National Institute for Health and Care Excellence

Brain tumours (primary) and brain metastases in adults

Evidence reviews for the investigation, management and follow-up of glioma

NICE guideline NG99

Evidence Report A

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Final

These evidence reviews were developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Investigation, management and follow-up of glioma

This Evidence Report contains information on 8 review

s relating to the investigation, management and follow-up of glioma. The Evidence Report is split into 3 sections:

- investigation of suspected glioma, which contains 2 reviews
  - imaging for suspected glioma
  - use of molecular markers to determine prognosis or guide treatment for glioma
- management of glioma, which contains 5 reviews
  - initial surgery for suspected low-grade glioma
  - further management of newly diagnosed low-grade glioma
  - management of newly diagnosed high-grade glioma following surgery or if surgery is not possible (or has been declined)
  - management of recurrent high-grade glioma (recurrent grade III and grade IV glioma)
  - techniques for resection of glioma
- follow-up for glioma, which contains 1 review
  - follow-up for glioma.

Investigation of suspected glioma

Imaging for suspected glioma

Review question

What is the most effective imaging strategy in newly diagnosed glioma and meningioma?

(Note that this review considers only the portion of the review question relating to glioma; see Evidence Report B for details on the portion of the review relating to meningioma.)

Introduction

The purposes of imaging at tumour presentation are to:

- identify the anatomical extent of tumour
- identify tumour relationship to critical brain areas/structures
- exclude non-tumour diagnoses
- predict tumour grade/biology/genetics
- predict likely future behaviour to stratify treatment
- identify sites for biopsy.

This systematic review explores the evidence for imaging strategies for patients with radiologically suspected glioma or meningioma. Under consideration are the imaging techniques, or combination of techniques, that provide the information necessary to make a putative diagnosis and plan appropriate treatment. MRI is the most commonly used imaging test after CT, although CT is usually the method by which a tumour is initially suspected and so MRI is used to give more information. Standard structural MRI can be performed in a number of different ways, including the use of a number of advanced techniques.

PICO table

Table 1: Summary of the protocol (PICO table)

Population	Adults with a radiologically (by CT scan or MRI scan) suspected glioma (high or low-grade)
Intervention	• Standard MRI alone: ○ standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2) Plus one of the following advanced tests: • advanced MRI: ○ MR Spectroscopy (chemical shift imaging) ○ diffusion imaging (DWI/DTI) tensor imaging (DTI) ○ perfusion imaging (DSC, DCE, ASL will not be looked at separately) ○ structural imaging • PET-CT (FDG: FET, MET, Choline-PET) • PET-MRI (FDG: FET, MET, Choline-PET)
Reference standard (test)	Pathology (histology and, where appropriate molecular testing) or clinical/radiological follow-up if there is not biopsy

Outcome	Critical:
	• health related quality of life
	• diagnostic test accuracy, including:
	  ○ sensitivity
	  ○ specificity
	  ○ likelihood ratios
	For detecting:
	  ○ high-grade glioma present (WHO grade III and IV) versus high-grade glioma absent
	  ○ low-grade glioma present (WHO grade I and II) versus low-grade glioma absent
	  ○ high-grade glioma (WHO grade III and IV) versus low-grade glioma (WHO grade I and II)

ASL arterial spin labelling; CT computer tomography; DCE dynamic contrast-enhancement; DSC dynamic susceptibility contrast; DTI diffusion tensor imaging; DWI diffusion weighted imaging; FDG 2-deoxy-2-(18)fluoro-D-glucose; FET (18)F-fluoro-ethyl-l-tyrosine; MET (11)C-methionine; MRI magnetic resonance imaging; PET-CT positron emission tomography - computed tomography; PET-MRI positron emission tomography - magnetic resonance imaging; WHO World Health Organisation.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Four studies (N=396) were included in the review (Caulo 2014, Law 2003, Qin 2017, and Zou 2011).

The evidence included in this review consisted of retrospective and prospective cohort studies meeting the PICO criteria and published from 2002 as it was when standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2) was first used. Of the included studies, 2 were from China (Zou 2011; Qin 2017), 1 from Italy (Caulo 2014) and 1 from the USA (Law 2003). The size of the population ranged from 30 (Zou 2011) to 160 (Law 2003).

Studies involved adults with a radiologically (by CT or MRI scan) suspected (high- or low-grade) glioma. No evidence was retrieved for meningioma. In all studies, adults underwent standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2) along with an advanced technique, including: diffusion weighted imaging (DWI), diffusion tensor imaging (DTI) and perfusion weighted imaging (PWI) (Caulo 2014); magnetic resonance spectroscopy (MRS) and DTI (Zou 2011); perfusion MRI and proton MRS (Law 2003) or DWI alone (Qin 2017). In order to assess whether standard MRI or standard MRI in combination with an advanced MRI technique had more sensitivity to characterise radiologically suspected glioma and meningioma, the results from both types of strategies are reported in the guideline review, provided the tests were conducted in the same sample of people. Studies that reported individual results for standard MRI or an advanced MRI technique were not included as they were non-comparative and therefore may have been influenced by factors such as patient characteristics.

No evidence was identified for PET-MRI or PET-CT. Data-driven models were run by the included studies and numerical cut-off values from the parameters generated by these advanced techniques were reported and published in the article. This permitted a determination of the sensitivity and specificity of the different imaging strategies for identification of high-grade glioma (WHO grade III and IV) versus low-grade glioma (WHO grade I and II). All the studies used histology as the reference standard.

This review reports diagnostic accuracy outcomes such as sensitivity and specificity for high-grade glioma versus low-grade glioma. No evidence was retrieved for high-grade glioma present versus high-grade glioma absent or for low-grade glioma present versus low-grade glioma absent. No test-and-treat trials were identified, therefore no patient-reported outcomes such as quality of life are reported in the review. Data from the included studies could not be pooled due to differences in imaging strategies, therefore the clinical evidence is descriptive and is presented study by study.

For details on clinical evidence which met the inclusion criteria of the second part of this review (on meningioma) see Evidence Report B.

A summary of these studies is provided in Table 2 and the results along with the quality of the evidence for each outcome are listed in Table 3 - Table 17 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Index test (1) and index test (2)	Reference standard	Population	Outcomes
Caulo 2014 Italy	Conventional MRI Pre- and postgandolinium enhanced Three-dimensional turbo field-echo T1-weighted Fluid-attenuated inversion recovery T1-weighted fast field echo Advanced MRI imaging Diffusion-weighted imaging Diffusion-tensor imaging MR spectroscopy Perfusion-weighted imaging	Histology	Adults with radiologically (MRI) suspected glioma (N=110)	Sensitivity and specificity for identification of high- versus low - grade glioma. Each suspected glioma was evaluated with 3 different methods: semi quantitative, qualitative and quantitative
Law 2003 USA	Conventional MRI 1.5 T unit	Histology	Adults with radiologically (MRI)	Sensitivity and specificity for identification of

Study	Index test (1) and index test (2)	Reference standard	Population	Outcomes
	Localising sagittal T1-weighted image obtained followed by non-enhanced axial T1-weighted, axial fluid-attenuated inversion-recovery, and T2-weighted images. Advanced MRI Dynamic contrast-enhanced perfusion MRI		suspected glioma (N=160)	high- versus low - grade glioma
Qin 2017 China	Conventional MRI T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Axial contrast-enhanced T1WI was repeated after intravenous administration of 0.1mmol/kg of gadolinium contrast gadopentetate dimeglumine. Advanced MRI DWI scans used the SE/EPI sequence, and the diffusion coefficient of sensitivity as selected as 0.1000 s/mm^2.	Histology	Adults with radiologically (MRI) suspected glioma (N=66)	Sensitivity and specificity for identification of high- versus low - grade glioma
Zou 2011 China	Conventional MRI T-1 weighted, T-2 weighted and FLAIR sequence Advanced MRI MRS imaging DTI	Histology	Adults with radiologically (MRI) suspected glioma (N=30)	Sensitivity and specificity for identification of high- versus low - grade glioma

DTI Diffusion tensor imaging; DWI diffusion weighted imaging; FDG fluorodeoxyglucose; FLAIR Fluid attenuation inversion recovery; MR magnetic resonance; MRI magnetic resonance imaging; MRS magnetic resonance spectroscopy; PET CT Positron emission tomography–computed tomography.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for the discrimination of high-grade glioma versus low-grade glioma are presented in Table 3 to Table 17.

Table 3: Summary clinical evidence profile for colour map images derived from PWI, MRS and the following cut-off data: 1.75 rCBV, 1.5 for Choline, 1.5 Cho/NAA (identification of high-grade glioma versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR +	LR-	N	Quality of the evidence (GRADE)	Comments/study
81.6% (71 to 90%)	50% (32 to 68%)	1.6	0.3	110	Low[1]	Results of semi quantitative analysis from Caulo 2014

CI confidence interval; LR likelihood ratio
[1] Unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 4: Summary clinical evidence profile for conventional MRI sequences (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR +	LR-	N	Quality of the evidence (GRADE)	Comments/study
83% (73 to 91%)	61% (42 to 77%)	2.1	0.2	110	Low[1]	Results of qualitative analysis from Caulo 2014

CI confidence interval; LR likelihood ratio
[1] Interval between index test and reference standard unclear; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 5: Summary clinical evidence profile for DWI (ADC maps generated), DTI, MRS (Cho/Cr, NAA/Cr, Cho/NAA, lactate/Cr, and lipids/Cr) and PWI (blood volume and mean transit maps were generated) with a cut-off value of -0.3096 (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/study
84% (74 to 92%)	100% (89 to 100%)	n/a	0.15	110	Low[1]	Results of quantitative analysis from Caulo 2014

ADC apparent diffusion coefficient; CI confidence interval; LR likelihood ratio
[1] unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data.

Table 6: Summary clinical evidence profile for DWI (ADC maps generated), DTI, MRS (Cho/Cr, NAA/Cr, Cho/NAA, lactate/Cr, and lipids/Cr) and PWI (blood volume and mean transit maps were generated) with a cut-off value of -0.3096

without including oligodendroglioma (ODG) (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/Study
88% (78 to 94%)	92% (75 to 99%)	11.39	0.13	110	Low[1]	Results of quantitative analysis from Caulo 2014

ADC apparent diffusion coefficient; CI confidence interval; LR likelihood ratio
[1] unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data.

Table 7: Summary clinical evidence profile for conventional MRI (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/Study
72% (64 to 80%)	65% (48 to 79%)	2.0	0.4	160	Low[1]	Law 2003

CI confidence interval; LR likelihood ratio
[1] unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 8: Summary clinical evidence profile for threshold values for rCBV [perfusion MRI] (identification of high- versus low-grade glioma)

Description	rCBV	Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments /Study
Minimum C2 error[2]	1.75	95% (89 to 98%)	57% (41 to 73%)	2.20	0.08	160	Low[1]	Law 2003
Minimum C1 error[3]	2.97	72% (64 to 80%)	88% (73 to 96%)	5.80	0.31	160	Low[1]	Law 2003
Same sensitivity as cMRI[4]	2.97	72% (64 to 80%)	88% (73 to 96%)	6.00	0.31	160	Low[1]	Law 2003
Same specificity as cMRI[5]	2.18	88% (80 to 93%)	65% (48 to 79%)	2.50	0.19	160	Low[1]	Law 2003

CI confidence interval, cMRI conventional magnetic resonance imaging; LR likelihood ratio; rCBV relative cerebral blood volume.
[1] unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
[2] C2 the percentage of observed data points misclassified
[3] C1 1 – (sensitivity)/2. This maximises the average of sensitivity and specificity
[4] Same sensitivity as cMRI = the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI
[5] Same specificity as cMRI= the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI

Table 9: Summary clinical evidence profile for threshold values for Cho/Cr (perfusion MRS) (identification of high- versus low-grade glioma)

Description	Cho/ Cr	Sensitivity (95%CI)	Specificity (95% CI)	LR +	LR-	N	Quality of the evidence (GRADE)	Comments /Study
Minimum C2 error[2]	1.08	97% (93 to 99%)	13% (0.4 to 27%)	1.1	0.2	160	Low[1]	Law 2003
Minimum C1 error[3]	1.56	76% (67 to 83%)	47% (32 to 64%)	1.4	0.5	160	Low[1]	Law 2003
Same sensitivity as cMRI[4]	1.61	72% (64 to 80%)	50% (34 to 66%)	1.4	0.5	160	Low[1]	Law 2003
Same specificity as cMRI[5]	1.88	55% (46 to 64%)	65% (48 to 79%)	1.5	0.6	160	Low[1]	Law 2003

Cho/Cr choline [Cho] / creatine [Cr]; CI confidence interval; cMRI conventional magnetic resonance imaging; LR likelihood ratio; rCBV relative cerebral blood volume.
[1] unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
[2] C2 the percentage of observed data points misclassified
[3] C1 1 – (sensitivity)/2. This maximises the average of sensitivity and specificity
[4] Same sensitivity as cMRI = the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI
[5] Same specificity as cMRI= the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI

Table 10: Summary clinical evidence profile for threshold values for Cho/NAA (perfusion MRS) (identification of high- versus low-grade glioma)

Description	Cho /NAA	Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments /Study
Minimum C2 error[3]	0.75	97% (92 to 99%)	10% (0.3 to 24%)	1.07	0.08	160	Low[1]	Law 2003
Minimum C1 error[4]	1.60	74% (65 to 82%)	63% (46 to 77%)	1.90	0.40	160	Low[1]	Law 2003
Same sensitivity as cMRI[5]	1.66	72% (64 to 80%)	63% (46 to 77%)	1.94	0.44	160	Very low[1,2]	Law 2003
Same specificity as cMRI[6]	1.78	68% (58 to 76%)	65% (48 to 79%)	1.94	0.49	160	Low[1]	Law 2003

Cho/NAA Cho/N-acetylaspartate; CI confidence interval; cMRI conventional magnetic resonance imaging; LR likelihood ratio; MRS magnetic resonance spectroscopy.
[1] unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
[2] The difference between confidence limits was >0.25 for sensitivity
[3] C2= the percentage of observed data points misclassified
[4] C1= 1 – (sensitivity)/2. This maximises the average of sensitivity and specificity
[5] Same sensitivity as cMRI = the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI
[6] Same specificity as cMRI= the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI

Table 11: Summary clinical evidence profile for threshold values for rCBV, and Cho/NAA ratio together (identification of high- versus low-grade glioma)

Description	Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments /Study
Minimum C2 error[2]	93% (87 to 97%)	60% (43 to 75%)	2.3	0.1	160	Low[1]	Law 2003
Minimum C1 error[3]	71% (62 to 79%)	93% (80 to 98%)	10.1	0.3	160	Low[1]	Law 2003
Same sensitivity as cMRI[4]	72% (64 to 80%)	88% (73 to 96%)	5.8	0.3	160	Low[1]	Law 2003
Same specificity as cMRI[5]	89% (82 to 94%)	65% (48 to 79%)	2.5	0.1	160	Low[1]	Law 2003

Cho/NAA Cho/N-acetylaspartate; CI confidence interval; cMRI conventional magnetic resonance imaging; LR likelihood ratio; MRS magnetic resonance spectroscopy; rCBV relative cerebral blood volume.
[1] unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
[2] C2 the percentage of observed data points misclassified
[3] C1 1 – (sensitivity)/2. This maximises the average of sensitivity and specificity
[4] Same sensitivity as cMRI = the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI
[5] Same specificity as cMRI= the threshold values used for rCBV were adjusted to provide the same sensitivity as cMRI

Results for MR spectroscopy and DTI

Table 12: Summary clinical evidence profile for conventional MRI (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/ study
72% (47 to 90%)	67% (35 to 90%)	2.1	0.4	30	Very low[1,2]	Zou 2011

CI confidence interval; MRI magnetic resonance imaging
[1] Unclear whether the results of the index test were interpreted without prior knowledge of the reference standard; the conduct or interpretation of the index test could have introduced bias; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
[2] The difference between confidence limits was >0.25 for sensitivity

Table 13: Summary clinical evidence profile for the combination of apparent diffusion coefficient (ADC) and N-acetylaspartate/choline ratio (NAA/Cho) [MRS and DTI] (identification of high- versus low-grade glioma)

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/s tudy
83% (59 to 96%)	100% (74 to 100%)	n/a	0.1	30	Low[1]	Zou 2011

ADC apparent diffusion coefficient; CI confidence interval; LR likelihood ratio; MRI magnetic resonance imaging.
[1] Unclear whether the results of the index test were interpreted without prior knowledge of the reference standard; the conduct or interpretation of the index test could have introduced bias; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Results for conventional MRI (T2 WI - FLAIR GLCM Cluster Shade and T1W1-CE GLCM Entropy on the T1W1-CE sequence) and DWI (ADC homogeneity on the ADC map)[a]

Table 14: Summary of clinical evidence profile for T2 WI - FLAIR GLCM Cluster Shade

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/ study
75% (59 to 87%)	84.6% (65 to 96%)	4.8	0.2	66	Very low[1,2]	Qin 2017

ADC apparent diffusion coefficient; CI confidence interval; DWI diffusion weighted imaging; FLAIR Fluid attenuation inversion recovery; GLCM Gray level co-occurrence matrix; LR likelihood ratio
[1] data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding
[2] The difference between 95% CI confidence limits was > 0.25 for sensitivity

Table 15: Summary clinical evidence profile for T1W1-CE GLCM Entropy on the T1W1-CE sequence

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/ study
97.5% (87 to 100%)	80.8% (61 to 93%)	5.07	0.03	66	Low[1]	Qin 2017

CI confidence interval; GLCM Gray level co-occurrence matrix; LR likelihood ratio
[1] data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding

Table 16: Summary clinical evidence profile for ADC homogeneity on the ADC map

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/ study
97.5% (87 to 100%)	80.8% (61 to 93%)	5.07	0.03	66	Low[1]	Qin 2017

CI confidence interval; GLCM Gray level co-occurrence matrix; LR likelihood ratio
[1] data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding

Table 17: Summary clinical evidence profile for combined features of conventional MRI, DWI and ADC

Sensitivity (95%CI)	Specificity (95% CI)	LR+	LR-	N	Quality of the evidence (GRADE)	Comments/ study
90% (76 to 97%)	89% (70 to 98%)	8.1	0.1	63	Low[1]	Qin 2017

CI confidence interval; LR likelihood ratio; MRI magnetic resonance imaging.

[a] This study only reported figures for radiomic features found to have statistical differential features for distinguishing HGG vs LGG

[1] data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding; not all patients underwent DWI

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

Conventional MRI, PWI, MRS, DWI and PWI for differentiation between high- and low-grade glioma

- One retrospective cohort study (N=110) reported that the sensitivity and specificity of:
  - PWI and MRS was 81.6% (71 to 90%) and 50% (32 to 68%) respectively (low quality);
  - conventional MRI yielded a sensitivity and specificity of 83% (73 to 91%) and 61% (42 to 77%) respectively (low quality evidence);
  - ROC analysis of the glioma grading index yielded a sensitivity and specificity of 84% (74 to 92%) and 100% (89 to 100%) respectively (low quality);
  - ROC analysis of the glioma grading index without including oligodendroglioma yielded a sensitivity and specificity of 88% (78 to 94%) and 92% (75 to 99%) respectively (low quality evidence).

Conventional MRI, perfusion MRI, and perfusion MRS for differentiation between high- and low-grade glioma

- One retrospective cohort study (N=160) reported that the sensitivity and specificity of:
  - conventional MRI was 72% (64 to 80%) and 65% (48 and 79%), respectively (low quality evidence);
  - perfusion MRI (rCBV cut-off of 1.75, minimum c2 error) was 95% (89 to 98%) and 57% (41 to 73%), respectively (low quality evidence);
  - perfusion MRI (rCBV cut-off of 2.97, minimum c1 error) was 72% (64 to 80%) and 88% (73 to 96%), respectively, (low quality evidence);
  - perfusion MRI (rCBV cut-off of 2.97, same sensitivity as cMRI) was 72% (64 to 80%) and 88% (73 to 96%) respectively (low quality evidence);
  - perfusion MRI (rCBV cut-off of 2.18, same specificity as cMRI) was 88% (80 to 93%) and 65% (48 to 79%), respectively (low quality evidence).
- One retrospective cohort study (N=160) reported that the sensitivity and specificity of:
  - perfusion MRS (Cho/Cr cut-off of 1.08, minimum c2 error) was 97% (93 to 99%) and 13% (0.4 to 27%), respectively, (low quality evidence);
  - perfusion MRS (Cho/Cr cut-off of 1.56, minimum c1 error) was 76% (67 to 83%) and 47% (32 to 64%), respectively, (low quality evidence);
  - perfusion MRS (Cho/Cr cut-off of 1.61, same sensitivity as cMRI) was 72% (64 to 80%) and 50% (34 to 66%), respectively, (low quality evidence);
  - perfusion MRI (Cho/Cr cut-off of 1.88, same specificity as cMRI) was 55% (46 to 64%) and 65% (48 to 79%), respectively, (low quality evidence).
- One retrospective cohort study (N=160) reported that the sensitivity and specificity of:

  - perfusion MRS (Cho/NAA cut-off of 0.75, minimum c2 error) was 97% (92 to 99%) and 10% (0.3 to 24%),respectively, (low quality evidence);
  - perfusion MRS (Cho/NAA cut-off of 1.60, minimum c1 error) was 74% (65 to 82%) and 63% (46 to 77%),respectively, (low quality evidence);
  - perfusion MRS (Cho/NAA cut-off of 1.66, same sensitivity as cMRI) was 72% (64 to 80%) and 63% (46 to 77%),respectively, (very low quality evidence);
  - perfusion MRI (Cho/NAA cut-off of 1.78, same specificity as cMRI) was 68% (58 to 76%) and 65% (48 to 79%), respectively, (low quality evidence).
- One retrospective cohort study (N=160) reported that the sensitivity and specificity of:
  - for threshold values for rCBV, and Cho/NAA ratio together (minimum c2 error) was 93% (87 to 97%) and 60% (43 to 75%),respectively, (low quality evidence);
  - perfusion MRS threshold values for rCBV, and Cho/NAA ratio together (minimum c1 error) was 71% (62 to 79%) and 93% (80 to 98%), respectively (low quality evidence);
  - threshold values for rCBV, and Cho/NAA ratio together (same sensitivity as cMRI) was 72% (64 to 80%) and 88% (73 to 96%),respectively, (low quality evidence);
  - threshold values for rCBV, and Cho/NAA ratio together (same specificity as cMRI) was 89% (82 to 94%) and 65% (48 to 79%), respectively, (low quality evidence).

MR spectroscopy and DTI and conventional MRI for differentiation between high- and low-grade glioma

- One prospective cohort study (N=30) reported that the sensitivity and specificity of:
  - conventional MRI was 72% (49 to 90%) and 67% (35 to 90%), respectively;
  - the combination of ADC and NAA/Cho [MRS and DTI] was 83% (59 to 96%) and 100% (74 to 100), respectively (low quality evidence).

Conventional MRI (T2 WI - FLAIR GLCM Cluster Shade and T1W1-CE GLCM Entropy on the T1W1-CE sequence) and DWI (ADC homogeneity on the ADC map) for differentiation between high- and low-grade glioma

- One retrospective cohort study (N=66) reported that the sensitivity and specificity of:
  - T2 WI - FLAIR GLCM Cluster Shade was 75% (59 to 87%) and 84.6% (65 to 96%) respectively (very low quality evidence);
  - T1W1-CE GLCM Entropy on the T1W1-CE sequence was 97.5% (87 to 100%) and 80.8% (61 to 93%), respectively (low quality evidence);
  - ADC GLCM homogeneity was 97.5% (87 to 100%) and 80.8% (61 to 93%), respectively (low quality evidence);
  - for the combination of T2 WI - FLAIR GLCM Cluster Shade, T1W1-CE GLCM Entropy on the T1W1-CE sequence and ADC homogeneity on the ADC map 90% (76 to 97%) and 89% (70 to 98%), respectively (low quality evidence).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Patient outcomes, as reflected by the sensitivity and specificity of the diagnostic test, were considered critical for decision-making in this review. Sensitivity was used to evaluate imprecision, as an early accurate identification of high-grade glioma confers benefits and reduces the harmful consequences of a misdiagnosis. Likelihood ratios were also considered to be critical diagnostic outcomes because they provide information about a test's usefulness in assisting the healthcare professional to make a diagnosis. Health-related quality of life

(especially anxiety) was also considered critical for decision-making, as waiting for additional imaging tests may delay a diagnosis.

The quality of the evidence

The quality of the evidence ranged from very low to moderate as assessed by a modified version of GRADE, using the same principles as GRADE for assessing the quality of the evidence, but a different form of presentation as GRADE is not yet available for diagnostic questions.

The domain 'risk of bias' was assessed with the QUADAS 2 checklist. The identified studies had serious or very serious risks of bias. Some of the main concerns were related to lack of information regarding the time interval between the index test and the reference standard being performed or lack of clarity about whether the index test was interpreted without prior knowledge of the results of the reference standard. None of the included studies used a pre-specified threshold for what constituted a positive test result, but rather chose a threshold based on the study data. This is an important source of bias that is associated with inflated test accuracy. The committee adjusted for this potential bias by interpreting the data on high- and low-grade tumour discrimination cautiously, and recommending further MR tests if appropriate.

No serious issues were found regarding inconsistency (heterogeneity) since only single studies were included. No serious issues were found regarding indirectness either.

In evaluating the accuracy and staging measures, imprecision was assessed using the 95% CI of sensitivity as the primary measure of interest because the harmful consequence of false negatives (for example, death caused by a WHO grade III or IV glioma incorrectly identified as WHO grade I or II) were considered to be worse than the harmful consequence of false positives (for instance, unnecessary surgery or treatment on a WHO grade I or grade II glioma). Most of the studies were considered to have 'serious' imprecision due to wide (>0.25) differences between the upper and lower limits of the 95% CI.

The committee believed the evidence was of good enough quality enough to make recommendations on, as it was consistent with their clinical experience.

The committee did not choose to make a research recommendation, as they believed the evidence base to be sufficient to justify their recommendations given the difficulty of conducting definitive trials in the area. The committee were aware of ongoing trials in on advanced scanning techniques and therefore believed that a research recommendation to help refine their existing recommendations would have a limited marginal impact on future imaging strategies once these trials had reported.

Benefits and harms

Low to moderate quality evidence from retrospective cohort studies showed that standard structural MRI has good sensitivity at discriminating high and low-grade gliomas, and excellent sensitivity and specificity at discriminating tumour from non-tumour. This is consistent with the committee's own knowledge and experience. The evidence was complex and demonstrated that optimal tumour characterisation depended on the exact parameters set on the MRI machine. The committee determined that these parameters should be left to the discretion of the operator, as it was not clear from the evidence whether the protocol used in the study would apply to all types of tumours across all types of machine however the committee were satisfied that even without the careful optimisation done in these papers that MRI would have value at identifying clinically important features of the glioma.

Following a consistent imaging protocol can reduce delays by reducing the need for repeat imaging. However, this could not be demonstrated from published evidence (which should follow a consistent protocol by definition). To avoid ambiguity the committee recommended an imaging protocol they believed was the minimum standard for imaging acquisition.

The committee described how the management of glioma required input from a wide variety of specialists, particularly in the determination of initial surgery (either for treatment of to get a biopsy). Consequently as soon as a possible glioma is identified the person with this glioma should be referred to a specialist multidisciplinary team. The committee explained how multidisciplinary teams would normally manage a glioma, but that this recommendation would bring the team together faster, which they hoped would improve the overall quality of the person's care.

The committee was concerned about the risk of MR imaging misclassifying low-grade and high-grade gliomas due to insufficient sensitivity and the potential harmful effect of this, such as delays in interventions. To help prevent this the committee recommended advanced MRI techniques, particularly MR perfusion and MR spectroscopy, should be considered for assessing malignant features in suspected low-grade glioma tumours. This recommendation was made on the basis of the committee's clinical experience that these techniques could sometimes help with classification. The committee considered the extra cost of these techniques and determined that this could be warranted as the images could show structural features of the tumour which conventional MRI could not (for example, perfusion hotspots). These could have a critical impact in planning later treatment.

The potential benefits of accurate diagnosis are improved characterisation of tumours that leads to different management strategies (for example, high-grade gliomas may require treatment to begin more quickly, and with different therapies). Other benefits include a better use of the resources available such as support groups or strategies to help cope with the symptoms. The committee believe a third benefit may be to empower the person with a brain tumour, allowing them to participate in long-term planning and to help develop realistic expectations, which can reduce stress.

The potential harms associated with inaccurate diagnosis are: inappropriate interventions, such as a low-grade glioma or non-tumour being treated more aggressively than necessary; or delay in treatment if a high-grade tumour is misclassified as low-grade. The concomitant morbidity and mortality may increase in both cases. These risks may occur through both the underuse and overuse of diagnostic imaging tests, and so represent a potential harm of the recommendations.

The committee discussed the consequences of false negatives (diagnosing a high-grade glioma as a low-grade glioma) and false positives (diagnosing a low-grade glioma as a high-grade glioma). In the context of this systematic review, the higher the sensitivity of an imaging strategy, the more likely it is that a high-grade glioma will be accurately identified. A higher specificity means an imaging strategy will be more likely to correctly identify a person with a low-grade glioma as having a low-grade glioma. In any given diagnostic test, there is normally a trade-off between these accuracy measurements. The committee prioritised sensitivity, as they wanted to identify as many true cases of high-grade glioma as possible, since the consequences for underdiagnosing the tumour are usually much worse than overdiagnosing it.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

There is currently variation in practice with different imaging protocols being used by different centres in different circumstances. For centres currently undertaking a reduced MR protocol when compared with the committee-recommended core sequences, there may be an increase in resource use in implementing the guideline recommendations through increased MR machine time, radiographer and radiologist time. However, these increases in resource use will be at least partially recouped through a clearer patient pathway reducing the need for repeat MR imaging; for example, when initial imaging is not compatible with neuronavigational equipment. Reduction in resource use will also be made through

reductions in misdiagnosis (leading to reimaging, inappropriate treatment and greater costs of treating adverse events) given the high sensitivity and specificity of standard structural MRI.

The committee believed that the recommendations around advanced imaging techniques, including MR perfusion and MR spectroscopy, may lead to minor increases in resource use but would not lead to major increases. There would be a large resource impact if hospitals without this technology were expected to provide it, but it is more likely that patients will be referred to appropriate specialist centres, where these techniques are usually available, and performed according to local expertise and experience. As the majority of these patients are already referred to specialist centres it was thought that any increase in referrals would be minimal.

While it was unclear what the overall impact on resource use would be, more diagnostically accurate imaging protocols would lead to increases in both life expectancy and quality of life in this patient group. Missed diagnoses can lead to potential harmful effects on both length and quality of life and lead to misuse of resources through inappropriate and potentially harmful interventions. Even if there were increases in resource use with the recommendations they would not be large.

Other factors the committee took into account

The committee was aware that imaging provision was variable at the moment. The recommendations they have made should improve consistency in both specialist and non-specialist centres (for example district general hospitals).

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Use of molecular markers to determine prognosis or guide treatment for glioma

Review question

What are the most useful molecular markers to determine prognosis / guide treatment for gliomas?

Introduction

Molecular markers are used for a variety of important decisions concerning the treatment of brain tumours, for example confirming the presence/absence of a tumour and improving stratification of known tumours. For each tumour type, molecular markers can be divided into 3 categories – those which are critical to test for, those which are not critical to test for but may offer benefit in uncommon cases, and those which offer no benefit if tested for.

Molecular markers are a new and emerging area in the treatment of brain tumours, and so guidance is needed to bring best practice to the attention of clinicians. It is thought that good molecular profiling can help to improve outcomes for people with tumours, but to perform molecular profiling well is difficult.

The objective of this review is to determine if there are any subgroups of patients for whom molecular markers which are currently regarded as noncritical might be valuable enough to always offer. Molecular markers of specific interest to the committee were: proto-oncogene B-Raf / v-Raf murine sarcoma viral oncogene homolog B (BRAF) v600e mutation; telomerase reverse transcriptase (TERT) promoter mutation; and epidermal growth factor receptor gene (EGFR) amplification. Other prognostic factors to be taken into account when evaluating these included isocetrate dehydrogenase (IDH) mutation.

PICO table

Table 18: Summary of the protocol (PICO table)

Population	Adults (aged 16 years and over) with initial glioma at the time of testing for the molecular markers (i.e., these people do not have recurrent glioma)
Prognostic factors	Molecular markers: • BRAF v600e mutation • TERT promoter mutation • EGFR amplification
Comparison	Analyses of eligible studies should control for the effect of the other prognostic factors listed below when examining the prognostic effect of the molecular markers (to examine the additional prognostic effect of the markers once the effect of other variables have been taken into account): • age • tumour grade • tumour histological subtype • treatment (first line) • IDH mutation • 1p19Q
Outcome	Critical: • overall survival

	• progression-free survival For BRAF v600e mutation group only: • response to BRAF inhibitors (vemurafenib, daburafenib, tremetanib)

BRAF proto-oncogene B-Raf / v-Raf murine sarcoma viral oncogene homolog B; EGFR epidermal growth factor receptor gene; IDH isocetrate dehydrogenase; TERT telomerase reverse transcriptase.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource impact

Table 19: Resource impact and unit costs associated with the use of molecular markers to determine prognosis or guide treatment for glioma

Resource	Unit costs	Source
MGMT methylation test	£90 per test	All Wales Genetics Laboratory (2016)
1p/19q test	£250 per test	All Wales Genetics Laboratory (2016)
1DH-1 test	£250 per test	All Wales Genetics Laboratory (2016)
BRAF Test	£85 per test	All Wales Genetics Laboratory (2016)
Unit costs only include cost of molecular marker test. Additional time and other costs collecting samples and interpreting results are not included		

Evidence statements

No evidence was identified.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised only 2 outcomes, which were both critical; overall survival and progression-free survival. This is because the molecular markers are only helpful if they guide treatment or inform prognosis, and survival is the best measure of this. The only

exception to this was in the BRAF group of tumours, where response to BRAF inhibitors is thought to represent a sufficiently primary endpoint that it could be used.

The quality of the evidence

The clinical evidence search identified no studies that met the inclusion criteria for this review.

The committee decided that it would be possible to make some weak recommendations on the basis of their clinical judgement as from their experience molecular markers were an area of considerable interest to clinicians and people with tumours.

The committee did not make any research recommendations in this area because several large trials are due to report after publication of the guideline and these should provide an evidence base relevant to this topic.

Benefits and harms

Molecular markers are a new and evolving area of the treatment of gliomas and they can be more complex than histology alone. Given the lack of evidence on the effectiveness of these markers, the committee agreed not to make recommendations listing which molecular markers should be used, or could be used in certain circumstances. The committee agreed they would highlight the WHO guidance, which would always be up to date, and contain technical detail and evidence which could not be reviewed by the committee because it was outside the scope of the guideline. The committee chose to highlight some markers in particular (IDH1 and IDH2 mutations, ATRX mutations, 1p/19q codeletion, histone H3.3 K27M mutations and BRAF fusion genes) to ensure that these tests were consistently performed, and to provide some guidance for people with tumours on what the molecular markers are for. The committee emphasised that these tests should only be used where the result will provide better diagnostic or prognostic information leading to either better targeted treatment or greater information.

Based on their experience, the committee additionally highlighted MGMT and TERT mutations as being ones which specifically helped establish prognosis, although they were of limited relevance in diagnosing the tumour (MGMT) or guiding treatment (TERT). The committee discussed how people with tumours would probably value the extra prognostic information from these tests even if they were not strictly required for diagnosis by the WHO standard.

The technology and understanding of molecular markers is evolving rapidly. In particular, several molecular markers are available for which there is not currently good evidence that the results of the marker can be used to guide treatment. The committee recommended that if such treatment became available that the markers be considered, on the basis of their clinical experience that similar markers have been useful in the past.

The committee described how there are 3 main benefits to establishing a molecular diagnosis; it can identify the type of tumour, help inform prognosis and help guide treatment. Depending on the precise type of tumour and diagnosis these can range from very large and obvious benefits to benefits of questionable value. Although there was no evidence for the markers which the committee looked for in this evidence review, the committee pointed to high quality evidence of the importance of more established markers coming from subgroup analysis in other reviews in this evidence report.

There are no meaningful harms to establishing a molecular diagnosis from an existing sample other than cost. However, obtaining a sample for testing requires a biopsy, which can carry risks for the person with the tumour. While the committee discussed how those with a tumour appearing high-grade would almost always be offered surgical treatment (and hence biopsy carries no additional risk), the balance of benefits and harms for people with a tumour appearing low-grade is discussed in the section on ‘Initial surgery for suspected low-grade

glioma'. Additionally, the committee discussed how explaining the results of the test to a person could distress them, particularly if the news was likely to be unwelcome.

The committee concluded that the benefits of establishing a molecular diagnosis far outweighed the potential harms, especially if surgery is to be undertaken anyway.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

Molecular markers are a new technology in the area of brain tumours and consequently there is large variation in practice across the NHS in England. Some centres already test widely and routinely while others will do very little. It is inevitable that this recommendation will lead to an increase in molecular tests being performed with associated costs. The time and costs of implementing these interventions will vary widely across centres depending on how mature their programme is.

The committee emphasised that these tests should only be used where the result will provide better diagnostic or prognostic information leading to either better targeted treatment or greater information, and a corresponding reduction in anxiety in patients and potential increase in quality of life. While the committee acknowledged these interventions would be cost increasing it would be balanced against improvements in quality of life. Molecular testing is also likely to become more cost effective as new targeted treatments become available and people better matched with interventions.

Other factors the committee took into account

The committee discussed how it was difficult to 'future proof' these recommendations, as the field was evolving so rapidly. In the future, there may be additional molecular markers available to clinicians which were not included in the review protocol.

The committee discussed tissue banking for therapeutic and research purposes. The described how tissue banking for later testing was an integral part of using molecular information to guide treatment, and that this should be automatically undertaken by anyone reporting to the WHO standard. However they also described how tissue banking for the purpose of research was not yet universal. Tissue banking for research would not directly benefit the individual offering the tissue and therefore the committee decided it was inappropriate to make a recommendation on the topic. However the committee explained that many clinicians would want to discuss tissue banking for the purpose of research with the person with the tumour, and that such discussions could be interesting and empowering for the person with the tumour.

References

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Management of glioma

Initial surgery for suspected low-grade glioma

Review question

What is the optimal timing and extent of initial surgery for suspected low-grade glioma?

Introduction

Low-grade gliomas are a heterogeneous group of slow-growing primary brain tumours (WHO grades I and II) and account for 20-30% of all gliomas. Median survival varies according to a number of factors including age, performance status and histological subtype. Grade I gliomas in adults are a diverse group of tumours which can remain static for prolonged periods. Their management is often dictated by issues such as seizure control

The committee believe there is an intuitive plausibility to the idea that resecting as much of a tumour as possible as early as possible leads to better outcomes. However surgical resection carries risk, and the precise point at which the benefits of resection are outweighed by the harms of surgery is not well defined. This is complicated by the range and complexity of factors that can affect the potential benefits of resection or harms of surgery.

This is an important question for NICE as surgery for low-grade gliomas has never been formally evaluated in a prospective randomised trial. Patients and clinicians may be faced with the possibility of extended survival after extensive resections but at the risk of permanent and disabling neurological deficits.

PICO table

Table 20: Summary of the protocol (PICO table)

Population	Adults (aged 16 years and over) with suspected low-grade glioma on imaging suitable for surgical resection or biopsy
Intervention	• Biopsy/image-guided biopsy • Subtotal resection (partial) • Gross total resection (maximal)
Comparison	• Each other • Active monitoring (no surgery/biopsy)
Outcome	Critical: • progression-free survival • epilepsy / seizure control • neurological function ○ Neurological Function Scale or NIH stroke scale Important: • overall survival • time to tumour transformation (from low-grade to high-grade) • health-related quality of life. Of limited importance: • surgical mortality (intra-operative and 30-day postoperative)

NIH National Institutes of Health

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Seven comparative observational studies were included in this review, 3 of which were conducted in the USA (Alattar, 2017; Schupper, 2017; Youland, 2013), 2 in Germany (Coburger, 2016; Gousias, 2014), 1 in France (Pallud, 2014) and 1 in China (Yang 2013). The studies examined overall survival, progression-free survival, malignant progression-free survival, and neurological function after gross total resection (GTR), subtotal resection (STR), partial resection (PaR), biopsy (Bx) or no surgery (active monitoring). However, the patient population in all 7 studies was people with confirmed grade II glioma (and not suspected low-grade glioma, as specified in the guideline review protocol). No studies were found that met the inclusion criteria for patients with suspected low-grade glioma.

A summary of these studies is provided in Table 21 and the results along with the quality of the evidence for each outcome are listed in Table 22 to Table 28 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 21 provides a summary of the included studies.

Table 21: Summary of included studies

Study	Glioma	Intervention groups	Other treatment	Outcomes	Comments
Alattar, 2017	Grade II oligodendroglioma	-No surgery: N = 438 -Local excision / Bx: N = 550 -STR: N = 557. -GTR: N = 833.	Radiotherapy yes / no: N = 816 / 1491 (not split by resection group)	-Overall survival (measured as 75ST = months at which 25% of the patient population had died)	Serious risk of bias (uncontrolled confounders); N = 146 aged < 18 years; Population had confirmed, not suspected, LGG
Coburger, 2016	Grade II diffuse astrocytoma / oligoastrocytoma / oligodendroglioma	-Preoperatively planned GTR: N = 179 -Preoperatively planned STR: N = 109 -Intraoperative decision for STR (despite intended GTR): N = 64	N = 57; 22/57 received chemotherapy only; 25/57 had radiotherapy only; 10/57 patients received combined radiochemotherapy; 5/57 patients had GTR; 23/57 had	-Progression-free survival -Neurological function (new deficits)	Low risk of bias; Population had confirmed, not suspected, LGG

Study	Glioma	Intervention groups	Other treatment	Outcomes	Comments
		-Intraoperative decision for GTR (despite intended STR): N = 40	failed GTR; 29/57 had STR; 16/57 had recurrent surgery		
Gousias, 2014	Grade II supra-tentorial astrocytoma, oligodendroglioma or oligoastrocytoma,	- Biopsy: N = 11 (as there were not at least 50 patients in this group no more information will be reported about it, although the analyses are only reported relative to biopsy and have been included as such. This should be borne in mind when evaluating the results of this study) -STR: N = 75. -GTR: N = 62	STR: 2-4 patients in this group also had radiation and/or chemotherapy	-Progression-free survival -Malignant progression-free survival	Moderate risk of bias (unclear re missing data); Biopsy: N = 11; Population had confirmed, not suspected, LGG
Pallud, 2014	Diffuse grade II supra-tentorial astrocytoma, oligodendroglioma or oligoastrocytoma,	-Bx: N = 619 -PaR: N = 427 -STR: N = 313. -GTR: N = 150.	-Radiotherapy: N = 424 -Chemotherapy: N = 251 (not split by resection group)	-Malignant progression-free survival	Low risk of bias; Population had confirmed, not suspected, LGG
Schupper, 2017	Grade II astrocytoma	-No surgery: N = 1487 -Bx: N = 806 -STR: N = 904 -GTR: N = 916	Radiotherapy yes / no: N = 2109 / 1884 (not split by resection group)	- Overall survival:	Serious risk of bias (uncon-trolled con-founders); N = 528 aged < 18 years; Population had confirmed, not suspected, LGG
Yang, 2013	Grade II astrocytoma, oligodendroglioma, or oligoastrocytoma	-GTR: N = 357. -STR: N = 474.	Radiotherapy given / not given / unknown: 315 / 70 / 445 Chemotherapy given / not given / unknown: 106 / 275 / 450 (not split by resection group)	-Progression-free survival -Overall survival	Serious risk of bias (uncon-trolled confounder; missing data); Population had confirmed, not

Study	Glioma	Intervention groups	Other treatment	Outcomes	Comments
					suspected, LGG
Youland, 2013	Grade II astrocytoma, oligodendroglioma or oligoastrocytoma	-GTR: N = 176. -Radical STR (rSTR): N = 55. -STR: N = 118. -Bx: N = 222	Radiotherapy alone / chemotherapy alone / chemotherapy + radiotherapy / observation: 244 / 13 / 88 / 226 (not split by resection group)	-Progression-free survival -Overall survival	Serious risk of bias (uncontrolled confounder); Population had confirmed, not suspected, LGG

Bx biopsy; GTR gross total resection; LGG low-grade glioma; PaR partial resection; rSTR radical subtotal resection; STR subtotal resection.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question are presented in Table 22 to Table 28.

No meta-analyses were performed either because there were only data from 1 study for the outcomes within each treatment comparison or, when more than 1 study contributed data to an outcome within a treatment comparison, because the hazard ratios were adjusted for different covariates within the individual studies, and thus were not directly comparable.

Table 22: Summary clinical evidence profile for local excision/biopsy compared to no surgery (active monitoring) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	No surgery (active monitoring)	Local excision/biopsy			
Overall survival Follow-up: NR	Not estimable[1]	Not estimable[1]	HR 1.69 (1.15 to 2.48)	988 (1 study)	⊕⊖⊖⊖ very low[2,3,4]

CI confidence interval; HR hazard ratio; NR not reported.
[1] Event rate not reported
[2] Uncontrolled confounders
[3] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[4] 95% CI crosses the upper threshold for appreciable benefit (i.e., 1.2 as per the review protocol).

Table 23: Summary clinical evidence profile for subtotal resection (STR) compared to no surgery (active monitoring) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	STR	No surgery (active monitoring)			

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival Follow-up: minimum 120 months	Not estimable[1]	Not estimable[1]	HR 1.32 (1.14 to 1.53)	3197 (1 study)	⊕⊖⊖⊖ very low[2,3,4]

CI confidence interval; HR hazard ratio.
[1] Event rate not reported
[2] Uncontrolled confounders
[3] N = 528 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[4] 95% CI crosses the upper threshold for appreciable benefit (i.e., 1.2 as per the review protocol).

Table 24: Summary clinical evidence profile for local excision/biopsy compared to subtotal resection (STR) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Local excision/biopsy	STR			
Overall survival Follow-up: NR	Not estimable[1]	Not estimable[1]	HR 1.21 (0.83 to 1.76)	1107 (1 study)	⊕⊖⊖⊖ very low[2,3,4]
Progression-free survival Follow-up: median 59 months	Not estimable[1]	Not estimable[1]	HR 0.23 (0.11 to 0.49) and 0.87 (0.31 to 2.42)	86 (1 study)	⊕⊖⊖⊖ very low[5, 6, 7, 8]
Malignant progression-free survival Follow-up: 59-82 months	Not estimable[1]	Not estimable[1]	HR 0.35 (0.15 to 0.82) and 0.43 (0.35 to 0.53)	1018 (2 studies)	⊕⊖⊖⊖ very low[6,9,10]

CI confidence interval; HR hazard ratio; NR not reported; STR subtotal resection.
[1] Event rate not reported
[2] Uncontrolled confounders
[3] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[4] The confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm (i.e., 1.2 as per the review protocol).
[5] Unclear how much missing data in the study
[6] Population had confirmed, not suspected, low-grade glioma
[7] For 1 of the 2 estimates, the confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm and the lower threshold for appreciable benefit (i.e., 1.2 and 0.8, respectively, as per the review protocol).
[8] The authors performed 2 multivariate analyses in which they varied the levels of 1 of the covariates (eloquence of location), having 2 levels in 1 of the analyses and 3 levels in the other. The former multivariate analysis returned a HR of 0.865 (95% CI 0.308-2.421), p = 0.78 for STR (v biopsy), whereas the latter analysis returned a HR of 0.234 (95% CI 0.111-0.493), p < 0.001 for STR (v biopsy),
[9] Unclear how much missing data in 1 of the studies
[10] For 1 of the 2 estimates, the confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol).

Table 25: Summary clinical evidence profile for local excision/biopsy compared to gross total resection (GTR) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Local excision/biopsy	GTR			

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival Follow-up: NR	Not estimable[1]	Not estimable[1]	HR 1.06 (0.73 to 1.54)	1383 (1 study)	⊕⊖⊖⊖ very low[2,3,4]
Progression-free survival Follow-up: median 59 months	Not estimable[1]	Not estimable[1]	HR 0.04 (0.02 to 0.1) and 0.22 (0.07 to 0.72)	73 (1 study)	⊕⊖⊖⊖ very low[5, 6, 7]
Malignant progression-free survival Follow-up: 59-82 months	Not estimable[1]	Not estimable[1]	HR 0.05 (0.02 to 0.15) and 0.22 (0.16 to 0.32)	842 (2 studies)	⊕⊖⊖⊖ very low[7, 8]

CI confidence interval; HR hazard ratio; NR not reported.
[1] Event rate not reported
[2] Uncontrolled confounders
[3] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[4] The confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm and the lower threshold for appreciable benefit (i.e., 1.2 and 0.8, respectively, as per the review protocol).
[5] Unclear how much missing data in the study
[6] The authors performed 2 multivariate analyses in which they varied the levels of 1 of the covariates (eloquence of location), having 2 levels in 1 of the analyses and 3 levels in the other. The former multivariate analysis returned a HR of 0.221 (95% CI 0.067-0.723), p = 0.013 for GTR (v biopsy), whereas the latter analysis returned a HR of 0.039 (95% CI 0.016-0.096), p < 0.001 for GTR (v biopsy),
[7] Population had confirmed, not suspected, low-grade glioma.
[8] Unclear how much missing data in 1 of the studies

Table 26: Summary clinical evidence profile for gross total resection (GTR) compared to subtotal resection (STR) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	STR	**GTR**			
Overall survival Follow-up: minimum 120 months	Not estimable[1]	Not estimable[1]	HR 0.72 (0.6 to 0.85) and 0.78 (0.53 to 1.16)	3340 (2 studies)	⊕⊖⊖⊖ **very low**[2,3,4]
Progression-free survival Follow-up: mean 52 months	Not estimable[1]	Not estimable[1]	HR 0.44 (0.27 to 0.72) and 0.93 (0.75 to 1.15)	1074 (2 studies)	⊕⊖⊖⊖ **very low**[3, 5, 6, 7]
New neurological deficit Follow-up: mean 52 months	200 per 1000	94 per 1000 (50 to 180)	RR 0.47 (0.25 to 0.9)	243 (1 study)	⊕⊖⊖⊖ **very low**[3, 5, 8]

CI confidence interval; HR hazard ratio; NR not reported; *OR: odds ratio*.
[1] Event rate not reported
[2] Uncontrolled confounders in both studies and missing data in 1 of the studies
[3] Population had confirmed, not suspected, low-grade glioma in both studies; in 1 of the studies N = 528 aged < 18 years
[4] The confidence interval includes 0 (no effect) and crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the

review protocol) in 1 of the studies.
[5] Uncontrolled confounders and missing data in 1 of the studies
[6] One of the studies reports a HR of 0.44 (95% CI 0.27-0.72), whereas the other study reports a HR of 0.93 (95% CI 0.74-1.15)
[7] The confidence interval includes 0 (no effect) and crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol) in 1 of the studies
[8] The confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol)

Table 27: Summary clinical evidence profile for biopsy compared to partial resection (PaR) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Biopsy	PaR			
Malignant progression-free survival Follow-up: mean 82 months	Not estimable[1]	Not estimable[1]	HR 0.68 (0.58 to 0.80)	1046 (1 study)	⊕⊖⊖⊖ very low[2]

CI confidence interval; HR hazard ratio.
[1] Event rate not reported
[2] Population had confirmed, not suspected, low-grade glioma

Table 28: Summary clinical evidence profile for gross total resection (GTR)/radical subtotal resection (rSTR) compared to subtotal resection (STR)/biopsy (Bx) for patients with low-grade glioma

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	STR/Bx	GTR/rSTR			
Overall survival Follow-up: median 8.7 years	Not estimable[1]	Not estimable[1]	RR 0.61 (0.43 to 0.87)	571 (1 study)	⊕⊖⊖⊖ very low[2, 3,4]
Progression-free survival Follow-up: median 8.7 years	Not estimable[1]	Not estimable[1]	RR 0.45 (0.35 to 0.58)	571 (1 study)	⊕⊖⊖⊖ very low[2, 3]

Bx biopsy; CI confidence interval; HR hazard ratio; GTR gross total resection; LGG low-grade glioma; PaR partial resection; RR risk ratio; rSTR radical subtotal resection; STR subtotal resection.
[1] Event rate not reported
[2] Uncontrolled confounder(s)
[3] Population had confirmed, not suspected, low-grade glioma
[4] The confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol).

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

Local excision/biopsy versus no surgery (active monitoring)

- One observational study (N=988) provided very low quality evidence that showed significantly shorter overall survival in patients treated with no surgery (active monitoring) compared to patients treated with local excision/biopsy (hazard ratio (HR) = 1.69; 95% confidence interval (CI) 1.15-2.48).

Subtotal resection versus no surgery (active monitoring)

- One observational study (N=3197) provided very low quality evidence that showed significantly shorter overall survival in patients treated with no surgery (active monitoring) compared to patients treated with subtotal resection (HR = 1.32; 95% CI 1.14-1.53).

Local excision/biopsy versus subtotal resection

- One observational study (N=1107) provided very low quality evidence that showed no difference in overall survival in patients treated with local excision/biopsy compared to patients treated with subtotal resection (HR = 1.21; 95% CI 0.83-1.76). Another observational study (N=86) provided very low quality evidence that showed either no difference (HR = 0.87; 95% CI 0.31-2.43) or longer progression-free survival in patients treated with subtotal resection compared to patients treated with local excision/biopsy (HR = 0.23; 95% CI 0.11-0.49). Two observational studies (N=1018) provided very low quality evidence that showed significantly longer malignant progression-free survival in patients treated with subtotal resection compared to patients treated with local excision/biopsy (HRs = 0.35; 95% CI 0.15-0.82; and HR = 0.43; 95% CI 0.35-0.53).

Local excision/biopsy versus gross total resection

- One observational study (N=1383) provided very low quality evidence that showed no difference in overall survival in patients treated with local excision/biopsy compared to patients treated with gross total resection (HR = 1.06; 95% CI 0.73-1.54). Another observational study (N=73) provided very low quality evidence that showed longer progression-free survival in patients treated with gross total resection compared to patients treated with local excision/biopsy (in 2 analyses; HR = 0.22; 95% CI 0.07-0.73, and HR = 0.04: 95% CI 0.02-0.1). Two observational studies (N=842) provided very low quality evidence that showed significantly longer malignant progression-free survival in patients treated with gross total resection compared to patients treated with local excision/biopsy (HR = 0.05; 95% CI 0.02-0.15, and HR = 0.22; 95% CI 0.16-0.32).

Subtotal resection versus gross total resection

- Two observational studies (N=3340) provided very low quality evidence that showed either no difference (HR = 0.78; 95% CI 0.53-1.16) or longer overall survival in patients treated with gross total resection compared to patients treated with subtotal resection (HR = 0.72; 95% CI 0.6-0.85). Two observational studies (N=1074) provided very low quality evidence that showed either no difference (HR = 0.93; 95% CI 0.74-1.15) or longer progression-free survival in patients treated with gross total resection compared to patients treated with subtotal resection (HR = 0.44; 95% CI 0.27-0.72). One observational study (N=243) provided very low quality evidence that showed a significantly lower rate of new neurological deficits in patients treated with gross total resection compared to patients treated with subtotal resection (RR = 0.47; 95% CI 0.25-0.9).

Biopsy versus partial resection

- One observational study (N=1046) provided very low quality evidence that showed significantly longer malignant progression-free survival in patients treated with partial resection compared to patients treated with biopsy (HR = 0.68; 95% CI 0.58-0.80).

Subtotal resection/biopsy versus gross total resection/radical subtotal resection

- One observational study (N=571) provided very low quality evidence that showed significantly longer overall survival (HR = 0.61; 95% CI 0.43-0.87) and progression-free survival in patients treated with gross total resection/radical subtotal resection compared to patients treated with subtotal resection/biopsy (HR = 0.45; 95% CI 0.35-0.58).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 3 outcomes of critical importance: progression-free survival, epilepsy or seizure control and neurological function as measured by the Neurological Function Scale or NIH stroke scale. These outcomes were selected as the most direct measures of the risks of a decision to resect or not resect. Progression-free survival was preferred to overall survival as it is a better measure of tumour-specific features of the decision to resect or not.

The committee identified 3 further outcomes as important. These were overall survival, time to tumour transformation (from low- to high-grade) and health-related quality of life. These were defined as important because they were also direct measures of the success of a decision to operate, but were not defined as critical because they are substantially affected by factors outside the clinician's control. No evidence was identified for health-related quality of life.

Surgical mortality was identified as an outcome of limited importance. The committee accepted it was an important outcome to be considered in whether to offer surgery or not, but was often influenced by factors independent of the tumour, or factors endogenous to the tumour but known before the operation (such as tumour size and location) such that a recommendation based solely on this outcome would not be helpful. No evidence was identified for surgical mortality.

The quality of the evidence

The quality of the evidence was assessed according to GRADE criteria. Included studies presented were of very low quality. The committee discussed how the evidence matched their clinical experience, but added that there were significant gaps in the evidence around how tumours with different molecular or histological profiles would respond to resection or biopsy.

More generally, the committee noted that much of the evidence presented was from before molecular profiling of gliomas was common, and from a time when histological profiling was less advanced than currently. The committee expected that the evidence would improve as published studies catch up with clinical best-practice, but added that it is extremely likely that conducting a resection or biopsy today will lead to better outcomes than reported in the older studies, as the ability to guide treatment based on molecular profile was not available to studies begun prior to the last decade or so.

The committee believed that although the evidence was low quality and prospective comparative data would have been better, it was still sufficient to justify considering resection or biopsy, as the importance of molecular diagnosis is established in evidence considered elsewhere in the guidance, such as the section on 'Management of newly diagnosed high-grade glioma following surgery or if surgery is not possible (or has been declined)'. The committee discussed how there was no evidence on the timing of intervention, but that their experience suggested that there was no benefit to long delays between diagnosis and initial management and sometimes the possibility of immediately improving symptoms with resection. The committee therefore recommended that resection take place within six months

to allow enough time to discuss treatment options with other clinicians and the person with the tumour, but not introduce unnecessary delays.

The committee chose not to make a research recommendation as they believed that their clinical consensus was sufficiently embedded that such research would be unlikely to change practice.

Benefits and harms

The committee discussed how decisions on whether to undertake complete resection, subtotal resection, biopsy only or no surgery were extremely complicated and based on a number of factors requiring specialist expertise. Non-expert surgical teams may not understand the balance of these factors, or have the equipment and specialisms available to ensure that more radical types of surgery can be safely undertaken. Consequently the committee agreed that the initial management of surgery for people with low-grade glioma should be undertaken by a multidisciplinary team with surgical expertise in low-grade glioma, as the evidence the committee considered was only conducted by expert surgical teams and the committee did not believe the evidence could be extended to non-expert teams. The committee explained that referral into this team would happen immediately following identification of a suspected glioma.

The committee was persuaded by very low quality evidence that resection improved overall survival and progression-free survival. The committee explained that the amount that would need to be resected in order to see a benefit was not known exactly, but that >80%-90% were common clinical estimates. Therefore neither 'maximal' nor 'complete' resection were quite adequate to describe the level of resection required, and the committee phrased their recommendation to allow for surgical clinical judgement. The committee was persuaded by similar evidence that overall survival was improved by offering a biopsy followed by appropriate oncological treatment compared to active monitoring, however the committee observed there was evidence that biopsy was inferior to excision where both options were available. Overall this led the committee to conclude that resection should be considered, and that biopsy alone should only be considered if resection was not possible. However if resection was not possible the committee believed biopsy alone would likely improve outcomes compared to active monitoring in this situation based on evidence, as well as being the only current proven technique to assess IDH status based on their clinical knowledge, and evidence shows IDH status has important prognostic value.

The committee described how there was little evidence that immediate excision improved outcomes, but on the basis of their clinical experience it was risky to leave a low-grade glioma untreated for a significant length of time. Consequently they recommended that surgery be considered as part of initial management, which should therefore mean that treatment would come within six months.

Evidence for which types of tumour would benefit especially from resection compared to active monitoring was low quality, and the committee qualified this evidence by identifying that the balance of risk and harms was likely to favour active monitoring in very low-risk tumours. They explained that by this they meant tumours which were unlikely to undergo malignant transformation and in which the surgery to remove them would still carry risk. However the committee explained that there are only a small number of tumour types which can be confidently identified as low-risk from imaging alone (for example DNETs and optic pathway glioma), and in all other tumours molecular and histological subtyping needs to be undertaken to establish the risk of transformation, meaning that resection should be undertaken at the same time if possible. This recommendation was based on the committee's experience.

The committee discussed how the recommendations might be seen as ambiguous with respect to people whose tumours have never been treated and who are in follow up but have no molecular/histological diagnosis (for example, people who have never had surgery).

Based on the evidence for resection in the initial treatment group and their experience, the committee agreed that this group could also receive resection if possible. Biopsy to establish molecular subtype and thereby guide treatment or prognosis may be less important in this group because tumour behaviour will have become apparent over time since initial discovery of the tumour. It was thought that this recommendation might also provide guidance for people with tumours currently receiving active monitoring who experience progression or new symptoms. This was based on the evidence, and is a clarification of the above recommendations.

The benefit to resecting a low-grade tumour early and aggressively is that the tumour is controlled before it has a chance to transform, which should lead to a better life expectancy and quality of life. Additionally, surgery is the only way to obtain a sample of the tumour for molecular and histological subtyping (particularly IDH status). Once the subtype of the tumour is known, the clinician may be able to discuss prognosis more accurately, or alter treatment decisions in light of the profile of the tumour. Knowing the prognosis can be of significant quality of life benefit for the person with the tumour, while modifying treatment decisions on the basis of optimal prognostic molecular information should improve length and quality of life. This benefit applies even if the tumour is only biopsied or partially resected.

The harms of resecting the tumour are mostly the risks of surgery, but also include the cost of the operation and the burden on the person with the tumour. Biopsy still carries risks to life and neurological function, as well as a financial cost. Some people may prefer not to know the molecular profile of their tumour, unless it can be used to make useful treatment decisions about care.

The committee balanced the benefits against the risks by prioritising gaining information about the tumour through biopsy where possible, but only resecting the tumour if the position of the tumour and its likely growth rate justified the potential side-effects of surgical intervention. With the additional information about the tumour gained through biopsy the clinician and person with the tumour can make a more informed decision about balancing risks and benefits of subsequent treatment.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

There is currently large variation in practice across the NHS in England around the treatment of low-grade glioma. In some centres low-grade glioma is managed by non-specialist surgical teams. The recommendations will lead to more patients being referred to a specialist multidisciplinary team. While it is anticipated that the shift in which type of specialist multidisciplinary team people are referred should be cost neutral in the immediate term it could potentially lead to greater access to resource intensive intraoperative interventions including awake craniotomy. While these are all associated with increased costs it could lead to greater progression-free survival, seizure control and neurological function. All three of these are likely to be strong determinants of quality of life. Any increase in costs is likely to be offset by reasonable increases in quality-adjusted life years (QALYs).

The other recommendations are likely to be cost neutral given they largely reflect current practice. Given the criteria for retroactive biopsies there will be a reduction in their use in already treated patients for which there is no consensus or evidence on benefit. This will reduce both costs and potentially reduce harm.

Other factors the committee took into account

The committee did not discuss any factors not already described above.

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Further management of newly diagnosed low-grade glioma

Review question

What is the optimal management (observation, surgery, radiotherapy, chemotherapy, or combinations of these) for histologically proven low-grade glioma?

Introduction

Though low-grade glioma is a relatively infrequent diagnosis, they occur principally in younger people and with improved survival long term, quality of life is of paramount importance. All brain tumour therapies have potential acute and late toxicities so clinical teams need to balance improving longevity whilst minimising long-term impact on physical, cognitive and psychological wellbeing.

Management of low-grade glioma remains controversial, with large variations in practice. Areas of controversy include the role and timing for radiotherapy and chemotherapy and whether to undertake more aggressive treatment, including surgical intervention, versus delayed intervention for people with a better prognosis.

PICO table

Table 29: Summary of the protocol (PICO table)

Population	People with newly histologically proven low-grade glioma (grade I and II) who have had surgery (resection or biopsy)
Intervention	• Active monitoring • Surgery • Radiotherapy • Chemotherapy • Combined treatments involving combinations of the above (including radiation versus radiation or chemotherapy versus chemotherapy)
Comparison	Any of the above-mentioned interventions
Outcome	Critical: • overall survival • cognitive function • neurological function (as measured by the Neurological Function Scale or NIH stroke scale) Important: • health-related quality of life • progression free survival • epilepsy/seizure control • grade 3 or 4 late toxicity (after 3 months)

NIH National Institutes of Health

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Included studies consisted of phase III randomised controlled trials (RCTs) enrolling patients with histologically proven low-grade glioma (LGG) (WHO grade I and II) who have had

surgery (resection or biopsy). Overall, interventions of the included studies consisted or radiotherapy (RT) (and different dosages of this) as well as chemotherapy (lomustine, temozolomide [TMZ] and the combination of procarbazine, lomustine and vincristine [PCV]). No studies reported active monitoring.

The identified trials were not deemed suitable for meta-analysis, therefore comparisons from individual studies have been reported.

A summary of these studies is provided in Table 30 and the results along with the quality of the evidence for each outcome are listed in Table 31 to Table 36 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 30 provides a brief summary of the included studies.

Table 30: Summary of included studies

Study	Population	Intervention	Comparison	Detail(s)
Eyre 1993	N= 54 adults with histopathologic diagnosis of LGG. N= 4 (8%) presented with grade I tumour and N= 50 (92%) presented with grade II tumour	RT + CCNU RT: 55-Gy delivered in 32 fractions Concurrent CCNU: 100 mg/m^2 every 6 weeks	RT 55-Gy delivered in 32 fractions	
EORTC 22844 Karim 1996	N= 343 adults with histopathologic diagnosis of LGG. N= 206 (60%) with grade 2 astrocytoma; N= 32 (9%) with grade I (pilocytic) astrocytoma; N= 73 (22%) oligodendroglioma and N=32 (9%) with mixed oligoastrocytoma	Low-dose RT (45-Gy in 25 fractions)	High-dose RT (59.4-Gy in 33 fractions)	Kiebert 1998 did a sub-analysis of this study and reported QoL for this population

Study	Population	Intervention	Comparison	Detail(s)
Shaw 2002	N= 203 adults with a histologic proof of a suprarentorial Kernohan grade 1 or 2 astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. N= 10 (5%) presented with Kernohan 1 grade and N=193 (95%) presented with Kernohan 2 grade	Low-dose RT (50.4- Gy in 28 fractions)	High-dose RT (64.8-Gy in 36 fractions)	Brown 2003 and Laack 2005 did a subanalysis of this study and presented the cognitive function and health related QoL in this population
Karim 2002	N= 290 adults with a definite histopathologic diagnosis of LGG. N= 7 (2.4%) with WHO grade I glioma And N= 173 (59.6%) with WHO grade II glioma N= 72 (25%) with oligodendroglioma N= 29 (10%) with mixed-oligo-astrocytoma N= 9 (3%) with unknown histology	Early RT within 8 weeks of the day of surgery 54 Gy in 30 fractions	Deferred RT Adults did not receive any RT until the tumour showed progression [defined as clinical-neurologic deterioration confirmed by definitive evidence of tumour activity clinically and on CT scan]	van den Bent 2005 provide the results of this same cohort at a median of 7.8 years of follow-up
Buckner 2016	N= 251 Either > 40 years old	RT + PCV	RT alone administered at	Shaw 2012 was the initial report that provided the

Study	Population	Intervention	Comparison	Detail(s)
	with any resection, or 18-39 years old with subtotal resection with grade 2 astrocytoma, oligodendroglioma, or oligoastrocytoma that was histologically confirmed on pathological review.	RT was administered at 54-Gy in 30 fractions of 1.8-Gy each over a period of 6 weeks later Procarbazine 60 mg/ m^2 orally day 8-21 of each cycle Lomustine 110 mg/ m^2 orally on day 1 of each cycle. Vincristine 4 mg/ m2 (max 2.0 mg) IV days 8 and 29 of each cycle. Each cycle 56 days, max 6 cycles.	54-Gy in 30 fractions	efficacy analyses for, as it was specified in the protocol. Prabhu 2014 did a sub-analyses of the above and reported the cognitive function
Baumert 2016	N=477 adults with histologically confirmed, supratentorial, diffusely, infiltrating WHO grade II glioma. N= 167 (35%) astrocytoma Who grade II; N= 118 (24%) oligoastrocytoma WHO grade II glioma and N= 192 (40%) oligodendro	TMZ 75 mg/m2 per day orally for 21 days, repeated every 28 days for up to 12 cycles or until disease progression or unacceptable toxicity)[b]	RT alone administered at 54 Gy in 28 fractions of 1.8 Gy each, 5 days per week, over a period of 5-6 weeks, and up to a maximum treatment period of 6.5 weeks.	Reijneveld 2016 reported the QoL and cognitive function for this population

Study	Population	Intervention	Comparison	Detail(s)
	glioma WHO grade II glioma			

CCNU lomustine CT computed tomography; Gy Grays; LGG low-grade glioma; QoL quality of life; RT radiotherapy; TMZ temozolomide; WHO World Health Organization.
a This was defined as repeated grade 4 haematological toxicity or grade 3-4 non haematological toxicity – with the exception of alopecia, nausea, and vomiting.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question (optimal management of low-grade glioma) are presented in Table 31 to Table 36.

Table 31: RT + CCNU versus RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT	RT + CCNU			
OS	The median survival time in the control group was 4.5 years	The median survival time in the intervention group was 7.4 years	Not applicable	54 (1 study)	⨁⊖⊖⊖ very low[1,2]

1 No details were given about randomisation and allocation concealment methods
2 Only descriptive data without p-values was reported, insufficient details given to assess the MID thresholds and imprecision

Table 32: Summary clinical evidence profile for low dose (45-Gy) versus high dose (59.4-Gy)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	High dose (59.4-Gy)	Low dose (45-Gy)			
OS Follow-up: median 76 months	314 per 1000	374 per 1000 (279 to 502)	RR 1.19 (0.89 to 1.60)	343 (1 study)	⨁⨁⊖⊖ low[1,2]
PFS Follow-up: median 76 months	407 per 1000	464 per 1000 (362 to 590)	RR 1.14 (0.89 to 1.45)	343 (1 study)	⨁⊖⊖⊖ very low[2,3]
Adverse events (fatigue, insomnia)	No events were reported	No events were reported	Data not reported to allow calculation	343 (1 study)	⨁⊖⊖⊖ very low[1,3,4]
Quality of life (leisure activity and emotional functioning)	Not applicable	Not applicable	Not estimable	343 (1 study)	⨁⊖⊖⊖ very low[1,3,4]

CI confidence interval; RR risk ratio; Gy Gray; OS overall survival; PFS progression free survival.

1 Unclear how randomisation was performed and concealed
2 95% CI crossed 1 default MID (1.25)
3 Unclear how randomisation was performed and concealed; unclear whether participants and assessors were blinded to treatment allocation
4 Only descriptive data without p-values was reported, insufficient details given to assess the MID thresholds and imprecision

Table 33: Summary clinical evidence profile for low dose (50.4-Gy) versus high dose (64.8-Gy)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	High dose (64.8 Gy)	Low dose (50.4 Gy)			
OS Follow-up: median 2 years[a]	186 per 1000	69 per 1000 (30 to 158)	RR 0.37 (0.16 to 0.85)	203 (1 study)	⊕⊕⊖⊖ low[1,2]
OS Follow-up: median 5 years[b]	471 per 1000	405 per 1000 (296 to 555)	RR 0.86 (0.63 to 1.18)	203 (1 study)	⊕⊕⊖⊖ low[1,2]
PFS Follow-up: median 2 years	314 per 1000	188 per 1000 (113 to 311)	RR 0.60 (0.36 to 0.99)	203 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
PFS Follow-up: median 5 years	392 per 1000	435 per 1000 (314 to 604)	RR 1.11 (0.80 to 1.54)	203 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Toxicity (grade 3, 4, and 5) at 5 years follow-up Follow-up: median 6.4 years	529 per 1000	418 per 1000 (307 to 556)	RR 0.79 (0.58 to 1.05)	203 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
MMSE	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable	97 (1 study)	⊕⊖⊖⊖ very low[1,3,5]
Cognitive function	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable	20 (1 study)	⊕⊖⊖⊖ very low[1,3,6]

CI confidence interval; RR risk ratio; Gy Gray; OS overall survival; PFS progression free survival.
aThese data represents the number of people who were alive at a median follow-up of 2 years (RR< 1 favours the low-dose [50.4 Gy])
bThese data represents the number of people who were alive at a median follow-up of 5 years (RR< 1 favours the low-dose [50.4 Gy])
1 Unclear how randomisation was concealed
2 95% CI crossed 1 default MID (0.80)
3 Unclear whether patients and assessors were blinded
4 95% CI crossed 2 default MIDs (0.80 and 1.25)
5 Data reported narratively, with insufficient details given to assess the MID thresholds and imprecision. Data reported overall and not per treatment arm (76%, 89% and 89% of adults presented with a stable MMSE score at year 1, 2 and 5, respectively. Adults with an abnormal score at baseline were more likely to have an improvement in cognitive abilities after radiotherapy)
6 Data reported narratively, with insufficient details given to assess the MID thresholds and imprecision. Analyses of these battery tests suggested a stable cognitive function amongst those adults who received low-dose (50.4-Gy) radiotherapy and those who received high-dose radiotherapy (64.8-Gy), although results have not been reported by treatment arm.

Table 34: Summary clinical evidence profile for early RT versus deferred RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Deferred RT	Early RT			
Time to progression Follow-up: median 5 years[1]	Not applicable	Not applicable	HR 0.71 (0.52 to 0.97)	290 (1 study)	⊕⊕⊖⊖ low[2,3]
Time to progression Follow-up: median 7.8 years[4]	Not applicable	Not applicable	HR 0.59 (0.45 to 0.77)	303 (1 study)	⊕⊕⊕⊖ moderate[2]
Overall survival Follow-up: median 5 years[1]	Not applicable	Not applicable	HR 1.04 (0.61 to 1.77)	290 (1 study)	⊕⊖⊖⊖ very low[2,5]
Overall survival Follow-up: median 7.8 years[4]	Not applicable	Not applicable	HR 0.97 (0.71 to 1.33)	303 (1 study)	⊕⊖⊖⊖ very low[2,5]

CI confidence interval; HR hazard ratio; RT radiotherapy
1 Karim 2002
2 Unclear how randomisation was concealed
3 95% CI crossed 1 default MID (0.80)
4 van den Bent 2005
5 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 35: Summary clinical evidence profile for RT + PCV versus RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT	RT + PCV			
Overall survival (total) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.59 (0.42 to 0.83)	251 (1 study)	⊕⊕⊖⊖ low[2]
Overall survival (grade 2 astrocytoma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.73 (0.40 to 1.33)	65 (1 study)	⊕⊖⊖⊖ very low[3]
Overall survival (grade 2 oligodendroglioma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.43 (0.23 to 0.80)	107 (1 study)	⊕⊕⊖⊖ low[2]
Overall survival (grade 2 oligoastrocytoma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.56 (0.32 to 0.98)	79 (1 study)	⊕⊕⊖⊖ low[2]
Overall survival among those with IDH1 R132H Mutation Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.42 (0.20 to 0.88)	125 (1 study)	⊕⊕⊖⊖ low[2]
Progression free survival (total) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.50 (0.36 to 0.69)	251 (1 study)	⊕⊕⊕⊖ moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Progression free survival (grade 2 astrocytoma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.58 (0.33 to 1.02)	65 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival (grade 2 oligodendroglioma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.36 (0.21 to 0.62)	107 (1 study)	⊕⊕⊕⊖ moderate[1]
Progression free survival (grade 2 oligoastrocytoma) Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.52 (0.30 to 0.90)	79 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival among those with IDH1 R132H Mutation Follow-up: median 11.9 years	Not applicable	Not applicable	HR 0.32 (0.17 to 0.60)	125 (1 study)	⊕⊕⊕⊖ moderate[1]
MMSE decline year 1	68 per 1000	39 per 1000 (8 to 195)	RR 0.58 (0.12 to 2.88)	125 (1 study)	⊕⊖⊖⊖ very low[1,2]
MMSE decline year 2	17 per 1000	7 per 1000 (0 to 160)	RR 0.40 (0.02 to 9.58)	110 (1 study)	⊕⊖⊖⊖ very low[1,2]
MMSE decline year 3	21 per 1000	8 per 1000 (0 to 185)	RR 0.37 (0.02 to 8.88)	91 (1 study)	⊕⊖⊖⊖ very low[1,2]
MMSE decline year 5	0 per 1000	No events were reported	RR 4.42 (0.22 to 87.44)	47 (1 study)	⊕⊖⊖⊖ very low[1,2]

CI confidence interval; RR risk ratio; HR hazard ratio; RT radiotherapy; PCV procarbazine, lomustine, vincristine; IDH isocetrate dehydrogenase
1 Unclear how randomisation was performed and how it was concealed
2 95% CI crossed 1 default MID (0.80)
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 36: Summary clinical evidence profile for TMZ versus RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk (± SD)	Corresponding risk (± SD)			
	RT	TMZ			
Progression free survival – PFS Total	Not applicable	Not applicable	HR 1.16 (0.90 to 1.5)	477 (1 study)	⊕⊕⊖⊖ low[1,24]
Progression free survival - PFS IDHmt/codel Follow-up: median 48 months	Not applicable	Not applicable	HR 1.04 (0.56 to 1.93)	104 (1 study)	⊕⊖⊖⊖ very low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk (± SD)	Corresponding risk (± SD)			
Progression free survival - PFS IDHmt/non-codel Follow-up: median 48 months	Not applicable	Not applicable	HR 1.86 (1.21 to 2.86)	165 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival - PFS IDHwt Follow-up: median 48 months	Not applicable	Not applicable	HR 0.67 (0.34 to 1.32)	49 (1 study)	⊕⊖⊖⊖ very low[1,3]
Global health-related quality of life - 3 months Follow-up: median 36 months	Not applicable	The mean global health-related quality of life – 3 months in the intervention group was 6 higher (5.8 to 6.2 higher)[4]	Not applicable	369 (1 study)	⊕⊕⊕⊖ moderate[1]
Global health-related quality of life - 6 months Follow-up: median 39 months	Not applicable	The mean global health related quality of life at 6 months in the intervention group was 2.5 lower (2.71 to 2.29 lower)[4]	Not applicable	340 (1 study)	⊕⊕⊕⊖ moderate[1]
Global health-related quality of life - 24 months Follow-up: median 60 months	Not applicable	The mean global health related quality of life at 24 months in the intervention group was 1.6 lower (1.87 to 1.33 lower)[4]	Not applicable	205 (1 study)	⊕⊕⊕⊖ moderate[1]
Global health-related quality of life - 36 months Follow-up: median 72 months	Not applicable	The mean global health-related quality of life at 36 months in the intervention group was 0.2 lower (2.82 to 2.78 lower)[4]	Not applicable	120 (1 study)	⊕⊕⊕⊖ moderate[1]
MMSE - 3 months Follow-up: median 36 months	Not applicable	The mean MMSE at 3 months in the intervention group was 2.8 lower (2.82 to 2.78 lower)[6]	Not applicable	369 (1 study)	⊕⊕⊖⊖ low[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk (± SD)	Corresponding risk (± SD)			
MMSE - 6 months Follow-up: median 39 months	Not applicable	The mean MMSE at 6 months in the intervention group was 3 lower (3.02 to 2.98 lower)[5]	Not applicable	340 (1 study)	⊕⊕⊖⊖ low[1]
MMSE - 24 months Follow-up: median 60 months	Not applicable	The mean MMSE at 24 months in the intervention group was 2.9 lower (2.93 to 2.87 lower)[5]	Not applicable	205 (1 study)	⊕⊕⊖⊖ low[1]
MMSE - 36 months Follow-up: median 72 months	Not applicable	The mean MMSE at 36 months in the intervention group was 2.9 lower (2.93 to 2.87 lower)[5]	Not applicable	120 (1 study)	⊕⊕⊖⊖ low[1]

CI confidence interval; HR hazard ratio; MMSE mini mental state examination; TMZ temozolomide; RT radiotherapy; IDHmt/non-codel isocetrate dehydrogenase mutated and 1p/19q co-deleted; IDHmt/non-codel isocetrate dehydrogenase mutated and1p/19q non co-deleted; IDHwt isocetrate dehydrogenase wild type
1 Unclear how randomisation was concealed, open label trial
2 95% CI crossed 1 default MID (1.25)
3 95% CI crossed 2 default MIDs (0.80 and 1.25)
4 Figures represent mean differences between both treatment groups (TMZ versus RT) for global quality of life. Changes between 5 to 10 represent a small difference, and between 10 and 20 represent a moderate difference (>10 points considered as clinically relevant)
5 Figures represent mean different between both treatment groups (TMZ versus RT) for MMSE scores. Changes >3 are considered to be clinically significant

See Appendix F for full GRADE tables.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource impact

Table 37: Resource impact and unit costs associated with further management of newly diagnosed low-grade glioma

Resource	Unit costs	Source
PCV Chemotherapy	£137 per week	Garside 2007
Preparation for Complex Conformal Radiotherapy	£687	NHS reference costs 2015-16 (SC23Z)
Deliver a Fraction of Complex Treatment on a	£153 per fraction	NHS reference costs 2015-16 (SC51Z)

Resource	Unit costs	Source
Megavoltage Machine		

Evidence statements

RT + CCNU (lomustine) versus RT

- Very low quality evidence from 1 randomised controlled trial (N=54) showed no difference in overall survival between radiotherapy in combination with lomustine - and radiotherapy alone in adults with a histopathologic diagnosis of low-grade glioma.

Low-dose RT (45-Gy) versus high-dose RT (59.4-Gy)

- Low to very low quality evidence from 1 randomised controlled trial (N=343) showed no difference between low-dose radiotherapy (45-Gy) and high-dose radiotherapy (54.9-Gy) in overall survival (relative risk (RR) = 1.19, 95% confidence interval (CI) 0.89-1.60) and progression free survival (RR = 1.14, 95% CI 0.89-1.45).
- A sub-analysis of this sample showed a significant increase in fatigue and insomnia immediately after radiotherapy, more impairment in leisure time activities, and poorer emotional functioning at 7-15 months post-randomisation for those who received high-dose radiotherapy as compared with low-dose radiotherapy. No other significant differences between the 2 arms were found for the remaining quality of life domains.

Low-dose RT (50.4-Gy) versus high-dose RT (64.8-Gy)

- Low to very low quality evidence from 1 randomised controlled trial (N=203) showed a significant difference in survival (RR = 0.37, 95% CI 0.16-0.85) and time to progression (RR = 0.60, 95% CI 0.36-0.99) in those who received low-dose radiotherapy (50.4-Gy) as compared to dose who received high-dose radiotherapy at a median of 2 years follow up. At 5 years follow-up, there were no differences in survival (RR = 0.86, 95% CI 0.63-1.18) and time to progression (RR = 1.11, 95% CI 0.8-1.54) between adults who received low-dose radiotherapy as compared to those who received high-dose radiotherapy. No differences were observed for toxicity (grade 3, 4 and 5) between both treatment arms (RR=0.79, 95% CI=0.58-1.05).
- A sub-analysis of this sample (N=97 adults available with MMSE baseline data) showed no differences in cognitive function in patients who received low-dose radiotherapy (50.4-Gy) as compared with those who received high-dose radiotherapy arm (64.8-Gy). Seventy six per cent, 89% and 89% of adults presented with a stable MMSE score at year 1, 2 and 5 respectively. Adults with an abnormal score at baseline were more likely to have an improvement in cognitive abilities after radiotherapy. A subset[c] of these adults (N=20) were evaluated prospectively at baseline (before radiotherapy) and at 18-month intervals subsequently with an extensive battery of psychometric tests [MMSE; Wechsler Adult Intelligence Scale-Revised (WAIS-R); Auditory Learning Verbal Test (AVLT); Benton Visual Retention Test (BVRT) and Trail-Making Test (TMT)]. Analyses of these battery tests suggested a stable cognitive function amongst those adults who received low-dose (50.4-Gy) radiotherapy and those who received high-dose radiotherapy (64.8-Gy), although results have not been reported by treatment arm.

Early (within 8 weeks after surgery) versus deferred RT

- Moderate to very low quality evidence from 1 randomised controlled trial (N=290) showed an improvement in time to progression in those who received radiotherapy within 8 weeks

[c] These subset of adults differed significantly in extent of resection compared with the main cohort. 18 adults had only a biopsy (90%) and 2 underwent GTR (10%)

after surgery as compared with those who received deferred radiotherapy at 5 years follow-up (HR = 0.71, 95% CI 0.52-0.97) and at 7.8 years follow-up (hazard ratio (HR) = 0.59, 95% CI 0.45-0.77). There were no differences between the treatment arms in overall survival at 5 years follow-up (HR = 1.04, 95% CI 0.61-1.77) or at 7.8 years (HR = 0.97, 95% CI 0.71-1.33) follow-up.

RT + PCV versus RT

- Moderate to very low quality evidence from 1 randomised controlled trial (N=251) showed that those who received radiotherapy in combination with PCV had longer overall survival (HR = 0.59, 95% CI 0.42-0.83) and progression-free survival (HR = 0.50, 95% CI 0.36-0.69) than those who received radiotherapy alone.
- There were no differences between the treatment arms in overall survival (HR = 0.73, 95% CI 0.4-1.33) or progression-free survival (HR = 0.58, 95% CI 0.33-1.02) for those adults with WHO grade 2 astrocytoma (N=65). Adults with WHO grade 2 oligodendroglioma (N=107) who received radiotherapy and PCV had longer overall survival (HR = 0.43, 95% CI 0.23-0.80) and progression-free survival (HR = 0.36, 95% CI 0.21-0.62) compared to those who received radiotherapy alone. Adults with WHO grade 2 oligoastrocytoma (N=79) who received radiotherapy and PCV had longer overall survival (HR = 0.56, 95% CI 0.32-0.98) and progression-free survival (HR = 0.52, 95% CI 0.3-0.9) compared to those who received radiotherapy alone. Adults with IDH1 32H (N=125) who received radiotherapy and PCV had longer overall survival (HR = 0.42, 95% CI 0.2-0.88) and progression-free survival (HR = 0.32, 95% CI 0.17-0.6) compared to those who received radiotherapy alone.
- Very low qyality evidence from 1 randomised controlled trial (N=125) provided very low quality evidence to show no differences in MMSE decline from baseline to year 1, 2, 3, and 5 in those who received radiotherapy in combination with PCV as compared to those who received radiotherapy alone.

TMZ versus RT

- Low to very low quality evidence from 1 randomised controlled trial (N=477) showed no differences in progression-free survival (HR = 1.16, 95% CI 0.9-1.5) between those who received temozolomide or radiotherapy. Differences in progression-free survival were not observed either between treatment arms for those with IDHmt/codel (N=104; HR = 1.04, 95% CI 0.56-1.93) and IDHwt (N=49; HR = 0.67, 95% CI 0.34-1.32). For those with IDHmt/non-codel who received radiotherapy, progression-free survival was longer when compared to those who received temozolomide (HR = 1.86; 95% CI 1.21-2.86).
- Moderate quality evidence from 1 randomised controlled trial (N=477) showed global-QLQ scores were higher in those who received temozolomide, with scores peaking 3 months after treatment, but within 24 months after intervention, there was no difference in scores between both groups.
- Low quality evidence from 1 randomised controlled trial (N=447) showed that MMSE scores remained steady across time, with clinically significant difference only observed at 3 months, in favour of those who received temozolomide.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify the optimal management of histologically proven low-grade glioma. The committee selected 3 outcomes as being critical: overall survival, cognitive function and neurological function as these were direct measures of the success of the interventions. As important outcomes, the committee identified health-related quality of

life, progression-free survival, impact on tumour-related epilepsy and grade 3 to 4 toxicity as these are indirect measures of the success of the intervention.

The quality of the evidence

The evidence consisted of 12 randomised controlled trials from six different cohorts of people with newly diagnosed low-grade glioma (WHO grade I and II). These studies examined overall survival, time to progression, quality of life, and toxicity. The quality of the evidence ranged from very low to moderate as assessed by GRADE. The main sources of bias were a lack of blinding of outcome assessors and participants (except for objective outcomes, such as overall survival, which were not downgraded despite lack of blinding) and concealment of allocation was unreported or unclear. The committee acknowledged the quality of the evidence, but suggested that it was expected that these studies were subject to bias as it was not possible to blind the clinicians or the participants of the studies due to the nature of the treatment.

The committee discussed that most of the trials presented only considered histological grade, since they were conducted prior to current understanding of the importance of molecular subtypes of the tumours. They commented that while histological grading is useful, molecular subtypes are more closely associated with prognosis (correlating with the biologic behaviour of the tumour) and consequently have important implications for patient management. Most of the evidence related to WHO grade II gliomas, with the trials conducted prior the year 2002, which included mixed WHO grade I and II gliomas.

The committee determined that despite the sources of bias and the fact the data did not present the most modern way of categorising low-grade glioma that the evidence was still robust enough to base recommendations upon. This was because there was no way to conduct the studies in a blinded fashion, and therefore it was appropriate to use their clinical expertise to interpret the results.

The committee discussed how there are still some areas of uncertainty for the management of low-grade gliomas, for instance whether high-risk low-grade glioma (IDH wildtype) would benefit from the same standard of care as patients with high-grade glioma, so they decided to make a research recommendation about this.

The committee discussed how active monitoring in combination with another treatment was specified in the protocol, but no evidence was found for this. Since this is an area of very significant importance to people with tumours but likely to have a high resource impact if implemented, the committee made a second research recommendation on supportive care clinics in addition to standard care.

Benefits and harms

Evidence showed that for high-risk low-grade gliomas, radiotherapy (54Gy administered in 30 fractions of 1.8Gy each) followed by PCV provided a significant increase in survival and time to progression when compared with radiotherapy alone. This overall effect appeared to be largest in those with 1p/19q codeletion and IDH mutation (oligodendroglioma), although the committee added that reliable assessment of 1p\19q status was not possible in the study on which this was based. The inclusion criterion of the trial reporting the outcomes the committee based this recommendation on was people aged under 40 years with residual disease or over 40 with or without residual disease on post-operative MRI scan and the committee did not believe they could extend the evidence to different subgroups. The committee concluded that the greatest benefit from this active approach was probably observed when 1p/19q codeletion was present, but that there also appeared to be benefit for non-codeleted tumours provided there was IDH mutation and hence made two recommendations of different strength.

Based on their experience, the committee concluded that those under 40 years old and presenting with IDH mutated low-grade glioma, with no residual tumour on postoperative MRI are less likely to benefit from an immediate treatment, and should be actively monitored, with regular imaging and clinical assessment to identify tumour progression. This was a balance of the harms of treatment against the risk of tumour transformation.

Based on moderate quality evidence showing a longer time to tumour progression, improved seizure control and improved neurological function, the committee recommended radiotherapy followed by PCV in those with progressive disease on radiology who have not previously had radiotherapy.

The committee discussed the trials which looked at the different radiotherapy regimens. They concluded the evidence on this topic was extremely difficult to interpret, as the two studies appeared to show contradictory outcomes (high dose better in 50.4 Gy versus 64.8 Gy comparison and worse in 45.0 Gy versus 59.4 Gy comparison). They inferred from the results higher doses of radiotherapy (59.4Gy to 64.8Gy) do not improve survival when compared to lower dose radiotherapy (45Gy to 50.4Gy) based on overall outcomes across both groups in each study, although this was based on their experience as much as the evidence. However, the trial examining radiotherapy followed by PCV which showed the most significant benefit across outcomes used 54Gy. For this reason, the committee decided to make a recommendation to limit the dose to a maximum of 54Gy for IDH-mutated low-grade gliomas.

The committee discussed case series suggesting the tumour behaviour for histologically proven low-grade glioma without IDH mutation (IDH wildtype) may be more in keeping with a glioblastoma, and should be considered when discussing management options. The evidence was too low quality to make a strong recommendation.

Low-grade gliomas are slow-growing tumours. However, over time most transform into high-grade gliomas, therefore interventions for low-grade gliomas aim to delay tumour enlargement and transformation. Consequently, the committee considered that low-grade gliomas with prognosis closer to a typical grade III glioma will benefit from radiotherapy followed by PCV as earlier intervention is associated with extended time to disease progression (considering radiotherapy within 8 weeks of surgery versus later radiotherapy). Furthermore, it can help to improve seizure control. One of the potential harms of this intervention is that radiotherapy can, in the long term, induce steady cognitive decline. However the committee considered that the survival benefits offset this harm.

For those people with more favourable prognostic factors, the committee considered that an active monitoring approach would be appropriate. The main benefit is that people may be well for a prolonged period of time without any symptoms, and active monitoring will not interfere with this. This means that people are not subjected to the potential risk of radiation-induced cognitive decline, secondary tumour and other late side effects. However, the potential risk is that the tumour may grow substantially, and the person would then need an intervention for a larger lesion which has greater risk of cognitive problems. In addition, the optimal frequency of monitoring for the tumour is not established as it varies from person to person.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

While the committee thought these recommendations would standardise practice across the NHS in England and therefore there could be changes in practice, the interventions recommended (radiotherapy and PCV) are not resource intensive and already widely used. Some of these recommendations will require molecular marker testing to be able to implement, which may have an additional resource impact, discussed in the section on ‘What

are the most useful molecular markers to determine prognosis / guide treatment for gliomas?'.

Other factors the committee took into account

The committee made an approximate age cutoff in their recommendations. This is based on moderate quality evidence that this treatment improved overall survival and progression free survival. The trial upon which this evidence was sourced used the age of 40 as the cutoff for entry. The committee were therefore sure that there was benefit to offering this treatment to those aged over 40, but unsure about the benefit of this treatment in those aged under 40 who did not meet the other entry criterion for the trial (residual tumour). Since the committee were uncertain about the benefits in this group of patients, they agreed that clinical judgement should be used at around the age cutoff of 40. Taken together, the recommendations constituting this potential equality issue are proportionate and justified with respect to the evidence. The committee highlighted that the balance of harms of treatment versus risk of no treatment favours non-intervention in younger patients and that therefore in the absence of evidence of benefit, people who are younger than the inclusion criteria for the trial (with no risk from residual tumour) should be especially considered for a non-intervention approach. This therefore means different recommendations in different groups are made only on the basis of differing clinical evidence in these groups.

The committee discussed how treatment options had changed significantly in recent years, and that those diagnosed prior to the use of these new treatments might be concerned that their management protocol differed substantially from that set out in the guideline. They explained that this will usually be to do with the availability of new evidence, especially molecular markers, but that this is unlikely to present an equality issue, as anyone who is stable having been treated in the past is unlikely to need further active treatment unless the tumour progresses. Therefore it was not necessary to make a recommendation about this group for reasons of equality.

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Management of newly diagnosed high-grade glioma following surgery or if surgery is not possible (or has been declined)

Review question

Following surgery, what is the optimal management (radiotherapy, chemotherapy, combinations of these, or other therapies such as metformin or tumour-treating fields) of initial high-grade glioma?

Introduction

Glioblastomas (WHO grade IV) and anaplastic astrocytoma/oligoastrocytoma/oligodendroglioma (WHO grade III) are the most frequent type of intrinsic primary brain tumours. Despite a greater understanding of molecular classification and improvements in treatment, survival – particularly for WHO grade IV tumours – remains very poor.

The aim of this review is to resolve areas of clinical uncertainty as to the optimal management of newly diagnosed high-grade glioma.

PICO table

Table 38: Summary of the protocol (PICO table)

Population	People with high-grade gliomas (anaplastic astrocytomas, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, gliosarcoma and glioblastoma, transformed low-grade gliomas that has not previously been treated) who have not previously had a high-grade glioma.
Intervention	Specified standard of care in the comparator group plus: • chemotherapy • immunotherapy • biological therapy • different radiotherapy schedules • tumour treating fields • metformin • statins • ketogenic diet • valgancyclovir • cannabis oil (Sativex)
Comparison	**Glioblastoma (WHO Grade IV)** • ≤70 years of age + Karnofsky performance status ≥70: Surgery/biopsy + radiotherapy + temozolomide • ≥70 years of age or Karnofsky performance status ≤70: Surgery/biopsy + Radiotherapy **Anaplastic astrocytoma/ oligoastrocytoma/ oligodendroglioma (WHO Grade III):** • surgery/biopsy + radiotherapy
Outcome	Critical: • overall survival. • progression-free survival / time to progression

	• health related quality of life Important: • neurological adverse events • wound infections • RTOG grade 3 and/or 4 toxicity • CTCAE grade 3 and/or 4 toxicity • fatigue (somnolence) • cognitive function

CTCAE Common Terminology Criteria for Adverse Events; RTOG Radiation Therapy Oncology Group; WHO World Health Organization.

For further details see the full review protocol in Appendix A.

Clinical evidence

The aim of this review was to determine following surgery, the optimal management (radiotherapy, chemotherapy, combinations of these, or other therapies such as metformin or tumour-treating fields) of initial high-grade glioma. A single literature search was conducted for WHO grade III (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma) and IV glioma (glioblastoma), however due to differences in the management of WHO grade III and WHO grade IV glioma, studies were reviewed separately. These differences were accounted for by pre-specifying interventional and comparator groups for included studies. For details, see Table 38.

Given the variability in response to interventions based on molecular markers, where possible, analyses were stratified accordingly. Pre-specified stratifications were 1p and 19q chromosomal status (with or without co-deletion); IDH-1 or -2 (isocitrate dehydrogenase 1 or 2) status (with or without mutation); and MGMT (O6-methylguanine-DNA-methyltransferase status) (with or without methylation).

In studies where a mixed population of WHO grade III and IV high-grade glioma were included, stratified results according to grade of glioma were extracted. Due to the limited evidence available in stratified adverse events, these results were still extracted, however the indirectness of the population was accounted for when assessing the quality of the evidence using GRADE.

In terms of health-related quality of life (HRQoL), a minimal clinically meaningful difference for the EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 and QLQ-BN20 scales in brain cancer was considered to be a change of 5 units, in line with published literature by Maringwa 2010.

Meta-analyses were conducted when appropriate. In the presence of heterogeneity, potential reasons for heterogeneity were explored and subgroup analyses were conducted when possible according to the pre-specified groups in the protocol.

Included studies

WHO grade III glioma

Included studies consisted of Phase III RCTs and 1 systematic review enrolling patients with newly diagnosed WHO grade III anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma. Patients may have undergone any form of surgery to reach a histological diagnosis (biopsy or resection).

A summary of these studies is provided in Table 39 and the results along with the quality of the evidence for each outcome are listed in Table 41 to Table 46 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

WHO grade IV glioma

Included studies consisted of Phase III randomised controlled trials (RCTs) enrolling patients with newly diagnosed WHO grade IV glioblastoma multiforme (GBM). Patients may have undergone any form of surgery to reach a histological diagnosis (biopsy or resection).

Current clinical practice has differences in management according to the performance status and age of the patient. For this reason, the protocol consisted of two different sets of inclusion criteria. The first set included those who were ≤70 years old and presented with a Karnofsky Performance Score (KPS) ≥70, group in which standard of care is radiotherapy [RT] in combination with temozolomide [TMZ]. The second set of inclusion criteria, reflected those adults in in which the standard of care is biopsy in combination with RT. This corresponds to those adults ≥ 60 years old and/or with a KPS status ≤ 70.

A summary of these studies is provided in Table 40 and the results along with the quality of the evidence for each outcome are listed in Table 47 to Table 61 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 39 and Table 40 provide a brief summary of the included studies.

Table 39: Summary of included studies for WHO grade III glioma

Study	Population	Intervention	Comparator	Outcomes	Comments
Lecavalier-Barsoum 2014	Two RCTs from this Cochrane systematic review were included: • Cairncross 2006 (RTOG 9402) N= 289 Newly diagnosed, AO or AOA (2 out of 5 anaplastic features) KPS > 60 • van den Bent 2006 (EORTC 26951) N= 368 Newly diagnosed, AO or AOA (3 out of 5 anaplastic features)	PCV + Radiotherapy	Radiotherapy	• OS • PFS • Grade 3 or 4 Toxicity • HRQoL	Cairncross 2006: Chemotherapy schedule: pre-RT Updated outcome data additional data on impact of 1p and 19 q chromosomes and IDH-1 or 2 mutation status: from Cairncross 2013, 2014 and Wang 2010. van den Bent 2006: Outcome data

Study	Population	Intervention	Comparator	Outcomes	Comments
	• WHO PS: 0-2				supplemented by data in sub-studies: Van den Bent 2013 and Taphoorn 2007. Chemotherapy schedule: post-RT For OS and PFS, results stratified for 1p and 19 q chromosomes, MGMT methylation, and IDH-1 or 2 mutation status
NOA-04 Wick 2009	N= 274 Newly diagnosed, AO, AOA, or AA (3 of 4 anaplastic features) KPS >70	Surgical resection/ biopsy + Radiotherapy, followed by temozolomide or PCV at progression	Surgical resection/ biopsy + temozolomide or PCV, followed by RT at progression	• OS • PFS • TTF	Outcome data supplemented by data in sub-studies: Wick 2016 For OS, TTF, and PFS, results stratified for IDH mutant + 1p and 19q co-deleted chromosomes
RTOG 9813 Chang 2016	N = 196 Newly diagnosed, AO and AA KPS > 60	Surgical resection/ biopsy + Radiotherapy + temozolomide	Surgical resection/ biopsy + Radiotherapy + nitrosourea * *BCNU 80mg/m^2 or CCNU 130mg/m^2 (up to a total of 6 cycles)	• OS • PFS • TTF • Grade > 3 Toxicity	
Henriksson 2006	N= 122 newly diagnosed high-grade astrocytoma; grade III, N=46; grade IV, N=76 WHO PS: 0-2	Surgical resection/ biopsy + estramustine + Radiotherapy	Surgical resection/ biopsy + Radiotherapy	• OS • HRQoL	For OS, results were stratified to grade III and IV astrocytoma. Only grade III astrocytoma participants

Study	Population	Intervention	Comparator	Outcomes	Comments
					were included in the analyses as per protocol. For HRQoL, results were not stratified for grade III and IV astrocytoma. However, this was accounted for in the GRADE assessment.
Thomas 2001	N= 674 newly diagnosed high-grade astrocytoma; grade III (anaplastic astrocytoma), N=113; grade IV (GBM), N= 449; others, N=112 <70 years of age	Surgical resection/ biopsy + Radiotherapy + PCV	Surgical resection/ biopsy + Radiotherapy	• OS	For OS, results were stratified to grade III and IV astrocytoma. Only grade III astrocytoma participants were included in the analyses as per protocol.
Malmström 2017	N= 41 adults with newly diagnosed, histologically confirmed AA.	TMZ followed by RT TMZ (200mg/m2, days 1-5, every 28 days) followed by RT (60-Gy in 30 fractions) N= 12 (60%) completed concTMZ*	Standard RT (60-Gy in 30 fractions) N=16 (76.1%) completed concTMZ*	• Median OS	*2 years and 2 months after randomisation, all adults receive a daily dose of TMZ (75mg/m2) concurrent with RT (concTMZ) as it became standard of treatment.

Study	Population	Intervention	Comparator	Outcomes	Comments
CATNON TRIAL van den Bent 2017	N= 745 adults with newly diagnosed AA without 1p-19q co-deletion.	Adjuvant TMZ Arm 3: RT (59.4-Gy in 33 fractions) followed with 12 cycles of adjuvant TMZ (150-200mg/m^2) Arm 4: RT (59.4-Gy in 33 fractions) with both concurrent TMZ (75/mg/m2) and 12 cycles of adjuvant TMZ (150-200mg/m2)	No adjuvant TMZ Arm 1: RT alone (59.4-Gy in 33 fractions) Arm 2: RT with concurrent daily TMZ (75/mg/m^2)	• OS adjusted for: ○ age ○ performance status ○ 1p loss of heterozygosity ○ methylation status	Ongoing study – estimated primary completion date is January 2022 MGMT status available for N=550 (74%) at the time of the interim analysis.

AA anaplastic astrocytoma; AO anaplastic oligoastrocytoma; AOA anaplastic oligodendroglioma; BCNU lomustine; CCNU lomustine; EORTC European Organisation for Research and Treatment of Cancer; HRQoL Health-related quality of life; GBM glioblastoma; Gy Gray (unit of radiation); IDH Isocitrate dehydrogenase; KPS Karnofsky performance status; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; PFS progression free survival; PCV procarbazine lomustine vincristine; RT radiotherapy; RTOG Radiation Therapy Oncology Group; TMZ temozolomide; TTF tumour treating fields; WHO World Health Organisation; WHO PS World Health Organisation performance status.

Table 40: Summary of included studies for WHO grade IV glioma

Study	Population	Intervention	Comparator	Outcomes	Comments
Chinot 2014	N= 921 Newly diagnosed, supratentorial glioblastoma	Surgical resection/ biopsy + chemo-radiation and adjuvant temozolomide plus Bevacizumab	Surgical resection/ biopsy + chemo-radiation and adjuvant Temozolomide	• OS • (methylated and non-methylated MGMT) • PFS • (methylated and non-methylated MGMT)	
Taphoorn 2015	N= 921 Newly diagnosed, supratentorial glioblastoma	Surgical resection/ biopsy + chemo-radiation and adjuvant temozolomide plus bevacizumab	Surgical resection/ biopsy + chemo-radiation and adjuvant temozolomide	• Time to deterioration (TTD) • Disease free survival (DFS)	Sub-study of Chinot 2014
Saran 2016	N= 921 Newly diagnosed, supratentorial glioblastoma	Surgical resection/ biopsy + chemo-radiation and adjuvant Temozolomide plus bevacizumab	Surgical resection/ biopsy + chemo-radiation and adjuvant temozolomide	• Adverse events > Grade 3 RTOG • Adverse events >10% - fatigue	Sub-study of Chinot 2014
Gilbert 2014	N = 621 Newly diagnosed glioblastoma. Additional eligibility criteria included a Karnofsky performance status of at least 70	Surgical resection + chemo-radiation and adjuvant temozolomide plus bevacizumab	Surgical resection + chemo-radiation and adjuvant temozolomide	• OS (methylated and non-methylated MGMT) • PFS (methylated and non-methylated MGMT) • Adverse events RTOG grade 3 + 4 (fatigue + wound dehiscence)	Only resected (partial or complete) patients were included in the study, no biopsy patients
Gilbert 2013	N= 833 newly diagnosed Glioblastoma (WHO grade 4 astrocytoma), KPS > 60	Surgical resection/ biopsy + chemoradiation then adjuvant dose-dense	Surgical resection/ biopsy +chemoradiation then standard adjuvant	• OS (methylated and non-methylated MGMT) • PFS	

Study	Population	Intervention	Comparator	Outcomes	Comments
		temozolomide (21 days in 28 days for up to 12 cycles)	temozolomide (5 days in 28 days for up to 12 cycles)	(methylated and non-methylated MGMT)	
Keime-Guibert 2007	N= 81 ≥70 years of age, newly diagnosed Glioblastoma or anaplastic astrocytoma, KPS of 70 or more	Surgical resection/ biopsy + supportive care + Radiotherapy (50-Gy in 25 fractions)	Surgical resection/ biopsy + supportive care	• OS • PFS • Health-related quality of life (EORTC QLQ-C30 + QLQ-BN20)	Patients with anaplastic astrocytoma were excluded as such a small population (2%)
Kim 2011	N=76 Newly diagnosed glioblastomas, KPS of 70 or more	Surgical resection/ biopsy then 2 cycles of neoadjuvant nimustine (ACNU) and cisplatin (CDDP) then radiotherapy (60-Gy in 30 fractions) and adjuvant temozolomide	Surgical resection/ biopsy then radiotherapy (60-Gy in 30 fractions) and adjuvant temozolomide	• OS • PFS • Adverse effects CTCAE Grade 3 + 4	Enrolment ceased after interim analysis revealed a frequency of toxicity related to the neoadjuvant chemotherapeutic agents that is not acceptable in modern cancer management.
Nordic trial Malmström 2012	N=342 Newly diagnosed glioblastoma, over 60 years of age	Surgical resection/ biopsy then either 6 cycles of Temozolomide or Hypofractionated Radiotherapy (34Gy in 10 fractions)	Standard radiotherapy (60Gy in 30 fractions)	• Health related quality of life (EORTC QLQ-30 + BN20)	
Roa 2004	N=95 Newly diagnosed glioblastoma, > 60 years, KPS > 50	3-week abbreviated course of Radiotherapy (40-Gy in 15 fractions)	Standard radiotherapy (60-Gy in 30 fractions)	• OS • Health related quality of life [Functional Assessment of Cancer Therapy–Brain (FACT-Br) + KPS]	

Study	Population	Intervention	Comparator	Outcomes	Comments
Roa 2015	N= 96 Older and/or frail people diagnosed with glioblastoma. Frail patients were defined as >50 years old with a KPS of 50% to 70%; older and frail patients were defined as >60 years old with a KPS of 50% to 70%, and older people were defined as >65 years old with a KPS of 80-100%.	Short-course radiotherapy (25-Gy in 5 fractions)	Commonly used radiotherapy (40-Gy in 15 fractions)	• OS • PFS • Health related quality of life – Global Health Status (EORTC QLQ-30)	de Castro 2017 provided a sub-analysis of this trial
CENTRIC EORTC 26071-22072 Stupp 2014	N= 545 Newly diagnosed Glioblastoma	Surgical resection chemo-radiation and adjuvant temozolomide plus cilengitide (twice weekly)	Surgical resection chemo-radiation and adjuvant temozolomide	• OS • PFS • Adverse effects RTOG 3 + 4 – fatigue and memory impairment	
Stupp 2015	N= 315 Newly diagnosed, supratentorial glioblastoma, completed standard concomitant chemoradiotherapy with Temozolomide, KPS > 70. Prior use of implanted carmustine wafers was allowed.	Surgical resection /biopsy + chemo-radiation and adjuvant temozolomide till progression plus Tumour-Treating Fields	Surgical resection /biopsy + chemo-radiation and adjuvant temozolomide till progression	• OS • PFS • Adverse events RTOG Grade 3 + 4	Very high drop-out rate – 90%. Zhu 2017 performed a sub-analysis to report quality of life, cognitive function and performance status. Patient enrolment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemoth

Study	Population	Intervention	Comparator	Outcomes	Comments
					erapy were not eligible for randomisation, thus excluding patients with very poor prognosis. Interim analysis from the first 315 patients with at least 18 months follow-up. However, for detailed and meaningful subgroup analysis, the mature data of the full data set will be needed (expected end of 2017).
Westphal 2015	N= 142 Newly diagnosed supratentorial glioblastoma multiforme that were deemed by the treating neurosurgeon to be amenable to complete resection, KPS > 70.	Surgical resection /biopsy chemo-radiation and adjuvant temozolomide plus I.V. Nimotuzumab	Surgical resection /biopsy chemo-radiation and adjuvant temozolomide	• OS (methylated and non-methylated MGMT) PFS (methylated and non-methylated MGMT) • Adverse events RTOG Grade 3 + 4 • Pre-specified adverse events – fatigue and memory impairment	
NOA-08 Wick 2012	N= 373 Newly diagnosed anaplastic astrocytoma or glioblastoma. Age older than 65 years and KPS of 60 or more.	Surgical resection/ biopsy + biopsy/resection then temozolomide alone	Surgical resection/ biopsy then radiotherapy (60-Gy in 30 fractions)	• OS • PFS	Indirect population: 10.7% of the included patients presented with anaplastic astrocytoma

Study	Population	Intervention	Comparator	Outcomes	Comments
ASPECT trial Westphal 2013	N= 236 Newly diagnosed supratentorial glioblastoma multiforme that were deemed by the treating neurosurgeon to be amenable to complete resection, KPS > 70.	Surgical resection + radiotherapy (60-Gy in 30 fractions) plus sitimagene ceradenovec + ganciclovir	Surgical resection + radiotherapy (60-Gy in 30 fractions)	• OS • (methylated and non-methylated MGMT) • Adverse events RTOG Grade 3 + 4	The use of concurrent and adjuvant temozolomide depended on institutional policy (65% control arm and 49% in experimental unit)
Malmström 2017	N= 103 adults with newly diagnosed, histologically confirmed glioblastoma multiforme.	TMZ followed by RT TMZ (200mg/m^2, days 1-5, every 28 days) followed by RT (60-Gy in 30 fractions) N=26 (51%) completed concTMZ*	Standard RT (60-Gy in 30 fractions) N= 36 (69%) completed concTMZ*	OS	*2 years and 2 months after randomisation, all adults receive a daily dose of TMZ (75mg/m^2) concurrent with RT (concTMZ) as it became standard of treatment. Standard RT arm: N= 12 adults from 1 center received 52-Gy (36-Gy whole brain plus 16-Gy tumour boost). One adult had palliative RT (34-Gy in 10 fractions)
Perry 2017	N= 562 older people (≥ 65 years old) with newly diagnosed, histologically confirmed glioblastoma multiforme	RT with concomitant and adjuvant TMZ	RT alone	• OS • PFS • QOL	N= 3 (0.6%) of the adults included presented with anaplastic oligodendroglioma.

ACNU-CDDP chemotherapy with nimustine – cisplatin; concTMZ concurrent temozolomide; CTCAE Common Terminology Criteria for Adverse events; DFS disease free survival; EORTC European Organisation for Research and Treatment of Cancer; Gy Gray (unit of radiation);KPS Karnofsky performance status; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; PFS progression free survival; QOL quality of life; RT radiotherapy; RTOG Radiation Therapy Oncology Group; TMZ temozolomide; TTD time to deterioration ; WHO World Health Organization.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

WHO grade III glioma

The clinical evidence profiles for Grade III glioma are presented in Table 41 to Table 46.

Table 41: Summary of clinical evidence profile for RT + TMZ versus RT + a nitrosourea (NU)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT + NU	RT + TMZ			
Overall Survival (univariate analysis)	Not applicable	Not applicable	HR 0.94 (0.67 to 1.32)	196 (1 study)	⊕⊕⊖⊖ low[1]
Progression-free survival (univariate analyses)	Not applicable	Not applicable	HR 0.85 (0.61 to 1.18)	196 (1 study)	⊕⊕⊖⊖ low[2,3]
Overall Toxicity (> Grade 3)	758 per 1000	477 per 1000 (379 to 606)	RR 0.63 (0.50 to 0.80)	195 (1 study)	⊕⊕⊖⊖ low[2,3]

CI confidence interval; HR hazard ratio; RR risk ratio; RT radiotherapy; NU nitrosourea.
1 95% CI crossed 2 MIDs (0.80 and 1.25)
2 95% CI crossed 1 MIDs (0.80)
3 Unclear if blinding of participants, personnel, and outcome assessors

Table 42: Summary of clinical evidence profile for RT + PCV versus RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT	RT + PCV			
Overall survival	Not applicable	Not applicable	HR 0.78 (0.67 to 0.91)	1331 (3 studies)	⊕⊕⊕⊖ moderate[1]
Overall survival with codeletion of chromosomes 1p + 19q	Not applicable	Not applicable	HR 0.58 (0.40 to 0.83)	206 (2 studies)	⊕⊕⊕⊖ moderate[1]
Overall survival without codeletion of chromosomes 1p + 19q	Not applicable	Not applicable	HR 0.84 (0.66 to 1.06)	373 (2 studies)	⊕⊕⊕⊖ moderate[1]
Overall survival with IDH-1 mutation	Not applicable	Not applicable	HR 0.53 (0.30 to 0.94)	81 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival without IDH-1 mutation	Not applicable	Not applicable	HR 0.78 (0.52 to 1.17)	97 (1 study)	⊕⊕⊕⊖ moderate[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival with methylated MGMT	Not applicable	Not applicable	HR 0.65 (0.43 to 0.98)	136 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival with non-methylated MGMT	Not applicable	Not applicable	HR 0.81 (0.44 to 1.49)	47 (1 study)	⊕⊕⊖⊖ low[2]
Overall survival with IDH-1 or 2 mutations	Not applicable	Not applicable	HR 0.59 (0.40 to 0.87)	156 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival without codeletion of chromosomes but with IDH-1 or 2	Not applicable	Not applicable	HR 0.56 (0.32 to 0.98)	66 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival without IDH-1 or 2 mutations	Not applicable	Not applicable	HR 1.14 (0.63 to 2.06)	54 (1 study)	⊕⊕⊖⊖ low[2]
Progression Free Survival	Not applicable	Not applicable	HR 0.67 (0.56 to 0.81)	1331 (2 studies)	⊕⊕⊖⊖ low[1,3]
Progression free survival with codeletion of chromosomes 1p + 19q	Not applicable	Not applicable	HR 0.45 (0.32 to 0.64)	206 (2 studies)	⊕⊕⊕⊖ moderate[3]
Progression free survival without codeletion of chromosomes 1p + 19q	Not applicable	Not applicable	HR 0.76 (0.61 to 0.94)	373 (2 studies)	⊕⊕⊖⊖ low[1,3]
Progression free survival with IDH-1 mutation	Not applicable	Not applicable	HR (0.49 (0.29 to 0.83)	81 (1 study)	⊕⊕⊖⊖ low[1,3]
Progression free survival without IDH-1 mutation	Not applicable	Not applicable	HR 0.56 (0.37 to 0.85)	97 (1 study)	⊕⊕⊖⊖ low[1,3]
Progression free survival with methylated MGMT	Not applicable	Not applicable	HR 0.52 (0.35 to 0.77)	136 (1 study)	⊕⊕⊕⊖ moderate[3]
Progression free survival with non-methylated MGMT	Not applicable	Not applicable	HR 0.63 (0.34 to 1.17)	47 (1 study)	⊕⊕⊖⊖ low[1,3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (**end of RT**)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - fatigue HRQoL scale (end of RT) in the intervention groups was	Not applicable	257 (1 study)	⊕⊕⊕⊖ moderate[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
		0.90 lower (4.93 lower to 3.13 higher)			
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (end of **RT + 1 year**)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - fatigue HRQoL scale (end of RT + 1 year) in the intervention groups was 0.50 higher (3.51 lower to 4.51 higher)	Not applicable	133 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (**end of RT + 2.5 years)**	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - fatigue HRQoL scale (end of RT + 2.5 years) in the intervention groups was 2.00 lower (6.01 lower to 2.01 higher)	Not applicable	94 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (**end of RT**)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - nausea and vomiting HRQoL scale (end of RT) in the intervention groups was 2.30 higher (0.29 to 4.31 higher)	Not applicable	257 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (end of **RT + 1** year)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - nausea and vomiting HRQoL scale (end of RT + 1 year) in the intervention groups was 1.80 higher (0.20 lower to 3.80 higher)	Not applicable	133 (1 study)	⊕⊕⊕⊖ moderate[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (end of **RT + 2.5 years**)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - nausea and vomiting HRQoL scale (end of RT + 2.5 years) in the intervention groups was 0.70 lower (2.71 lower to 1.31 higher)	Not applicable	94 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - physical functioning HRQoL scale (end of RT) in the intervention groups was 8.50 higher (4.06 to 12.94 higher)	Not applicable	257 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT + 1 year)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - physical functioning HRQoL scale (end of RT + 1 year) in the intervention groups was 2.50 higher (2.01 lower to 7.01 higher)	Not applicable	133 (1 study)	⊕⊕⊕⊖ moderate[3]
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT + 2.5 years)	Not applicable	The mean health related quality of life - qlq-c30 + qlq-bn20 - physical functioning HRQoL scale (end of RT + 2.5 years) in the intervention groups was 2.20 higher (2.30 lower to 6.70 higher)	Not applicable	94 (1 study)	⊕⊕⊕⊖ moderate[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Toxicity - Overall Toxicity (Grade 3 or 4)	50 per 1000	644 per 1000 (310 to 1000)	RR 12.97 (6.24 to 26.97)	287 (1 study)	⊕⊕⊕⊖ moderate[3]

CI confidence interval; HR hazard ratio; HRQoL Health-related quality of life; PCV procarbazine lomustine vincristine; HRQoL Health-related quality of life; IDH Isocitrate dehydrogenase mutations; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; PCV procarbazine lomustine vincristine; RR risk ratio; RT radiotherapy; TMZ temozolomide
[1] 95% CI crossed 1 default MID (0.80)
[2] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[3] Unclear blinding of participants, personnel and outcome assessors

Table 43: Summary of clinical evidence profile for estramustine + RT versus RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT	Estramustine + RT			
Overall survival for Grade III Astrocytoma	Not applicable	Not applicable	HR 0.99 (0.92 to 1.07)	122 (1 study)	⊕⊕⊕⊖ moderate[1]
Toxicity - Grade III + IV Nausea/vomiting	44 per 1000	34 per 1000 (6 to 96)	RR 0.77 (0.13 to 4.44)	122 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Health Related Quality of Life - QLQ-30 - Global QoL Scale from: 0 to 100.	Not applicable	The mean health related quality of life - QLQ-30 - global QoL in the intervention groups was 2.1 higher (not possible to calculate CI)	Not applicable	66 (1 study)	⊕⊖⊖⊖ very low[1,2,4,5]

CI confidence interval; HR hazard ratio; RT radiotherapy; QoL quality of life.
1 Randomisation process nor allocation concealment not described in methods
2 Unblinded to participants, personnel, and assessors
3 95% CI crossed 2 default MIDs (0.80 and 1.25)
4 Grade III and IV astrocytoma analysed together, not stratified per grade
5 No SDs were reported to assess the MID thresholds or imprecision

Table 44: Summary of clinical evidence profile for PCV or TMZ + RT on progression versus RT + PCV or TMZ on progression

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	PCV or TMZ + RT on progression	RT + PCV or TMZ on progression			

Overall survival (long-term analysis, median follow-up time 9.5 years)	Not applicable	Not applicable	HR 1.11 (0.80 to 1.54)	274 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free-survival (long-term analysis, median follow-up 9.5 years)	Not applicable	Not applicable	HR 0.97 (0.74 to 1.27)	274 (1 study)	⊕⊖⊖⊖ very low[3,4]
Time to treatment failure (long-term follow-up, 9.5 years)	Not applicable	Not applicable	HR 0.99 (0.75 to 1.31)	274 (1 study)	⊕⊖⊖⊖ very low[3,4]
Differential treatment outcomes[a] in **IDH mutant + 1p/19q co-deleted -** Progression-Free Survival Follow-up: median 9.5 years	Not applicable	Not applicable	HR 1.30 (0.70 to 2.41)	68 (1 study)	⊕⊖⊖⊖ very low [3,4]
Differential treatment outcomes[b] in **IDH mutant + 1p/19q co-deleted -** Time-to-Treatment Failure Follow-up: median 9.5 years	Not applicable	Not applicable	HR 1.35 (0.68 to 2.68)	68 (1 study)	⊕⊖⊖⊖ very low[3,4]
Differential treatment outcomes[c] in **IDH mutant + 1p/19q co-deleted -** Overall Survival Follow-up: median 9.5 years	Not applicable	Not applicable	HR 0.46 (0.04 to 5.56)	68 (1 study)	⊕⊖⊖⊖ very low [1,3]

CI confidence interval; HR hazard ratio; IDH Isocitrate dehydrogenase; RR risk ratio; RT radiotherapy; TMZ temozolomide; n/r not reached

[a]Differential treatment outcomes refers to treatment differences in progression free survival in those with IDH mutant and 1p/19q co-deletion
[b]Differential treatment outcomes refers to treatment differences in time to treatment failure in those with IDH mutant and 1p/19q co-deletion
[c]Differential treatment outcomes refers to treatment differences in overall survival in those with IDH mutant and 1p/19q co-deletion
1 Unclear risk of allocation concealment and no mention of loss to follow-up
2 95% CI crosses 1 MID (1.25)
3 95% CI crosses 2 MIDs (0.80 and 1.25)
4 Unclear risk of allocation concealment, no mention of loss to follow-up, un-blinded

Table 45: TMZ followed by RT versus RT alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT alone	TMZ followed by RT			
Overall survival	Not applicable	Not applicable	HR 0.40 (0.19 to 0.84)	41 (1 study)	⊕⊕⊕⊖ moderate[1]

CI confidence interval; HR hazard ratio; RT radiotherapy; TMZ temozolomide
[1] 95% CI crossed 1 default MID (0.80)

Table 46: RT with adjuvant TMZ versus RT without adjuvant therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT without adjuvant therapy	RT with adjuvant TMZ			
Overall survival	Not applicable	Not applicable	HR 0.65 (0.45 to 0.94)	745 (1 study)	⊕⊕⊕⊖ moderate[1]
Progression free survival	Not applicable	Not applicable	HR 0.58 (0.47 to 0.72)	745 (1 study)	⊕⊕⊕⊕ high
Adjusted analyses for adjuvant TMZ only - Age (>50 y/o versus ≤ 50 y/o)[a]	Not applicable	Not applicable	HR 4.04 (2.78 to 5.87)	373 (1 study)	⊕⊕⊕⊕ high
Adjusted analyses for adjuvant TMZ only - WHO performance status score (>0 versus 0)[a]	Not applicable	Not applicable	HR 1.36 (0.94 to 1.97)	373 (1 study)	⊕⊕⊕⊖ moderate[2]
Adjusted analyses for adjuvant TMZ only - 1p loss of heterozygosity (yes versus no)[a]	Not applicable	Not applicable	HR 1.56 (0.84 to 2.90)	373 (1 study)	⊕⊕⊕⊖ moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Adjusted analyses for adjuvant TMZ only - Methylated versus non-methylated MGMT status [a]	Not applicable	Not applicable	HR 1.81 (1.44 to 2.27)	373 (1 study)	⊕⊕⊕⊕ high

CI confidence interval; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; RT radiotherapy; TMZ temozolomide; WHO World Health Organization.
[a]These analyses correspond to within group differences of those who received RT with adjuvant TMZ
[1] 95% CI crossed 1 default MID (0.80)
[2] 95% CI crossed 1 default MID (1.25)

See Appendix F for full GRADE tables.

WHO grade IV glioma

The clinical evidence profiles for Grade IV glioma are presented in Table 47 to Table 61.

Table 47: Bevacizumab plus TMZ+RT versus TMZ+RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ+RT	Bevacizumab plus TMZ+RT			
Overall survival	Not applicable	Not applicable	HR 0.99 (0.77 to 1.26)	1542 (2 studies)	⊕⊖⊖⊖ very low[1,2,3]
Overall survival MGMT methylated	Not applicable	Not applicable	HR 1.20 (0.42 to 3.46)	412 (2 studies)	⊕⊖⊖⊖ very low[1,2,6]
Overall survival MGMT non-methylated	Not applicable	Not applicable	HR 1.02 (0.98 to 1.06)	890 (2 studies)	⊕⊕⊕⊖ moderate[1]
Overall survival RPA class 3	Not applicable	Not applicable	HR 0.93 (0.66 to 1.30)	234 (2 studies)	⊕⊕⊖⊖ low[1,4]
Overall survival RPA class 4	Not applicable	Not applicable	HR 0.97 (0.88 to 1.06)	959 (2 studies)	⊕⊕⊕⊖ moderate[1]
Overall survival RPA class 5	Not applicable	Not applicable	HR 0.93 (0.73 to 1.19)	335 (2 studies)	⊕⊕⊖⊖ low[1,4]

Progression free survival	Not applicable	Not applicable	HR 0.71 (0.58 to 0.87)	1542 (2 studies)	⊕⊖⊖⊖ very low[1,3,5]
Progression free survival MGMT methylated	Not applicable	Not applicable	HR 0.93 (0.53 to 1.64)	412 (2 studies)	⊕⊕⊖⊖ very low[1,3,5,6]
Progression free survival MGMT non-methylated	Not applicable	Not applicable	HR 0.59 (0.49 to 0.70)	890 (2 studies)	⊕⊕⊕⊖ moderate[1]
Progression free survival RPA grade 3	Not applicable	Not applicable	HR 0.67 (0.49 to 0.91)	234 (2 studies)	⊕⊕⊖⊖ low[1,3]
Progression free survival RPA grade 4	Not applicable	Not applicable	HR 0.69 (0.60 to 0.79)	959 (2 studies)	⊕⊕⊖⊖ low[1,5]
Progression free survival RPA grade 5	Not applicable	Not applicable	HR 0.71 (0.56 to 0.90)	335 (2 studies)	⊕⊕⊖⊖ low[1,3]
Adverse events overall - Grade ≥3	158 per 1000	325 per 1000 (252 to 418)	RR 2.06 (1.60 to 2.65)	911 (1 study)	⊕⊕⊕⊖ moderate[1]
Wound complications	11 per 1000	23 per 1000 (11 to 48)	RR 2.16 (1.03 to 4.52)	1514 (2 studies)	⊕⊕⊖⊖ low[1,4]
Fatigue	70 per 1000	112 per 1000 (66 to 189)	RR 1.60 (0.95 to 2.70)	603 (1 study)	⊕⊕⊖⊖ low[1,3]

CI confidence interval; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; RR risk ratio; RPA recursive portioning analysis; RT radiotherapy; TMZ temozolomide.
1 Unclear how allocation concealment was performed
2 I^2 ≥75%
3 95% CI crossed 1 default MID (0.80)
4 95% CI crossed 1 MID (1.25)
5 I^2 between 50 and 74.99%
6 95% CI crossed 2 default MIDs (0.8 and 1.25)

Table 48: Nimotuzumab plus TMZ+RT versus TMZ+RT

Outcomes	Illustrative comparative risks* (95% CI)			Quality of the

	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of Participants (studies)	evidence (GRADE)
	TMZ+RT	Nimotuzumab plus TMZ+RT			
Overall survival	Not applicable	Not applicable	HR 0.86 (0.57 to 1.31)	142 (1 study)	⊕⊖⊖⊖ very low[1,2]
Overall survival MGMT methylated	Not applicable	Not applicable	HR 0.86 (0.27 to 2.74)	31 (1 study)	⊕⊖⊖⊖ very low[1,2]
Overall survival MGMT non-methylated	Not applicable	Not applicable	HR 0.80 (0.45 to 1.42)	65 (1 study)	⊕⊖⊖⊖ very low[1,2]
Progression free survival	Not applicable	Not applicable	HR 0.95 (0.93 to 1.14)	142 (1 study)	⊕⊕⊖⊖ low[1,3]
Progression free survival MGMT methylated	Not applicable	Not applicable	HR 0.93 (0.76 to 1.14)	31 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Grade 3/4 adverse events	85 per 1000	310 per 1000 (134 to 718)	RR 3.67 (1.58 to 8.50)	142 (1 study)	⊕⊕⊖⊖ low[1,3]
Fatigue	437 per 1000	275 per 1000 (188 to 402)	RR 1.26 (0.90 to 1.76)	142 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Memory impairment	113 per 1000	28 per 1000 (9 to 90)	RR 0.50 (0.16 to 1.59)	142 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

CI confidence interval; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; RR risk ratio; RT radiotherapy; TMZ temozolomide.
[1] Unclear how randomisation was done, only randomisation by fax was described. High risk of performance bias
[2] 95% CI crossed 2 default MID (0.80 and 1.25)
[3] Open label study
[4] 95% CI crossed 1 default MID (1.25)

Table 49: Cilengitide plus TMZ+RT versus TMZ+RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ+RT	Cilengitide plus TMZ+RT			

Overall survival	Not applicable	Not applicable	HR 1.02 (0.81 to 1.28)	545 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival RPA grade 3	Not applicable	Not applicable	HR 0.63 (0.31 to 1.28)	86 (1 study)	⊕⊕⊖⊖ low[2]
Overall survival RPA grade 4-5	Not applicable	Not applicable	HR 1.08 (0.84 to 1.39)	521 (1 study)	⊕⊕⊕⊖ moderate[1]
Progression free survival	Not applicable	Not applicable	HR 0.92 (0.75 to 1.13)	521 (1 study)	⊕⊕⊖⊖ low[1,3]
Grade 3 and 4 toxicity	579 per 1000	619 per 1000 (544 to 712)	RR 1.07 (0.94 to 1.23)	521 (1 study)	⊕⊕⊕⊖ moderate[3]
Fatigue	31 per 1000	53 per 1000 (23 to 125)	RR 1.72 (0.73 to 4.02)	521 (1 study)	⊕⊖⊖⊖ very low[2,3]
Memory impairment	4 per 1000	4 per 1000 (0 to 58)	RR 0.98 (0.06 to 14.91)	521 (1 study)	⊕⊖⊖⊖ very low[2,3]

CI confidence interval; HR hazard ratio; RR risk ratio; RPA recursive portioning analysis; RT radiotherapy; TMZ temozolomide
1 95% CI crossed 1 default MID (1.25)
2 95% CI crossed 2 default MID (0.80 and 1.25)
3 Open label study

Table 50: Summary clinical evidence profile for TMZ+RT plus DD TMZ (150-200 mg/m^2) versus TMZ+RT plus standard TMZ (75-100mg/m^2)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ+RT plus standard TMZ (75-100mg/m2)	TMZ+RT plus DD TMZ (150-200 mg/m2)			
Overall survival	Not applicable	Not applicable	HR 1.03 (0.88 to 1.21)	823 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival for patients with MGMT methylated status	Not applicable	Not applicable	HR 1.19 (0.87 to 1.63)	245 (1 study)	⊕⊕⊖⊖ low[1,2]
Overall survival for patients with MGMT non-	Not applicable	Not applicable	HR 0.99 (0.82 to 1.20)	517 (1 study)	⊕⊕⊕⊖ moderate[1]

methylated status					
Progression free survival	Not applicable	Not applicable	HR 0.87(0.75 to 1.01)	823 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Progression free survival for patients with MGMT methylated status	Not applicable	Not applicable	HR 0.87 (0.66 to 1.15)	245 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Progression free survival for patients with MGMT non-methylated status	Not applicable	Not applicable	HR 0.88 (0.73 to 1.06)	517 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Grade 3-4 toxicity	342 per 1000	536 per 1000 (441 to 626)	RR 1.54 (1.29 to 1.83)	720 (1 study)	⊕⊕⊖⊖ low[1,3]
Fatigue	34 per 1000	90 per 1000 (47 to 170)	RR 2.62 (1.37 to 4.98)	45 (1 study)	⊕⊕⊖⊖ low[1,3]

CI confidence interval; DD dose dense; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; RR risk ratio; RT radiotherapy; TMZ temozolomide.
[1] Unclear allocation concealment
[2] 95% CI crossed 1 MID (1.25)
[3] Not blinded
[4] 95% CI crossed 1 MID (0.80)

Table 51: Summary clinical evidence profile for ceradenovec followed by ganciclovir plus TMZ+RT versus TMZ+RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ+RT	Ceradenovec followed by ganciclovir plus TMZ+RT			
Overall survival	Not applicable	Not applicable	HR 1.18 (0.86 to 1.62)	236 (1 study)	⊕⊕⊖⊖ low[1,2]

Overall survival for patients with MGMT non-methylated status	Not applicable	Not applicable	HR 1.40 (0.92 to 2.13)	236 (1 study)	⊕⊕⊖⊖ low[1,2]
Adverse events (grade 3 and 4)	373 per 1000	582 per 1000 (444 to 761)	RR 1.56 (1.19 to 2.04)	250 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

CI confidence interval; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; RR risk ratio; RT radiotherapy; TMZ temozolomide
1 Incomplete outcome data, insufficient detail regarding randomisation process
2 95% CI crossed 1 MID (1.25)
3 Unclear whether outcome assessors were blinded to treatment allocation

Table 52: Summary clinical evidence profile for ACNU-CDDP and TMZ+ RT versus TMZ+RT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ+RT	ACNU-CDDP and TMZ+ RT			
Overall survival	Not applicable	Not applicable	HR 0.59 (0.33 to 1.05)	82 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival	Not applicable	Not applicable	HR 0.76 (0.43 to 1.34)	82 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Adverse events grade ≥3	158 per 1000	684 per 1000 (417 to 867)	RR 4.33 (2.64 to 5.49)	76 (1 study)	⊕⊕⊖⊖ low[1,4]

ACNU-CDDP chemotherapy with nimustine – cisplatin; CI confidence interval; HR hazard ratio; RR risk ratio; RT radiotherapy; TMZ temozolomide.
[1] No details on actual randomisation process; no details reported on whether any form of allocation concealment was used
[2] 95% crossed 1 MID (0.80)
[3] 95% crossed 2 MIDs (0.80 and 1.25)
[4] No blinding of outcome assessors

Table 53: Summary clinical evidence profile for TTF (tumour treating fields) + TMZ versus TMZ

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	TMZ	TTF + TMZ			
Overall survival	Not applicable	Not applicable	HR 0.74 (0.56 to 0.98)	315 (1 study)	⊕⊕⊕⊖ moderate[1]

Progression free survival	Not applicable	Not applicable	HR 0.62 (0.43 to 0.89)	315 (1 study)	⊕⊕⊖⊖ low[1,2]
Fatigue	40 per 1000	40 per 1000 (12 to 128)	RR 1.00 (0.31 to 3.23)	304 (1 study)	⊕⊖⊖⊖ very low[2,3]

CI confidence interval; HR hazard ratio; RR risk ratio; TTFields tumour treating fields; TMZ temozolomide.
1 95% CI crossed 1 MID (0.80)
2 Open label study
3 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 54: Summary clinical evidence profile for TMZ versus standard RT in older people[d]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard RT	TMZ			
Overall survival	Not applicable	Not applicable	HR 0.88 (0.57 to 1.36)	566 (2 studies)	⊕⊖⊖⊖ very low[1,3,5]
Overall survival for people between 60 and 70 years old	Not applicable	Not applicable	HR 0.87 (0.59 to 1.28)	110 (1 study)	⊕⊖⊖⊖ very low[2,5]
Overall survival for people ≥70 years old	Not applicable	Not applicable	HR 0.35 (0.21 to 0.58)	193 (1 study)	⊕⊕⊕⊖ moderate[2]
Overall survival for MGMT methylated versus non - methylated	Not applicable	Not applicable	HR 0.62 (0.42-0.91)	373 (1 study)	⊕⊕⊖⊖ low[2,3]
Grade 3-4 fatigue	73 per 1000	84 per 1000 (48 to 144)	RR 1.14 (0.66 to 1.97)	558 (2 studies)	⊕⊖⊖⊖ very low[2,4,5]
Grade 3-4 neurological symptoms	140 per 1000	184 per 1000 (115 to 295)	RR 1.31 (0.82 to 2.10)	373 (1 study)	⊕⊖⊖⊖ very low[2,4,6]

CI confidence interval; HR hazard ratio; OS overall survival; RR risk ratio; RT radiotherapy; TMZ temozolomide
[1] I^2>75%
[2] some of the patients presented with de-novo anaplastic astrocytoma (3%)
[3] 95% CI crossed 1 default MID (0.80)
[4] No blinding of outcome assessors
[5] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[6] 95% CI crossed 1 default MID (1.25)

[d] Malmstrom 2012 included people above 60 years and older; Wick 2012 included people 65 years and older

Table 55: Summary clinical evidence profile for hypofractionated RT versus standard RT in those aged 60 years over

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard RT	Hypofractionated RT			
Overall survival	Not applicable	Not applicable	HR 0.85 (0.64 to 1.13)	198 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival people > 70 years old	Not applicable	Not applicable	HR 0.59 (0.37 to 0.94)	198 (1 study)	⊕⊕⊕⊖ moderate[1]
Grade 3 and 4 fatigue	Not applicable	Not applicable	RR 5 (0.24 to 102.78)	190 (1 study)	⊕⊖⊖⊖ very low[2,3]

CI confidence interval; HR hazard ratio; OS overall survival; RR risk ratio; RT radiotherapy.
[1] 95% CI crossed 1 default MID (0.80)
[2] No blinding of outcome assessors
[3] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 56: Summary clinical evidence profile for RT schedules in older people [60-Gy versus 40-Gy]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	40-Gy	60-Gy			
Overall survival	Not applicable	Not applicable	HR 0.90 (0.60 to 1.35)	96 (1 study)	⊕⊕⊖⊖ low[1]

CI confidence interval; Gy Gray (unit of radiation); HR hazard ratio; RT radiotherapy.
[1] 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 57: Summary clinical evidence profile for RT schedules in older/frail people [40-Gy versus 25-Gy]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	25-Gy	40-Gy			
Overall survival	Not applicable	Not applicable	HR 0.95 (0.75 to 1.2)	98 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival	Not applicable	Not applicable	HR 0.99 (0.80 to 1.23)	98 (1 study)	⊕⊕⊖⊖ low[1,2]

Quality of life	Not applicable	The mean quality of life in the intervention group was 3.6 lower (17.17 lower to 9.97 higher)	Not applicable	37 (1 study)	⊕⊖⊖⊖ very low[1,3,4]

CI confidence interval; HR hazard ratio; Gy Gray; RT radiotherapy.
1 Insufficient details on allocation concealment
2 95% CI crossed 1 default MID (0.80)
3 unclear whether outcome assessors were blinded to treatment allocation
4 95% CI crossed 2 default MIDs (±17.6 x ± 0.5= ± 8.08)

Table 58: Summary clinical evidence profile for subanalysis of RT schedules in older/frail people [40-Gy versus 25-Gy][a]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Commonly used RT	Short course RT			
Median overall survival	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable	61 (1 study)	⊕⊖⊖⊖ very low[1,2,5]
Median progression free survival	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable	61 (1 study)	⊕⊖⊖⊖ very low[2,3,6]
QoL - 4 weeks after treatment – older people	Not applicable	The mean QOL - 4 weeks after treatment - older people in the intervention groups was 6.5 higher (0.81 lower to 13.81 higher)	Not applicable	61 (1 study)	⊕⊖⊖⊖ very low[3,4]
QoL - 8 weeks after treatment - older people	Not applicable	The mean - 8 weeks after treatment - older people in the intervention groups was 3.1 higher (4.21 lower to 10.41 higher)	Not applicable	24 (1 study)	⊕⊖⊖⊖ very low[3,4]

CI confidence interval; Gy Gray (unit of radiation); OS overall survival; QoL quality of life; RT radiotherapy.
[a]This is a subset analysis of RT schedules in older/frail people [40-Gy versus 25-G] (Table 57). This subset included only those ≥ 65 years old.
[1] Unclear how randomisation was performed
[2] Only descriptive data reported, insufficient details given to assess the MID threshold and imprecision
[3] Unclear how randomisation was performed and concealed; unclear whether outcome assessors and participants were blinded to treatment allocation
[4] 95% CI crossed 1 default MID (8.6 [17.2 x ± 0.5 = ± 8.6])

[5] Not calculable as only medians have been reported. The median OS in the short course RT arm = 6.8 months (95% CI, 4.5-9.1 months) and the median OS in the commonly used RT = 6.2 months (95% CI, 4.7-7.7 months)
[6] Not calculable as only medians have been reported. The median PFS in the short course RT arm = 4.3 months (95% CI, 2.6- 5.9 months) and the median PFS in the commonly used RT= 3.2 months (95% CI, 0.1-6.3 months)

Table 59: Summary clinical evidence profile for RT and supportive care versus supportive care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Supportive care	RT + supportive care			
Overall survival	Not applicable	Not applicable	HR 0.47 (0.29 to 0.76)	85 (1 study)	⊕⊕⊕⊖ moderate[1]
Progression free survival	Not applicable	Not applicable	HR 0.28 (0.17 to 0.46)	85 (1 study)	⊕⊕⊖⊖ low[1,2]
Quality of life (QLQ-C30)	Not applicable	The mean quality of life in the intervention groups was 10.50 higher (9.37 to 11.63 higher)	Not applicable	81 (1 study)	⊕⊕⊖⊖ low[1,2]

CI confidence interval; HR hazard ratio; RT radiotherapy.
[1] No details on how randomisation was performed or how randomisation concealment was used.
[2] Outcome assessors were aware of treatment allocation

Table 60: TMZ followed by RT versus RT alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT alone	TMZ followed by RT			
Overall survival	Not applicable	Not applicable	HR 1.40 (0.93 to 2.09)	103 (1 study)	⊕⊕⊕⊖ moderate[1]

CI confidence interval; HR hazard ratio; RT radiotherapy; TMZ temozolomide.
[1] 95% CI crossed 1 default MID (1.25)

Table 61: RT with concomitant and adjuvant TMZ versus RT alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	RT alone	RT with concomitant and adjuvant TMZ			
Overall survival	Not applicable	Not applicable	HR 0.67 (0.56 to 0.80)	562 (1 study)	⊕⊕⊕⊕ high
Overall survival patients 65 to 70 y/o	Not applicable	Not applicable	HR 0.93 (0.68 to 1.27)	165 (1 study)	⊕⊕⊖⊖ low[1]
Overall survival patients 71 to 75 y/o	Not applicable	Not applicable	HR 0.63 (0.48 to 0.83)	231 (1 study)	⊕⊕⊕⊖ moderate[2]
Overall survival patients ≥ 76 y/o	Not applicable	Not applicable	HR 0.53 (0.38 to 0.74)	166 (1 study)	⊕⊕⊕⊕ high
Overall survival MGMT methylated	Not applicable	Not applicable	HR 0.53 (0.38 to 0.74)	165/354 (1 study)[5]	⊕⊕⊕⊕ high
Overall survival MGMT non-methylated	Not applicable	Not applicable	HR 0.75 (0.56 to 1.00)	189/354 (1 study)[5]	⊕⊕⊕⊖ moderate[2]
Progression free survival	Not applicable	Not applicable	HR 0.50 (0.41 to 0.61)	562 (1 study)	⊕⊕⊕⊖ moderate[3]
Progression free survival patients 65 to 70 y/o	Not applicable	Not applicable	HR 0.76 (0.55 to 1.05)	165 (1 study)	⊕⊕⊖⊖ low[2,3]
Progression free survival patients 71 to 75 y/o	Not applicable	Not applicable	HR 0.42 (0.30 to 0.59)	231 (1 study)	⊕⊕⊕⊖ moderate[3]
Progression free survival patients ≥ 76 y/o	Not applicable	Not applicable	HR 0.49 (0.35 to 0.69)	166 (1 study)	⊕⊕⊕⊖ moderate[3]
Progression free survival MGMT methylated	Not applicable	Not applicable	HR 0.33 (0.23 to 0.47)	165/354 (1 study)[4]	⊕⊕⊕⊖ moderate[3]
Progression free survival MGMT non-methylated	Not applicable	Not applicable	HR 0.79 (0.59 to 1.06)	189/354 (1 study)[4]	⊕⊕⊖⊖ low[2,3]
Time to quality of life deterioration - Emotional	Not applicable	Not applicable	HR 0.86 (0.69 to 1.07)	562 (1 study)	⊕⊕⊖⊖ low[2,3]
Time to quality of life deterioration - Role	Not applicable	Not applicable	HR 0.94 (0.76 to 1.16)	562 (1 study)	⊕⊕⊖⊖ low[2,3]
Time to quality of life deterioration - Social	Not applicable	Not applicable	HR 0.94 (0.76 to 1.16)	562 (1 study)	⊕⊕⊖⊖ low[2,3]
Time to quality of life deterioration - Cognitive	Not applicable	Not applicable	HR 0.84 (0.68 to 1.04)	562 (1 study)	⊕⊕⊖⊖ low[2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Time to quality of life deterioration - Constipation	Not applicable	Not applicable	HR 1.11 (0.88 to 1.40)	562 (1 study)	⊕⊕⊖⊖ low[3,4]
Time to quality of life deterioration - Nausea and vomiting	Not applicable	Not applicable	HR 1.00 (0.79 to 1.27)	562 (1 study)	⊕⊖⊖⊖ very low[1,3]
Time to quality of life deterioration - Fatigue	Not applicable	Not applicable	HR 0.90 (0.73 to 1.11)	562 (1 study)	⊕⊕⊖⊖ low[2,3]

CI confidence interval; HR hazard ratio; MGMT O6-methylguanine-DNA-methyltransferase; OS overall survival; RT radiotherapy; TMZ temozolomide.
1 95% CI crossed 2 default MIDs (0.80 and 1.25)
2 95% CI crossed 1 default MID (0.80)
3 Not blinded
4 MGMT status was obtained from 354 samples (N= 181 from RT+ TMZ and N= 173 from RT alone)

Economic evidence

Included studies

One cost utility and 1 cost effectiveness analysis (Kovic 2015 and Bernard-Arnoux 2016) were included in the current review of published economic evidence for this topic.

Health economic evidence profile

Table 62: Health economic evidence profile

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Study 1										
Kovic 2015 Canada	Adults with a newly diagnosed GBM after biopsy or resection with a WHO performance score between 0 and 2	Standard of Care (SOC)	CA$17,000	0.83	Reference			Deterministic Sensitivity Analysis A range of deterministic sensitivity analyses were performed. The ICER was consistently greater than CA$350,000	Partially Applicable	Minor Limitations.
		Bevacizumab +SOC	CA$80,000	0.96	CA$63,000	0.13	CA$607,966			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
								per QALY Probabilistic Sensitivity Analysis Bevacizumab + SOC only had a non-zero probability of being the preferred option when the cost per QALY threshold was CA$210,000.		
	Comments:									
Study 2										
Bernard-Arnoux 2016 France	Patients with newly diagnosed grade IV astrocytoma and a Karnofsky performance status≥ 70	Standard Chemotherapy and radiotherapy	€$57,665	1.5 LYs	Reference			Deterministic Sensitivity Analysis Deterministic sensitivity analyses were performed around the majority of variables with the	Partially Applicable	Minor Limitations.
		Standard Chemotherapy and radiotherapy with the addition of tumor treating fields	€243,131	1.84 LYs	€185,466	0.34	€596,411 per life year			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
		therapy (TTF)						results consistently above €450,000. The ICER appeared most sensitive to the cost of TTF with the ICER reducing to €71,220 per LY when the cost of TTF was reduced by 80%. Probabilistic Sensitivity Analysis The probability TTF was cost effective at a cost per LY threshold of €100,000 was 0%. For TTF to be the preferred option more than 50% of the time a		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
								cost per LY threshold greater than $600,000 was needed.		
	Comments:									

Summary of studies included in the economic evidence review

Kovic 2015 is a cost utility study comparing bevacizumab in addition to standard of care to standard of care alone in patients with newly diagnosed glioblastoma (GBM). The study took a Canadian healthcare payer perspective and reported outcomes in terms of cost per QALY. Effectiveness data and resource use was taken from the AVAglio trial (Chinot 2014) reported in detail in the clinical evidence review. Utility data were taken from a UK general population using standard gamble techniques. Costs were taken from publically available Canadian costing data.

Bernard-Arnoux 2016 is a cost effectiveness study comparing standard chemotherapy and radiotherapy with the addition of tumour treating field therapy compared to standard chemotherapy and radiotherapy alone in patients with grade IV astrocytoma. The study took a French health insurance perspective and reported outcomes in terms of cost per life year gained. Effectiveness data were taken from EF-14 trial (Stupp 2015) discussed in detail in the accompanying clinical evidence review.

Both studies were deemed partially applicable to the decision problem that we are evaluating. This is because they did not take a NHS and PSS perspective.

Both studies were considered to only have minor limitations in terms of methodological quality. Both studies used the best available evidence and performed a wide range of deterministic sensitivity analyses as well as a comprehensive probabilistic sensitivity analysis

The base-cases in Kovic 2015 and Bernard-Arnoux 2016 suggested an incremental cost-effectiveness ratio (ICER) of CA$607,966 per QALY and €596,411 per life year gained respectively when the addition of the interventions to standard of care alone was compared to standard of care. This was deemed significantly above a cost per QALY for which interventions are accepted for the considered perspectives.

Deterministic sensitivity analysis suggested the preferred option was robust to plausible alternative values across variables of interest with standard of care alone consistently the preferred option across all alternative assumptions. This was confirmed during probabilistic sensitivity analysis where both interventions had a 0% chance of being the preferred option, compared to standard care at the conventionally held cost per QALY thresholds. While neither study considered a NHS and PSS perspective it was considered that the results maybe generalizable to other developed nations given the potentially prohibitive costs associated with both bevacizumab and tumour treating fields (TTF).

For full economic evidence tables and economic evidence profiles see Appendix H.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

WHO grade III glioma

RT + TMZ versus RT + NU (nitrosourea)

- One randomised controlled trial (N=196) provided low quality evidence that showed no difference in overall survival (HR=0.94, 95% CI 0.67-1.32) and progression free survival (HR= 0.85, 95% CI 0.61-1.18) between those who received radiotherapy and temozolomide compared to those who received radiotherapy and a nitrosourea (NU).
- Low quality evidence showed a significant decrease in the risk of any grade 3, 4 or 5 adverse events in those who received radiotherapy and temozolomide compared to radiotherapy and a nitrosourea (NU) (RR=0.63, 95% CI 0.50-0.80).

RT + PCV versus RT (KPS > 60 or WHO 0-2)

- Three randomised controlled trials (N=1331) provided moderate quality evidence that showed radiotherapy and procarbazine, lomustine and vincristine was associated with longer overall survival compared to radiotherapy only (HR= 0.78, 95% CI 0.67-0.91).
- Low to moderate quality evidence showed longer overall survival in those with codeletion of chromosomes 1p/19q (HR= 0.58, 95% CI 0.40-0.83), those with IDH-1 mutation (HR=0.53, 95% CI 0.30-0.94) and those with MGMT methylated status (HR=0.65, 95% CI 0.43-0.98) when receiving radiotherapy and procarbazine, lomustine and vincristine compared to radiotherapy only. No differences in overall survival were observed between the treatments in those without codeletion of 1p/19q (HR= 0.84, 95% CI 0.66-1.06), without IDH-1 mutation (HR= 0.78, 95% CI 0.52-1.17) or with MGMT non-methylated status (HR= 0.81, 95% CI 0.44-1.49).
- Subgroups analyses of 1 randomised controlled trial (N=54 to 156) provided low to moderate quality evidence that showed that radiotherapy and procarbazine, lomustine and vincristine was associated with longer overall survival in those with IDH-1 or 2 mutations (HR= 0.59, 95% CI 0.4-0.87) and in those without codeletion of chromosomes but with IDH-1 or 2 (HR= 0.56, 95% CI 0.32-0.98) compared to those who received radiotherapy only. No differences were observed for those without IDH-1 or 2 mutations (HR=1.14, 95% CI 0.63-2.06).
- Three randomised controlled trials (N=1331) provided low quality evidence that showed radiotherapy and procarbazine, lomustine and vincristine was associated with longer progression free survival compared to radiotherapy only (HR= 0.67, 95% CI 0.56-0.81).
- Low to moderate quality evidence from 1 sub-analysis showed longer progression free survival in those with (HR = 0.45, 95% CI 0.32-0.64) or without codeletion of chromosomes 1p/19q (HR= 0.76, 95% CI 0.61-0.94) who received radiotherapy and procarbazine, lomustine and vincristine compared with those who received radiotherapy only.
- Low to moderate quality evidence from a sub-analysis showed longer progression free survival in those with (HR= 0.49, 95% CI 0.29-0.83) and without IDH-1 mutation (HR= 0.56, 95% CI 0.37-0.85) and those with MGMT methylated status (HR= 0.52, 95% CI 0.35-0.77) who received radiotherapy and procarbazine, lomustine and vincristine compared with those who received radiotherapy only. No significant differences between

treatment arms were observed in those with MGMT non-methylated status (HR= 0.63, 95% CI 0.34-1.17).

- Moderate quality evidence from 1 randomised controlled trial (N=287) showed that those who received radiotherapy only showed a significant decrease of grade 3 or 4 toxicity compared to those who received radiotherapy and procarbazine, carmustine and vincristine (RR=12.97, 95% CI 6.24-26.97).
- Moderate quality evidence from 1 randomised controlled trial (N=287) showed similar B-QoL- fatigue scores with the use of PCV and RT compared to RT, with values remaining constant in the mid-upper range over time. In those who received PCV and RT, mean values at the end of RT, at 1 year and at 2 years, were -0.90 (95% CI -4.93 to 3.13), 0.50 (95% CI -3.51 to 4.51), and -2.00 (95% CI -6.01 to 2.01), respectively, compared to RT only.
- Moderate quality evidence from 1 randomised controlled trial (N=287) showed similar B-QoL- nausea and vomiting scores with the use of PCV and RT compared to RT, with values remaining constant in the mid-upper range over time. In those who received PCV and RT, mean values at the end of RT, at 1 year and at 2 years, were 2.30 (95% CI 0.29 to 4.31), 1.8 (95% CI -0.20 to 3.80), and -0.7 (95% CI -2.71 to 1.31), respectively, compared to RT only.
- Moderate quality evidence from 1 randomised controlled trial (N=287) that showed similar B-QoL- physical functioning scores with the use of PCV and RT compared to RT, with values remaining constant in the mid-upper range over time. In those who received PCV and RT, mean values at the end of RT, at 1 year and at 2 years, were 8.50 (95% CI 4.06 to 12.94), 2.5 (95% CI -2.01 to 7.01), and 2.2 (95% CI -0.30 to 6.7), respectively, compared to RT only.

Estramustine + RT versus RT

- One RCT (N=122) provided moderate quality evidence that showed no differences in overall survival in those who received estramustine and radiotherapy compared to those who received radiotherapy (HR= 0.99, 95% CI 0.92-1.07)
- Very low quality evidence from 1 randomised controlled trial (N=127) showed similar rates of grade 3-4 nausea/vomiting after treatment with estramustine and RT and RT alone in a mixed population of newly diagnosed grade III and IV initial high-grade glioma (RR=0.77, 95% CI 0.13-4.44).
- Very low quality evidence from 1 randomised controlled trial (N=66) showed similar scores on the global domain of HRQoL as measured with the QLQ-30 – Global after treatment with estramustine and RT compared to RT in a mixed population of newly diagnosed grade III and IV initial high-grade glioma (mean = 2.1 higher in the estramustne + RT group; the uncertainty around this result could not be calculated).

PCV or TMZ + RT on progression versus RT + PCV or TMZ on progression

- One randomised controlled trial (N=274) provided low to very low quality evidence that showed no differences in overall survival (HR= 1.11, 95% CI 0.80-1.54), progression free survival (HR= 0.97, 95% CI 0.74-1.27), or time to treatment failure (HR= 0.99, 95% CI 0.75-1.31) in the ordering of receiving procarbazine, carmustine and vincristine or temozolomide and radiotherapy on progression as compared to radiotherapy and procarbazine, carmustine and vincristine or temozolomide on progression.
- One randomised controlled trial (N=68) provided very low quality evidence that showed no differences in the ordering of receiving the treatments between both groups on progression in progression-free survival (HR= 1.30, 95% CI 0.70-2.41), time-to-treatment failure (HR=1.35, 95% CI 0.68-2.68), and overall survival (HR= 0.46, 95% CI 0.04-5.56) in those who are IDH mutant and 1p/19q co-deleted.

TMZ followed by RT versus RT alone

- Moderate quality evidence from 1 randomised controlled trial (N=41) showed that temozolomide followed by radiotherapy was associated with longer overall survival compared with radiotherapy alone (HR= 0.40, 95% CI 0.19-0.84).

RT with adjuvant TMZ versus RT without adjuvant therapy

- Moderate to high quality evidence from 1 randomised controlled trial (N=745) showed that radiotherapy with concurrent and adjuvant temozolomide was associated with longer overall survival (HR = 0.65 95%CI 0.45-0.94) and progression free survival (HR= 0.58, 95% CI 0.47-0.72) compared with those who received radiotherapy without an adjuvant therapy. Amongst those treated under arms with adjuvant temozolomide, age (≤ 50 years) (HR=4.04, 95% CI 2.78-5.87) and MGMT methylation (HR= 1.81, 95% CI 1.44-2.27) status were prognostic factors for extended overall survival. 1p loss of heterozygosity (yes versus no) (HR= 1.56, 95% CI 0.84-2.90) and WHO performance status (>0 vs 0) (HR= 1.36, 95% CI 0.94-1.97) were not prognostic factors for improvement.

WHO grade IV glioma

Bevacizumab plus TMZ and RT versus TMZ and RT alone

- Two RCTs (N= 1542) provided very low quality evidence that showed no difference in overall survival (hazard ratio (HR) =0.99, 95% confidence interval (CI) 0.77-1.26) in those who received the combination of bevacizumab plus temozolomide and radiotherapy compared to those who received temozolomide and radiotherapy alone.
- Very low to moderate evidence from 2 randomised controlled trials showed no differences in overall survival between treatment arms amongst those with methylated MGMT status (HR=1.20, 95% CI 0.42-3.46) or non-methylated MGMT status (HR=1.02, 95% CI 0.98-1.06); or amongst those ≤50 years old and KPS ≥ 90 (RPA class 3) (HR=0.93, 95% CI 0.66-1.3); amongst those ≤50 years old and KPS ≤ 90 (RPA class 4) (HR=0.97, 95% CI 0.88-1.06);or amongst those ≥50 years old and KPS ≥ 70 (RPA class 5) (HR=0.93, 95% CI 0.73-1.19).
- Low quality evidence from 2 randomised controlled trials showed that those who received the combination of bevacizumab plus temozolomide and radiotherapy experienced longer progression free survival compared to those who received temozolomide and radiotherapy alone (HR=0.71, 95% CI 0.58-0.87).
- Low to moderate quality evidence from 2 randomised controlled trials showed no differences in progression free survival between treatment arms amongst those with methylated MGMT status (HR=0.93, 95% CI 0.53-1.64), and longer progression free survival in those who received the combination of bevacizumab plus temozolomide and radiotherapy who had the following prognostic factors (compared to those who received temozolomide and radiotherapy): MGMT non-methylated (HR=0.59, 95% CI 0.49-0.70); those ≤50 years old and KPS ≥ 90 (RPA class 3) (HR=0.67, 95% CI 0.49-0.91); those ≤50 years old and KPS ≤ 90 (RPA class 4) (HR=0.69, 95% CI 0.60-0.79);or those ≥50 years old and KPS ≥ 70 (RPA class 5) (HR=0.71, 95% CI 0.56-0.90).
- Low quality evidence showed a significant increase in wound complications (RR=2.16, 95% CI 1.03-4.52) and grade 3 and 4 adverse events (RR=2.06, 95% CI 1.6-2.65) in those who received bevacizumab plus TMZ and RT compared with TMZ and RT alone, but no difference in the risk of fatigue between the treatments (RR= 1.60, 95% CI 0.95-2.70).

Nimotuzumab plus TMZ+RT versus TMZ+RT alone

- One randomised controlled trial (N=142) provided very low to low quality evidence that showed no difference in overall survival (HR= 0.86, 95% CI 0.57-1.31) or progression free survival (HR= 0.95, 95% CI 0.93-1.14) between those who received nimotuzumab plus TMZ and RT compared with TMZ and RT alone. Subgroup analyses amongst those with

MGMT methylated (HR=0.86, 95% CI 0.27-2.74) or non-methylated status (HR= 0.80, 95% CI 0.45-1.42) showed no differences between the treatments in overall survival and no difference in progression free survival between the treatment arms for those with MGMT methylated status (HR= 0.93, 95% CI 0.76-1.14).

- Very low to low quality evidence showed that in the TMZ and RT alone group, fewer people experienced grade 3 adverse events as compared to those who received nimotuzumab plus temozolomide and radiotherapy (RR= 3.67, 95% CI 1.58-8.50), but no differences between the treatments in fatigue (RR=1.26, 95% CI 0.90-1.76) or memory impairment (RR=0.50, 95% CI 0.16-1.59).

Cilengitide plus TMZ+RT versus TMZ+RT alone

- One randomised controlled trial (N=545) provided very low to moderate quality evidence that showed no difference in overall survival (HR= 1.02, 95% CI 0.81-1.28) or progression free survival (HR= 0.92, 95% CI 0.75-1.13) between those who received cilengitide plus TMZ and RT compared with TMZ and RT alone. No differences were found between the treatments in overall survival amongst those ≤50 years old and KPS ≥ 90 (RPA class 3) (HR= 0.63, 95% CI 0.31-1.28) or amongst those ≤50 years old and KPS ≥ 70 (RPA class 4-5) (HR=1.08, 95% CI 0.84-1.39).
- Very low to moderate quality evidence showed no difference between the treatment groups in grade 3 and 4 toxicity (RR= 1.07, 95% CI 0.94-1.23); fatigue (RR= 1.72, 95% CI 0.73-4.02) or memory impairment (RR= 0.98, 95% CI 0.06-14.91).

TMZ+RT plus DD TMZ (150-200 mg/m^2) versus TMZ+RT plus standard TMZ (75-100mg/m^2)

- One randomised controlled trial (N=823) provided very low to moderate quality evidence that showed no difference in overall survival (HR= 1.03, 95% CI 0.88-1.21) or progression free survival between (HR= 0.87, 95% CI 0.75-1.01) between those who received TMZ and RT plus dose dense temozolomide compared to those who received TMZ and RT plus standard temozolomide. In subgroup analyses no differences were found between the treatments in overall survival for those with MGMT methylated (HR=1.19, 95% CI 0.87-1.63) or non-methylated status (HR=0.99, 95% CI 0.82-1.20) or in progression free survival for those with MGMT methylated (HR=0.87, 95% CI 0.66-1.15) or non-methylated status (HR=0.88, 95% CI 0.73-1.06).
- Low quality evidence showed that in the TMZ and RT plus standard temozolomide group, fewer patients experienced grade 3 and 4 toxicities (RR=1.54, 95% CI 1.29-1.83) and fatigue (RR=2.62, 95% CI 1.37-4.89) compared to those who received TMZ and RT plus dose dense temozolomide.

Ceradenovec followed by intravenous ganciclovir plus TMZ +RT versus TMZ+RT alone

- One randomised controlled trial (N=236) provided very low to low quality evidence that showed no difference in overall survival (HR= 1.18, 95% CI 0.86-1.62) between those who received ceradenoved followed by intravenous ganciclovir plus TMZ and RT compared to those who received TMZ and RT and either for those with MGMT non-methylated status (HR= 1.40, 95% CI 0.92-2.13), whereas treatment with TMZ and RT alone was associated with a lower risk of grade 3 and 4 adverse events (RR= 1.56 95% CI 1.19-2.04) compared to treatment with ceradenoved followed by intravenous ganciclovir plus TMZ and RT alone.

ACNU-CDDP plus TMZ+ RT versus TMZ+ RT alone

- One randomised controlled trial (N=82) provided very low to low quality evidence that showed no difference in overall survival (HR = 0.59, 95% CI 0.33-1.05), or progression free survival (HR= 0.76, 95% CI 0.43-1.34) between those who received ACNU-CDDP plus TMZ and RT compared to those who received TMZ and RT alone, whereas treatment with TMZ and RT alone was associated with a reduced risk of grade 3 and 4 adverse events (RR=4.33, 95% CI 2.64-5.49) compared to ACNU-CDDP plus TMZ+RT.

Tumour treating fields (TTF) + TMZ versus TMZ alone

- One randomised controlled trial (N=315) provided very low to moderate quality evidence that showed longer overall survival (HR= 0.74, 95% CI 0.56-0.98) and progression free survival (HR= 0.62, 95% CI 0.43-0.89) in the tumour treating fields treatment group compared to the temozolomide only treatment group, but no difference between the treatments in fatigue (RR=1.00, 95% CI 0.31-3.23).

TMZ versus standard RT in older people

- Two randomised controlled trials (N=566) provided very low quality evidence that showed no differences in overall survival in those who received TMZ compared to those who received standard RT (HR= 0.88, 95% CI 0.57-1.36). One of this RCTs provided low quality evidence that showed no differences between both treatment arms for people between 60 and 70 years old (HR= 0.87, 95% CI 0.59 – 1.28), however moderate quality evidence showed that in patients aged 70 years or above, overall survival was longer after treatment with TMZ compared to treatment with RT (HR=0.35, 95% CI 0.21-0.58).
- One randomised controlled trial (N=373) provided low quality evidence that showed that those with MGMT methylated status presented with a longer overall survival as compared to those with MGMT unmethylated status (HR=0.62, 95% CI 0.42-0.91).
- Very low quality evidence showed that there were no differences in grade 3 and 4 fatigue (RR=1.14, 95% CI 0.66-1.97) or in grade 3 and 4 neurological symptoms (RR = 1.31, 95% CI 0.82-2.10) between the treatment groups.

Hypofractionated RT versus standard RT in those aged 60 years and over

- One randomised controlled trial (N=198) provided very low to moderate quality evidence that showed no differences in overall survival (HR =0.85, 95% CI 0.64-1.13) or grade 3 and 4 fatigue (RR=5, 95% CI 0.24-102.78) between treatment with either hypofractionated or standard RT. Subgroup analysis of patients aged 70 years or older showed longer overall survival after treatment with hypofractionated radiotherapy compared to standard radiotherapy (HR= 0.59, 95% CI 0.37-0.94).

RT schedules in older people [60-Gy versus 40-Gy]

- One randomised controlled trial (N=96) provided low quality evidence that showed no difference in overall survival between those who received 40-Gy or 60-Gy radiotherapy (HR= 0.90, 95% CI 0.60-1.35).

RT schedules in older/frail people [40-Gy versus 25-Gy]

- One randomised controlled trial (N= 98) provided low quality evidence that showed no differences in overall survival (HR = 0.95, 95% CI 0.75-1.2), progression free survival (HR = 0.99, 95% CI 0.8-1.23) or quality of life (mean in the intervention group was 3.6 lower [17.17 lower to 9.97 higher]) between RT with 40 Gy and 25 Gy.
- Subgroup analyses[e] (N=61, very low quality evidence) showed no differences in overall survival in those who received 40-Gy radiotherapy (median survival in the short course RT arm = 6.8 months [95% CI 4.5-9.1 months];median survival in the commonly used RT = 6.2 months [95% CI, 4.7-7.7 months]) and those who received 25-Gy radiotherapy or in progression free survival in those who received 40-Gy and those who received 25-Gy radiotherapy (median progression free survival in the short course RT arm = 4.3 months [95% CI 2.6- 5.9 months] and the median progression free survival in the commonly used RT= 3.2 months [95% CI 0.1-6.3 months], whereas the mean quality of life score was significantly higher in those who received 40-Gy radiotherapy (mean score = 6.50 higher, 95% CI -0.81 to 13.81) as compared to those who received 25-Gy radiotherapy 4 weeks after treatment, however this difference was no longer significant 8 weeks after treatment (mean score= 3.1 higher in the intervention group, 95% CI 4.21-0.41).

[e] This is a subset analysis of RT schedules in elderly/frail patients [40-Gy versus 25-Gy]. It included those ≥ 65 years old.

RT and supportive care versus supportive care

- One randomised controlled trial (N=85) provided low to moderate quality evidence that showed that radiotherapy and supportive care is associated with longer overall survival (HR= 0.47, 95% CI 0.29-0.76), longer progression free survival (HR= 0.28, 95% CI 0.17-0.46) and higher quality of life (mean score= 10.50, 95% CI 9.37-11.63) compared with supportive care.

TMZ followed by RT versus RT alone

- One randomised controlled trial (N=103) provided moderate quality evidence that showed no difference in overall survival between TMZ followed by RT and RT alone (HR= 1.40, 95% CI 0.93-2.09).

RT with concomitant and adjuvant TMZ versus RT (KPS ≥ 70)

- One randomised controlled trial (N=562) provided moderate to high quality evidence that showed radiotherapy with concomitant and adjuvant temozolomide was associated with longer overall survival (HR= 0.67, 95% CI 0.56-0.80) and progression free survival(HR= 0.50, 95% CI 0.41-0.61).
- Low to high quality evidence from subgroup analyses showed that adults between 71 and 75 years old (HR=0.63, 95% CI 0.48-0.83), those 76 years and older (HR= 0.53, 95% CI 0.38-0.74), and those with MGMT methylated status (HR= 0.53, 95% CI 0.38-0.74) (high to moderate quality evidence), who received radiotherapy with concomitant and adjuvant temozolomide had longer overall survival compared to those who received radiotherapy only. There were no differences in overall survival in those between 65 and 70 years old (HR= 0.93, 95% CI 0.68-1.27) and those with MGMT non-methylated status (HR= 0.75, 95% CI 0.56-1).
- Low to moderate quality evidence from subgroup analyses showed that adults between 71 and 75 years old (HR=0.42, 95% CI 0.3-0.59), those 76 years and older (HR= 0.49, 95% CI 0.35-0.69), and those with MGMT methylated status (HR= 0.33, 95% CI 0.23-0.47) who received radiotherapy with concomitant and adjuvant temozolomide experienced longer progression free survival compared to those who received radiotherapy only. No differences in progression free survival were observed between the treatments in those aged between 65 and 70 years old (HR=0.76, 95% CI0.55-1.05) and those with MGMT non-methylated status (HR= 0.79, 95% CI 0.59-1.06).
- Low quality evidence showed no differences in time to quality of life deterioration in any of the different scales (emotional [HR=0.86, 95% CI 0.69-1.07], role [HR=0.94, 95% CI 0.76-1.16], social [HR=0.94, 95% CI 0.76-1.16], cognitive [HR=0.84, 95% CI 0.68-1.04], constipation [HR= 1.11, 95% CI 0.88-1.4], vomiting [HR=1, 95% CI 0.79-1.27] or fatigue[HR= 0.9, 95% CI 0.73 to 1.11]) between those who received radiotherapy with concomitant and adjuvant temozolomide compared to radiotherapy only.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 3 outcomes of critical importance to people with brain tumours. These were: overall survival, progression-free survival, and quality of life. These 3 outcomes were selected to provide direct evidence about the effectiveness of an intervention. The committee discussed how it was sometimes difficult, due to post-treatment changes and tumour progression looking similar on MRI scans, to determine whether progression-free survival was the most accurate measure of a treatment effectiveness. They also discussed how health-related quality of life can be a useful measure to provide more detail on whether extra-life years were of value to a person with a high-grade glioma. However, quality of life is often poorly reported.

The committee identified 5 other outcomes of importance to people with a high-grade glioma. These were RTOG/CTAE grade 3 and/or 4 toxicity; fatigue; cognitive function; wound infections, and neurological adverse events. These outcomes were important because they can have an important detrimental impact on quality of life.

The quality of the evidence

Twenty-three phase III randomised controlled trials were included in the review. The quality of the evidence ranged from very low to high as assessed by GRADE. The main sources of potential bias were: lack of information on the randomisation method used; concealment of allocation unreported or unclear and lack of blinding of investigators. Objective outcomes, such as overall survival, was not downgraded for lack of blinding as being aware of the treatment allocation cannot change the survival rate of the participants. The committee acknowledged that outcomes that were not objective (such as progression-free survival, adverse events or quality of life) may be subject to bias, but agreed that it was not possible to blind the assessors, investigators or participants due to the nature of the interventions used.

The committee believed the evidence was high quality, and consequently made strong recommendations.

The committee identified that evidence was low quality on whether early referral to palliative care improves outcomes for people with glioblastoma, which could have a major impact on quality of life but is also likely to be expensive. The committee determined they could not make a recommendation in this area without more evidence which leaves a substantial evidence gap between therapeutic and palliative care for this condition.

Benefits and harms

Management of newly diagnosed grade III glioma following surgery or where surgery is not possible (or has been declined)

The committee made all recommendations on temozolomide in accordance with existing NICE guidance.

Based on some RCT evidence, the committee concluded that radiotherapy and PCV led to increased overall survival in those with good performance status and grade III tumours with the 1p/19q co-deletion. The committee justified restricting the intervention to those with good performance status based on the entry criteria to the trial, since they did not think it was appropriate to extrapolate beyond the results of this trial. The committee justified restricting the intervention to those with the 1p/19q co-deletion based on evidence showing improvement in overall survival was only significant in this subgroup.

The committee recommended radiotherapy and PCV for those with grade III tumours with the 1p/19q co-deletion based on 2 trials which demonstrated improved survival compared to radiotherapy alone, with 1 study using radiotherapy before PCV and the other PCV before radiotherapy. Consequently, the committee concluded the sequence does not appear to impact on outcome, so the order should be decided based on the preference of the person with the tumour. The committee noted that most UK centres used radiotherapy then PCV as this was felt to result in less fatigue and give more time for fertility preservation, but that these were both preferences that could be discussed with the person with the tumour.

Based on some RCT evidence, the committee concluded that radiotherapy followed by adjuvant temozolomide chemotherapy increased overall and progression-free survival in people with good performance status and grade III glioma without 1p/19q co-deletion (non-codeleted). The committee based the number of adjuvant cycles on the protocol of the trial which reported the positive outcomes compared to radiotherapy alone. The committee justified the restriction in their recommendation on the basis that this mirrored the inclusion

criteria for the trial they drew the evidence from. As before, the committee did not believe it had the ability to extrapolate beyond the inclusion criteria of this trial.

Based on some RCT evidence, the committee concluded that nitrosoureas (for example CCNU) should not be used concurrently with radiotherapy as it did not improve overall survival or progression-free survival, but resulted in significant side-effects.

The committee searched for evidence on a number of interventions for grade III glioma which they were frequently asked about in clinic. When they found no evidence on these interventions, they concluded it would be helpful to inform clinicians and people with tumours of this fact, so that they could have better-informed discussions. The committee emphasised that there were several other interventions of uncertain benefit not included in this evidence search – for example Vitamin C – and the non-appearance of a particular therapy on the list should not be taken as an endorsement of benefit of that therapy.

Grade III glioma has a variety of prognoses depending on the molecular characteristics. Unlike grade I or II glioma, it would be very unusual not to intervene and treat a grade II glioma unless the risk of harm to quality of life was very great. In general, the committee viewed the best balance of benefits and harms occurring when almost all individuals were treated with some combination of radiotherapy and either PCV or TMZ, with the exact combination and schedules determined by personal characteristics.

Management of newly diagnosed grade IV glioma (glioblastoma) following surgery or where surgery is not possible (or has been declined)

The committee made all recommendations on temozolomide in accordance with existing NICE guidance.

Based on some RCT evidence, which showed an improvement in overall survival and progression-free survival, the committee recommended that a 6-week course of radiotherapy with concurrent and adjuvant temozolomide should be offered to people aged 70 years or younger, with a good performance status, who have undergone maximal safe debulking of their tumour. The committee based the radiotherapy schedule in this group on the schedule used in the trial, which they explained was also the standard schedule used in most treatment centres.

Based on evidence showing an extended overall survival and progression-free survival, the committee recommended radiotherapy with concurrent and adjuvant temozolomide for people over the age of 70 years with a good performance status and methylation of MGMT. The committee based the radiotherapy schedule in this group on evidence demonstrating no difference in survival between 60 Gy and 40 Gy in this group, and therefore judged that there was no reason to expose people to greater risk of radiation-induced side-effects if the same clinical outcomes could be obtained with a lower radiotherapy dose.

There was debate on the role of the addition of temozolomide in this group of people with unmethylated MGMT as the randomised trial showed marginal improvement in overall survival, but no improvement in progression free survival. Consequently, for this group of people the committee suggested the recommendation should be ‘considered’ as other factors such as extent of surgery or size of radiotherapy volumes need also to be taken into account when deciding on optimal management. The committee based the radiotherapy schedule in this group on evidence demonstrating no difference in survival between 60 Gy and 40 Gy in this group, and therefore judged that there was no reason to expose people to greater risk of radiation-induced side-effects if the same clinical outcomes could be obtained with a lower radiotherapy dose.

The committee stressed the importance of performance status in interpreting the outcome of the trials, particularly in those aged over 70 where there was evidence that performance status could affect treatment outcomes. They described how the evidence for improvement in

overall survival was for those with a Karnofsky performance status of 70 or higher. Consequently, the committee considered that best supportive care alone may be the most appropriate management strategy for older patients with poor performance status (particularly if MGMT is unmethylated), who are less likely to derive survival gain from additional interventions.

Based on their clinical experience the committee concluded they did not have enough information to make a definitive judgement about the best management for people not in these defined groups. They recommended a series of potential management options that they considered to be reasonable treatments, to be considered depending on various factors, such as; extent of surgery (maximum safe debulking versus biopsy only), performance status, extent of radiotherapy volume, age, molecular subtype (particularly methylated versus unmethylated MGMT) and patient preference.

Based on their clinical experience, the committee explained that most clinicians were aware that performance status may change (both improve and deteriorate) in the period between surgery and starting radiotherapy, but that this was occasionally forgotten. Since this could lead to people with tumours being treated with inappropriate management for their pre-radiotherapy performance score, the committee ensured that this recommendation was given sufficient prominence to highlight this. Although the committee had no evidence, they argued that failing to assess a change in performance status could lead to significant harm for the patient, and so the recommendation could be strong.

Based on very low quality evidence the committee concluded there was no improvement in overall survival from offering bevacizumab as part of management of a grade IV glioma. Published cost effectiveness evidence also suggested it was unlikely to be an efficient use of NHS & PSS resources. The committee therefore recommended against its use.

Based on RCT evidence and published cost effectiveness evidence, the committee concluded that tumour treating fields did not offer sufficient improvement in overall survival and progression free survival to justify the additional cost. As this recommendation was based largely on cost effectiveness considerations, the committee drew on evidence identified in the health economic evidence review.

The committee searched for evidence on a number of interventions for grade IV glioma which they were frequently asked about in clinic. When they found no evidence on these interventions, they concluded it would be helpful to inform clinicians and people with tumours of this fact, so that they could have better-informed discussions. The committee emphasised that there were several other interventions of uncertain benefit not included in this evidence search – for example Vitamin C – and the non-appearance of a particular therapy on the list should not be taken as an endorsement of benefit of that therapy.

Grade IV glioma has a very poor prognosis, and hence the balance of benefits and harms will almost always favour intervention. Determining which combination of therapies to give is extremely complex, since different combinations offer different balances of survival improvement, quality of life and patient acceptability. In general, the committee viewed the best balance of benefits and harms occurring when those with higher performance status and greater response to treatment were treated more intensively, and treatment in those with lower performance status focussed more on preserving quality of life.

Cost effectiveness and resource use

Grade III and grade IV glioma

The economic evidence review identified 2 previous economic evaluations for this topic. No studies were identified which took a NHS and PSS (Personal Social Services) perspective. All studies were considered to have minor limitations with their methodology.

One study compared the addition of tumour treating field (TTF) to standard of care (SOC) to SOC alone from a French public healthcare payer perspective. This study, based on 1 trial identified in the evidence review, estimated that the addition of TTF to SOC would cost an additional €185,466 and bring 0.34 life years over the lifetime of 1 person, equal to a cost of €596,411 per life year gained. This result was robust to probabilistic sensitivity analysis (PSA) with a zero probability of the addition of TTF being cost effective below a cost per life year threshold of €100,000. While outcomes in terms of QALYs were not reported the committee thought the difference would likely be of a similar magnitude to those reported in life years. The committee thought that the TTF arm of the study may underestimate the effectiveness of the intervention by not adequately considering any potential long-term survivors as the follow-up in this study is relatively short, and therefore evidence is lacking to accurately estimate the size of this potential benefit. Consequently, the study may have overestimated the size of the incremental cost effectiveness ratio (ICER), but given the outcomes of the sensitivity analyses it was unlikely to change any conclusions.

The other study identified compared the addition of bevacizumab to SOC to SOC alone from a Canadian public payer perspective. The study estimated a cost per QALY of CA$607,966 based on outcomes reported in the Avaglio trial with utility values collected from a UK population. Again, the results were robust to PSA with a cost per QALY threshold of $210,000 needed before any non-zero probability of the addition of bevacizumab being cost effective. The committee thought that there was unlikely to be a large difference in QALYs between the 2 groups given the significant number of grade III & IV adverse events and high cost associated with bevacizumab and therefore a large ICER is to be expected.

The committee discussed how conclusions made from non-UK studies (such as those predominantly based in the USA) may be different from conclusions that would be drawn if the trial was conducted in the UK setting. The committee considered that the health outcomes would be largely similar to what they would expect in a NHS setting given the evidence identified in the clinical evidence review. The interventions considered were still likely to be prohibitively expensive if a NHS & PSS perspective was taken and that any ICER would almost certainly be above thresholds conventionally held by NICE for accepting new technologies. It was therefore decided these interventions would not be an efficient use of NHS resources and a ‘do not do’ recommendation was made for both interventions.

No economic evidence was identified for the other interventions covered by the question. The committee thought that while the recommendation to offer radiotherapy and adjuvant temozolomide was likely to increase the use of radiotherapy and TMZ with a resulting increase in costs, this treatment is already widely considered the standard of care in much of the NHS and thus the overall resource impact was likely to be small. Given that age is a protected characteristic the discussion around recommendations based on age explicitly did not consider cost effectiveness. None the less, the recommendation to offer best supportive care to frail older people will likely be health improving given the reduction in treatment related adverse events as well as cost saving, avoiding unnecessary and ineffective treatment.

Other factors the committee took into account

The committee made recommendations with approximate age cutoffs for those with grade IV glioma. This is based on a variety of very low to moderate quality pieces of evidence showing this technique improved overall survival and progression free survival in which the age cutoff for inclusion in the trial was either 65 or 70. The committee discussed how the best quality evidence typically came from trials with a 70 year cutoff, and therefore agreed that clinical judgement should be used around this age range. They subgroup analysis show that the group aged >70 benefit more from the addition of temozolomide to their treatment. Another trial shows that there is no clinically important difference in outcomes between standard radiotherapy (60 Gy) and short-course radiotherapy (40 Gy) in those aged >65. Since lower doses of radiotherapy are likely to lead to better outcomes, the committee justified a

recommendation to use clinical judgement at around age 70 and over on the basis that there was specific evidence on optimal treatment in those aged >70 and indirect evidence that the same therapies at a lower radiotherapy dose would therefore be appropriate in this group.

Taken together, the recommendations constituting this potential equality issue are proportionate and justified by evidence. While people of different ages are recommended treatment which is mutually exclusive, these recommendations are only made where there is evidence that this differentiation will improve outcomes in a particular group. The only case where there is no related evidence is recommendation 1.2.22, and this does not prevent any individual receiving any treatment as it is only a weak 'consider' recommendation, intended to highlight the decreasing balance of risks and benefits to treatment as KPS drops (which is to say, age is not the differentiator of when treatment is recommended and not; KPS is).

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Management of recurrent high-grade glioma (recurrent grade III and grade IV glioma)

Review question

What is the optimal management (surgery, radiotherapy, chemotherapy, combinations of these, or other therapies such as metformin or tumour-treating fields) of recurrent high-grade glioma?

Introduction

Recurrent high-grade glioma is particularly difficult to treat, since many treatment options will already have been used at the initial diagnosis of glioma, limiting future use and effectiveness. Unfortunately the treatment of recurrent high-grade glioma is, therefore, often ineffective, and additionally there is significant variation in clinical practice at present. The committee described how people with recurrent high-grade glioma were often very keen to explore any possible treatment option, which could lead to treatment harms and additional costs for no clinical benefit.

This review is aimed at identifying whether any management strategy is more effective than any other in patients with high-grade glioma which has previously been treated.

PICO table

Table 63: Summary of the protocol (PICO table)

Population	People with high-grade gliomas (anaplastic astrocytomas, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, gliosarcoma and glioblastoma, not otherwise excluded in the scope) who have previously had a high-grade glioma
Intervention	• TMZ • PCV (procarbazine, CCNU, vincristine) • Single agent nitrosourea (CCNU or BCNU) • Other systemic anti-cancer agents (including immunotherapy and viral therapy) • Metformin • Statins • Ketogenic diet • Valgancyclovir • Cannabis oil (Sativex) • Tumour-treating fields • Combinations of the above
Comparison	• All versus each other • Clinicians choice • Best supportive care

Outcome	• Critical:
	  ○ overall survival
	  ○ progression free survival/time to progression
	  ○ health related quality of life
	• Important:
	  ○ neurological adverse events
	  ○ wound infections

	○ RTOG grade 3 and/or grade 4 toxicity ○ CTAE grade 3 and/or grade 4 toxicity ○ fatigue (somnolence) ○ cognitive function

BCNU carmustine; CCNU lomustine; CTAE Common Terminology Criteria for Adverse Events PCV procarbaine, lomustine, vincristine; RTOG Radiation Therapy Oncology Group; TMZ temozolomide.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Included studies consisted of Phase II and III randomised controlled trials (RCTs) enrolling patients with recurrent high-grade glioma. Overall, patients underwent magnetic resonance imaging (MRI) or histology in order to confirm disease progression. All studies included patients with recurrent World Health Organization (WHO) Grade IV Glioblastoma (GBM). There were not identified trials for recurrent WHO Grade III – anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), anaplastic oligoastrocytoma (AOA) or gliosarcoma.

Given the great variability in trial characteristics, especially with regard to outcomes and interventions, the included studies were not deemed suitable for meta-analysis, therefore separate analyses were required for the different combinations of interventions. See below an overview of the comparisons included.

A summary of these studies is provided in Table 64 and the results along with the quality of the evidence for each outcome are listed in Table 65 to Table 78 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 64 provides a brief summary of the included studies.

Table 64: Summary of included studies

Study	Population	Intervention	Comparator	Outcomes	Comments
REGAL trial Batchelor 2013	Recurrent GBM; Median age = 54 y/o; >50% population had a KPS 90-100	CED alone (N=131) **or** CED + LOM CED (30 mg daily, 20 mg oral daily + LOM 110mg/m2) (N=129)	Placebo + LOM (110mg/m2) (N =65)	PFS OS AE (≥3) Fatigue	Participants had previously received radiation and TMZ

Study	Population	Intervention	Comparator	Outcomes	Comments
Dirven 2015	Recurrent GBM; age range: 24 to 77 y/o; >50% population had a WHO 1 Performance Status	BEV + LOM 90 (N=44)	LOM (N=46) **or** BEV (N=50)	QoL	Sub analyses of Taal 2014 (BELOB trial)
Field 2015	Recurrent GBM; median age: 55; >40% population had KPS 70-80	BEV 10 mg/kg every 2 weeks **+** carboplatin AUC 5 every 4 weeks (N=60)	BEV 10 mg/kg monotherapy (N= 62)	PFS OS AE ≥ grade 3 adverse event Wound healing complications	Phase II trial Participants had previously been treated with TMZ and RT.
Friedman 2009	Recurrent GBM; median age:55; >50% population had KPS 70-80	BEV 10mg/kg intravenously every other week **+** CPT-11 (N=82)	BEV 10mg/kg intravenously every other week (N=85)	OS PFS Wound healing complications Aphasia Fatigue	Phase II trial Participants had previously been treated with standard RT and received TMZ. Wefel 2011 reported the neurocognitive function of the participants treated in this trial.
RTOG 0625 Gilbert 2016	Recurrent GBM; >50% of the population were ≥ 50 y/o; >50% population had a KPS 70-80.	BEV 10mg/kg intravenously every other week **+** CPT 125mg/m2 very 2 weeks along with bevacizumab (N=57)	BEV **+** TMZ (N= 60)	PFS OS	Phase II trial No limits placed on the number of prior treatment regimens.
Socha 2016	Recurrent GBM; >50% of the population	Active treatment (RT, surgery or chemotherapy)	BSC	PPS OS	

Study	Population	Intervention	Comparator	Outcomes	Comments
	were ≥ 65 y/o; >50% population had a KPS ≤60%.				
Stupp 2012	Recurrent GBM; median age = 54 y/o; KPS ≥ 70%	TTF monotherapy (without chemotherapy) (N= 120)	Best available chemotherapy at the local investigators discretion (N=117)	OS PFS Cognitive disorder	Phase III trial Prior therapy must have included RT (with and without adjuvant TMZ). More than 80% of patients had failed 2 or more prior lines of chemotherapy (≥ second recurrence) and 20% of the patients had failed bevacizumab therapy prior to enrolment.
BELOB trial Taal 2014	Recurrent GMB; age range: 24-77; >50% of the population had WHO 1	BEV **+** LOM 90 (N=44)	Single-agent LOM (N=46) **or** Single-agent BEV (N=50)	OS PFS AE	Phase II trial Dirven 2015 reported QoL for participants included in this trial Participants had previously been treated with TMZ chemo-radiotherapy The trial was started after the negative ruling of the European Medicines Agency regarding the use of BEV in recurrent GBM, the trial was modified into a 3-group study by the addition of LOM to the control group – only results for BEV+LOM 90 have been reported
van den Bent 2009	Recurrent GBM; median age = 54 y/o; >50% of the	Erlotinib (N=54)	TMZ—**or** carmustine (BCNU) (N=54) if TMZ was part of initial treatment**.**	PFS OS	Phase II RCT Patients could have previously received a max of 1 prior chemotherapy regimen given as adjuvant therapy

Study	Population	Intervention	Comparator	Outcomes	Comments
	population had a KPS 90-100				
Weathers 2016	Recurrent GBM; >60% of the participants had a KPS 90-100; >60% of the participants had a KPS 90-100.	BEV + CCNU (N= 33)	BEV intravenously (N=35)	PFS OS AE	Phase II trial LOM was initially given at 90 mg/m2 every 6 weeks but was later reduced to 75mg/m2 following the occurrence of 17 grade 3 and 7 grade 4 hematologic adverse events. Study included patients at 1st 2nd or 3rd relapse.
Wefel 2011	Recurrent GBM; median age=55; >50% population had KPS 70-80	BEV 10mg/kg intravenously every other week + CPT-11 (N=82)	BEV 10mg/kg intravenously every other week (N=85)	Neurocognitive outcome	Sub analyses from Friedman 2009
Brem 1995	N= 222 adults with recurrent GBM, AA, AO or AOA.	Carmustine discs (7.7 mg of carmustine per wafer for a maximum patient dose of 62 mg)	Placebo polymer	OS adjusted for the following; ○ KPS ○ WHO grade	
Kesari 2017	N=204 with radiologically confirmed disease progression (Macdonald criteria).	TTF + maintenance chemotherapy TTF were fitted with four transducer arrays placed on the shaved scalp. This was connected to a power-operated device set to generate alternating electric fields of 200 kHz	Maintenance TMZ (150-200 mg/m2 per day for 5 days, every 28 days for 6-12 cycles)	OS and grade 3-4 adverse events	Post-hoc analysis of the EF-14 trial (Stupp 2012)

Study	Population	Intervention	Comparator	Outcomes	Comments
		qo within the brain. Maintenance TMZ (150-200 mg/m^2 per day for 5 days, every 28 days for 6-12 cycles)			

AA anaplastic astrocytoma; AE adverse events; AO anaplastic oligodendroglioma; AOA anaplastic oligoastrocytoma; AUC area under the concentration-time curve; BEV Bevacizumab; BSC best supportive care; CED Cediranib; CCNU lomustine; CPT cisplatin; GBM glioblastoma; kHz kilohertz; KPS Karnofsky Performance Status; LOM lomustine; NR not reported; OS overall survival; PFS progression free survival; PPS post-progression survival; QoL quality of life; RCT randomised controlled trial; REGAL Recetin in Glioblastoma Alone and With Lomustine; RT radiotherapy; TMZ temozolomide; TTF tumour treating fields; WHO World Health Organization; y/o years old.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles are presented in Table 65 to Table 78.

Table 65: Summary clinical evidence profile for Erlotinib versus TMZ or BCNU

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Erlotinib	BCNU/TMZ			
PFS (Erlotinib)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[4]	110 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
PFS (BCNU/TMZ)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[4]	110 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
OS (Erlotinib)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[4]	110 (1 study)	⊕⊕⊖⊖ low[1,3,4]
OS (BCNU/TMZ)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[4]	110 (1 study)	⊕⊕⊖⊖ low[1,3,4]

BCNU lomustine; CI: confidence interval; OS overall survival; PFS progression free survival; TMZ temozolomide.
[1] Selective reporting of outcomes
[2] Unclear blinding
[3] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
[4] Not calculated as standard deviations or interquartile range of the outcomes were not reported. Median overall survival in the control group = 7.7 months; median progression free survival = 1.8 months; median overall survival in the BCNU/TMZ arm= 7.3 months and median progression free survival= 2.4 months

Table 66: Summary clinical evidence profile for Cediranib alone versus cediranib + lomustine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Cediranib alone	Cediranib + lomustine			
OS	Not applicable	Not applicable	HR 1.43 (0.96 to 2.13)	260 (1 study)	⊕⊕⊕⊖ moderate[1]
PFS	Not applicable	Not applicable	HR 1.05 (0.74 to 1.49)	260 (1 study)	⊕⊕⊖⊖ low[2]
Adverse events	797 per 1000	606 per 1000 (518 to 717)	RR 0.76 (0.65 to 0.90)	251 (1 study)	⊕⊕⊕⊖ moderate[3]
Fatigue	147 per 1000	29 per 1000 (19 to 44)	RR 0.20 (0.13 to 0.30)	260 (1 study)	⊕⊕⊕⊕ high

CI: confidence interval; HR: hazard ratio; OS overall survival; PFS progression free survival; RR: risk ratio.
[1] 95% CI crossed 1 default MID (1.25)
[2] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[3] 95% CI crossed 1 default MID (0.80)

Table 67: Summary clinical evidence profile for Cediranib + lomustine versus lomustine + placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Lomustine + placebo	Cediranib + lomustine			
OS	Not applicable	Not applicable	HR 1.15 (0.77 to 1.71)	196 (1 study)	⊕⊕⊖⊖ low[1]
PFS	Not applicable	Not applicable	HR 0.76 (0.53 to 1.08)	196 (1 study)	⊕⊕⊕⊖ moderate[2]
Fatigue	94 per 1000	147 per 1000 (62 to 351)	RR 1.57 (0.66 to 3.74)	193 (1 study)	⊕⊕⊕⊖ moderate[1]
Adverse events	600 per 1000	762 per 1000 (612 to 948)	RR 1.27 (1.02 to 1.58)	194 (1 study)	⊕⊕⊕⊖ moderate[3]

CI confidence interval; HRhazard ratio; OS overall survival; PFS progression free survival; RR risk ratio
[1] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[2] 95% CI crossed 1 default MID (0.80)
[3] 95%CI crossed 1 default MID (1.25)

Table 68: Summary clinical evidence profile for Bevacizumab versus Bevacizumab + irinotecan

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	BEV + irinotecan	BEV			
OS	Not applicable	Not applicable	HR 1.04 (0.85 to 1.28)	163 (1 study)	⊕⊕⊖⊖ low[1,2]
PFS	Not applicable	Not applicable	HR 1.01 (0.83 to 1.22)	163 (1 study)	⊕⊕⊖⊖ low[1,2]
Wound healing complications	13 per 1000	24 per 1000 (2 to 257)	RR 1.88 (0.17 to 20.30)	163 (1 study)	⊕⊖⊖⊖ very low[1,3]
Aphasia	76 per 1000	36 per 1000 (9 to 137)	RR 0.47 (0.12 to 1.80)	163 (1 study)	⊕⊖⊖⊖ very low[1,3]
Fatigue	89 per 1000	35 per 1000 (11 to 133)	RR 0.40 (0.12 to 1.50)	163 (1 study)	⊕⊖⊖⊖ very low[1,3]

BEV bevacizumab; CI: confidence interval; HR: hazard ratio; OS overall survival; PFS progression free survival; RR: risk ratio.
[1] Unclear how randomisation was performed
[2] 95% CI crossed 1 default MID (1.25)
[3] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 69: Summary clinical evidence profile for Bevacizumab / lomustine 90 versus lomustine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Lomustine	Bevacizumab / lomustine 90			
OS	Not applicable	Not applicable	HR 0.68 (0.42 to 1.10)	90 (1 study)	⊕⊕⊕⊖ moderate[1]
PFS	Not applicable	Not applicable	HR 0.58 (0.37 to 0.90)	90 (1 study)	⊕⊕⊖⊖ low[1,2]
Fatigue	65 per 1000	182 per 1000 (52 to 642)	RR 2.79 (0.79 to 9.84)	90 (1 study)	⊕⊖⊖⊖ very low[2,3]

CI: confidence interval; HR: hazard ratio; OS overall survival; PFS progression free survival; RR: risk ratio.
[1] 95% CI crossed 1 default MID (0.80)
[2] Outcome assessors not blinded
[3] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 70: Summary clinical evidence profile for Bevacizumab / lomustine 90 versus Bevacizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Bevacizumab	Bevacizumab / lomustine 90			
OS	Not applicable	Not applicable	HR 0.64 (0.40 to 1.02)	94 (1 study)	⊕⊕⊕⊖ moderate[1]
PFS	Not applicable	Not applicable	HR 0.60 (0.38 to 0.95)	94 (1 study)	⊕⊕⊖⊖ low[1,2]
Fatigue	40 per 1000	170 per 1000 (41 to 563)	RR 4.55 (1.02 to 20.28)	94 (1 study)	⊕⊕⊖⊖ low[2,3]

CI: confidence interval; HR: hazard ratio; OS overall survival; PFS progression free survival; RR: risk ratio.
[1] 95% CI crossed 1 default MID (0.80)
[2] Outcome assessors not blinded
[3] 95% CI crossed 1 default MID (1.25)

Table 71: Summary clinical evidence profile for HRQOL for Bevacizumab or lomustine versus a combination of bevacizumab + lomustine

Interventions	Mean change from baseline to 2 weeks[1,2,3,4]	Mean change from baseline to 4 weeks[1,2,3,4]	Mean change from baseline to 6 weeks[1,2,3,4]	No of Participants at baseline (studies)	Quality of evidence[5]
Lomustine	Mean change from baseline was of -5.8	Mean change from baseline was of -3.5	Mean change from baseline was of 5.3	27 (1 study)	⊕⊖⊖⊖ very low[5,6]
Bevacizumab	Mean change from baseline was of 0.6	Mean change from baseline was of –0.9	Mean change from baseline was of -15.5	36 (1 study)	⊕⊖⊖⊖ very low[5,6]
Bevacizumab + lomustine	Mean change from baseline was of -4.5	Mean change from baseline was of -1.1	Mean change from baseline was of -5.1	44 (1 study)	⊕⊖⊖⊖ very low[5,6]

HRQoL Health-related quality of life.
[1] Values are the means from the individual study and are not pooled
[2] A higher score represents a higher quality of life
[3] The standard deviations were not reported
[4] Differences in the mean value of ≥ 10 points are classified as being clinically meaningful, whereas changes of >20 points represents a very large effect
[5] Not blinded
[6] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision

Table 72: Summary clinical evidence profile for Bevacizumab + carboplatin versus bevacizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Bevacizumab	Bevacizumab + carboplatin			
PFS	Not applicable	Not applicable	HR 0.92 (0.64 to 1.32)	122 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
OS	Not applicable	Not applicable	HR 1.18 (0.82 to 1.69)	122 (1 study)	⊕⊕⊖⊖ low[1,4]
Adverse events grade ≥ 3	581 per 1000	639 per 1000 (476 to 848)	RR 1.10 (0.82 to 1.46)	120 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Wound healing complications	No events were reported	No events were reported	Not estimable	120 (1 study)	⊕⊕⊖⊖ low[1,2]
Fatigue	65 per 1000	86 per 1000 (25 to 305)	RR 1.34 (0.38 to 4.73)	120 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; OS overall survival; PFS progression free survival.
[1] Unclear how randomisation was performed
[2] outcome assessors not blinded
[3] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[4] 95% CI crossed 1 default MID (1.25)

Table 73: Summary clinical evidence profile for Bevacizumab + irinotecan versus bevacizumab + DD TMZ

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Bevacizumab + DD TMZ	Bevacizumab + irinotecan			
OS	Not applicable	Not applicable	HR 0.86 (0.64 to 1.15)	117 (1 study)	⊕⊕⊖⊖ low[1,2]
PFS	Not applicable	Not applicable	HR 1.03 (0.81 to 1.30)	117 (1 study)	⊕⊖⊖⊖ very low[3,4]
Neurologic adverse events	53 per 1000	100 per 1000 (26 to 381)	RR 1.90 (0.50 to 7.24)	117 (1 study)	⊕⊖⊖⊖ very low[3,5]

CI: confidence interval; DD dose dense; HR: hazard ratio; OS overall survival; PFS progression free survival; RR: Risk ratio; TMZ temozolomide.
[1] Unclear how randomisation was performed
[2] 95% CI crossed 1 default MID (0.80)
[3] Unclear how randomisation was done; outcome assessors not blinded
[4] 95% CI crossed 1 default MID (1.25)
[5] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 74: Summary clinical evidence profile for Low dose bevacizumab + CCNU (lomustine) versus Standard dose Bevacizumab monotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Bevacizumab	Bevacizumab + CCNU			
PFS (patients at 1st ,2nd and 3rd recurrence)	Not applicable	Not applicable	HR 0.71 (0.43 to 1.17)	69 (1 study)	⊕⊕⊖⊖ low[1,2,3]
PFS (patients at 1st recurrence only)	Not applicable	Not applicable	HR 0.58 (0.31 to 1.08)	56 (1 study)	⊕⊕⊖⊖ low[1,2,3]
OS in patients at 1st recurrence	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[7]	47 (1 study)	⊕⊖⊖⊖ very low[1,4,6]
Adverse events (grade ≥ 3)	114 per 1000	31 per 1000 (3 to 257)	RR 0.27 (0.03 to 2.25)	56 (1 study)	⊕⊖⊖⊖ very low[1,2,5]

CI: Confidence interval; HR: Hazard ratio; MD mean difference; OS overall survival; PFS progression free survival; RR risk ratio.
[1] Selective reporting of outcomes
[2] Not blinded
[3] 95% CI crossed 1 default MID (0.80)
[4] Only descriptive data have been reported, insufficient details given to assess the MID threshold and imprecision
[5] 95% crossed 2 default MIDs (0.80 and 1.25)
[6] Only descriptive data have been reported, insufficient details given to assess the MID threshold and imprecision
[7] Not calculable as only medians have been reported. Median OSin the low dose bevacizumab + lomustine 90 arm= 13.05 months (7.08 to 17.82) and median OS in the bevacizumab monotherapy group= 8.8 (6.42 to 20.22)

Table 75: Summary clinical evidence profile for NovoTTF-100A versus active control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Active control	TTF			
OS	Not applicable	Not applicable	HR 0.86 (0.60 to 1.23)	237 (1 study)	⊕⊕⊖⊖ low[1,2]
PFS	Not applicable	Not applicable	HR 0.81 (0.60 to 1.09)	237 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Cognitive disorder (grade ≥ 2)	Not applicable	Not applicable	RR 0.78 (0.11 to 5.46)	237 (1 study)	⊕⊖⊖⊖ very low[1,3,4]

CI: Confidence interval; HR: Hazard ratio; RR risk ratio; OS overall survival; PFS progression free survival; TTF tumour treating fields.
[1] Unclear method of allocation; high risk of attrition bias
[2] 95% CI crossed 1 default MID (0.80)
[3] not blinded
[4] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 76: Summary clinical evidence profile for post-hoc analysis[a] of NOVO-TTF-100A + second line chemotherapy versus second line chemotherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Second line chemotherapy alone	TTF + second line chemotherapy			
OS -overall	Not applicable	Not applicable	HR 0.70 (0.48 to 1.02)	204 (1 study)	⊕⊕⊖⊖ low[1,2]
OS- patients treated with bevacizumab only	Not applicable	Not applicable	HR 0.61 (0.37 to 1.01)	204 (1 study)	⊕⊕⊖⊖ low[1,2]
Grade 3/4 adverse events	333 per 1000	487 per 1000 (327 to 723)	RR 1.46 (0.98 to 2.17)	204 (1 study)	⊕⊕⊖⊖ low[1,3]

CI: confidence interval; HR: hazard ratio; RR risk ratio; OS overall survival; TTF tumour treating fields.
[a]This is a post-hoc analysis of Stupp 2015 and comprises those patients who experienced tumour progression after the initial treatment.
1 Unclear how randomisation was concealed
2 95% CI crossed 1 default MID (0.80)
3 95% CI crossed 1 default MID (1.25)

Table 77: Summary clinical evidence profile for active treatment (TMZ, surgery, surgery + TMZ, surgery + RT, RT only) versus best supportive care in older and/or frail people

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Best supportive care	Active treatment			
Overall survival	Not applicable	Not applicable	HR 0.31 (0.17 to 0.57)	79 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival - age <65 versus ≥ 65 years	Not applicable	Not applicable	HR 0.91 (0.54 to 1.53)	79 (1 study)	⊕⊕⊖⊖ low[1,2]
Overall survival – KPS at relapse ≤50% versus ≥60%	Not applicable	Not applicable	HR 1.60 (0.93 to 2.73)	79 (1 study)	⊕⊕⊖⊖ low[1,3]
Post-progression survival	Not applicable	Not applicable	HR 0.34 (0.19 to 0.60)	79 (1 study)	⊕⊕⊖⊖ low[1,4]
Post-progression survival - age <65 versus ≥ 65 years	Not applicable	Not applicable	HR 0.75(0.45 to 1.24)	79 (1 study)	⊕⊕⊖⊖ low[1,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Post-progression survival – KPS at relapse ≤50% versus ≥60%	Not applicable	Not applicable	HR 0.31 (0.17 to 0.57)	79 (1 study)	⊕⊕⊖⊖ low[1,4]

CI: confidence interval; HR: hazard ratio; KPS Karnofsky performance status; RT radiotherapy; TMZ temozolomide.
1 Selection criteria for treatment modalities were not consistent- the decision was left to the discretion of doctors
2 95% CI crossed 2 default MIDs (0.80 and 1.25)
3 95% CI crossed 1 default MID (1.25)
4 Not blinded
5 95% CI crossed 1 default MID (0.80)

Table 78: Summary clinical evidence profile for carmustine polymer versus placebo polymer

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo polymer	Carmustine polymer			
Overall survival	Not applicable	Not applicable	HR 0.83 (0.63 to 1.09)	222 (1 study)	⊕⊕⊕⊖ moderate[1]
Overall survival - KPS ≥70 versus KPS≤ 70	Not applicable	Not applicable	HR 0.53 (0.40 to 0.70)	222 (1 study)	⊕⊕⊕⊕ high
Overall survival - AA versus GBM	Not applicable	Not applicable	HR 0.60 (0.40 to 0.90)	222 (1 study)	⊕⊕⊕⊖ moderate[2]
Overall survival - Oligodendroglioma versus glioblastoma	Not applicable	Not applicable	HR 0.39 (0.26 to 0.59)	222 (1 study)	⊕⊕⊕⊕ high

AA anaplastic astrocytoma; CI Confidence interval; GBM glioblastoma; HR Hazard ratio; KPS Karnofsky Performance Score.
1 95% CI crossed 1 default MID (0.80)

See Appendix F for full GRADE tables.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

Erlotinib versus TMZ or BCNU

- Very low quality evidence from 1 phase II randomised controlled trial (N=110) showed no significant differences in overall survival and progression free survival between those who received erlotinib (median overall survival = 7.7 months; median progression free survival = 1.8) and those who received temozolomide in combination with lomustine (median overall survival = 7.3 months; median progression free survival = 2.4).

Cediranib alone versus cediranib + lomustine

- Low to moderate quality evidence from 1 phase III randomised controlled trial (N=251) showed no difference in overall survival (HR=1.43, 95% CI 0.96-2.13) and progression free survival (HR=1.05, 95% CI 0.74-1.49) in those who received cediranib alone compared to those who received cediranib in combination with lomustine.
- Moderate to high quality evidence showed a significant reduction in overall adverse events (RR=0.75, 95% CI 0.65-0.90) and fatigue (RR= 0.20, 95% CI 0.13-0.30) in those who received cediranib only compared to those who received cediranib in combination with lomustine.

Cediranib + lomustine versus lomustine + placebo

- Low to moderate quality evidence from 1 phase III randomised controlled trial (N= 196) showed no difference in overall survival (HR=1.15, 95% CI 0.77-1.71) and progression free survival (HR=0.76, 95% CI 0.53-1.08) between those who received cediranib in combination with lomustine compared to those who received lomustine in combination with placebo.
- Moderate quality evidence showed no differences in fatigue between the treatment arms (RR=1.57, 95% CI 0.66-3.74) and an increased risk of adverse events in those who received cediranib in combination with lomustine (RR=1.27, 95% CI 1.02-1.58).

Bevacizumab versus bevacizumab + irinotecan

- Low quality evidence from 1 phase II randomised controlled trial (N=163) showed no differences in overall survival (HR=1.04, 95% CI 0.85-1.28) and progression free survival (HR 1.01, 95% CI 0.83-1.22) between those who received bevacizumab compared to those who received bevacizumab and irinotecan.
- Very low quality evidence showed no differences in the risk of wound healing complications (RR=1.88, 95% CI 0.17-20.3); aphasia (RR= 0.47, 95% CI 0.12-1.80) or fatigue (RR=0.40, 95% CI 0.12-1.50) between those who received bevacizumab compared to those who received bevacizumab and irinotecan.

Bevacizumab/lomustine 90 versus lomustine

- Low to moderate quality evidence from 1 phase II randomised controlled trial (N=153) showed no differences in overall survival (HR=0.68, 95% CI 0.42-1.10) between those who received bevacizumab in combination with lomustine compared with lomustine alone. However, this same trial showed longer progression free survival in those who received bevacizumab in combination with lomustine compared to those who received lomustine only (HR=0.58, 95% CI 0.37-0.90).
- Very low quality evidence showed no differences in fatigue between the treatment arms (RR = 2.79, 95% CI 0.79 - 9.84).
- Very low quality evidence showed that quality of life scores remained stable at 2, 4, and 6 weeks after treatment in those who received bevacizumab in combination with lomustine (mean change from baseline scores= -4.5; -1.1 and -5.1 respectively), with no clinically significant changes observed. In those who received lomustine only, quality of life scores

also remained stable, at 2, 4, and 6 weeks after treatment (mean change from baseline scores= -5.8; -3.5 and 5.3 respectively), with no clinically significant changes observed.

Bevacizumab/lomustine 90 versus bevacizumab

- Low to moderate quality evidence from 1 phase II randomised controlled trial (N=153) showed no differences in overall survival (HR=0.64, 95% CI 0.40-1.02) between those who received bevacizumab in combination with lomustine compared with those who received bevacizumab only. However, this same trial showed longer progression free survival in those who received bevacizumab in combination with lomustine compared to those who received bevacizumab only (HR= 0.60, 95% CI 0.38 - 0.95).
- Low quality evidence showed that those who received bevacizumab only experienced less fatigue than those who received bevacizumab in combination with lomustine (RR= 4.55, 95% CI 1.02-20.28)
- Very low quality evidence showed that quality of life scores remained stable at 2, 4, and 6 weeks after treatment in those who received bevacizumab in combination with lomustine (mean change from baseline scores= -4.5; -1.1 and -5.1 respectively), with no clinically significant changes observed. In those who received bevacizumab only, there was a clinically significant decrease in quality of life scores 6 weeks after the intervention (mean change from baseline = 0.6, -0.9 and -15.5 at 2, 4 and 6 weeks respectively). No other clinically significant changes were observed.

Bevacizumab + carboplatin versus bevacizumab

- Very low to low quality evidence from 1 phase II randomised controlled trial (N=120) showed no differences in overall survival (HR= 1.18, 95% CI 0.82-1.69) and progression free survival (HR= 0.92, 95% CI 0.64-1.32) between those who received bevacizumab in combination with carboplatin compared to those who received bevacizumab monotherapy.
- Low to very low quality evidence showed no differences in the risk of grade ≥3 adverse events (RR=1.10, 95% CI 0.82-1.46), wound healing complications (HR not estimable, none of the groups had any event) or fatigue (RR= 1.34, 95% CI 0.38-4.73) between those who received bevacizumab in combination with carboplatin compared to those who received bevacizumab monotherapy.

Bevacizumab + irinotecan versus bevacizumab + DD TMZ

- Low to very low quality evidence from 1 randomised controlled trial (N=117) showed no differences in overall survival (HR= 0.86, 95% CI 0.64-1.15) and progression free survival (HR = 1.03, 95% CI 0.81-1.30) between those who received bevacizumab in combination with irinotecan or bevacizumab in combination with dose dense temozolomide.
- Very low quality evidence showed no differences in the risk of neurologic adverse events between the treatment arms (RR= 1.90, 95% CI 0.50-7.24).

Low dose bevacizumab + CCNU (lomustine) versus standard dose bevacizumab monotherapy

- Low to very low quality evidence from 1 phase II randomised controlled trial showed no differences in progression free survival at 1st, 2nd and 3rd recurrence (N=71) (HR=0.71, 95% CI 0.43-1.17) or at first recurrence (N=56) (HR=0.58, 95% CI 0.31-1.08) between those who received low dose bevacizumab in combination with lomustine compared to those who received standard dose bevacizumab monotherapy.
- There were also no differences in overall survival at first recurrence (median overall survival in the low dose bevacizumab + lomustine 90 arm= 13.05 months [7.08 to 17.82] and median overall survival in the bevacizumab monotherapy group= 8.8 [6.42 to 20.22]) or in adverse events grade ≥ 3 (RR=0.27, 95% CI 0.03-2.25) between the treatment arms.

Novo-TTF 100A versus active control

- Very low to low quality evidence from 1 phase III randomised controlled trial (N=337) showed no differences in overall survival (HR= 0.86, 95% CI 0.60-1.23) and progression free survival (HR=0.81, 95% CI 0.60-1.09) between those who received tumour treating fields (TTF) compared to those who received active control. Both treatment arms experienced a similar risk of cognitive disorder (grade ≥ 2; RR= 0.78, 95% CI 0.11-5.46).

TTF + second line chemotherapy versus chemotherapy alone

- A post-hoc analysis analysed people treated under this regimen plus second-line chemotherapy after first recurrence. Low quality evidence from 1 randomised controlled trial (N=204) showed that tumour-treating fields (TTF) in combination with second line chemotherapy had similar effects on overall survival as chemotherapy alone (HR = 0.70, 95% CI 0.48-1.02). Low quality evidence showed no statistically significant differences in overall survival (HR=0.61, 95% CI 0.37-1.01) or in risk of grade 3 or 4 adverse events (RR= 1.46, 95% CI 0.98-2.17) between those who received tumour-treating fields (TTF) in combination with bevacizumab compared to those who received bevacizumab only.

Active treatment (TMZ, surgery, surgery + TMZ, surgery + RT, RT only) versus best supportive care in older and/or frail people

- Low to moderate quality evidence from 1 randomised controlled trial (N=79) showed that those who received an active treatment had longer overall survival (HR=0.31, 95% CI 0.17-0.56) and post progression survival (HR=0.34, 95% CI 0.19-0.60) compared to best supportive care. Low quality evidence from a sub-analysis of this trial showed no differences in overall survival between those under 65 years old and those 65 years or older (HR=0.91, 95% CI 0.54-1.53) or between those with a KPS of 50% or less and those with a KPS of 60% or above (HR = 1.60, 95% CI 0.93 – 2.73). Very low to low quality evidence from a sub analysis of this trial showed no differences in post progression survival in those under 65 years old compared to those 65 years or older (HR=0.75, 95% CI 0.45-1.24), and a longer post- progression survival in those with a KPS at relapse of 50% or less compared to those with a KPS of 60% or more (HR=0.31, 95% CI 0.17-0.57).

Carmustine polymer versus placebo polymer

- Moderate quality evidence from 1 randomised controlled trial (N=222) showed no difference in overall survival for those who received a carmustine polymer compared to those who received a placebo polymer (HR=0.83, 95% CI 0.63-1.09). Moderate to high quality evidence from this randomised controlled trial showed that those with the following prognostic factors experienced longer overall survival: those with a KPS score ≥70 compared to those with a KPS ≤ 70 (HR=0.53, 95% CI 0.40-0.70), those with anaplastic astrocytoma compared to those with glioblastoma (HR=0.60, 95% CI 0.40-0.90), and those with oligodendroglioma compared to those with glioblastoma (HR 0.39, 95% CI 0.26-0.59).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 3 outcomes of critical importance to people with brain tumours, which were overall survival, progression-free survival and health-related quality of life. These 3 outcomes were prioritised because they all provide direct evidence of the 'success' of a treatment. The committee discussed how it was sometimes difficult to determine whether

overall survival or progression-free survival was the most accurate measure of a treatment's success, and discussed how health-related quality of life was a useful but often poorly reported outcome measure that provided more detail on whether the extra life-years were of value to a person with a tumour.

The committee identified 6 other outcomes of importance to people with brain tumours. These were neurological adverse events, wound infections, RTOG grade 3 or grade 4 toxicity, CTAE grade 3 or grade 4 toxicity, fatigue and cognitive function. These outcomes were important because they were also measures of the success of a treatment, but were not critical because they were indirect measures. Significant treatment-related adverse events indicate that the person with a tumour is unlikely to be experiencing as high a quality of life as when those events could have been avoided. The adverse events themselves are sometimes a source of mortality, limiting overall survival.

The quality of the evidence

Eight phase II RCTs and 5 phase III RCTs have been included in this review. The quality of the evidence was assessed with GRADE. The main sources of bias were: lack of blinding of investigators and outcome assessors; not reporting the method of randomisation; incomplete outcome data or selective reporting of outcomes; and systematic differences in withdrawal between groups. Objective outcomes, such as overall survival, were not downgraded if participants, outcome assessors or investigators were not blinded to treatment, since being aware of treatment allocation is unlikely to change the survival rate of the participants included. The committee acknowledged the bias in the remaining outcomes and suggested that the bias limited the wider applicability of the evidence.

The committee noted that all the evidence related to grade IV gliomas or a mixed group of grade III and IV gliomas. They agreed that it was appropriate to make recommendations for grade III and IV gliomas on mixed evidence because the response of the tumour to particular kinds of treatment was likely to be somewhat similar once it became recurrent (although not identical) and therefore grade IV recurrent glioma could be regarded as indirect evidence for grade II recurrent glioma.

The committee was aware of some ongoing trials which would not be published during development of the guideline, such as the EORTC 26101 trial looking at CCNU (lomustine) and bevacizumab. They believed that these trials would be unlikely to significantly alter the recommendations they had made, but cautioned that the trials could provide definitive evidence for or against certain treatment options.

The committee determined that the evidence was sufficient to support some weak positive recommendations and some stronger 'do not' recommendations. This was because if there was no evidence to support the use of particular treatments it was likely to be beneficial to patients not to suffer the side effects of those treatments, but that most patients would prefer some treatment if their prognosis was good.

Benefits and harms

The prognosis for people with recurrent high-grade glioma is affected by their performance status, prior treatment, and the tumour's molecular markers. For some people the prognosis can be very limited. Based on their clinical experience and judgement the committee recommended that clinicians treating patients with recurrent high-grade glioma should take all of these factors into account (including the person's wishes) when considering the possible treatment options. The committee also noted, based on low to moderate quality evidence, that older or frail people have an improved survival with treatment over supportive care alone, so these factors should not be the sole determinants of treatment.

Based on some direct evidence for CCNU (lomustine) and indirect evidence for PCV (evidence supporting the use of individual components of PCV but not all three components

of PCV together) the committee recommended that the treatment options for people with recurrent high glade glioma include TMZ, PCV or single agent CCNU (lomustine). The committee stressed that the choice between TMZ, PCV and CCNU (lomustine) should be made on the basis of clinical features of the tumour outlined in the recommendation since there was no evidence to overwhelmingly support one or the other.

The committee made all recommendations on temozolomide in accordance with existing NICE guidance.

Based on clinical experience and judgement, the committee recommended best supportive care alone if the person with the tumour is unlikely to benefit from treatment. This was in order to prevent unnecessary treatment that would not improve the outcome for the person. The committee set out this recommendation to remind clinicians that symptom management alone is an option, and empower people with tumours to ask for this if they felt it was right for them, although they did not have any evidence and so could not make a strong recommendation.

The committee determined that people with focal recurrent enhancing disease may benefit from surgery or re-irradiation. There was moderate quality evidence to suggest carmustine wafers did not have a substantial effect on outcomes (though not of sufficient quality to make a recommendation either way). The committee agreed that people who had diffuse recurrent enhancing disease or those with multi-focal recurrent enhancing disease should not be considered for surgery or radiotherapy and so did not make a recommendation in this group. Although there was a lack of evidence in this area, the committee was aware of ongoing trials and so chose not make a research recommendation.

The committee recommended against the use of erlotinib and cediranib as there was no evidence of effect in either case and the committee believed it was likely to cause side effects. While there was some limited evidence for bevacizumab on progression free survival, the committee agreed that this could be explained by the specific method of action of bevacizumab, so scans appear better but there is no actual impact on overall survival. For this reason, and because no other effect had been shown, the committee also recommended against using bevacizumab.

The committee recommended against the use of tumour treating fields on the basis of a study showing insufficient clinical effectiveness to make the technology cost effective. As the economic evidence was for newly diagnosed glioma, the committee treated this as indirect evidence for the non cost effectiveness of tumour treating fields.

The committee searched for evidence on a number of interventions for recurrent glioma which they were frequently asked about in clinic. When they found no evidence on these interventions, they concluded it would be helpful to inform clinicians and people with tumours of this fact, so that they could have better-informed discussions. The committee emphasised that there were several other interventions of uncertain benefit not included in this evidence search – for example Vitamin C – and the non-appearance of a particular therapy on the list should not be taken as an endorsement of benefit of that therapy.

The average survival of somebody who has a recurrent high-grade glioma is around 6 months for grade IV and 12 to 18 months for grade III (but can vary considerably). Consequently the benefits of treatment in this population are specifically to extend life by a further few months, or to improve the quality of life by – for example – preventing degradation of neurological and cognitive function following diagnosis.

Consequently the clinical decision the committee considered was at what point the benefits of treatment were offset by the side effects. Side effects included a variety of treatment-induced adverse events (such as CTAE grade 3 or grade 4 toxicity) and a variety of negative impacts on the lifestyle of the person with the tumour (such as having to attend hospital frequently for chemotherapy).

The committee additionally considered the clinically complex question of using therapies that were highly unlikely to work (and carried side effects) against the benefit of allowing people to take control of decisions about their treatment.

The committee balanced these benefits and harms and made recommendations which should prevent the treatments with the worst ratio of benefits to side effects from being offered, and should allow clinicians to discuss with people with tumours their preferred profile of side effects given that there is insufficient evidence to support one treatment over another.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

The committee considered that these recommendations would lead to a reduction in resource use while also potentially improving quality of life.

The recommendations will have little or no impact upon the treatment for the vast majority of people with high-grade glioma as they are already usual practice in the NHS in England.

The committee highlighted that while very costly treatments such as tumour treating fields, bevacuzimab, erlotinib and cediranib are not widely used, the recommendations would lead to a reduction in the number of people receiving these treatments. Even very small reductions in the frequency of these treatments could lead to significant reductions in costs. The recommendations will also likely decrease the number of unnecessary adverse events experienced by people receiving these interventions, again reducing resource use from treating adverse events and potentially improving quality of life.

Other factors the committee took into account

The committee discussed how the TMZ TA contained recommendations around not excluding people who had a poor performance status from treatment. The committee agreed with this sentiment, (though added in discussion that a poor performance status was often an indication that treatment decisions needed to be taken very carefully). Consequently the committee did not make a specific recommendation on this topic, as it was already covered by existing NICE guidance.

Based on their experience the committee was aware that people with brain tumours often consulted sources of information about their condition that may not be accurate (for example, websites), and felt it important to state when there was no evidence that a treatment was or was not effective. The committee noted that prescribing therapies with no underpinning evidence base and potentially harmful side effects (including offering false hope) was not recommended. Explanation regarding this should be offered to people with recurrent high-grade glioma.

The committee had a detailed discussion about the choice of words ‘best supportive care’, as this can sometimes be interpreted in too vague a sense to be useful for people with brain tumours. They determined that the current phrasing in close proximity to a reference to NICE’s end of life care guideline would make it clear what meant by the recommendation, and that it was unlikely to confuse anyone reading the guideline.

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Techniques for resection of glioma

Review question

What is the most effective method for optimising maximal safe resection of glioma (for example with 5-ALA, awake craniotomy, intraoperative ultrasound, intraoperative MRI)?

Introduction

Neurosurgical resection is the initial treatment for many gliomas, however – depending on features of the tumour such as location and shape – removing all of the tumour can be very difficult. For high-grade tumours, cure is essentially impossible, but benefits for complete or near-complete (>95%) resection of the tumour have been observed in the committee's experience. Similarly for low-grade glioma, survival benefits have been shown for maximal surgical resection of the non-enhancing tumour. However, increased extent of resection may increase the risk of post-operative neurological disability from damage to surrounding eloquent brain. Traditional surgical resective techniques rely on visual assessment by the operating surgeon, with image guidance using neuro-navigation based on pre-operative radiological imaging. Resection can be limited by difficulty in discerning tumour from normal brain tissue and by intra-operative shift of structures as surgery progresses. Adjuncts to surgery have been introduced to attempt to help maximise the extent and safety of tumour resection, including 5-Amino-Levulinic Acid (5-ALA) fluorescence, awake craniotomy with electrophysiological stimulation, intra-operative ultrasound and intra-operative MRI. This review will examine the effect of these adjunctive techniques on neurosurgical resection of gliomas and the evidence base for their usage.

PICO table

Table 79: Summary of the protocol (PICO table)

Population	Adults due to undergo surgical resection for glioma (primary presentation or first surgery)

Intervention	• Standard craniotomy with techniques (neuronavigation, microscope)
	
	• Surgical resection guided by:
	  ○ 5-ALA (Gliolan)
	  ○ awake craniotomy
	  ○ subcortical stimulation
	  ○ cortical stimulation
	  ○ bipolar stimulation
	  ○ mono-polar stimulation
	
	• Intraoperative ultrasound
	• Intraoperative MRI
	• Endoscopic resection
	• BrainPath
	• MRI ablation

Comparison	Each other
Outcome	Critical: • overall survival. • gross total resection margins (as determined by post-operative MRI)

	• progression-free survival
	• neurological function
	  ○ Karnofsky performance status (KPS)
	  ○ Neurological Function Scale
	  ○ language
	
	<u>Important:</u>
	• treatment-related mortality
	• treatment-related morbidity:
	  ○ wound infection
	• length of surgery
	
	<u>Of limited importance:</u>
	• epilepsy / seizure control

5-ALA 5-Amino-Levulinic Acid; *iMRI image guided magnetic resonance imaging; MRI magnetic resonance imaging.*

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Included studies consisted of phase III randomised controlled trials (RCTs) enrolling patients due to undergo surgical resection for glioma at primary presentation or first surgery, presenting with low-grade glioma (LGG), high-grade glioma (HGG) or a mixed combination of gliomas.

The majority of studies covered image-guided surgery (with the exception of a single study which used awake craniotomy). The identified trials were not deemed suitable for meta-analysis, therefore only comparisons from individual studies were considered for inclusion.

Overall, studies were at significant risk of bias, some of them being significantly underpowered and stopped early.

One Cochrane systematic review examining image-guided surgery for the resection of brain tumours (Barone 2014) was identified. The Cochrane review compared image-guided surgery with either surgery without any image guidance or surgery using a different type image guidance. Patients with a presumed new or recurrent central nervous system (CNS) tumour (any location or histology) from clinical examination and imaging (CT but ideally contrast enhanced MRI) were included. The Cochrane review included 4 RCTs and all met the inclusion criteria for this review also (that is, the target populations in the trials were all patients with glioma, although 1 trial also included patients with cerebral metastasis [15%; Willems 2006]; Senft 2011, Stummer 2006, Willems 2006, Wu 2007). However, the Cochrane review did not include any meta-analyses which, along with the identification of another 2 eligible studies, meant that the individual RCTs from the Cochrane review were included instead of the Cochrane review itself in the current evidence review. The 2 additional included studies were not included in the Cochrane review because they were either published after the Cochrane review (Wu 2014) or covered a different intervention to the ones considered in the Cochrane review (awake craniotomy; Gupta 2007). Although the participants included in both Wu 2014 and Senft 2011 received the same interventions, surgery with iMRI and surgery with conventional neuronavigation, the studies were not deemed suitable for meta-analysis as the patient characteristics varied widely (in Wu 2014, >50% of patients presented with LGG, whereas in Senft 2011, >70% of patients presented with HGG).

A summary of these studies is provided in Table 80 and the results along with the quality of the evidence for each outcome are listed in Table 81 to Table 86 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Summary of clinical studies included in the evidence review

Table 80 provides a brief summary of the included studies.

Table 80: Summary of studies included in Barone 2014

Study	Population	Intervention	Comparator	Outcomes
Senft 2011	2% of patients presented with WHO grade I glioma; 4% of patients presented with WHO grade III glioma and 94% with WHO grade IV glioma. Mean age (SD) = 55.3 (12.5) in the iMRI group and 55 (13.6) in the conventional microsurgery group; median KPS in both groups was 90.	iMRI (N=24)	Conventional microsurgery (N=25)	• Complete tumour resections • Adverse events • PFS
Stummer 2006	4% of patients presented with WHO grade III glioma and 96% of patients had WHO grade IV glioma. Ages ranged between 18 and 72 years old; >70% of the patients had a KPS >70.	5-ALA (N=139)	Conventional microsurgery with white light (N=131)	• Complete resection • PFS • OS • KPS
Willems 2006	17% of patients presented with WHO grade III	Surgery with neuronavigation (N=23)	Standard surgery (N=22)	• Gross total removal

Study	Population	Intervention	Comparator	Outcomes
	glioma; 68% of patients with WHO grade IV glioma and 15% of patients with cerebral metastasis. Mean age was 60 years old. Median KPS score was 80			• Neurological deficits • Survival • QoL
Wu 2007	54% of patients presented with WHO grade III glioma and 46% of patients with WHO grade IV glioma. All the patients had gliomas involving pyramidal tracts. Median age or KPS have not been reported.	DTI-based functional neuronavigation (N=118)	Routine neuronavigation (N=120)	• Extent of resection • OS • Postoperative motor function • KPS score
Gupta 2007	All patients presented with intrinsic lesions of eloquent cortex (motor and speech areas). Median age was 43 years old. KPS was not reported	Awake craniotomy (N=26)	Surgery under general anaesthesia (N=27)	• Deteriorated speech area lesion • Deteriorated motor cortex lesions • Residual tumour • KPS
Wu 2014	57.4% of patients presented with LGG; 42.6% presented with HGG.59.7% presented with tumours in eloquent areas; 40.3% of patients presented with tumours in noneloquent areas. 90% of people had of people in the iMRI group and 88% in the neuronavigation group had a KPS of 100.	iMRI (N=58)	Neuronavigation (N=56)	• Rate of gross total resection • Extent of resection • PFS • New or aggravated language deficits

Study	Population	Intervention	Comparator	Outcomes

5-ALA 5-Amino-Levulinic Acid; HGG high-grade glioma; iMRI intraoperative magnetic resonance imaging; KPS Karnofsky performance status; OS overall survival; PFS progression free survival; QoL quality of life; WHO World Health Organization.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question (surgical adjuncts to optimise maximal safe resection of glioma) are presented in Table 81 to Table 86.

Table 81: Summary clinical evidence profile for 5-ALA versus white light microsurgery

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WL microsurgery	5-ALA			
Complete tumour resection	359 per 1000	646 per 1000 (499 to 840)	RR 1.80 (1.39 to 2.34)	270 (1 study)	⊕⊕⊖⊖ low[1]
PFS	Not applicable	Not applicable	HR 0.73 (0.57 to 0.93)	270 (1 study)	⊕⊖⊖⊖ very low[1,2]
OS - Age ≤55	Not applicable	Not applicable	HR 1.04 (0.64 to 1.70)	88 (1 study)	⊕⊖⊖⊖ very low[3,4]
OS - Age >55	Not applicable	Not applicable	HR 0.73 (0.53 to 1.01)	182 (1 study)	⊕⊕⊖⊖ low[2,3]
OS- combined	Not applicable	Not applicable	HR 0.82 (0.62 to 1.08)	270 (1 study)	⊕⊕⊖⊖ low[2,3]
Convulsions	8 per 1000	18 per 1000 (2 to 205)	RR 2.38 (0.30 to 26.84)	270 (1 study)	⊕⊖⊖⊖ very low[1,4]
Grade 3/4 neurological AEs	53 per 1000	72 per 1000 (28 to 183)	RR 1.35 (0.53 to 3.43)	270 (1 study)	⊕⊖⊖⊖ very low[1,4]

AEs adverse events; CI confidence interval; OS overall survival; PFS progression free survival; RR Risk ratio; HR Hazard ratio; WL white light.
[1] Outcome assessors not blinded; participants excluded due to major violations of MRI inclusion criteria and due to histological criteria. High selective reporting of outcomes.
[2] 95% CI crossed 1 default MID (0.80)
[3] Participants excluded due to major violations of MRI inclusion criteria and due to histological criteria. High selective reporting of outcomes.
[4] 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 82: Summary clinical evidence profile for iMRI versus neuronavigation[a]

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Neuronavigation	iMRI			

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Complete tumour resection	320 per 1000	959 per 1000 (721 to 1000)	RR 1.14 (1.06 to 1.87)	49 (1 study)	⊕⊖⊖⊖ very low[1,2]
Progression	640 per 1000	1000 per 1000 (653 to 1000)	RR 1.85 (1.02 to 3.36)	49 (1 study)	⊕⊖⊖⊖ very low[1,2]
New or aggravated language deficits	80 per 1000	125 per 1000 (23 to 684)	RR 1.56 (0.29 to 8.55)	49 (1 study)	⊕⊖⊖⊖ very low[1,3]

CI: confidence interval; iMRI intraoperative magnetic resonance imaging; PFS progression free survival; RR: risk ratio.
[1] Not blinded; unclear risk of attrition bias; study stopped early due to an interim analysis resulting in a reduced sample size.
[2] 95% CI crossed 1 default MID (1.25)
[3] 95% CI crossed 2 default MIDs (0.80 and 1.25)
a Senft 2011

Table 83: Summary clinical evidence profile for iMRI versus neuronavigation[b]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Neuronavigation	iMRI			
Rate of gross total resection	768 per 1000	760 per 1000 (622 to 929)	RR 0.99 (0.81 to 1.21)	49 (1 study)	⊕⊕⊕⊖ moderate[1]
PFS	Not applicable	Not applicable	HR 1 (0.96 to 1.04)	49 (1 study)	⊕⊕⊕⊖ moderate[1]
New or aggravated language deficits	232 per 1000	104 per 1000 (42 to 253)	RR 0.45 (0.18 to 1.09)	49 (1 study)	⊕⊕⊖⊖ low[1,2]

CI: confidence interval; HR: hazard ratio; iMRI intraoperative magnetic resonance imaging; PFS progression free survival; RR: risk ratio.
[1] Unclear whether all the pre-determined outcomes have been reported
[2] 95% CI crossed 1 default MID (0.80)
b Wu 2014

Table 84: Summary clinical evidence profile for DTI based functional neuronavigation versus routine neuronavigation

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Routine neuronavigation	DTI based functional neuronavigation			

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Complete tumour resection HGG	326 per 1000	762 per 1000 (479 to 1000)	RR 2.34 (1.47 to 3.72)	85 (1 study)	⊕⊕⊖⊖ low[1]
Complete tumour resection LGG	618 per 1000	655 per 1000 (506 to 852)	RR 1.06 (0.82 to 1.38)	129 (1 study)	⊕⊖⊖⊖ very low[1,2]
OS	Not applicable	Not applicable	HR 0.57 (0.33 to 1.00)	238 (1 study)	⊕⊕⊖⊖ low[3,4]
KPS	Not applicable	Not applicable	MD 12 (5.37 to 18.63)	238 (1 study)	⊕⊖⊖⊖ very low[1,5]
Postoperative motor function deterioration	325 per 1000	153 per 1000 (94 to 250)	RR 0.47 (0.29 to 0.77)	238 (1 study)	⊕⊕⊖⊖ low[1]

CI: confidence interval; DTI diffusion tensor imaging; HGG high-grade glioma; KPS Karnofsky performance status; LGG low-grade glioma OS overall survival; RR: risk ratio; HR: hazard ratio.
[1] High risk of selection bias and incomplete outcome data. Outcome assessors not blinded to intervention
[2] 95% CI crossed 1 default MID (1.25)
[3] High risk of selection bias and incomplete outcome data
[4] 95% CI crossed 1 default MID (0.80)
[5] 95% CI crossed 1 default MID (+14) (±0.5 x ±28=±14)

Table 85: Summary clinical evidence profile for surgery with neuronavigation versus standard surgery

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard surgery	Surgery with neuronavigation			
Complete tumour resection	773 per 1000	873 per 1000 (657 to 1000)	RR 1.13 (0.85 to 1.48)	45 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

CI: confidence interval; RR: risk ratio.
[1] Selective reporting of outcomes; trial significantly underpowered and terminated prematurely; perioperative evaluations and postoperative motor function and surgical complications conducted by the resident neurosurgeon and operating neurosurgeon who were not blinded
[2] 15% of patients presented with cerebral metastases
[3] 95% CI crossed 1 default MID (1.25)

Table 86: Summary clinical evidence profile for awake craniotomy versus surgery under general anaesthesia

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Surgery under general anaesthesia	Awake craniotomy			
Deteriorated speech area lesion - Immediate postoperatively	74 per 1000	153 per 1000 (31 to 770)	RR 2.08 (0.42 to 10.39)	53 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Deteriorated speech area lesion - At 3-month follow up	74 per 1000	135 per 1000 (42 to 433)	RR 1.56 (0.26 to 6.21)	53 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Deteriorate motor cortex lesions - Immediate postoperatively	74 per 1000	270 per 1000 (64 to 664)	RR 3.64 (0.87 to 8.97)	53 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Deteriorate motor cortex lesions - At 3-month follow up	333 per 1000	383 per 1000 (170 to 660)	RR 1.15 (0.51 to 1.98)	53 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Residual tumour	368 per 1000	523 per 1000 (236 to 796)	RR 1.42 (0.64 to 2.16)	40 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
KPS score	Not applicable	The mean KPS score in the intervention arm was 7.80 lower (from 13.25 to 2.35 lower)	Not applicable	53 (1 study)	⊕⊖⊖⊖ very low[1,2,5]

CI: confidence interval; KPS Karnofsky performance status; RR: risk ratio.
[1] Drop outs not accounted for; no data regarding survival or adverse events has been reported. Outcome assessors not blinded to intervention
[2] One patient presented with a metastatic lesion
[3] 95% CI crossed 1 default MID (1.25)
[4] 95% CI crossed 2 default MIDs (0.80 and 1.25)
[5] 95% CI crossed 1 default MID (-4.15) (8.3 x ±0.5=±4.15)

See Appendix F for full GRADE tables.

Economic evidence

Included studies

Four hundred and ninety-six possibly relevant papers were identified. Of these, 8 full-text papers relating to this topic were obtained for appraisal. Three cost utility analyses (Slof 2015, Eseonu 2017 and Martino 2013) were included in the current review of published economic evidence for this topic.

Health economic evidence profile

Table 87: Health economic evidence profile

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Slof 2015 Spain	People with Grade III and Grade IV glioma.	Conventional resection under White Light	Not reported	Not reported	Reference			Deterministic sensitivity analyses: A range of one way sensitivity analyses were undertaken with the ICER remaining under €20,000	Partially Applicable	Potentially serious limitations
		Fluorescent-guided resection with 5-ALA	Not reported	Not reported	€1010	0.11 QALYs	€9,021 per QALY			
	Comments:									
Study	**Population**	**Comparators**	**Costs**	**Effects**	**Incr costs**	**Incr effects**	**ICER**	**Uncertainty**	**Applicability**	**Limitations**
Esenou 2017 USA	Adults with WHO grade II, III and IV glioma in the perirolandic motor area location.	Surgery under general anaesthesia	$46,798	0.47 QALYs	Reference			No exploration of uncertainty performed.	Partially applicable	Very Serious Limitations
		Awake Craniotomy	$34,804	0.97 QALYs	-$11,994	0.50 QALYs	Awake craniotomy dominant			
	Comments:									
Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Martino 2013 Spain	Adults with WHO grade II glioma involv	Surgery under general anaesthesia	€32,116	2.9 QALYs	Reference			No exploration of uncertainty performed.	Partially applicable	Very Serious Limitations
		Surgery under general anaesthesia/	€38,663	4.8 QALYs	€6,547	1.9 QALYs	€3,500 per QALY			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
	ing an eloquent area	Awake/ surgery under general anaesthesia								
	Comments:									

Summary of studies included in the economic evidence review

Slof 2015 is a cost utility study comparing fluorescent guided resection with 5-ALA to conventional white light resection (resection alone) in people with grade III and grade IV glioma. The study took a Spanish healthcare payer perspective and reported outcomes in terms of cost per QALY. Effectiveness data was taken from retrospective patient records with a sensitivity analysis using the Stummer 2006 trial effectiveness data described in detail in the clinical evidence review and de-novo economic model. Utility values were taken from one UK cost utility analysis comparing intracranial implantation of carmustine wafers as an adjunct to resection to resection and radiotherapy alone in patients with high-grade glioma. A publically available database of prices was used to estimate costs in the model.

Both Eseonu 2017 and Martino 2013 compared awake craniotomy to resection under general anaesthesia. Both reported outcomes in terms of cost per QALY. Eseonu 2017 compared the interventions in a population of adults with WHO grade II, III and IV glioma. Effectiveness data was taken from a retrospective case-control study of 40 previous patient receiving the interventions. Utility data was calculated by dividing Karnofsky performance status of patients by 100. All costs were taken from one hospitals database.

Martino 2013 studied very similar interventions in patients with WHO grade II glioma involving an eloquent area. All patients were in active employment. The study presented two analyses, one taking a Spanish healthcare payer perspective (direct) and one taking a Spanish societal perspective (indirect). Costs were reported in US dollars. Effectiveness data was taken from 11 consecutive patients' records receiving awake craniotomy which were matched to 11 retrospective records of patients receiving resection under general anaesthesia. Utility values were estimated by dividing Karnofsky performance status of patients by 100. All costs were taken from publically available databases of Spanish unit costs of healthcare. Losses in productivity for the indirect analysis were assumed to equal the wage rate of the patient.

All 3 studies were deemed partially applicable to the decision problem. This is because they did not take a NHS and PSS perspective.

Eseonu 2017 and Martino 2013 were considered to have very serious limitations in terms of methodological quality. The main limitation in both studies was the lack of exploration of uncertainty. Slof 2015 was deemed to have potentially serious limitations. The study did not present any probabilistic sensitivity analysis and was funded by a manufacturer of 5-ALA.

Slof 2015 estimated in the base-case that the addition of 5-ALA to resection would lead to increase in costs of €1,010 and an increase in QALYs of 0.11 resulting in an ICER of €9,021 per QALY, a value for which technologies are usually adopted in the Spanish healthcare system. These results were robust to range of one way sensitivity analyses. Even when a combination of unfavourable assumptions towards 5-ALA was used the ICER equalled €19,222 per QALY again below the value at which technologies are usually adopted in the Spanish healthcare system. No probabilistic sensitivity analysis was performed by this study.

Eseonu 2017 reported that awake craniotomy reduces costs by $11,994 and increases QALYs by 0.5 compared to resection under general anaesthesia. Martino 2013, when considering direct healthcare costs, also led to an increase in QALYs through the use of awake craniotomy (1.9 QALYs) compared to resection under general anaesthesia although this was at an increased cost of €6,547 per patient. This results in an ICER of €3,500 per QALY below values for which technologies are often accepted by the Spanish health service. Again no exploration of uncertainty was undertaken. Limited weight should be given to the comparison of these studies as different perspectives and methodologies have been used which may explain conflicting results.

For full economic evidence tables see Appendix H.

Economic model

See Appendix I for full details of economic model.

Overview of Methods

A decision analytical model in the form of a partitioned survival analysis was developed to estimate the cost effectiveness of the addition of 5-ALA to surgical resection of WHO grade IV glioma relative to surgical resection alone. The main outcome of the economic model was incremental cost per QALY of the addition of 5-ALA. A NHS and PSS perspective was taken. The model had a time horizon of 5 years which was deemed sufficient to capture the lifetime of the majority of the cohort.

Clinical data for the model was solely taken from the 1 RCT identified by the clinical evidence review. This study reported both higher progression free survival and overall survival (not statistically significant) for 5-ALA. The cost of a vial of 5-ALA was estimated at £1,032 and the cost of the addition of a surgical microscope was estimated £39,483 with an active lifespan of 8 years both taken from 1 previous economic evaluation of 5-ALA. The model tried to estimate outcomes for 2 costing scenarios; A base-case analysis where a centre already had the module as part of their surgical microscope (and therefore this cost was not included) and a alternate analysis where the module had to be purchased. Given the variation in throughput at different centres and difficulty in obtaining information around other diseases for which 5-ALA is used in the NHS the alternate scenario was difficult to model. We therefore looked at the number of patients who needed to be treated annually with 5-ALA for 5-ALA to remain cost effective (if so in the base-case) when the capital costs of purchasing the module were included. All other costs were taken from NHS Reference Costs.

Quality of life weights were taken from cost utility study comparing carmustine wafers as an adjunct to resection to resection with radiotherapy in people with high-grade glioma. This study used a UK general population sample of 93 people of which 36 responded to this health state elicitation exercise. Hypothetical health states were developed using the EORTC QLQ-30 alongside the brain cancer module BC20 and standard gamble techniques used to estimate quality of life weights. This estimated a quality of life weight for unprogressed and progressed disease of 0.89 and 0.73 respectively. The committee considered these values to be higher than would have been expected from their clinical experience so extensive sensitivity analysis was carried out around them.

All health and cost outcomes were discounted at a rate of 3.5% per annum.

Results of the economic model

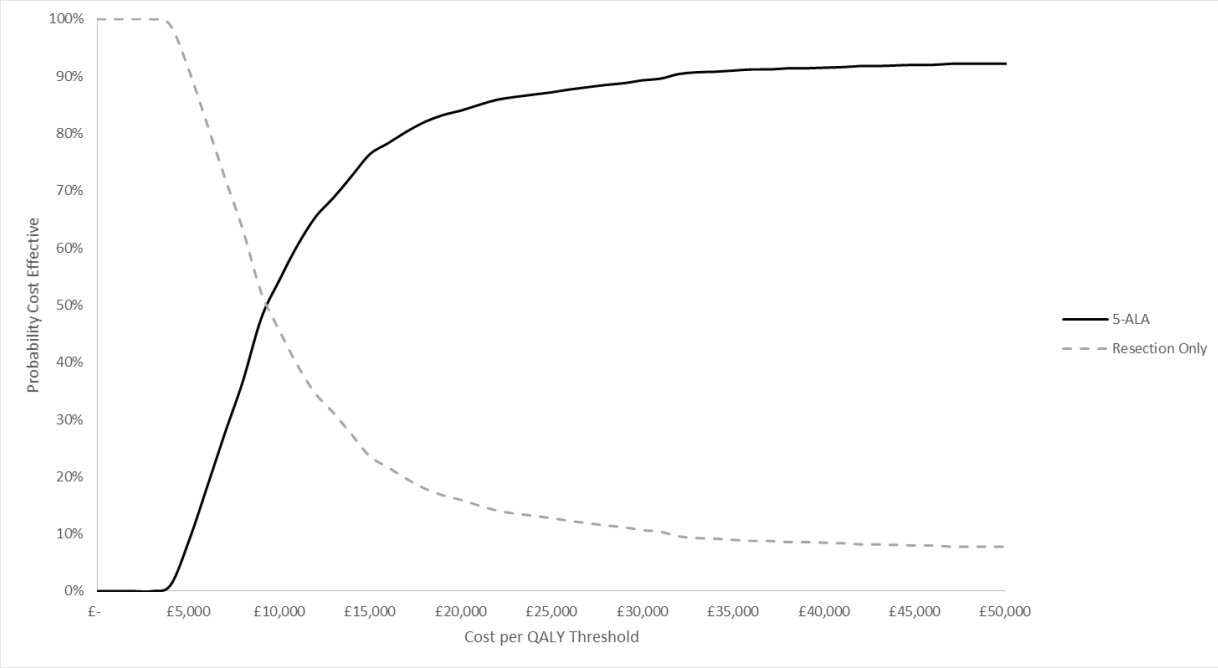
The addition of 5-ALA to standard resection led to an increase in costs of £1,257 and an increase in QALYs of 0.14 equating to an ICER of £8,991 per QALY below the NICE threshold of £20,000 per QALY. (Table 88) The conclusions were consistent when the mean of the stochastic results were used.

Table 88: Base-case analysis results

Intervention	Life Months	QALY	Disc. QALY	Cost	Disc Cost	Inc. QALY	Inc. COST	ICER
Resection Alone	18.58	1.1872	1.1504	£1,947	£1,874	Ref	Ref	
5-ALA	20.75	1.3353	1.2903	£3,220	£3,131	0.1398	£1257	£8,991

When module costs were included in the model, even at the highest estimate of cost, a centre would only need to treat 5 people per year with 5-ALA (for any condition) for it to remain cost effective. (Figure 1) This is reduced to 4 people per year when the middle or lower estimates are considered respectively.

Figure 1: Relationship between patient throughput and the ICER



During deterministic sensitivity analysis 5-ALA was not the most cost effective option in only 2 scenarios for a £20,000 per QALY. Despite poor quality evidence around quality of life the conclusions were robust to a range of differing assumptions. Even when no difference was assumed between progressed and unprogressed health states, an assumption that would strongly bias against 5-ALA, it still remains the preferred option. During probabilistic sensitivity analysis 84% of iterations were cost effective at a £20,000 per QALY threshold although all iterations were cost increasing.

Conclusions

Using 5-ALA as an adjunct to surgery strongly appears to be a cost effective use of NHS resources. When the additional costs of purchasing the necessary module for addition to the surgical microscope only a small number of patients need to be treated per year for 5-ALA to remain cost effective for which even small centres should be able to comfortably achieve. 5-ALA remained the preferred option under deterministic and probabilistic sensitivity analyses with 5-ALA always being resulting in higher QALYs and higher costs.

This clinical evidence for the model was based on 1 RCT. The quality of this evidence was either low or very low as rated by GRADE in the clinical evidence review. Despite these weaknesses the committee were persuaded by this RCT and their own clinical experience that 5-ALA was likely to lead to greater percentage of resected glioma and greater progression free survival and overall survival in line with that reported by the trial. No high quality evidence around quality of life was identified for the economic model however the conclusions of the model were robust to a large range of alternative assumptions around quality of life.

The conclusions were in line with 1 previous economic evaluations of the use of 5-ALA as an adjunct to resection alone from the perspective of the Spanish healthcare system.

Resource Impact

Unit costs and resource impact presented as part of the de novo economic model.

Evidence statements

5-ALA versus white light microsurgery

- Low to very low quality evidence (N=270) from 1 randomised controlled trial showed that 5-ALA was associated with a higher rate of complete tumour resection (relative risk (RR)= 1.80, 95% confidence interval (CI) 1.39-2.34) and with a longer time to progression (hazard ratio (HR)= 0.73, 95% CI 0.57-0.93) compared to white light microsurgery. There were no differences in overall survival between the treatments in those aged 55 years or below (HR= 1.04, 95% CI 0.64 – 1.70); in those aged over 55 years old (HR= 0.73, 95% CI 0.53 – 1.01) or in the combined overall survival (HR=0.82, 95% CI 0.62-1.08). There were no differences in grade 3-4 adverse events as measured by the Common Terminology Criteria for Adverse Events (CTCAE) (RR= 1.35, 95% CI 0.53-3.43) or in risk of convulsions in between both groups (RR= 2.38, 95% CI 0.3-26.84).

iMRI versus neuronavigation

- Very low quality evidence from 1 randomised controlled trial (N=49) in which >50% of people presented with WHO grade IV glioma showed that iMRI was associated with a higher rate of complete tumour resection (RR= 1.14, 95% CI 1.06-1.87) and with a longer time to progression compared to neuronavigation (RR=1.85, 95%CI 1.02-3.36). There were no differences in the risk of new or aggravated language deficits between the treatment arms (RR=1.56, 95% CI 0.29-8.55). Conversely, low to moderate to moderate quality evidence from 1 RCT in which > 50% of people presented with WHO grade I/II gliomas (N=114) showed no differences between iMRI and neuronavigation in the rate of gross total resection (RR=0.99, 95% CI 0.81-1.21); progression-free survival (HR= 1, 95% CI 0.96-1.04) and new or aggravated language deficits (RR= 0.45, 95% CI 0.18-1.09).

DTI based functional neuronavigation versus routine neuronavigation in gliomas involving the pyramidal tracts

- Low to very low quality evidence from 1 randomised controlled trial (N=238) showed that DTI based functional neuronavigation was associated with a higher rate of complete tumour resection in comparison with routine neuronavigation in those with high-grade glioma (HR= 2.34, 95% CI 1.47-3.72), but no difference in the rate of complete tumour resection was observed in those with low-grade glioma (HR= 1.06, 95% CI 0.82-1.38). Those who received DTI based neuronavigation, had longer overall survival (HR= 0.57, 95% CI 0.33-1) than those who received routine neuronavigation. Those who received DTI based neuronavigation experienced less postoperative motor function problems

(RR=0.47, 95% CI 0.29-0.77) and an improved functional status compared to those who received routine neuronavigation (MD= 12, 95% CI 5.37 to 18.63).

Surgery with neuronavigation versus standard surgery

- Very low quality evidence from 1 randomised controlled trial (N=55) showed that surgery with neuronavigation was associated with a higher rate of complete resection in comparison with gross total removal (standard surgery) (RR=1.13, 95% CI 0.85-1.48).

Awake craniotomy versus surgery under general anaesthesia

- Very low quality evidence from 1 randomised controlled trial (N=56) showed no differences in residual tumour rate in those who received awake craniotomy compared to those who received surgery under general anaesthesia (RR= 1.42, 95% CI 0.64-2.16). Very low quality evidence showed that there were no differences in the status of the speech area lesion either immediately postoperatively (RR 2.08, 95% CI 0.42-10.39) or 3 months postoperatively (RR= 1.56, 95% CI 0.26-6.21). Very low quality evidence showed that there were no differences in motor cortex lesions either immediately postoperatively (RR=3.64, 95% CI 0.87-8.97) or at 3 months follow-up (RR= 1.15, 95% CI 0.51-1.98). Very low quality evidence showed that those who received surgery under general anaesthesia presented with a higher Karnofsky performance status as compared to those who received awake craniotomy (MD= -7.80, 95% CI -13.25 to -2.35).

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 6 outcomes of critical importance: overall survival; gross total resection margins; progression-free survival; neurological function as measured by Karnofsky performance status; neurological function as measured by the neurological function scale; and language outcomes. The committee accepted that it was unusual to identify 6 outcomes as 'critical', but noted that in this case the phenomenon being studied was so ephemeral that all 6 outcomes were required in order to ensure that all tumour had been removed (overall survival, gross total resection margins and progression-free survival, where the success of the removal is based on a holistic interpretation of all 3 outcome measures) and that no functional brain had been damaged (neurological function and language, where language is an especially important measure of neurological function).

The committee identified 3 further outcomes as important. These were treatment-related mortality and morbidity (specifically wound infection), and length of surgery. These were defined as important because they were indirect measures of the success of surgery, with longer and more dangerous surgery being taken as a proxy measure for increasing difficulty in resecting all visible tumour.

The committee identified 1 outcome of limited importance. This was epilepsy/seizure control. The committee accepted it was of very high importance to people with tumours, but considered that most people would accept an increase in seizures in exchange for a longer, higher-quality life on average. There was also little rationale for why any single technique would worsen seizure control above the baseline effect of surgery.

The quality of the evidence

The quality of the evidence was assessed according to GRADE criteria. Included studies presented outcomes with evidence classified as very low to moderate quality. The main sources of bias were lack of information regarding the selection of participants in the studies: most of the studies stated 'randomisation' but did not provide further information about the

method used, which could have made the selection of participants into each of treatment groups predictable. Another common source of bias amongst the included studies was the lack of blinding, although this is expected due to the nature of the interventions in the studies. Overall, studies did not provide information regarding drop outs, which also accounts for the very low quality of the evidence reported in some studies.

Given the low quality of evidence, the committee chose to make weak recommendations with the exception of the recommendation for 5-ALA where an economic model developed for the guideline allowed them to make stronger recommendations.

The committee chose not to make a research recommendation, as the evidence for 5-ALA was robust enough to base recommendations on once combined with an economic model, and all other recommendations were in line with current clinical practice.

Benefits and harms

The committee was persuaded by evidence that using 5-ALA probably improved the extent of tumour resection and progression-free survival and may also improve overall survival although the effect was not statistically significant. Health economic analysis suggested that the use of 5-ALA as an adjunct to surgical resection of high grade glioma would be an efficient use of NHS resources. The committee discussed how the quality of important outcomes in this trial were low, but that they still believed that the trial provided enough evidence to make a strong recommendation because it would have been impossible to blind the trial and this was a significant reason the trial was downgraded; therefore the trial represented the best possible quality evidence for this intervention.

The evidence for intraoperative MRI was mixed. One trial showed significantly improved complete resection rates and rates of tumour progression. A second trial showed no statistical significance at all. The committee discussed whether these two trials could be reconciled, as meta-analysis was not suitable for these results. Their conclusion was that both studies were well conducted, and that therefore the results were unlikely to reflect statistical chance. However they argued that it was possible for even a well-conducted study to find a null result, for example if the tumours being operated on were not situated in a location where MRI would make a definitive clinical difference. This therefore led them to conclude that it was likely that there were circumstances where intraoperative MRI would make a difference, and that therefore they favoured the Senft (2011) study for the purpose of making recommendations.

The committee did not see any evidence for intraoperative ultrasound, but were aware many centres used this instead of intraoperative MRI. Based on their experience, the committee concluded that there was unlikely to be a significant difference between the effect of intraoperative MRI and ultrasound and that therefore clinicians should continue to use whichever they preferred. This was especially important given the significant capital cost of replacing an intraoperative ultrasound machine with an intraoperative MRI machine. The committee added that intraoperative MRI and intraoperative ultersound were not ‘alternatives’, but options to be considered; there may be times when one, neither or both would be the most clinically appropriate imaging strategy. The recommendations were therefore drafted to make this clear.

Based on the evidence for MRI and their judgement, the committee concluded that MRI and ultrasound both had advantages and disadvantages, and both could be used to assess tumour size, location and resection extent. There was little to choose between them other than surgical preference and local availability, although there was additional evidence for MRI compared to ultrasound.

Evidence showed the rate of complete resection, overall survival and postoperative motor function were all improved by using DTI over conventional neuronavigation. While the evidence focused on the pyramidal tract, based on their experience the committee agreed

DTI may be important to prevent damage to all functionally important fibre tracts, though the technique is not standardised across different MRI platforms.

While evidence was limited, the committee found the evidence on awake craniotomy was in line with their clinical experience that it could be beneficial in some groups of patients and harmful in others. The strength of the recommendation was based on the committee's conclusion that there was no UK-wide consensus on what areas of the brain the treatment should be limited to, and they decided that clinical judgement should be used. This therefore meant the committee focussed on improving the ratio of patients likely to benefit compared to patients likely to be harmed by the choice of offering awake craniotomy.

When discussing the evidence for awake craniotomy, the committee described how – while this technique was extremely powerful in preserving language, motor and visual function – for some patients it was also one of the most anxiety-provoking procedures available through the NHS. Based on their experience, the committee discussed how the physical and psychological effects of this could be better managed by both considering the characteristics of the person who might receive the craniotomy and through better management by the surgical team.

On the basis of their experience the committee concluded that management should not be left to the anaesthetist alone, and that a multi-professional team should psychologically screen and prepare people for this procedure to ensure that there will be no lasting psychological implications. In general, however, the evidence suggests the procedure is well tolerated by people with a brain tumour who are correctly prepared psychologically so the committee did not want to deny a useful procedure just because it was difficult to perform psychological management. This was based on the committee's experience.

The benefits of intraoperative imaging are that more tumour can be resected, which is believed to lead to better outcomes and a reduced rate of reoperation/retreatment.

The harms of intraoperative imaging are that it can be expensive and time consuming. It can provoke anxiety in a person with a brain tumour if not properly explained to them, especially if an awake craniotomy is being considered.

Overall, however, the risk of poorer outcomes if insufficient imaging was used led the committee to recommend the maximum amount of imaging possible, subject to the low quality of evidence.

The committee discussed a subtle effect where the use of intraoperative imaging might de-skill surgeons, such that when a particular imaging method was inappropriate the patient might be harmed. The committee agreed that imaging was so widespread that if such a deskilling effect occurred in practice it would have been detected already, and therefore the imaging techniques were viewed as only enhancing surgical skill.

Cost effectiveness and resource use

One previously published economic evaluation was identified around 5-ALA versus standard resection from a Spanish healthcare payer perspective. Given the potential resource implications of recommendations around the use of 5-ALA a bespoke economic model was also created to consider the same decision problem but from a NHS and PSS perspective. During their deliberations the committee put greater weight on the conclusions from the bespoke model than the previous evidence although the conclusions were largely the same.

The base-case results of the economic model estimated that using 5-ALA as an adjunct to resection would lead to an increase of 0.14 QALYs and an increase in costs of £1,257. This result was robust to a range of deterministic sensitivity analyses. If a £50,000 threshold, a higher cost per QALY, which NICE consider for interventions which increase life expectancy by at least 3 months in people in their final 24 months of life relative to current treatment, was

used the robustness of these results increased. Stummer 2006 reported a median overall survival in the 5-ALA group of 15.2 months and an increase in median overall survival between the 2 groups of 1.7 months with a 95% upper confidence interval of 4.0 months increased survival. The criteria for the higher threshold could potentially be met.

The base-case analysis excluded the capital cost of purchasing the module required for the surgical microscope to be able to use 5-ALA. Even when the higher estimate of this cost of the module was included in the analysis a centre would need to treat only 5 people per year, for any condition, with 5-ALA for 5-ALA to remain the most cost effective option. The committee considered that this could be achieved comfortably by all centres.

The probabilistic sensitivity analysis reinforced the robustness of the results with a 84% probability that 5-ALA was cost effective at a £20,000 per QALY threshold increasing to 92% when a £50,000 per QALY threshold was used. All iterations of the probabilistic sensitivity analysis resulted in 5-ALA being the more costly intervention.

The committee acknowledged that this analysis was based largely on the 1 RCT included in the clinical evidence review with the quality of this evidence being either very low or low as rated using GRADE. The committee was persuaded by this evidence and their own clinical experience that 5-ALA was likely to lead to a greater percentage of resected glioma and consequently greater PFS and OS in line with that reported by this trial. They therefore agreed that the conclusions of the model were valid. The committee was confident that recommending 5-ALA, while being cost increasing, would be an efficient use of NHS resources.

Two previously published cost utility analyses compared awake craniotomy to surgery under general anaesthesia craniotomy from a Spanish healthcare payer perspective, with 1 analysis also including societal costs such as foregone wages. The patient groups considered were grade II glioma and grade II, III and IV glioma. Both these studies found awake craniotomy to be cost effective compared to surgery under general anaesthesia with one study finding awake craniotomy both cost saving and health improving. The cost saving was largely driven by a reduction in hospital inpatient days and reduced treatment for adverse events. Neither study was directly applicable to a NHS setting. Both studies had potentially serious methodological issues. The committee therefore gave limited consideration to the conclusions.

The committee considered that cost savings could potentially be achieved as reduction in bed days and adverse events from awake craniotomy would be true for a UK NHS setting as much as for a Spanish healthcare setting. Neither study included the cost of providing specialists to assist before, during and after awake craniotomy. There is currently wide variation across the NHS in England around the provision of these specialists and this may add significant costs on top of those considered by the previous economic evidence. On balance the committee considered awake craniotomy to be an efficient use of NHS resources although given the absence of evidence from an NHS and PSS perspective and potential for a significant resource impact a weaker recommendation was made.

The committee acknowledge the difficulty in considering resource impact and cost effectiveness around intraoperative ultrasound and intraoperative MRI. Both interventions are associated with very large capital costs especially where operating theatres need to be adapted or built to allow the movement of patients to an MRI without the need to close up the patients head. These capital costs could potentially reach the millions of pounds per centre although the ward and technology are likely to have a long active life span. Therefore, these fixed capital costs could be spread across a large number of patients albeit with this number differing largely by centre.

This technology is already available in some centres. In these centres the use of intraoperative imaging may be no more costly than using post-operative imaging. It may also reduce the need for post-operative imaging or the need to operate again where optimal

resection has not been achieved. There would also be less demand on already stretched imaging services. Some of the cost savings discussed for awake craniotomy above are also likely to be true for intraoperative imaging with reduced bed days and lower adverse events.

While an economic model would have been useful for formulating recommendations in this area the committee acknowledged with the available clinical evidence and wide variation in costs across centres, results of such a model would give uncertain conclusions. The committee therefore made a consider recommendation around this intervention although it would almost certainly be cost effective and health improving in centres where the technology is already available.

Other factors the committee took into account

The committee discussed how their recommendations targeted a range of slightly different clinical scenarios that might not immediately be apparent to nonspecialists reading the guideline. Recommendations on 5-ALA, MRI and ultrasound effectively aim to maximise resection, but these techniques are less accurate in determining whether such a resection will cause a clinical deficit. Recommendations on awake craniotomy and DTI aim to make any resection undertaken functionally safe, without specifically adding new information about which areas should be resected. Consequently the only real way to maximise safe resection is to use a combination of techniques appropriate to the particular tumour being resected, and the recommendations reflect this.

The committee described how techniques such as 5-ALA could be used on low-grade tumours with less success; the committee estimated that around 90% of grade IV tumours would fluoresce under the 5-ALA technique while around 10% of grade II tumours would fluoresce under the same technique. There was some discussion about whether fluorescing low-grade tumours were in fact hidden high-grade tumours, but it was concluded that there was insufficient evidence to make a recommendation, especially given the cost of 5-ALA.

The committee discussed the phenomenon of ‘neuroplasticity’, where the region of a brain that is responsible for a particular function (for example speech), may not be where it would be assumed to be based on standard neuroanatomical knowledge. A particular function may in fact have moved to an adjacent brain area due to gradual encroachment by a growing tumour. Equally importantly, function may have been preserved in an area that appears unequivocally as tumour on MRI. The committee discussed how they would never resect such eloquent areas, and cautioned that the only way to detect neuroplasticity reliably was with functional measures of cognitive performance such as awake craniotomy, possibly aided by pre-operative measures such as functional MRI, transcranial magnetic stimulation and neuropsychology. There was insufficient evidence on this phenomenon to make a specific recommendation, and the committee concluded it would be covered by their recommendations on functional imaging.

Although the committee repeatedly highlighted the importance of psychological preparation before and during awake craniotomy to prevent trauma, they added that there were some people who found the operation quite interesting and enjoyed talking to the surgeons throughout – the level of support should, therefore, be matched to the needs of the person undergoing the procedure and the prominence the committee gave to recommendations ensuring patients are well prepared for the procedure should not be taken to mean all patients will need extensive preparation.

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Follow-up for glioma

Follow-up for glioma

Review question

What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?

Introduction

Glioma is the most common primary brain cancer in adults. Long-term and progression-free survival are very dependent on the type and grade of glioma, as well as the extent of resection and post-operative treatments. Asymptomatic or untreated gliomas may require follow up with only regular MRI scans (or CT for patients unable to tolerate MRIs). Early detection and treatment of recurrence may improve outcomes but the impact on overall morbidity is unknown. If routine imaging is recommended, the preferred image modality, frequency and duration of scanning is uncertain given the different subtypes of gliomas.

PICO table

Table 89: Summary of the protocol (PICO table)

Population	People treated for glioma
Intervention	Follow-up protocol including duration, and frequency of tests (e.g., MRI/CT scans)
Comparison	• Any other follow-up protocol • No follow up (wait until patient reports symptoms of recurrence)

Outcome	Critical:
	• treatment for recurrence
	• overall survival.
	• cognition
	• symptomatic versus asymptomatic presentation
	Important:
	• health-related quality of life
	  ○ neurological outcomes
	  ○ seizures

CT computer tomography; MRI magnetic resonance imaging.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource impact

Table 90: Resource impact and unit costs associated with follow-up for glioma

Resource	Unit costs	Source
Follow-Up Appointment	£188	NHS reference costs 2015-16 (WF01A)
MRI Scan	£145	NHS reference costs 2015-16 (RD01A)

Evidence statements

No evidence was identified.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee designated 4 outcomes as critical. These were cognitive function, treatment for recurrence, overall survival and the numbers of patients with symptomatic versus asymptomatic presentation. As the committee was unsure whether identifying early progression of a tumour would be clinically beneficial, they identified these outcomes as the easiest to interpret, so that the benefit or harm of treatment would be most obvious on review.

Health-related quality of life was also important, although not critical as the committee agreed the link between recurrence and health-related quality of life was not as direct.

The quality of the evidence

The clinical evidence search identified no studies that met the inclusion criteria for this review.

The committee decided that since the question was so important and the evidence so limited they would make weak recommendations to provide guidance for clinicians based on their clinical knowledge.

The committee determined that a research recommendation was important to standardise practice in this area. They determined that the major outstanding clinical question was how valuable early detection of recurrence was compared to later detection. This was true for all 3 questions on follow-up the committee looked at (for glioma, meningioma and brain metastases) but the committee elected to prioritise glioma as treatment options for recurrence of glioma had significant evidence, so it was more likely that findings would influence clinical practice.

For full details see Appendix L.

Benefits and harms

On the basis of their clinical experience and judgement, the committee recommended that clinical review in a person with glioma might be useful to detect recurrence, based on changes in the person's symptoms and function. Clinical assessment can also lead to intervention or onward referral, if indicated. This may improve a person's quality of life by alleviating symptoms or helping the person develop adaptive strategies. Although the committee identified no evidence that early detection of changes in clinical status could improve outcomes, they agreed that failing to detect a change had happened at all could have severely negative consequences for the person with a tumour. Consequently they made a strong recommendation for offering a review that could detect recurrence or other changes in clinical condition, but weaker recommendations on what should be in that review.

The committee identified no evidence on which to make recommendations about when to arrange regular clinical review. From reviews on the management of the tumour, however, the committee believed it had indirect evidence of factors that would make a recurrence more dangerous. Consequently they made a weak recommendation to consider the factors that could alter the urgency of the review. The recommendation on taking into account the person's preferences was made on the basis of the committee's experience.

While there was no evidence for or against the use of MRI or other scans to detect recurrence, the committee recommended that MRI scanning could be useful to detect recurrence on the basis that it is standard practice to do this already and that unstandardised MRI is not as useful as standard structural MRI. The committee explained how under certain circumstances not all of the sequence would be necessary, for example if the tumour had very well-defined characteristics which could be adequately monitored with only some of the suggested sequence. Consequently they made a weaker recommendation than for the equivalent sequence in the investigation of the tumour, because in the investigation of the tumour it is not yet known what characteristics the tumour will have and therefore clinicians cannot determine if there are any aspects of the sequence which can be left out whereas in the follow up there is more scope for the use of clinical judgement in determining which steps were necessary.

The committee agreed that there were situations in which advanced MRI techniques might also be helpful. For example, for newly-diagnosed gliomas advanced imaging techniques can inform discussions on whether a person's best option is watchful waiting or early surgery (see section on 'Imaging for suspected glioma'). They can also help distinguish between recurrence of tumour and the after effects of treatment. Therefore this recommendation was based on their clinical experience, and evidence examined in a separate review on methods of MRI scanning.

Based on their experience, the committee recommended that clinicians be aware that routine imaging (and waiting for the result) may cause anxiety. In addition, the committee recommended that the possibility of uncertain results (such as ambiguous growth) be explained. The committee made this recommendation because in their experience the potential harms of scanning very frequently were sometimes not appreciated by all clinicians.

The committee recommended clinical review in response to new or changing neurological symptoms (outside the usual schedule of scans). This is based on the fact that the purpose of routine follow-up is to identify changes to the tumour in order for treatment to be started before symptoms arise (if this is possible). New or changing symptoms likely mean that the tumour has grown between scans, and therefore waiting until the next routine scan could limit treatment options. In addition, the review would represent an opportunity for the clinician to discuss how the change might affect the risk of negative effects (such as infection and swelling). The committee discussed how they had not reviewed the evidence for how long a clinical review could be delayed in the case of new or changing symptoms and therefore could not specifically recommend a timeframe for review, but discussed how similar clinical

considerations would apply in the case of a changing symptom as a new cancer referral and that therefore the timing might be related to that in practice.

The committee suggested a schedule of scans for a person with glioma as a possible guide to discuss with the person with the tumour. Although there was no evidence the committee felt that consensus recommendations would be valuable to help standardise practice and reduce inequity from clinical variation, and suggested a follow-up schedule that could be used as a guide. Detail on the link between the committee's judgement and the recommendations is given below.

Example initial scanning schedule (all tumour grades)

Based on their clinical experience and judgement, the committee chose to make a recommendation on a scan within 72 hours following surgery as this gives a post-surgical baseline, confirms that the intended extent of resection was achieved, and can identify areas of tissue injury that may otherwise be mistaken for residual or recurrent tumour on later imaging studies.

The committee also chose to make a recommendation of a scan 3 months following the end of treatment, consistent with current clinical practice.

Example schedule for grade I

In the judgement of the committee, grade I glioma could sometimes be effectively treated. If the tumour is effectively treated (no tumour visible on imaging 12 months after treatment) it may therefore be appropriate to discharge the person from follow-up altogether. However if tumour is visible on imaging the committee described how the best response was uncertain – it may also be appropriate to discharge the person from follow-up, but the clinician may want to ensure no growth or transformation is occurring, in which case a regular but infrequent follow-up would offer the best balance of risks and benefits. Finally there are certain cases where even if the tumour is not visible it should still be considered a candidate for follow-up, for example if the tumour is a completely excised pilocytic astrocytoma the committee recommended monitoring for recurrencing with an increasing-length imaging interval.

Example schedule for grade II non codeleted, IDH mutated and grade II or III co-deleted

In the experience of the committee, most recurrence in this group occurs within the first 5 years. Therefore they recommended frequent follow-up during this period, followed by a long period of regular but infrequent follow-up. Ten years after treatment if there is no tumour recurrence or new side effects there should be a discussion about whether the person with the tumour can be discharged or whether the schedule of regular but infrequent follow-up should be maintained. The outcome will depend on clinical features of the tumour and the committee did not have the evidence to be specific about what should be considered when making this judgement.

Example schedule for grade II IDH wildtype, grade III non-codeleted and grade IV

In the experience of the committee, the life expectancy of someone with a grade IV glioma or an astrocytoma was very limited, and was unknown in the case of a grade II IDH wildtype tumour. Consequently they suggested that scanning should be initially very frequent, in order to maximise the potential for and quality of life. If the person with the tumour survives for a long time, the committee explained that they might assume the tumour was stable (depending on other clinical factors) and therefore reduce the scanning interval to be more in line with a grade II or oligodendroglioma.

Overall benefits and harms

The committee agreed that the overall benefits of the recommendations would be that more people who have undergone treatment of glioma will have longer overall survival because

more recurrences will be picked up while they are still asymptomatic (which is when recurrences are easiest to treat). However, the committee also recognised that scanning is associated with psychological stress and anxiety for some people. The committee discussed whether more frequent scanning would provoke or reduce anxiety in people with brain tumours, but reached no consensus as it might be different for different people – for example reassurance of regular contact versus anxiety induction of worrying results (especially results of uncertain significance). While there was no absolute balance to be struck – the actual balance in all cases should depend on individual factors to do with the person – the committee believed their suggested follow-up schedule was a useful guide to balancing these benefits and harms.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

The committee believed these recommendations to be in line with current practice nationally and therefore did not think they would lead to any significant change in practice. The committee acknowledged that a small number of centres may not be using a follow-up protocol similar or identical to the schedule they recommended, and in these centres increased follow-up imaging and some service reconfiguration may be needed if the centre wishes to implement the recommended schedule. This would lead to increased costs and resource use, although given the small number of centres this is unlikely to be significant. These additional cost may also be somewhat offset by quicker identification of recurrence and resultantly more effective treatment leading to reduced costs of treating adverse events.

Other factors the committee took into account

The committee also discussed that people with physical disabilities might find it difficult to attend very frequent scanning, and that consideration should therefore be given to alternative modalities of assessment for these people. They did not make a specific recommendation on this point as the types of physical disability experienced by people with brain tumours were very variable, and in not referring specifically to disability the committee believed they would make it clear that all people with tumours should be offered appropriate follow up, regardless of the presence of a disability.

The committee recognised that if the recommendations meant that follow-up scans had to be undertaken during the weekend then this would incur an additional cost. The committee therefore decided to use ranges of time for scanning that were at least 3 days long in order to ensure that weekend scanning could be minimised.

References

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Appendices

Appendix A – Review protocols

Review protocol for review 1a - imaging for suspected glioma and meningioma

Field (based on PRISMA-P)	Content
Key area in the scope	Diagnosing radiologically identified glioma, meningioma and brain metastases.
Actual review question	What is the most effective imaging strategy in newly diagnosed glioma and meningioma?
Type of review question	Diagnostic
Objective of the review	This protocol explores the evidence for imaging strategies for patients with radiologically suspected glioma or meningioma. Under consideration are the imaging techniques, or combination of techniques, that provide the information necessary to make a putative diagnosis and plan appropriate treatment. Standard CT will not be considered further as this is commonly the modality on which the diagnosis is first suspected. The purpose of this review is to identify the diagnostic accuracy of advanced MRI, PET-CT and PET-MRI for the characterisation of radiologically suspected glioma and meningioma in addition to standard MRI
Eligibility criteria – **population**/disease/condition/issue/domain	Adults with a radiologically (by CT scan or MRI scan) suspected glioma (high or low-grade) or meningioma

Field (based on PRISMA-P)	Content

Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)/ Index test	Standard MRI alone:
	• Standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2)
	
	Standard MRI plus 1 of the following advanced tests:
	
	• Advanced MRI:
	  ○ MR Spectroscopy (chemical shift imaging)
	  ○ diffusion imaging (DWI/DTI) tensor imaging (DTI)
	  ○ perfusion imaging (DSC, DCE, ASL will not be looked at separately)
	  ○ structural imaging
	
	• PET-CT (including FDG: FET, MET, Choline-PET)
	
	• PET-MRI
	(including FDG: FET, MET, Choline-PET)

Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• Pathology (histology and, where appropriate molecular testing) or clinical /radiological follow-up if there is not biopsy
Outcomes and prioritisation	• Quality of life / anxiety Diagnostic accuracy including: • sensitivity

Field (based on PRISMA-P)	Content
	• specificity • likelihood ratios For: • high-grade glioma present (WHO grade III and IV) versus high–grade glioma absent • low-grade glioma present (WHO grade I and II) versus low-grade glioma absent
Eligibility criteria – **study design**	• Only published full text English language papers • Studies published from the year 2002 as it was when standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2) was first used **Study design:** • cross-sectional studies (>20) • prospective comparative cohort studies (>20) • retrospective comparative cohort studies (>20) • nested case control (1 gate) studies (>20) Only direct comparisons were considered.
Other **exclusion criteria**	• Recurrent meningioma, low-grade glioma or high-grade glioma • Children and young people (under 16 years old)

Field (based on PRISMA-P)	Content
	The following list of tumour types: ○ neuronal and mixed neuronal-glial tumours ○ tumours of the pineal region ○ embryonal tumours ○ tumours of the cranial and paraspinal nerves ○ melanocytic tumours ○ lymphomas ○ mesenchymal, histiocytic, germ cell, sellar originating and choroid plexus tumours. ○ brain metastases
Proposed sensitivity/**sub-group analysis**, or meta-regression	Stratification: • suspected low-grade glioma • suspected high-grade glioma (grade III, IV) • suspected meningioma • axial versus volume imaging
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will be undertaken for this review. In addition, included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	Pairwise meta-analyses will be performed using STATA. STAR will be used for bibliographies/citations, text mining, study sifting, data extraction, and quality assessment/critical appraisal.
Information sources – databases and dates	See Appendix B for full list of databases.

Field (based on PRISMA-P)	Content
	Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limit to studies published from the year 2002 as it was when standard structured MRI (core protocol) +/- contrast (T1 pre and post contrast and T2) was first used Limit to English language only (Medline and Embase). Limit to RCTs and systematic reviews and observational studies unless overall return is small Supplementary search techniques: No supplementary search techniques were used Key papers: 1. Gliomas: Predicting Time to Progression or Survival with Cerebral Blood Volume Measurements at Dynamic Susceptibility-weighted Contrast-enhanced Perfusion MR Imaging. Meng Law, Robert J. Young, James S. Babb, Nicole Peccerelli, Sophie Chheang, Michael L. Gruber, Douglas C. Miller, John G. Golfinos, David Zagzag, and Glyn Johnson Radiology 2008 247:2, 490-498 2. Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging. Zonari, P., Baraldi, P. & Crisi, G. Neuroradiology (2007) 49: 795. doi:10.1007/s00234-007-0253-x
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.

Field (based on PRISMA-P)	Content
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using the following checklist: • QUADAS -II
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	The quality of the evidence for an outcome (i.e. across studies) will be assessed using QUADAS –II. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimally important differences: Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual extraction and quality assessment was not performed for this review, as it was not prioritised for dual extraction, This was because the evidence base was complex, and required support from the committee, which served the same function as dual extraction and quality assessment.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 1d – molecular markers to inform prognosis / guide treatment

Field (based on PRISMA-P)	Content
Key area in the scope	Diagnosing radiologically identified glioma, meningioma and brain metastases.
Actual review question	1d What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?
Type of review question	Prognostic
Objective of the review	Molecular markers are used for a variety of important decisions concerning the treatment of brain tumours, for example confirming the presence/absence of a tumour and improving stratification of known tumours. For each tumour type molecular markers can be divided into 3 types – those which are critical to test for, those which are not critical to test for but may offer benefit in uncommon cases and those which offer no benefit if tested for. The objective of this review is to determine if there are any subgroups of patients for whom molecular markers which are currently regarded as noncritical might be valuable enough to always offer.

Field (based on PRISMA-P)	Content
Eligibility criteria – **population**/disease/condition/issue/domain	Adults (aged 16 years and over) with initial glioma at the time of testing for the molecular markers (i.e., these people do not have recurrent glioma)
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Molecular markers: • BRAF • TERT • EGFR
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	The analyses of eligible studies have to control for the effect of the following other prognostic factors when examining the prognostic effect of the molecular markers (in order to be able to examine the additional prognostic effect of the markers once the effect of these variables have been taken into account): • age • tumour grade • tumour histological subtype • treatment (firstline) • IDH mutation • 1p19Q
Outcomes and prioritisation	Overall survival Progression free survival For BRAF group only: • response to BRAF inhibitors (Vemurafenib, daburafenib, tremetanib)
Eligibility criteria – **study design**	Only published full text English language papers Systematic reviews

Field (based on PRISMA-P)	Content
	Cohort studies (N ≥ 100)
Other inclusion **exclusion criteria**	NA
Proposed sensitivity/**sub-group analysis**, or meta-regression	Tumour grade
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Dual extraction and quality assessment was not performed for this review, as it was not prioritised for dual extraction, This was because the evidence base was complex, and required support from the committee, which served the same function as dual extraction and quality assessment.
Data management (software)	If meta-analyses undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase. Limit to 2008 as this was when the role of IDH was discovered. Limit to English language only (Medline and Embase). Supplementary search techniques: No supplementary search techniques were used.
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	NA
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not rgistered in PROSPERO

Review protocol for review 1c – timing and extent of initial surgery for low-grade glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Diagnosing radiologically identified glioma, meningioma and brain metastases.
Actual review question	1c What is the optimal timing and extent of initial surgery for suspected low-grade glioma?
Type of review question	Intervention
Objective of the review	This review aims to explore the benefits and risks of surgery, including awake craniotomy, for suspected low-grade gliomas and to determine whether there is sufficient evidence to support a policy of maximal surgical resection.

Field (based on PRISMA-P)	Content
Eligibility criteria – **population**/disease/condition/issue/domain	Adults (aged 16 years and over) with suspected low-grade glioma on imaging suitable for surgical resection or biopsy
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Biopsy/image-guided biopsy • Subtotal resection (partial) • Gross total resection (maximal)
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• Each other • Active monitoring (no surgery/biopsy)
Outcomes and prioritisation	Critical: • progression-free survival • epilepsy / seizure control • neurological function ○ Neurological Function Scale or NIH stroke scale Important: • overall survival • time to tumour transformation (from low-grade to high-grade) • health-related quality of life. Of limited importance: • surgical mortality (intra-operative and 30-day postoperative)
Eligibility criteria – **study design**	Only published full text papers

Field (based on PRISMA-P)	Content
	Systematic reviews RCTs Comparative cohort (50 per arm) or observational (50 per arm) studies
Other inclusion **exclusion criteria**	None
Proposed sensitivity/**sub-group analysis**, or meta-regression	• IDH status • 1p\19q status • histological subtype (astrocytoma versus oligodendroglioma) if applicable
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality assessment: Double sifting will be performed by the systematic reviewer and senior systematic reviewer. Data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer.
Data management (software)	If pairwise meta-analyses undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Date limit: 1980, which was chosen because that was when MRI became available and none of the interventions listed above would be used today without MRI. Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews and observational studies unless overall return is small

Field (based on PRISMA-P)	Content
	Supplementary search techniques: No supplementary search techniques were used Key papers: 1: Le Rhun E, Taillibert S, Chamberlain MC. Current Management of Adult Diffuse Infiltrative Low-grade Gliomas. Curr Neurol Neurosci Rep. 2016 Feb;16(2):15. 2: Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol. 2016 May 12. [Epub ahead of print] Review. 3: Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir (Wien). 2016 Jan; 158(1):51-8. doi: 10.1007/s00701-015-2621-3. Epub 2015 Nov 3. 4: Aghi MK, Nahed BV, Sloan AE, Ryken TC, Kalkanis SN, Olson JJ. The role of surgery in the management of patients with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline. J Neurooncol. 2015 Dec; 125(3):503-30. doi: 10.1007/s11060-015-1867-1. Epub 2015 Nov 3. 5. Shaw EG, Berkey B, Coons SW, Bullard D, Brachman D, Buckner JC, Stelzer KJ, Barger GR, Brown PD, Gilbert MR, Mehta M. Recurrence following neurosurgeon-determined gross-total resection of adult supratentorial low-grade glioma: results of a prospective clinical trial. J Neurosurg. 2008 Nov; 109(5):835-41. 6. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgård G, Solheim O. Comparison of a strategy favoring early surgical resection versus a strategy favoring watchful waiting in low-grade gliomas. JAMA. 2012 Nov 14;308(18):1881-8. 7. Watts, C., & Sanai, N. Surgical approaches for the gliomas. In MS Berger, & M. Weller (Eds), Handbook of Clinical Neurology, Vol 134. 2016. Pages 51-69.

Field (based on PRISMA-P)	Content
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	N/A
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 2a – further management of low-grade glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Managing low-grade glioma
Actual review question	2a What is the optimal management (observation, surgery, radiotherapy, chemotherapy or combinations of these) for histologically proven low-grade glioma?
Type of review question	Intervention

Field (based on PRISMA-P)	Content
Objective of the review	Though low-grade glioma are relatively infrequent diagnosis, they occur principally in younger people and with improved survival long term quality of life is of paramount importance. All brain tumour therapies have potential acute and long term toxicities so clinical teams need to balance improving longevity whilst minimising long term impact on physical, cognitive, psychological wellbeing. The principal management options are: 1) Watchful waiting where patients are followed up with clinical assessment of symptoms and imaging, usually with MRI scans. 2) Surgery which can consist of a biopsy only, partial removal or attempted maximal removal (debulking) 3) Radiotherapy which can be delivered using a variety of techniques and doses 4) Chemotherapy Often the treatments above are used in combination. Which combination should be used and in what situations is an important clinical question so review of the literature will help provide guidance for clinical teams, patients and their families.
Eligibility criteria – **population**/disease/condition/issue/domain	People with newly histologically proven low-grade glioma (grade I and II) who have had surgery (resection or biopsy)
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Active monitoring • Surgery • Radiotherapy • Chemotherapy • Combined treatments involving combinations of the above (including radiation versus radiation or Chemotherapy versus chemotherapy)
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	Any of the above interventions

Field (based on PRISMA-P)	Content
Outcomes and prioritisation	Critical: • overall survival • cognitive function • neurological function • Neurological Function Scale or NIH stroke scale Important: • health-related quality of life. • progression-free survival • epilepsy / seizure control • grade 3 or 4 late toxicity (after 3 months)
Eligibility criteria – **study design**	Only published full text English language papers Systematic reviews RCTs
Other **exclusion criteria**	Children and young people (up to age 15)
Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	• 1p/19q • IDH • By histological subtype if possible • Extent of resection (biopsy, subtotal, total)

Field (based on PRISMA-P)	Content
Selection process – duplicate screening/selection/analysis	No duplicate screening/selection/analysis will be undertaken for this review as the topic is so technically complex that the clinical advisor is required to support the reviewer, and is therefore judged to be performing the quality assurance function of a conventional dual sift.
Data management (software)	Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations, text mining, and study sifting Data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limit to 1985 as the radiotherapy techniques used before then are not applicable to current practice. Limit to English language only (Medline and Embase). Limit to RCTs and systematic reviews unless overall return is small Supplementary search techniques: No supplementary search techniques were used
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group Please document any deviations/alternative approach when GRADE isn't used or if a modified GRADE approach has been used for non-intervention or non-comparative studies.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • Cochrane risk of bias tool for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Meta-analysis will be conducted where appropriate. Minimally important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed will not be performed.

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. Consider exploring publication bias for review questions where it may be more common, such as pharmacological questions, certain disease areas, etc. Describe any steps taken to mitigate against publication bias, such as examining trial registries.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds [add name of developer] to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 2c – initial management of high-grade glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Managing Glioma
Actual review question	2c Following surgery, what is the optimal management (radiotherapy, chemotherapy, combinations of these, or other therapies such as metformin or tumour-treating fields) of initial high-grade glioma?
Type of review question	Intervention

Field (based on PRISMA-P)	Content
Objective of the review	This review is aimed at identifying whether any management strategy is more effective than any other in patients with high-grade glioma which has not previously been systemically treated
Eligibility criteria – population/disease/condition/issue/domain	People with high-grade gliomas (anaplastic astrocytomas, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, gliosarcoma and glioblastoma, transformed low-grade glioma that has not previously been treated, not otherwise excluded in the scope) who have not previously had a high-grade glioma Also grade III / IV glioma or the words 'high-grade glioma'
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Specified standard of care in the comparator group plus one or more of the following interventions: • chemotherapy • immunotherapy • biological therapy • different radiotherapy schedules • tumour treating fields • metformin • statins • ketogenic diet • valgancyclovir / Valganciclovir • cannabis oil (Sativex)
Eligibility criteria – comparator(s)/control or reference (gold) standard	In people with Glioblastoma who are ≤70 years of age + Karnofsky performance status ≥70: • surgery/biopsy + radiotherapy + Temozolomide In people with Glioblastoma who are ≥70 years of age or Karnofsky performance status ≤70: • surgery/biopsy + radiotherapy

Field (based on PRISMA-P)	Content
	In people with an Astrocytoma/ Oligoastrocytoma/ Oligodendroglioma: • surgery/biopsy + radiotherapy In all groups, comparator is standard of care versus standard of care plus one or more intervention therapy
Outcomes and prioritisation	<u>Critical outcomes:</u> • overall survival. • progression-free survival / Time to progression • health Related Quality of Life <u>Important outcomes:</u> • neurological adverse events ○ wound infections • RTOG grade 3 and/or 4 toxicity • CTCAE grade 3 and/or 4 toxicity • fatigue (somnolence) • cognitive function
Eligibility criteria – study design	Only published full text English language papers Systematic reviews RCTs (Phase III) Cohort where RCTs are not available No sample size criteria, 1977 publication date justified because of changes in radiotherapy technique in this year making comparisons before this not standard of care.

Field (based on PRISMA-P)	Content
Other inclusion exclusion criteria	The following list of tumour types: • neuronal and mixed-neuronal-glial tumours • tumours of the pineal region • embryonal tumours • tumours of the cranial and paraspinal nerves • melanocytic tumours • lymphomas • mesenchymal, histiocytic, germc cell, sellar originating and chroid plexus tumours Populations with mixed initial / recurrent glioma will be extracted separately if possible. If results are not reported by initial / recurrent subgroup they will be included if they are more than 75% initial, included in the sister review of recurrent glioma if they are less than 25% initial and included in a 'mixed' review if more than 10% of the population has a glioma which is not described as either initial or recurrent or if the population is between 25% and 75% initial. Populations including children <16 included will be considered if the number of children is low (<10%) or the average age of the cohort is high (>40) or results are reported separately for children and adults Mixed treatment populations will not be considered unless treatment outcomes are reported separately for each treatment arm
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Pre-specified Stratification analyses: The following populations will be reviewed, analysed and presented separately where possible: • glioblastoma • MGMT Methylation Status

Field (based on PRISMA-P)	Content
	• age (>65/70 – papers have different cutoffs and their value for 'high age' will be used as long as it is 1 of these 2 values) • Karnofsky performance status (<70) • astrocytoma/ oligoastrocytoma/ oligodendroglioma • 1p\19q codeleted versus non-codeleted • IDH-1 or 2 mutations Pre-specified Subgroup analyses: • Age (>65/70) for astrocytoma/oligastrocytoma/ oligodendroglioma • Grade 3 versus Grade 4 adverse effects (ie analysing groups that have one type of adverse effect differently from the other type)
Selection process – duplicate screening/selection/analysis	Owing to high stakeholder interest in this question, a complete duplicate review was undertaken where two reviewers did duplicate screening of the search. In addition to this formal method of validation, the excluded study list is checked by the committee prior to making recommendations.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews and observational studies unless overall return is small

Field (based on PRISMA-P)	Content
	Supplementary search techniques: No supplementary search techniques were used
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment

Field (based on PRISMA-P)	Content
	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction was performed.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 2d – management of recurrent high-grade glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Managing Glioma

Field (based on PRISMA-P)	Content
Actual review question	2d What is the optimal management (surgery, radiotherapy, chemotherapy, combinations of these, or other therapies such as metformin or tumour-treating fields) of recurrent high-grade glioma?
Type of review question	Intervention
Objective of the review	This review is aimed at identifying whether any management strategy is more effective than any other in patients with high-grade glioma which has previously been systematically treated
Eligibility criteria – population/disease/condition/issue/domain	Adults with high-grade gliomas who have previously had a high-grade glioma
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Temozolomide (TMZ) • Procarbazine, CCNU (lomustine), vincristine (PCV) • Single agent nitrosourea (CCNU) or Carmustine (BCNU) • Other systemic anti-cancer agents (SACT) (including immunotherapy and viral therapy) • Metformin • Statins • Ketogenic diet • Valgancyclovir • Cannabis oil (Sativex) • Tumour-treating fields • Combinations of the above • Bevacizumab • Surgery (meaning re-resection after first wasn't comprehensive enough) • Radiotherapy (RT) [3D conformal RT; intensity-modulated radiation therapy (IMRT); volumetric modulated arc radiotherapy (VAMT); tomotherapy; stereotactic RT; proton beam treatment; carbon ion treatment; boron neutron capture; chemoradiation; sequential radiochemotherapy; stereotactic radiosurgery (SRS)]

Field (based on PRISMA-P)	Content
	• Gliadel wafers (carmustine) • Combinations of the above
Eligibility criteria – comparator(s)/control or reference (gold) standard	There is no accepted comparator in this field. Consequently any of the following comparisons will be accepted: • any intervention versus best supportive care (BSC) • any specific intervention versus clinicians' choice of intervention • any intervention versus any other intervention
Outcomes and prioritisation	<u>Critical outcomes:</u> • overall survival (OS) • progression free survival/time to progression (PFS/TTP) • health related quality of life (HRQoL) <u>Important outcomes:</u> • neurological adverse events • wound infections • RTOG grade 3 and/or grade 4 toxicity • CTAE grade 3 and/or grade 4 toxicity • fatigue (somnolence) • cognitive function
Eligibility criteria – study design	Only published full text English language papers Systematic reviews RCTs

Field (based on PRISMA-P)	Content
Other inclusion exclusion criteria	• Second new surgery • Children and young people under 16 years old The following list of tumour types: • neuronal and mixed neuronal-glial tumours • tumours of the pineal region • embryonal tumours • tumours of the cranial and paraspinal nerves • melanocytic tumours • lymphomas • mesenchymal, histiocytic, germ cell, sellar originating and choroid plexus tumours. • Populations with mixed initial / recurrent glioma will be extracted separately if possible. If results are not reported by initial / recurrent subgroup they will be included if they are more than 75% recurrent, included in the sister review of initial glioma if they are less than 25% recurrent and included in a 'mixed' review if more than 10% of the population has a glioma which is not described as either initial or recurrent or if the population is between 25% and 75% initial. • Populations including children <16 included will be considered if the number of children is low (<10%) or the average age of the cohort is high (>40) or results are reported separately for children and adults. • Mixed treatment populations will not be considered unless treatment outcomes are reported separately for each treatment arm.
Proposed sub-group analysis	• Age (>65/70 – papers report different thresholds for their definition of 'high age' and both of these age cutoffs will be considered) • IDH 1 or 2 mutant glioma (1p/19q codeleted oligodendroglioma versus noncodelteted astrocytomas) • MGMT methylation • Grade III versus grade IV

Field (based on PRISMA-P)	Content
	• Primary versus transformed/secondary
Selection process – duplicate screening/selection/analysis	Dual sifting was performed by both systematic reviewers. Data extraction and quality appraisal was performed by one systematic reviewer. In order to ensure accuracy, all results are checked by a senior systematic reviewer and the excluded study list is checked by the committee prior to making recommendations.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews unless overall return is small. Date cutoff of 1990 for all publications, as this is when TMZ came in and as TMZ is recommended in NICE Technology Appraisal it would not be possible to consider evidence before this. Further date cutoff of 2000 for pharmaceutical-funded Phase II studies as there is major risk of bias in these trials which do not make it to Phase III. Supplementary search techniques: No supplementary search techniques were used
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see Appendix B of the full evidence report

Field (based on PRISMA-P)	Content
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction was performed on at least 10% of the records.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 2b – resection of glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Managing glioma
Actual review question	2b Which surgical adjuncts optimise maximal safe resection of glioma?
Type of review question	Intervention
Objective of the review	Adjuncts to surgery have been introduced to attempt to help maximise the extent and safety of tumour resection, including 5-ALA fluorescence, awake craniotomy with electrophysiological stimulation, intra-operative ultrasound and intra-operative MRI. This review will examine the effect of these adjunctive techniques on neurosurgical resection of gliomas and the evidence base for their usage.
Eligibility criteria – population/disease/condition/issue/domain	Adults due to undergo surgical resection for glioma (Primary presentation or first surgery) • Low-grade glioma

Field (based on PRISMA-P)	Content
	• High-grade glioma • Mixed glioma

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Surgical resection guided by:
	• 5-ALA (Gliolan)
	• awake craniotomy
	  ○ subcortical stimulation
	  ○ cortical stimulation
	  ○ bipolar stimulation
	  ○ mono-polar stimulation
	• intraoperative ultrasound
	• intraoperative MRI
	• endoscopic resection
	• BrainPath
	• MRI ablation
	
	• combinations of the above, for example awake craniotomy and 5-ALA

Eligibility criteria – comparator(s)/control or reference (gold) standard	• Standard craniotomy with standard neuronavigation techniques (eg microscope) • Advanced technique (ie those in the list of interventions) compared against a different advanced technique
Outcomes and prioritisation	<u>Critical outcomes:</u> • overall survival. • gross total resection margins (as determined by post-operative MRI)

Field (based on PRISMA-P)	Content

	• progression-free survival
	• neurological function
	  ○ Karnofsky performance status
	• Neurological Function Scale
	• language
	<u>Important outcomes:</u>
	• treatment-related mortality
	• treatment-related morbidity:
	  ○ wound infection
	• length of surgery
	• <u>Of limited importance:</u>
	• epilepsy / seizure control

Eligibility criteria – study design	• Only published full text papers in English language • Systematic reviews • RCTs except in the case of cortical stimulation where: • Comparative cohort (>30 participants per arm) • Only include papers from 2000 or later, as this date is when standard craniotomy with neuronavigation techniques started to be used – anything before this date will be of no use as it will not be standard of care
Other exclusion criteria	Children and young people (under 16 years old) Recurrent high or low-grade glioma The following list of tumour types: • neuronal and mixed neuronal-glial tumours

Field (based on PRISMA-P)	Content
	• tumours of the pineal region • embryonal tumours • tumours of the cranial and paraspinal nerves • melanocytic tumours • lymphomas • mesenchymal, histiocytic, germ cell, sellar originating and choroid plexus tumours.
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Stratification: • low-grade glioma • high-grade glioma
Selection process – duplicate screening/selection/analysis	No duplicate screening/selection/analysis will be undertaken for this review as the topic is so technically complex that the clinical advisor is required to support the reviewer, and is therefore judged to be performing the quality assurance function of a conventional dual sift. In order to ensure accuracy, all results are checked by a senior systematic reviewer and the excluded study list is checked by the committee prior to making recommendations.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase

Field (based on PRISMA-P)	Content
	Limits (e.g. date, study design): Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews and observational studies unless overall return is small Supplementary search techniques: No supplementary search techniques were used Key papers: Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. The lancet oncology. 2006 May 31; 7(5):392-401. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. Journal of Clinical Oncology. 2012 Apr 23; 30(20):2559-65. Leuthardt EC, Lim CC, Shah MN, Evans JA, Rich KM, Dacey RG, Tempelhoff R, Chicoine MR. Use of movable high-field-strength intraoperative magnetic resonance imaging with awake craniotomies for resection of gliomas: preliminary experience. Neurosurgery. 2011 Jul 1; 69(1):194-206. Unsgård G, Solheim O, Lindseth F, Selbekk T. Intra-operative imaging with 3D ultrasound in neurosurgery. InIntraoperative Imaging 2011 (pp. 181-186). Springer Vienna.
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist:

Field (based on PRISMA-P)	Content
	• ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.80 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction was performed on at least 10% of the records.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
	Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 5a – follow-up for glioma

Field (based on PRISMA-P)	Content
Key area in the scope	Follow-up care after treatment for glioma, meningioma or brain metastases
Actual review question	5a What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?
Type of review question	Intervention

Field (based on PRISMA-P)	Content
Objective of the review	A glioma is the most common primary brain cancer in adults. Long term and progression free survival is very dependent on the type and grade of glioma, as well as the extent of resection and post-operative treatments. Oligodendrogliomas have a more favourable outcome than Astrocytomas and molecular markers pay an increasing role in predicting the behaviour and treatment of these tumours. Asymptomatic / untreated gliomas may only require follow up with regular MRI scans (or CT for those unable to tolerate MRIs) Scanning routinely has costs to healthcare resources, patient time and potentially psychological health as well as excess radiation in those imaged with CT scan. Early detection and treatment of recurrence improves outcomes but is associated with higher morbidity. If routine imaging is recommended, the preferred image modality, frequency and duration of scanning is uncertain given the different subtypes of gliomas.
Eligibility criteria – **population**/disease/condition/issue/domain	Adults treated for glioma
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Any follow-up protocol including duration and frequency of any tests (e.g., MRI/CT scans)
Eligibility criteria – **comparator(s)/**control or reference (gold) standard	• Any other follow-up protocol • No follow up (wait until patient reports symptoms of recurrence)
Outcomes and prioritisation	Critical: • cognitive function, • treatment for recurrence • overall survival, • numbers of patients with symptomatic versus asymptomatic presentation Important:

Field (based on PRISMA-P)	Content
	• health-related quality of life
Eligibility criteria – **study design**	Only published full text papers Systematic reviews RCTs Comparative observational studies
Other inclusion **exclusion criteria**	We will include papers that have more than 90% of patients who have been treated for glioma
Proposed sensitivity/**sub-group analysis**, or meta-regression	Adults treated for: • high-grade versus low-grade at initial presentation • grade I versus II versus III versus IIII
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Dual sifting, quality assessment and data extraction was not performed as the review was not prioritised for dual extraction.
Data management (software)	If pairwise meta-analyses undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting.

Field (based on PRISMA-P)	Content
	Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews and cohort studies unless overall return is small Date limit: 1990 (CT/MRI not available/comparable to present time before 1990) Supplementary search techniques: No supplementary search techniques were used
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	NA
Search strategy – for one database	For details please see Appendix B of the full evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D.
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.80 and 1.2 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. No evidence was identified. No explorations of publication bias were therefore undertaken.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists

Field (based on PRISMA-P)	Content
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Appendix B – Literature search strategies

Literature search strategy for review 1a - imaging for suspected glioma and meningioma

Date of initial search: 30/03/2017

Database: Embase 1974 to 2017 March 29, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017
Database: Embase 1974 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp glioma/ or exp astrocytoma/ or oligodendroglioma/
2	exp Glioblastoma/
3	1 or 2 use ppez
4	exp glioma/ use oemezd or exp astrocytoma/ use oemezd
5	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
6	or/3-5
7	Meningioma/ use ppez
8	Meningeal Neoplasms/ use ppez
9	exp meningioma/ use oemezd
10	meningioma*.tw.
11	(mening* adj3 (neoplas* or cancer* or carcin* or tumo* or malign* or h?emangiopericytoma* or h?emangioblastoma*)).tw.
12	or/7-11
13	6 or 12
14	Diagnostic Imaging/ use ppez
15	diagnostic imaging/ use oemezd
16	exp Neuroimaging/ use ppez
17	exp neuroimaging/ use oemezd
18	Multimodal Imaging/ use ppez
19	multimodal imaging/ use oemezd
20	Radionuclide Imaging/ use ppez
21	exp brain scintiscanning/ use oemezd
22	Perfusion Imaging/ use ppez
23	Neuronal Tract-Tracers/ use ppez
24	neuronal tract tracer/ use oemezd
25	exp Magnetic Resonance Imaging/ use ppez
26	exp nuclear magnetic resonance imaging/ use oemezd
27	Diffusion Magnetic Resonance Imaging/ use ppez
28	exp Magnetic Resonance Spectroscopy/ use ppez
29	proton nuclear magnetic resonance/ use oemezd
30	magnetic resonance.tw.
31	(MRI or MR*1 or NMR*1).tw.
32	(MR adj2 (imag* or neuroimag* or scan* or spectroscop* or elastogra* or examination)).tw.
33	(magnet* adj2 (imag* or neuroimag* or spectroscop* or scan* or elastogra* or examination)).tw.
34	(magneti?ation adj2 imaging).tw.
35	exp Positron-Emission Tomography/ use ppez

#	Searches
36	positron emission tomography/ use oemezd
37	computer assisted emission tomography/ use oemezd
38	(PET adj (scan* or imag* or examination)).tw.
39	positron emission tomogra*.tw.
40	(PET or PET-CT or PETCT or PET MR*1).tw.
41	(spin adj2 (imag* or neuroimag* or spectroscop* or resonance)).tw.
42	(advanced adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
43	(chemical shift adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
44	(structural adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
45	(functional adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
46	(diffusion adj2 (imag* or spectroscop* or tractogra* or neuroimag* or scan* or MR* or NMR*)).tw.
47	(perfusion adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR* or CT)).tw.
48	((axial or transverse) adj2 (imag* or neuroimag* or scan* or CT or tomogra*)).tw.
49	(T1W*1 or T2W*1).tw.
50	((T1 or T2) adj2 (imag* or neuroimag* or scan* or MR* or NMR*)).tw.
51	(DWI or DTI or DSC or DCE or ASL).tw.
52	exp nuclear magnetic resonance imaging agent/ use oemezd
53	dynamic contrast.tw.
54	Fluorodeoxyglucose F18/ use ppez
55	fluorodeoxyglucose f 18/ use oemezd
56	("18F fluorodeoxyglucose" or FDG).tw.
57	Tyrosine/ use ppez
58	"18F fluoro ethyl tyrosine".tw.
59	18F FET.tw.
60	Methionine/ use ppez
61	methionine c 11/ use oemezd
62	((11C or "carbon 11") adj methionine).tw.
63	MET PET.tw.
64	Gadolinium DTPA/ use ppez
65	gadolinium pentetate/ use oemezd
66	gadolinium.tw.
67	or/14-66
68	13 and 67
69	limit 68 to english language
70	limit 69 to yr="2002-Current"
71	Letter/ use ppez
72	letter.pt. or letter/ use oemezd
73	note.pt.
74	editorial.pt.
75	Editorial/ use ppez
76	News/ use ppez
77	exp Historical Article/ use ppez
78	Anecdotes as Topic/ use ppez
79	Comment/ use ppez
80	Case Report/ use ppez
81	case report/ or case study/ use oemezd
82	(letter or comment*).ti.
83	or/71-82
84	randomized controlled trial/ use ppez
85	randomized controlled trial/ use oemezd
86	random*.ti,ab.
87	or/84-86
88	83 not 87
89	animals/ not humans/ use ppez
90	animal/ not human/ use oemezd
91	nonhuman/ use oemezd
92	exp Animals, Laboratory/ use ppez
93	exp Animal Experimentation/ use ppez
94	exp Animal Experiment/ use oemezd
95	exp Experimental Animal/ use oemezd

#	Searches
96	exp Models, Animal/ use ppez
97	animal model/ use oemezd
98	exp Rodentia/ use ppez
99	exp Rodent/ use oemezd
100	(rat or rats or mouse or mice).ti.
101	or/88-100
102	70 not 101
103	Meta-Analysis/
104	Meta-Analysis as Topic/
105	systematic review/
106	meta-analysis/
107	(meta analy* or metanaly* or metaanaly*).ti,ab.
108	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
109	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
110	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
111	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
112	(search* adj4 literature).ab.
113	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
114	cochrane.jw.
115	((pool* or combined) adj2 (data or trials or studies or results)).ab.
116	or/103-104,107,109-114 use ppez
117	or/105-108,110-115 use oemezd
118	or/116-117
119	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
120	119 use ppez
121	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
122	121 use ppez
123	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
124	123 use oemezd
125	120 or 122
126	124 or 125
127	Epidemiologic Studies/
128	Case Control Studies/
129	Retrospective Studies/
130	Cohort Studies/
131	Longitudinal Studies/
132	Follow-Up Studies/
133	Prospective Studies/
134	Cross-Sectional Studies/
135	or/127-134 use ppez
136	clinical study/
137	case control study/
138	family study/
139	longitudinal study/
140	retrospective study/
141	prospective study/
142	cohort analysis/
143	or/136-142 use oemezd
144	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
145	135 or 143 or 144
146	118 or 126 or 145
147	102 and 146
148	remove duplicates from 147

Date of initial search: 05/07/2017

Database: The Cochrane Library, Issue 3 of 12, March 2017

Date of re-run: 05/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	(glioma* or glioblastoma* or gliosarcoma* or astrocytoma* or astroblastoma* or oligodendroglioma* or oligodendrocytoma* or oligoastrocytoma* or GBM)
#3	(glial near/3 (neoplas* or cancer* or tumo* or carcin* or malign* or metasta*))
#4	{or #1-#3}
#5	MeSH descriptor: [Meningioma] explode all trees
#6	MeSH descriptor: [Meningeal Neoplasms] explode all trees
#7	meningioma*
#8	(mening* near/3 (neoplas* or cancer* or carcin* or tumo* or malign* or metasta*))
#9	{or #5-#8}
#10	#4 or #9
#11	MeSH descriptor: [Diagnostic Imaging] this term only
#12	MeSH descriptor: [Neuroimaging] explode all trees
#13	MeSH descriptor: [Multimodal Imaging] explode all trees
#14	MeSH descriptor: [Radionuclide Imaging] this term only
#15	MeSH descriptor: [Perfusion Imaging] explode all trees
#16	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#17	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
#18	MeSH descriptor: [Magnetic Resonance Spectroscopy] explode all trees
#19	(MRI or MR*1 or NMR*1)
#20	(MR near/2 (imag* or neuroimag* or scan* or spectroscop* or elastogra* or examination))
#21	(magnet* near/2 (imag* or neuroimag* or spectroscop* or scan* or elastogra* or examination))
#22	(magneti?ation near/2 imaging)
#23	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#24	(PET near (scan* or imag* or examination))
#25	positron emission tomogra*
#26	(PET or PET-CT or PETCT or PET MR*1)
#27	MeSH descriptor: [Spin Labels] explode all trees
#28	(spin near/2 (imag* or neuroimag* or spectroscop* or resonance))
#29	(advanced near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#30	(chemical shift near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#31	(structural near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#32	(functional near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#33	(diffusion near/2 (imag* or spectroscop* or tractogra* or neuroimag* or scan* or MR* or NMR*))
#34	(perfusion near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR* or CT))
#35	((axial or transverse) near/2 (imag* or neuroimag* or scan* or CT or tomogra*))
#36	(T1W*1 or T2W*1)
#37	((T1 or T2) near/2 (imag* or neuroimag* or scan* or MR* or NMR*))
#38	(DWI or DTI or DSC or DCE or ASL)
#39	dynamic contrast
#40	MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
#41	("18F fluorodeoxyglucose" or FDG)
#42	MeSH descriptor: [Tyrosine] this term only
#43	"18F fluoro ethyl tyrosine"
#44	18F FET
#45	MeSH descriptor: [Methionine] this term only
#46	((11C or "carbon 11") and methionine)
#47	MET PET

ID	Search
#48	MeSH descriptor: [Gadolinium DTPA] this term only
#49	gadolinium
#50	{or #11-#49}
#51	#10 and #50

Literature search strategy for review 1d – molecular markers to inform prognosis / guide treatment

Date of initial search: 27/06/2017

Database: Embase 1980 to 2017 Week 26, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017
Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp glioma/ or exp astrocytoma/ or oligodendroglioma/
2	exp Glioblastoma/
3	1 or 2 use ppez
4	exp glioma/ use emez or exp astrocytoma/ use emez
5	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
6	or/3-5
7	Proto-Oncogene Proteins B-raf/ use ppez
8	B Raf kinase/ use emez
9	(BRAF or B-RAF or NS7 or RAFB1).tw.
10	or/7-9
11	Receptor, Epidermal Growth Factor/ use ppez
12	epidermal growth factor receptor/ use emez
13	(epidermal growth factor or egf receptor or (growth factor adj3 receptor) or (erbb-1 adj3 receptor) or (erbb-1 adj3 protein)).tw.
14	(EGFR or ERBB or HER1 or mENA or ERBB1 or PIG61 or NISBD2).tw.
15	or/11-14
16	Telomerase/ use ppez
17	telomerase reverse transcriptase/ use emez
18	telomerase reverse transcriptase.tw.
19	(TERT or hTERT or TERTmut or TP2 or TRT or CMM9 or EST2 or TCS1 or hTRT or DKCA2 or DKCB4 or hEST2 or PFBMFT1).tw.
20	or/16-19
21	10 or 15 or 20
22	6 and 21
23	6 and 10
24	exp Disease Free Survival/ use ppez
25	disease free survival/ use emez
26	survival.tw.
27	exp Prognosis/ use ppez
28	prognosis.tw.
29	exp Survival Rate/ use ppez
30	survival rate/ use emez
31	or/24-30
32	exp Treatment Outcome/ use ppez
33	exp treatment outcome/ use emez
34	((treatment* or therap*) adj (outcome* or response*)).tw.
35	or/32-34
36	23 and (31 or 35)
37	22 and 31
38	36 or 37
39	limit 38 to english language

#	Searches
40	limit 39 to yr="2008 -Current"
41	Letter/ use ppez
42	letter.pt. or letter/ use emez
43	note.pt.
44	editorial.pt.
45	Editorial/ use ppez
46	News/ use ppez
47	exp Historical Article/ use ppez
48	Anecdotes as Topic/ use ppez
49	Comment/ use ppez
50	Case Report/ use ppez
51	case report/ or case study/ use emez
52	(letter or comment*).ti.
53	or/41-52
54	randomized controlled trial/ use ppez
55	randomized controlled trial/ use emez
56	random*.ti,ab.
57	or/54-56
58	53 not 57
59	animals/ not humans/ use ppez
60	animal/ not human/ use emez
61	nonhuman/ use emez
62	exp Animals, Laboratory/ use ppez
63	exp Animal Experimentation/ use ppez
64	exp Animal Experiment/ use emez
65	exp Experimental Animal/ use emez
66	exp Models, Animal/ use ppez
67	animal model/ use emez
68	exp Rodentia/ use ppez
69	exp Rodent/ use emez
70	(rat or rats or mouse or mice).ti.
71	or/58-70
72	40 not 71
73	remove duplicates from 72

Date of initial search: 27/06/2017

Database: The Cochrane Library, Issue 6 of 12, June 2017

Date of re-run: 07/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*)
#3	{or #1-#2}
#4	MeSH descriptor: [Proto-Oncogene Proteins B-raf] this term only
#5	(BRAF or B-RAF or NS7 or RAFB1)
#6	MeSH descriptor: [Receptor, Epidermal Growth Factor] this term only
#7	(epidermal growth factor or egf receptor or (growth factor near/3 receptor) or (erbb-1 near/3 receptor) or (erbb-1 near/3 protein))
#8	(EGFR or ERBB or HER1 or mENA or ERBB1 or PIG61 or NISBD2)
#9	MeSH descriptor: [Telomerase] this term only
#10	(telomerase and reverse and transcriptase)
#11	(TERT or hTERT or TERTmut or TP2 or TRT or CMM9 or EST2 or TCS1 or hTRT or DKCA2 or DKCB4 or hEST2 or PFBMFT1)

ID	Search
#12	{or #3-#11}
#13	#3 and #12 Publication Year from 2008 to 2017

Literature search strategy for review 1c – timing and extend of initial surgery for low-grade glioma

Systematic reviews and RCTs

Date of initial search: 11/07/2017

Database: Embase 1980 to 2017 Week 28, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017

Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/su use ppez or exp Astrocytoma/su use ppez or Oligodendroglioma/su use ppez
2	exp glioma/su use emez or exp astrocytoma/su use emez
3	1 or 2
4	Neoplasm Grading/ use ppez
5	cancer grading/ use emez
6	4 or 5
7	3 and 6
8	((grade* 2 or two or II) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
9	((grade* 1 or one or I) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oliogastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
10	((low-grade or non-invasive or mixed or premalignant or pre-malignant or atypical or discrete or diffuse or local* or myxopapillary or pilocytic or cerebellar or pilomyxoid or angiocentric or fibrillary or protoplasmic or chordoid) adj3 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
11	or/7-10
12	exp Neurosurgical Procedures/ use ppez
13	Neurosurgery/ use ppez
14	exp Biopsy/ use ppez
15	Watchful Waiting/ use ppez
16	Observation/ use ppez
17	exp Monitoring, Physiologic/ use ppez
18	or/12-17
19	exp neurosurgery/ use emez
20	brain biopsy/ use emez
21	craniotomy/ use emez
22	watchful waiting/ use emez
23	observation/ use emez
24	physiologic monitoring/ use emez
25	patient monitoring/ use emez
26	or/19-25
27	18 or 26
28	(craniotom* or craniectom* or lesionectom*).tw.

#	Searches
29	((partial or subtotal or gross or total or maxim* or extent or extensive or complete or greater or awake or wakeful) adj3 (ablat* or biops* or cytoreduc* or debulk* or excis* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*)).tw.
30	((watch* adj2 wait*) or (wait adj2 see)).tw.
31	((active or expect* or watch* or patient* or regular* symptom*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
32	or/27-31
33	11 and 32
34	limit 33 to english language
35	limit 34 to yr="1980 –Current"
36	Letter/ use ppez
37	letter.pt. or letter/ use emez
38	note.pt.
39	editorial.pt.
40	Editorial/ use ppez
41	News/ use ppez
42	exp Historical Article/ use ppez
43	Anecdotes as Topic/ use ppez
44	Comment/ use ppez
45	Case Report/ use ppez
46	case report/ or case study/ use emez
47	(letter or comment*).ti.
48	or/36-47
49	randomized controlled trial/ use ppez
50	randomized controlled trial/ use emez
51	random*.ti,ab.
52	or/49-51
53	48 not 52
54	animals/ not humans/ use ppez
55	animal/ not human/ use emez
56	nonhuman/ use emez
57	exp Animals, Laboratory/ use ppez
58	exp Animal Experimentation/ use ppez
59	exp Animal Experiment/ use emez
60	exp Experimental Animal/ use emez
61	exp Models, Animal/ use ppez
62	animal model/ use emez
63	exp Rodentia/ use ppez
64	exp Rodent/ use emez
65	(rat or rats or mouse or mice).ti.
66	or/53-65
67	35 not 66
68	Meta-Analysis/
69	Meta-Analysis as Topic/
70	systematic review/
71	meta-analysis/
72	(meta analy* or metanaly* or metaanaly*).ti,ab.
73	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
74	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
75	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77	(search* adj4 literature).ab.
78	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
79	cochrane.jw.
80	((pool* or combined) adj2 (data or trials or studies or results)).ab.
81	or/68-69,72,74-79 use ppez
82	or/70-73,75-80 use emez
83	or/81-82

#	Searches
84	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
85	84 use ppez
86	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
87	86 use ppez
88	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
89	88 use emez
90	85 or 87
91	89 or 90
92	83 or 91
93	67 and 92
94	remove duplicates from 93

Observational Studies

Date of initial search: 11/07/2017

Database: Embase 1980 to 2017 Week 28, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017

Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/su use ppez or exp Astrocytoma/su use ppez or Oligodendroglioma/su use ppez
2	exp glioma/su use emez or exp astrocytoma/su use emez
3	1 or 2
4	Neoplasm Grading/ use ppez
5	cancer grading/ use emez
6	4 or 5
7	3 and 6
8	((grade* 2 or two or II) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
9	((grade* 1 or one or I) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
10	((low-grade or non-invasive or mixed or premalignant or pre-malignant or atypical or discrete or diffuse or local* or myxopapillary or pilocytic or cerebellar or pilomyxoid or angiocentric or fibrillary or protoplasmic or chordoid) adj3 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
11	or/7-10
12	exp Neurosurgical Procedures/ use ppez
13	Neurosurgery/ use ppez
14	exp Biopsy/ use ppez
15	Watchful Waiting/ use ppez
16	Observation/ use ppez
17	exp Monitoring, Physiologic/ use ppez
18	or/12-17
19	exp neurosurgery/ use emez
20	brain biopsy/ use emez
21	craniotomy/ use emez

#	Searches
22	watchful waiting/ use emez
23	observation/ use emez
24	physiologic monitoring/ use emez
25	patient monitoring/ use emez
26	or/19-25
27	18 or 26
28	(craniotom* or craniectom* or lesionectom*).tw.
29	((partial or subtotal or gross or total or maxim* or extent or extensive or complete or greater or awake or wakeful) adj3 (ablat* or biops* or cytoreduc* or debulk* or excis* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*)).tw.
30	((watch* adj2 wait*) or (wait adj2 see)).tw.
31	((active or expect* or watch* or patient* or regular* symptom*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
32	or/27-31
33	11 and 32
34	limit 33 to english language
35	limit 34 to yr="1980 -Current"
36	Letter/ use ppez
37	letter.pt. or letter/ use emez
38	note.pt.
39	editorial.pt.
40	Editorial/ use ppez
41	News/ use ppez
42	exp Historical Article/ use ppez
43	Anecdotes as Topic/ use ppez
44	Comment/ use ppez
45	Case Report/ use ppez
46	case report/ or case study/ use emez
47	(letter or comment*).ti.
48	or/36-47
49	randomized controlled trial/ use ppez
50	randomized controlled trial/ use emez
51	random*.ti,ab.
52	or/49-51
53	48 not 52
54	animals/ not humans/ use ppez
55	animal/ not human/ use emez
56	nonhuman/ use emez
57	exp Animals, Laboratory/ use ppez
58	exp Animal Experimentation/ use ppez
59	exp Animal Experiment/ use emez
60	exp Experimental Animal/ use emez
61	exp Models, Animal/ use ppez
62	animal model/ use emez
63	exp Rodentia/ use ppez
64	exp Rodent/ use emez
65	(rat or rats or mouse or mice).ti.
66	or/53-65
67	35 not 66
68	Epidemiologic Studies/
69	Case Control Studies/
70	Retrospective Studies/
71	Cohort Studies/
72	Longitudinal Studies/
73	Follow-Up Studies/
74	Prospective Studies/
75	Cross-Sectional Studies/
76	or/68-75 use ppez
77	clinical study/
78	case control study/

#	Searches
79	family study/
80	longitudinal study/
81	retrospective study/
82	prospective study/
83	cohort analysis/
84	or/77-83 use emez
85	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section*) adj3 (stud* or research or analys*)).ti.
86	76 or 84 or 85
87	67 and 86
88	remove duplicates from 87

Date of initial search: 11/07/2017

Database: The Cochrane Library, Issue 7 of 12, July 2017

Date of re-run: 07/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees and with qualifier(s): [Surgery - SU]
#2	MeSH descriptor: [Astrocytoma] explode all trees and with qualifier(s): [Surgery - SU]
#3	MeSH descriptor: [Oligodendroglioma] explode all trees and with qualifier(s): [Surgery - SU]
#4	{or #1-#3}
#5	MeSH descriptor: [Neoplasm Grading] this term only
#6	#4 and #5
#7	((grade* 2 or two or II) near/3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#8	((grade* 1 or one or I) near/3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oliogastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#9	((low-grade or non-invasive or mixed or premalignant or pre-malignant or atypical or discrete or diffuse or local* or myxopapillary or pilocytic or cerebellar or pilomyxoid or angiocentric or fibrillary or protoplasmic or chordoid) near/3 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#10	{or #6-#9}
#11	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#12	MeSH descriptor: [Neurosurgery] this term only
#13	MeSH descriptor: [Biopsy] explode all trees
#14	MeSH descriptor: [Watchful Waiting] this term only
#15	MeSH descriptor: [Observation] this term only
#16	MeSH descriptor: [Monitoring, Physiologic] explode all trees
#17	(craniotom* or craniectom* or lesionectom*)
#18	((partial or subtotal or gross or total or maxim* or extent or extensive or complete or greater or awake or wakeful) near/3 (ablat* or biops* or cytoreduc* or debulk* or excis* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*))
#19	((watch* near/2 wait*) or (wait near/2 see))
#20	((active or expect* or watch* or patient* or regular* symptom*) near/2 (manag* or monitor* or surveill* or observ* or control*))
#21	{or #11-#20}
#22	#10 and #21 Publication Year from 1980 to 2017

Literature search strategy for review 2a – further management of low-grade glioma

Date of initial search: 18/07/2017

Database(s): Embase 1980 to 2017 Week 29, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	((grade* 2 or two or II) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
2	((grade* 1 or one or I) adj3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oliogastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
3	((low-grade or low-grade or non invasive or non-invasive or mixed or premalignant or pre-malignant or atypical or discrete or diffuse or local* or myxopapillary or pilocytic or cerebellar or pilomyxoid or angiocentric or fibrillary or protoplasmic or chordoid) adj3 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*)).tw.
4	LGG.tw.
5	or/1-4
6	(dt or rt or su or th).fs.
7	Neurosurgery/ use ppez
8	exp Neurosurgical Procedures/ use ppez
9	Surgical Procedures, Operative/ use ppez
10	exp Biopsy/ use ppez
11	exp Stereotaxic Techniques/ use ppez
12	Neuroendoscopy/ use ppez
13	exp cancer surgery/ use emez
14	exp neurosurgery/ use emez
15	tumor ablation/ use emez
16	brain biopsy/ use emez
17	craniotomy/ use emez
18	exp stereotactic procedure/ use emez
19	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or remov* or aspirat* or shunt*)).tw.
20	(neurosurg* or craniotom* or craniectom* or lesionectom*).tw.
21	(ventriculostom* or ventriculocisternostom*).tw.
22	((intra-operat* or intraoperat*) adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
23	or/6-22
24	exp Radiotherapy/ use ppez
25	exp radiotherapy/ use emez
26	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
27	((proton* or particle* or hadron or neutron) adj2 (therap* or treatment* or procedure* or modalit*)).tw.
28	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT or CPT).tw.
29	Radiation Oncology/ use ppez
30	(chemoradiotherap* chemo-radiotherap* or chemoradiat* or chemo-radiat* or chemoirradiat* or chemo-irradiat* or radiochemotherap* or radio-chemotherap*).tw.
31	or/24-30
32	exp Antineoplastic Agents/ use ppez
33	exp antineoplastic agent/ use emez
34	exp Combined Modality Therapy/ use ppez
35	multimodality cancer therapy/ use emez
36	exp combination drug therapy/ use emez
37	antineoplastic protocols/ use ppez or antineoplastic combined chemotherapy protocols/ use ppez or drug therapy, combination/ use ppez

#	Searches
38	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
39	CCRT.tw.
40	exp chemotherapy/ use emez
41	chemotherap*.tw.
42	((anticancer or anti-cancer or systemic or antineoplas* or anti-neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
43	PCV.tw.
44	Lomustine/ use ppez
45	lomustine/ use emez
46	(belustine or ccnu or cecenu or ceenu or lomustine or nsc?79037).tw.
47	Procarbazine/ use ppez
48	procarbazine/ use emez
49	(matulan or natulan or procarbazine).tw.
50	temozolomide/ use emez
51	(temozolomide or temodal or temodar).tw.
52	Vincristine/ use ppez
53	vincristine/ use emez
54	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
55	or/32-54
56	Watchful Waiting/ use ppez
57	watchful waiting/ use emez
58	Observation/ use ppez
59	observation/ use emez
60	physiologic monitoring/ use emez
61	patient monitoring/ use emez
62	((watch* adj2 wait*) or (wait adj2 see)).tw.
63	((active or expect* or watch* or patient* or regular* symptom*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
64	or/56-63
65	23 or 31 or 55 or 64
66	5 and 65
67	Letter/ use ppez
68	letter.pt. or letter/ use emez
69	note.pt.
70	editorial.pt.
71	Editorial/ use ppez
72	News/ use ppez
73	exp Historical Article/ use ppez
74	Anecdotes as Topic/ use ppez
75	Comment/ use ppez
76	Case Report/ use ppez
77	case report/ or case study/ use emez
78	(letter or comment*).ti.
79	or/67-78
80	randomized controlled trial/ use ppez
81	randomized controlled trial/ use emez
82	random*.ti,ab.
83	or/80-82
84	79 not 83
85	animals/ not humans/ use ppez
86	animal/ not human/ use emez
87	nonhuman/ use emez
88	exp Animals, Laboratory/ use ppez
89	exp Animal Experimentation/ use ppez
90	exp Animal Experiment/ use emez
91	exp Experimental Animal/ use emez
92	exp Models, Animal/ use ppez
93	animal model/ use emez
94	exp Rodentia/ use ppez

#	Searches
95	exp Rodent/ use emez
96	(rat or rats or mouse or mice).ti.
97	or/84-96
98	66 not 97
99	limit 98 to english language
100	limit 99 to yr="1985 -Current"
101	Meta-Analysis/
102	Meta-Analysis as Topic/
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
108	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
109	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
110	(search* adj4 literature).ab.
111	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
112	cochrane.jw.
113	((pool* or combined) adj2 (data or trials or studies or results)).ab.
114	or/101-102,105,107-112 use ppez
115	or/103-106,108-113 use emez
116	or/114-115
117	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
118	117 use ppez
119	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
120	119 use ppez
121	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
122	121 use emez
123	118 or 120
124	122 or 123
125	116 or 124
126	100 and 125
127	remove duplicates from 126

Date of initial search: 18/07/2017

Database: The Cochrane Library, Issue 7 of 12, July 2017

Date of re-run: 07/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	((grade* 2 or two or II) near/3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#2	((grade* 1 or one or I) near/3 (glioma* or astrocytoma* or ganglioglioma* or oligodendroglioma* or oliogastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#3	((low-grade or low-grade or non invasive or non-invasive or mixed or premalignant or pre-malignant or atypical or discrete or diffuse or local* or myxopapillary or pilocytic or cerebellar or pilomyxoid or angiocentric or fibrillary or protoplasmic or chordoid) near/3 (glioma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma* or oligo-astrocytoma* or xanthoastrocytoma*))
#4	LGG
#5	{or #1-#4} Publication Year from 1985 to 2017
#6	MeSH descriptor: [Neurosurgery] this term only

ID	Search
#7	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#8	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#9	MeSH descriptor: [Biopsy] explode all trees
#10	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#11	MeSH descriptor: [Neuroendoscopy] this term only
#12	(((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) near/2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or remov* or aspirat* or shunt*)) or neurosurg* or craniotom* or craniectom* or lesionectom* or ventriculostom* or ventriculocisternostom*)
#13	((intra-operat* or intraoperat*) near/3 (technolog* or modalit* or procedur* or technique* or method*))
#14	MeSH descriptor: [Radiotherapy] explode all trees
#15	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron)
#16	((proton* or particle* or hadron or neutron) near/2 (therap* or treatment* or procedure* or modalit*))
#17	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT or CPT)
#18	(chemo*radiotherap* or chemo*radiat* or chemo*irradiat* or radio*chemotherap*)
#19	MeSH descriptor: [Antineoplastic Agents] explode all trees
#20	MeSH descriptor: [Combined Modality Therapy] explode all trees
#21	MeSH descriptor: [Antineoplastic Protocols] explode all trees
#22	MeSH descriptor: [Drug Therapy, Combination] this term only
#23	((combin* or concomitant or concurrent) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#24	chemotherap*
#25	((anti*cancer or systemic or anti*neoplas* or cytotoxi*) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#26	PCV
#27	MeSH descriptor: [Lomustine] explode all trees
#28	(belustine or ccnu or cecenu or ceenu or lomustine)
#29	MeSH descriptor: [Procarbazine] explode all trees
#30	(matulan or natulan or procarbazine)
#31	(temozolomide or temodal or temodar)
#32	MeSH descriptor: [Vincristine] explode all trees
#33	(citomid or farmistin or leucocristine or oncovin* or onkocristin or vincasar or vincristin* or vincrisul or vintec)
#34	MeSH descriptor: [Watchful Waiting] this term only
#35	MeSH descriptor: [Monitoring, Physiologic] explode all trees
#36	((watch* near/2 wait*) or (wait near/2 see))
#37	((active or expect* or watch* or patient* or regular* symptom*) near/2 (manag* or monitor* or surveill* or observ* or control*))
#38	{or #6-#37}
#39	#5 and #38

Literature search strategy for review 2c – initial management of high-grade glioma

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to

ID	Search
1	exp Glioma/ or exp Astrocytoma/ or Oligodendroglioma/
2	Anaplasia/ or Neoplasm Recurrence, Local/
3	secondary.fs.
4	2 or 3
5	1 and 4
6	exp Glioblastoma/

ID	Search
7	5 or 6
8	(glioblastoma* or GBM).tw.
9	gliosarcoma*.tw.
10	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
11	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
12	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
13	or/7-12
14	Neurosurgery/
15	exp Neurosurgical Procedures/
16	Surgical Procedures, Operative/
17	exp Stereotaxic Techniques/
18	Neuroendoscopy/
19	surgery.fs.
20	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
21	(neurosurg* or craniotom* or craniectom*).tw.
22	(ventriculostom* or ventriculocisternostom*).tw.
23	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
24	or/14-23
25	exp Radiotherapy/
26	radiotherapy.fs.
27	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
28	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
29	Radiation Oncology/
30	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
31	or/25-30
32	exp Antineoplastic Agents/
33	exp Combined Modality Therapy/
34	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or drug therapy, combination/
35	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
36	CCRT.tw.
37	stupp.tw.
38	exp Antibodies, Monoclonal/
39	exp Angiogenesis Inhibitors/
40	exp Vascular Endothelial Growth Factors/
41	Cancer Vaccines/
42	exp Immunotherapy/
43	Oncolytic Virotherapy/
44	exp Antiviral Agents/
45	(virotherap* or anti?viral*).tw.
46	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
47	(anti?angiogenic or (angiogenesis and inhibit*)).tw.

ID	Search
48	vascular endothelial growth factor*.tw.
49	(VEGF or VEGFR or VEGF-R).tw.
50	drug therapy.fs.
51	chemotherap*.tw.
52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
53	Bevacizumab/
54	(bevacizumab or altusan or avastin).tw.
55	exp Bleomycin/
56	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
57	Carboplatin/
58	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
59	Carmustine/
60	exp Absorbable Implants/
61	exp Drug Implants/
62	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
63	(cilcane or cilengitide or impetreve).tw.
64	Cisplatin/
65	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
66	Cyclophosphamide/
67	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
68	Cytarabine/
69	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
70	Dacarbazine/
71	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
72	Dactinomycin/
73	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
74	Etoposide/
75	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
76	Ganciclovir/
77	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
78	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
79	(DC?vax or (dentric cell? adj (vaccin* or immunotherap*))).tw.
80	Ifosfamide/
81	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
82	(Ipilimumab or yervoy).tw.
83	(irinotecan or campto*).tw.
84	Lomustine/
85	(belustine or ccnu or cecenu or ceenu or lomustine or nsc?79037).tw.
86	Methotrexate/
87	(amethopterin or methotrexate or mexate).tw.
88	Nimustine/
89	(acnu or nimustine or nsc?245382).tw.

ID	Search
90	(nivolumab or opdivo).tw.
91	Procarbazine/
92	(matulan or natulan or procarbazine).tw.
93	(rindopepimut or rintega).tw.
94	(sitimagene ceradenovec or cerepro).tw.
95	Tamoxifen/
96	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
97	(temozolomide or temodal or temodar).tw.
98	Teniposide/
99	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
100	Vinblastine/
101	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastin*).tw.
102	Vincristine/
103	(citomid or farmistin or leucocristine or oncovin? or onkocristin or pcv or vincasar or vincristin? or vincrisul or vintec).tw.
104	or/32-103
105	exp Metformin/
106	(dimethylbiguandine or glucophage or metformin).tw.
107	105 or 106
108	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
109	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlyglutaryl adj2 inhibitor*)).tw.
110	(atorvastatin or lipitor or liptonorm or ci?981).tw.
111	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
112	(meglutol or methylglutar* acid).tw.
113	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
114	(rosuvastatin or crestor or zd?4522).tw.
115	(simvastatin or mk?733 or synvinolin or zocor).tw.
116	or/108-115
117	Ketogenic Diet/
118	Caloric Restriction/
119	Diet, Carbohydrate-Restricted/
120	Diet, Protein-Restricted/

ID	Search
121	diet therapy.fs.
122	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
123	or/117-122
124	Cannabis/
125	exp Cannabinoids/
126	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
127	or/124-126
128	exp Electric Stimulation Therapy/
129	Electromagnetic Fields/
130	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
131	(TTField* or TTF or NovoTTF).tw.
132	or/128-131
133	Watchful Waiting/
134	Observation/
135	(watch* adj2 wait*).tw.
136	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
137	(best supportive care or BSC).tw.
138	supportive care.tw.
139	or/133-138
140	or/24,31,104,107,116,123,127,132,139
141	13 and 140
142	limit 141 to english language
143	limit 142 to yr="1977 -Current"
144	Letter/
145	Editorial/
146	News/

ID	Search
147	exp Historical Article/
148	Anecdotes as Topic/
149	Comment/
150	Case Report/
151	(letter or comment* or abstracts).ti.
152	or/144-151
153	Randomized Controlled Trial/ or random*.ti,ab.
154	152 not 153
155	Animals/ not Humans/
156	exp Animals, Laboratory/
157	exp Animal Experimentation/
158	exp Models, Animal/
159	exp Rodentia/
160	(rat or rats or mouse or mice).ti.
161	or/154-160
162	143 not 161
163	randomized controlled trial.pt.
164	controlled clinical trial.pt.
165	pragmatic clinical trial.pt.
166	randomi#ed.ab.
167	placebo.ab.
168	drug therapy.fs.
169	randomly.ab.
170	trial.ab.
171	groups.ab.
172	or/163-171

ID	Search
173	Clinical Trials as topic.sh.
174	trial.ti.
175	or/163-167,169,173-174
176	162 and 175

Database: Cochrane Library, Issue 11 of 12, November 2016

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	MeSH descriptor: [Astrocytoma] explode all trees
#3	Oligodendroglioma
#4	{or #1-#3}
#5	MeSH descriptor: [Anaplasia] explode all trees
#6	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#7	#5 or #6
#8	#4 and #7
#9	MeSH descriptor: [Glioblastoma] explode all trees
#10	(glioblastoma* or GBM)
#11	gliosarcoma*
#12	((grade* 4 or four or IV) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*))
#13	((grade* 3 or three or III) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*))
#14	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligoastrocytoma*))
#15	{or #8-#14}
#16	MeSH descriptor: [Neurosurgery] explode all trees
#17	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#18	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#19	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#20	MeSH descriptor: [Neuroendoscopy] this term only
#21	Any MeSH descriptor with qualifier(s): [Surgery - SU]
#22	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) near/2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*))
#23	(neurosurg* or craniotom* or craniectom* or ventriculostom* or ventriculocisternostom*)
#24	(intraoperat* near/3 (technolog* or modalit* or procedur* or technique* or method*))
#25	{or #16-#24}
#26	MeSH descriptor: [Radiotherapy] explode all trees
#27	Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#28	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron)
#29	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT)
#30	(chemoradiotherap* or chemoradiat* or chemoirradiat* or radiochemotherap*)
#31	{or #26-#30}

ID	Search
#32	MeSH descriptor: [Antineoplastic Agents] explode all trees
#33	MeSH descriptor: [Combined Modality Therapy] explode all trees
#34	MeSH descriptor: [Antineoplastic Protocols] explode all trees
#35	MeSH descriptor: [Drug Therapy, Combination] explode all trees
#36	((combin* or concomitant or concurrent) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#37	(CCRT or stupp)
#38	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#39	MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#40	MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees
#41	MeSH descriptor: [Cancer Vaccines] explode all trees
#42	MeSH descriptor: [Immunotherapy] explode all trees
#43	MeSH descriptor: [Oncolytic Virotherapy] explode all trees
#44	MeSH descriptor: [Antiviral Agents] explode all trees
#45	(virotherap* or anti-viral*)
#46	((virus or viral or anti-virus or anti-viral) near/2 (therap* or treatment* or regimen* or protocol* or agent* or drug*))
#47	(anti-angiogenic or (angiogenesis and inhibit*))
#48	(vascular endothelial growth factor* or VEGF or VEGFR or VEGF-R)
#49	Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#50	MeSH descriptor: [Absorbable Implants] explode all trees
#51	chemotherap*
#52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#53	(bevacizumab or altusan or avastin or blanoxan or blenoxane or bleo cell or bleolem or bleomycin* or peplomycin or phleomycin* or blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo)
#54	MeSH descriptor: [Drug Implants] explode all trees
#55	MeSH descriptor: [Absorbable Implants] explode all trees
#56	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitrosourea* or nitrosourea or nitrumon or cilcane or cilengitide or impetreve or biocisplatinum or cddp or cisplatin or cisdiamminedichloroplatinum or cisplatinum or dichlorodiammineplatinum or platidiam or platino* or platinum or cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc-26271 or neosar or procytox or sendoxan or ara-c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*)
#57	(biocarbazine or carboxamide or dtic or dticdome or dacarbazine or deticene or icdt or nsc-45388 or actinomycin or cosmegan or dactinomycin or meractinomycin or celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc-141540 or onkoposid or riboposid or toposar or vp-16-213 or vepesid)
#58	(biolf-62 or bw-759 or cytovene or gangciclovir or gancyclovir or rs-21592 or virgan or valganciclovir or valgancyclovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt* or valixa)
#59	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide or ipilimumab or yervoy or irinotecan or campto* or belustine or ccnu or cecenu or ceenu or lomustine or nsc-79037 or amethopterin or methotrexate or mexate or acnu or nimustine or nsc-245382 or nivolumab or opdivo)
#60	(matulan or natulan or procarbazine or rindopepimut or rintega or sitimagene ceradenovec or cerepro or nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium or temozolomide or temodal or temodar or nsc-122819 or teniposide or vm-26 or vumon or lemblastine or velban or velbe or vinblastin* or vincaleukoblastin* or citomid or farmistin or leucocristine or oncovin* or onkocristin or pcv or vincasar or vincristin* or vincrisul or vintec)
#61	(dimethylbiguandine or glucophage or metformin)
#62	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#63	(hmg-coa reductase inhibitor* or statin* or (hydroxymethlyglutaryl near/2 inhibitor*))

ID	Search
#64	(atorvastatin or lipitor or liptonorm or ci-981 or lovastatin or 6-methylcompactin or mk-803 or mevacor or mevinolin or monacolin or meglutol or methylglutar* acid or pravastatin or bristacol or cs-514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravacol or pravasin or rms-431 or sq-31000 or selektine or vasten or rosuvastatin or crestor or zd-4522 or simvastatin or mk-733 or synvinolin or zocor)
#65	MeSH descriptor: [Ketogenic Diet] explode all trees
#66	MeSH descriptor: [Diet Therapy] explode all trees
#67	((calor* or carbohydrate* or protein*) near/2 (low or restrict* or diet*))
#68	MeSH descriptor: [Cannabinoids] explode all trees
#69	MeSH descriptor: [Cannabis] explode all trees
#70	(cannabi* or hashish* or hemp* or mari?uana* or sativex)
#71	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#72	MeSH descriptor: [Electromagnetic Fields] explode all trees
#73	((electr* or tumo* treat*) near/2 (field* or therap* or treatment*))
#74	(TTField* or TTF or NovoTTF)
#75	{or #32-#74}
#76	MeSH descriptor: [Watchful Waiting] explode all trees
#77	(watch* near/2 wait*)
#78	((active or expect* or symptom* or watch*) near/2 (manag* or monitor* or surveill* or observ* or control*))
#79	supportive care
#80	{or #76-#79}
#81	#25 or #31 or #75 or #80
#82	#15 and #81 Publication Year from 1977 to 2016

Database: Embase 1974 to 2016 Week 48

ID	Search
1	exp glioma/
2	exp astrocytoma/
3	1 or 2
4	anaplastic carcinoma/
5	tumor recurrence/ or "oncogenesis and malignant transformation"/
6	exp "oncogenesis and malignant transformation"/
7	exp Glioma/ or exp Astrocytoma/
8	anaplastic carcinoma/
9	exp "oncogenesis and malignant transformation"/
10	8 or 9
11	7 and 10
12	glioblastoma/
13	11 or 12
14	(glioblastoma* or GBM).tw.
15	gliosarcoma*.tw.
16	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
17	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.

ID	Search
18	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
19	or/13-18
20	exp neurosurgery/
21	exp cancer surgery/
22	surgery.fs.
23	exp stereotactic procedure/
24	tumor ablation/
25	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
26	(neurosurg* or craniotom* or craniectom*).tw.
27	(ventriculostom* or ventriculocisternostom*).tw.
28	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
29	or/20-28
30	exp radiotherapy/
31	radiotherapy.fs.
32	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
33	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
34	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
35	or/30-34
36	exp antineoplastic agent/
37	multimodality cancer therapy/
38	exp combination drug therapy/
39	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
40	CCRT.tw.
41	stupp.tw.
42	exp chemotherapy/
43	exp monoclonal antibody/
44	oncolytic virotherapy/
45	exp antivirus agent/
46	exp cancer vaccine/
47	cancer gene therapy/
48	exp angiogenesis inhibitor/
49	vasculotropin/
50	exp cancer immunotherapy/
51	target cell destruction/
52	drug therapy.fs.
53	chemotherap*.tw.
54	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
55	(virotherap* or anti?viral*).tw.
56	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
57	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
58	vascular endothelial growth factor*.tw.

ID	Search
59	(VEGF or VEGFR or VEGF-R).tw.
60	bevacizumab/
61	(bevacizumab or avastin or altusan).tw.
62	exp Bleomycin/
63	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
64	carboplatin/
65	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
66	carmustine/
67	biodegradable implant/
68	drug implant/
69	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
70	cilengitide/
71	(cilcane or cilengitide or impetreve).tw.
72	cisplatin/
73	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
74	cyclophosphamide/
75	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
76	cytarabine/
77	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
78	dacarbazine/
79	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
80	dactinomycin/
81	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
82	dendritic cell vaccine/
83	(DCVAX or (dentri* cell? adj (vaccin* or immnuotherap*))).tw.
84	etoposide/
85	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
86	ganciclovir/
87	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
88	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
89	ifosfamide/
90	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
91	ipilimumab/
92	(Ipilimumab or yervoy).tw.
93	irinotecan/
94	(Irinotecan or campto*).tw.
95	lomustine/
96	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
97	methotrexate/
98	(amethopterin or methotrexate or mexate).tw.
99	nimustine/
100	(acnu or nimustine or nsc?245382).tw.

ID	Search
101	nivolumab/
102	(Nivolumab or opdivo).tw.
103	procarbazine/
104	(matulan or natulan or procarbazine).tw.
105	rindopepimut/
106	(rindopepimut or rintega).tw.
107	sitimagene ceradenovec/
108	(sitimagene ceradenovec or cerepro).tw.
109	tamoxifen/
110	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
111	temozolomide/
112	(temozolomide or temodal or temodar).tw.
113	teniposide/
114	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
115	vinblastine/
116	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
117	vincristine/
118	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
119	or/36-118
120	metformin/
121	(dimethylbiguandine or glucophage or metformin).tw.
122	120 or 121
123	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
124	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlglutaryl adj2 inhibitor*)).tw.
125	(atorvastatin or lipitor or liptonorm or ci?981).tw.
126	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.

ID	Search
127	(meglutol or methylglutar* acid).tw.
128	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
129	(rosuvastatin or crestor or zd?4522).tw.
130	(simvastatin or mk?733 or synvinolin or zocor).tw.
131	or/123-130
132	ketogenic diet/
133	caloric restriction/
134	low calory diet/
135	low carbohydrate diet/
136	protein restriction/
137	diet therapy.fs.
138	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
139	or/132-138
140	exp cannabinoid/
141	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
142	140 or 141
143	exp electrotherapy/
144	electromagnetic field/
145	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
146	(TTField* or TTF or NovoTTF).tw.
147	or/143-146
148	watchful waiting/
149	conservative treatment/
150	clinical observation/
151	(watch* adj2 wait*).tw.
152	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.

ID	Search
153	(best supportive care or BSC).tw.
154	supportive care.tw.
155	or/148-154
156	or/29,35,119,122,131,139,142,147,155
157	19 and 156
158	limit 157 to english language
159	limit 158 to yr="1977 -Current"
160	letter.pt. or letter/
161	note.pt.
162	editorial.pt.
163	case report/ or case study/
164	(letter or comment*).ti.
165	or/160-164
166	randomized controlled trial/ or random*.ti,ab.
167	165 not 166
168	animal/ not human/
169	nonhuman/
170	exp Animal Experiment/
171	exp Experimental Animal/
172	animal model/
173	exp Rodent/
174	(rat or rats or mouse or mice).ti.
175	or/167-174
176	159 not 175
177	random*.ti,ab.
178	factorial*.ti,ab.

ID	Search
179	(crossover* or cross over*).ti,ab.
180	((doubl* or singl*) adj blind*).ti,ab.
181	(assign* or allocat* or volunteer* or placebo*).ti,ab.
182	crossover procedure/
183	single blind procedure/
184	randomized controlled trial/
185	double blind procedure/
186	or/177-185
187	176 and 186

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

ID	Search
1	exp Glioma/ or exp Astrocytoma/ or Oligodendroglioma/
2	Anaplasia/ or Neoplasm Recurrence, Local/
3	secondary.fs.
4	2 or 3
5	1 and 4
6	exp Glioblastoma/
7	5 or 6
8	(glioblastoma* or GBM).tw.
9	gliosarcoma*.tw.
10	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
11	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
12	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
13	or/7-12
14	Neurosurgery/
15	exp Neurosurgical Procedures/
16	Surgical Procedures, Operative/
17	exp Stereotaxic Techniques/
18	Neuroendoscopy/
19	surgery.fs.
20	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.

ID	Search
21	(neurosurg* or craniotom* or craniectom*).tw.
22	(ventriculostom* or ventriculocisternostom*).tw.
23	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
24	or/14-23
25	exp Radiotherapy/
26	radiotherapy.fs.
27	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
28	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
29	Radiation Oncology/
30	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
31	or/25-30
32	exp Antineoplastic Agents/
33	exp Combined Modality Therapy/
34	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or drug therapy, combination/
35	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
36	CCRT.tw.
37	stupp.tw.
38	exp Antibodies, Monoclonal/
39	exp Angiogenesis Inhibitors/
40	exp Vascular Endothelial Growth Factors/
41	Cancer Vaccines/
42	exp Immunotherapy/
43	Oncolytic Virotherapy/
44	exp Antiviral Agents/
45	(virotherap* or anti?viral*).tw.
46	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
47	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
48	vascular endothelial growth factor*.tw.
49	(VEGF or VEGFR or VEGF-R).tw.
50	drug therapy.fs.
51	chemotherap*.tw.
52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
53	Bevacizumab/
54	(bevacizumab or altusan or avastin).tw.
55	exp Bleomycin/
56	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
57	Carboplatin/
58	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
59	Carmustine/
60	exp Absorbable Implants/
61	exp Drug Implants/
62	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.

ID	Search
63	(cilcane or cilengitide or impetreve).tw.
64	Cisplatin/
65	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
66	Cyclophosphamide/
67	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
68	Cytarabine/
69	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
70	Dacarbazine/
71	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
72	Dactinomycin/
73	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
74	Etoposide/
75	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
76	Ganciclovir/
77	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
78	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
79	(DC?vax or (dentric cell? adj (vaccin* or immunotherap*))).tw.
80	Ifosfamide/
81	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
82	(Ipilimumab or yervoy).tw.
83	(irinotecan or campto*).tw.
84	Lomustine/
85	(belustine or ccnu or cecenu or ceenu or lomustine or nsc?79037).tw.
86	Methotrexate/
87	(amethopterin or methotrexate or mexate).tw.
88	Nimustine/
89	(acnu or nimustine or nsc?245382).tw.
90	(nivolumab or opdivo).tw.
91	Procarbazine/
92	(matulan or natulan or procarbazine).tw.
93	(rindopepimut or rintega).tw.
94	(sitimagene ceradenovec or cerepro).tw.
95	Tamoxifen/
96	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
97	(temozolomide or temodal or temodar).tw.
98	Teniposide/
99	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
100	Vinblastine/
101	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastin*).tw.
102	Vincristine/
103	(citomid or farmistin or leucocristine or oncovin? or onkocristin or pcv or vincasar or vincristin? or vincrisul or vintec).tw.

ID	Search
104	or/32-103
105	exp Metformin/
106	(dimethylbiguandine or glucophage or metformin).tw.
107	105 or 106
108	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
109	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlglutaryl adj2 inhibitor*)).tw.
110	(atorvastatin or lipitor or liptonorm or ci?981).tw.
111	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
112	(meglutol or methylglutar* acid).tw.
113	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
114	(rosuvastatin or crestor or zd?4522).tw.
115	(simvastatin or mk?733 or synvinolin or zocor).tw.
116	or/108-115
117	Ketogenic Diet/
118	Caloric Restriction/
119	Diet, Carbohydrate-Restricted/
120	Diet, Protein-Restricted/
121	diet therapy.fs.
122	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
123	or/117-122
124	Cannabis/
125	exp Cannabinoids/
126	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
127	or/124-126
128	exp Electric Stimulation Therapy/
129	Electromagnetic Fields/

ID	Search
130	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
131	(TTField* or TTF or NovoTTF).tw.
132	or/128-131
133	Watchful Waiting/
134	Observation/
135	(watch* adj2 wait*).tw.
136	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
137	(best supportive care or BSC).tw.
138	supportive care.tw.
139	or/133-138
140	or/24,31,104,107,116,123,127,132,139
141	13 and 140
142	limit 141 to english language
143	limit 142 to yr="1977 -Current"
144	Letter/
145	Editorial/
146	News/
147	exp Historical Article/
148	Anecdotes as Topic/
149	Comment/
150	Case Report/
151	(letter or comment* or abstracts).ti.
152	or/144-151
153	Randomized Controlled Trial/ or random*.ti,ab.
154	152 not 153
155	Animals/ not Humans/

ID	Search
156	exp Animals, Laboratory/
157	exp Animal Experimentation/
158	exp Models, Animal/
159	exp Rodentia/
160	(rat or rats or mouse or mice).ti.
161	or/154-160
162	143 not 161
163	Meta-Analysis/
164	Meta-Analysis as Topic/
165	(meta analy* or metanaly* or metaanaly*).ti,ab.
166	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
167	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
168	(search strateg* or search criteria or systematic search or study selection or data extraction).ab.
169	(search* adj4 literature).ab.
170	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
171	cochrane.jw.
172	or/163-171

Literature search strategy for review 2d – management of recurrent high-grade glioma

Systematic reviews

Date of initial search: 24/11/2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017
Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/ or exp Astrocytoma/ or Oligodendroglioma/

#	Searches
2	Anaplasia/ or Neoplasm Recurrence, Local/
3	secondary.fs.
4	2 or 3
5	1 and 4
6	exp Glioblastoma/
7	5 or 6
8	(glioblastoma* or GBM).tw.
9	gliosarcoma*.tw.
10	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
11	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
12	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
13	or/7-12
14	Neurosurgery/
15	exp Neurosurgical Procedures/
16	Surgical Procedures, Operative/
17	exp Stereotaxic Techniques/
18	Neuroendoscopy/
19	surgery.fs.
20	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
21	(neurosurg* or craniotom* or craniectom*).tw.
22	(ventriculostom* or ventriculocisternostom*).tw.
23	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
24	or/14-23
25	exp Radiotherapy/
26	radiotherapy.fs.
27	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
28	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
29	Radiation Oncology/
30	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
31	or/25-30
32	exp Antineoplastic Agents/
33	exp Combined Modality Therapy/
34	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or drug therapy, combination/
35	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
36	CCRT.tw.
37	stupp.tw.
38	exp Antibodies, Monoclonal/
39	exp Angiogenesis Inhibitors/
40	exp Vascular Endothelial Growth Factors/
41	Cancer Vaccines/
42	exp Immunotherapy/
43	Oncolytic Virotherapy/
44	exp Antiviral Agents/
45	(virotherap* or anti?viral*).tw.
46	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
47	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
48	vascular endothelial growth factor*.tw.
49	(VEGF or VEGFR or VEGF-R).tw.
50	drug therapy.fs.
51	chemotherap*.tw.
52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
53	Bevacizumab/

#	Searches
54	(bevacizumab or altusan or avastin).tw.
55	exp Bleomycin/
56	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
57	Carboplatin/
58	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
59	Carmustine/
60	exp Absorbable Implants/
61	exp Drug Implants/
62	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
63	(cilcane or cilengitide or impetreve).tw.
64	Cisplatin/
65	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
66	Cyclophosphamide/
67	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
68	Cytarabine/
69	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
70	Dacarbazine/
71	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
72	Dactinomycin/
73	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
74	Etoposide/
75	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
76	Ganciclovir/
77	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
78	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
79	(DC?vax or (dentric cell? adj (vaccin* or immunotherap*))).tw.
80	Ifosfamide/
81	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
82	(Ipilimumab or yervoy).tw.
83	(irinotecan or campto*).tw.
84	Lomustine/
85	(belustine or ccnu or cecenu or ceenu or lomustine or nsc?79037).tw.
86	Methotrexate/
87	(amethopterin or methotrexate or mexate).tw.
88	Nimustine/
89	(acnu or nimustine or nsc?245382).tw.
90	(nivolumab or opdivo).tw.
91	Procarbazine/
92	(matulan or natulan or procarbazine).tw.
93	(rindopepimut or rintega).tw.
94	(sitimagene ceradenovec or cerepro).tw.
95	Tamoxifen/
96	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
97	(temozolomide or temodal or temodar).tw.
98	Teniposide/
99	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
100	Vinblastine/
101	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastin*).tw.
102	Vincristine/
103	(citomid or farmistin or leucocristine or oncovin? or onkocristin or pcv or vincasar or vincristin? or vincrisul or vintec).tw.
104	or/32-103
105	exp Metformin/
106	(dimethylbiguandine or glucophage or metformin).tw.
107	105 or 106

#	Searches
108	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
109	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlglutaryl adj2 inhibitor*)).tw.
110	(atorvastatin or lipitor or liptonorm or ci?981).tw.
111	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
112	(meglutol or methylglutar* acid).tw.
113	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
114	(rosuvastatin or crestor or zd?4522).tw.
115	(simvastatin or mk?733 or synvinolin or zocor).tw.
116	or/108-115
117	Ketogenic Diet/
118	Caloric Restriction/
119	Diet, Carbohydrate-Restricted/
120	Diet, Protein-Restricted/
121	diet therapy.fs.
122	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
123	or/117-122
124	Cannabis/
125	exp Cannabinoids/
126	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
127	or/124-126
128	exp Electric Stimulation Therapy/
129	Electromagnetic Fields/
130	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
131	(TTField* or TTF or NovoTTF).tw.
132	or/128-131
133	Watchful Waiting/
134	Observation/
135	(watch* adj2 wait*).tw.
136	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
137	(best supportive care or BSC).tw.
138	supportive care.tw.
139	or/133-138
140	or/24,31,104,107,116,123,127,132,139
141	13 and 140
142	limit 141 to english language
143	limit 142 to yr="1977 -Current"
144	Letter/
145	Editorial/
146	News/
147	exp Historical Article/
148	Anecdotes as Topic/
149	Comment/
150	Case Report/
151	(letter or comment* or abstracts).ti.
152	or/144-151
153	Randomized Controlled Trial/ or random*.ti,ab.
154	152 not 153
155	Animals/ not Humans/
156	exp Animals, Laboratory/
157	exp Animal Experimentation/
158	exp Models, Animal/
159	exp Rodentia/
160	(rat or rats or mouse or mice).ti.
161	or/154-160
162	143 not 161
163	Meta-Analysis/
164	Meta-Analysis as Topic/
165	(meta analy* or metanaly* or metaanaly*).ti,ab.
166	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.

#	Searches
167	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
168	(search strateg* or search criteria or systematic search or study selection or data extraction).ab.
169	(search* adj4 literature).ab.
170	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
171	cochrane.jw.
172	or/163-171
173	162 and 172

Systematic reviews

Date of initial search: 24/11/2016

Database: Embase 1974 to 2016 Week 48

Date of re-run: 07/09/2017
Database: Embase 1980 to 2016 Week 35

#	Searches
1	exp glioma/
2	exp astrocytoma/
3	1 or 2
4	anaplastic carcinoma/
5	tumor recurrence/ or "oncogenesis and malignant transformation"/
6	exp "oncogenesis and malignant transformation"/
7	exp Glioma/ or exp Astrocytoma/
8	anaplastic carcinoma/
9	exp "oncogenesis and malignant transformation"/
10	8 or 9
11	7 and 10
12	glioblastoma/
13	11 or 12
14	(glioblastoma* or GBM).tw.
15	gliosarcoma*.tw.
16	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
17	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
18	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
19	or/13-18
20	exp neurosurgery/
21	exp cancer surgery/
22	surgery.fs.
23	exp stereotactic procedure/
24	tumor ablation/
25	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
26	(neurosurg* or craniotom* or craniectom*).tw.
27	(ventriculostom* or ventriculocisternostom*).tw.
28	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
29	or/20-28
30	exp radiotherapy/
31	radiotherapy.fs.
32	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.

#	Searches
33	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
34	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
35	or/30-34
36	exp antineoplastic agent/
37	multimodality cancer therapy/
38	exp combination drug therapy/
39	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
40	CCRT.tw.
41	stupp.tw.
42	exp chemotherapy/
43	exp monoclonal antibody/
44	oncolytic virotherapy/
45	exp antivirus agent/
46	exp cancer vaccine/
47	cancer gene therapy/
48	exp angiogenesis inhibitor/
49	vasculotropin/
50	exp cancer immunotherapy/
51	target cell destruction/
52	drug therapy.fs.
53	chemotherap*.tw.
54	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
55	(virotherap* or anti?viral*).tw.
56	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
57	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
58	vascular endothelial growth factor*.tw.
59	(VEGF or VEGFR or VEGF-R).tw.
60	bevacizumab/
61	(bevacizumab or avastin or altusan).tw.
62	exp Bleomycin/
63	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
64	carboplatin/
65	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
66	carmustine/
67	biodegradable implant/
68	drug implant/
69	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
70	cilengitide/
71	(cilcane or cilengitide or impetreve).tw.
72	cisplatin/
73	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
74	cyclophosphamide/
75	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
76	cytarabine/
77	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
78	dacarbazine/
79	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
80	dactinomycin/
81	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
82	dendritic cell vaccine/
83	(DCVAX or (dentri* cell? adj (vaccin* or immnuotherap*))).tw.
84	etoposide/

#	Searches
85	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
86	ganciclovir/
87	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
88	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
89	ifosfamide/
90	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
91	ipilimumab/
92	(Ipilimumab or yervoy).tw.
93	irinotecan/
94	(Irinotecan or campto*).tw.
95	lomustine/
96	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
97	methotrexate/
98	(amethopterin or methotrexate or mexate).tw.
99	nimustine/
100	(acnu or nimustine or nsc?245382).tw.
101	nivolumab/
102	(Nivolumab or opdivo).tw.
103	procarbazine/
104	(matulan or natulan or procarbazine).tw.
105	rindopepimut/
106	(rindopepimut or rintega).tw.
107	sitimagene ceradenovec/
108	(sitimagene ceradenovec or cerepro).tw.
109	tamoxifen/
110	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
111	temozolomide/
112	(temozolomide or temodal or temodar).tw.
113	teniposide/
114	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
115	vinblastine/
116	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
117	vincristine/
118	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
119	or/36-118
120	metformin/
121	(dimethylbiguandine or glucophage or metformin).tw.
122	120 or 121
123	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
124	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlglutaryl adj2 inhibitor*)).tw.
125	(atorvastatin or lipitor or liptonorm or ci?981).tw.
126	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
127	(meglutol or methylglutar* acid).tw.
128	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
129	(rosuvastatin or crestor or zd?4522).tw.
130	(simvastatin or mk?733 or synvinolin or zocor).tw.
131	or/123-130
132	ketogenic diet/
133	caloric restriction/
134	low calory diet/
135	low carbohydrate diet/
136	protein restriction/
137	diet therapy.fs.
138	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
139	or/132-138
140	exp cannabinoid/
141	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
142	140 or 141

#	Searches
143	exp electrotherapy/
144	electromagnetic field/
145	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
146	(TTField* or TTF or NovoTTF).tw.
147	or/143-146
148	watchful waiting/
149	conservative treatment/
150	clinical observation/
151	(watch* adj2 wait*).tw.
152	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
153	(best supportive care or BSC).tw.
154	supportive care.tw.
155	or/148-154
156	or/29,35,119,122,131,139,142,147,155
157	19 and 156
158	limit 157 to english language
159	limit 158 to yr="1977 -Current"
160	letter.pt. or letter/
161	note.pt.
162	editorial.pt.
163	case report/ or case study/
164	(letter or comment*).ti.
165	or/160-164
166	randomized controlled trial/ or random*.ti,ab.
167	165 not 166
168	animal/ not human/
169	nonhuman/
170	exp Animal Experiment/
171	exp Experimental Animal/
172	animal model/
173	exp Rodent/
174	(rat or rats or mouse or mice).ti.
175	or/167-174
176	159 not 175
177	systematic review/
178	meta-analysis/
179	(meta analy* or metanaly* or metaanaly*).ti,ab.
180	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
181	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
182	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
183	(search* adj4 literature).ab.
184	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
185	((pool* or combined) adj2 (data or trials or studies or results)).ab.
186	cochrane.jw.
187	or/177-186
188	176 and 187
174	(rat or rats or mouse or mice).ti.
175	or/167-174
176	159 not 175
177	systematic review/
178	meta-analysis/
179	(meta analy* or metanaly* or metaanaly*).ti,ab.
180	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
181	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
182	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
183	(search* adj4 literature).ab.
184	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
185	((pool* or combined) adj2 (data or trials or studies or results)).ab.

#	Searches
186	cochrane.jw.
187	or/177-186
188	176 and 187

Randomised controlled trials

Date of initial search: 24/11/2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/ or exp Astrocytoma/ or Oligodendroglioma/
2	Anaplasia/ or Neoplasm Recurrence, Local/
3	secondary.fs.
4	2 or 3
5	1 and 4
6	exp Glioblastoma/
7	5 or 6
8	(glioblastoma* or GBM).tw.
9	gliosarcoma*.tw.
10	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
11	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
12	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
13	or/7-12
14	Neurosurgery/
15	exp Neurosurgical Procedures/
16	Surgical Procedures, Operative/
17	exp Stereotaxic Techniques/
18	Neuroendoscopy/
19	surgery.fs.
20	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
21	(neurosurg* or craniotom* or craniectom*).tw.
22	(ventriculostom* or ventriculocisternostom*).tw.
23	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
24	or/14-23
25	exp Radiotherapy/
26	radiotherapy.fs.
27	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
28	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
29	Radiation Oncology/
30	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
31	or/25-30
32	exp Antineoplastic Agents/
33	exp Combined Modality Therapy/

#	Searches
34	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or drug therapy, combination/
35	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
36	CCRT.tw.
37	stupp.tw.
38	exp Antibodies, Monoclonal/
39	exp Angiogenesis Inhibitors/
40	exp Vascular Endothelial Growth Factors/
41	Cancer Vaccines/
42	exp Immunotherapy/
43	Oncolytic Virotherapy/
44	exp Antiviral Agents/
45	(virotherap* or anti?viral*).tw.
46	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
47	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
48	vascular endothelial growth factor*.tw.
49	(VEGF or VEGFR or VEGF-R).tw.
50	drug therapy.fs.
51	chemotherap*.tw.
52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
53	Bevacizumab/
54	(bevacizumab or altusan or avastin).tw.
55	exp Bleomycin/
56	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
57	Carboplatin/
58	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
59	Carmustine/
60	exp Absorbable Implants/
61	exp Drug Implants/
62	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
63	(cilcane or cilengitide or impetreve).tw.
64	Cisplatin/
65	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
66	Cyclophosphamide/
67	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
68	Cytarabine/
69	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
70	Dacarbazine/
71	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
72	Dactinomycin/
73	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
74	Etoposide/
75	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
76	Ganciclovir/
77	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
78	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
79	(DC?vax or (dentric cell? adj (vaccin* or immunotherap*))).tw.
80	Ifosfamide/
81	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
82	(Ipilimumab or yervoy).tw.
83	(irinotecan or campto*).tw.
84	Lomustine/
85	(belustine or ccnu or cecenu or ceenu or lomustine or nsc?79037).tw.
86	Methotrexate/

#	Searches
87	(amethopterin or methotrexate or mexate).tw.
88	Nimustine/
89	(acnu or nimustine or nsc?245382).tw.
90	(nivolumab or opdivo).tw.
91	Procarbazine/
92	(matulan or natulan or procarbazine).tw.
93	(rindopepimut or rintega).tw.
94	(sitimagene ceradenovec or cerepro).tw.
95	Tamoxifen/
96	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
97	(temozolomide or temodal or temodar).tw.
98	Teniposide/
99	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
100	Vinblastine/
101	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastin*).tw.
102	Vincristine/
103	(citomid or farmistin or leucocristine or oncovin? or onkocristin or pcv or vincasar or vincristin? or vincrisul or vintec).tw.
104	or/32-103
105	exp Metformin/
106	(dimethylbiguandine or glucophage or metformin).tw.
107	105 or 106
108	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
109	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlyglutaryl adj2 inhibitor*)).tw.
110	(atorvastatin or lipitor or liptonorm or ci?981).tw.
111	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
112	(meglutol or methylglutar* acid).tw.
113	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
114	(rosuvastatin or crestor or zd?4522).tw.
115	(simvastatin or mk?733 or synvinolin or zocor).tw.
116	or/108-115
117	Ketogenic Diet/
118	Caloric Restriction/
119	Diet, Carbohydrate-Restricted/
120	Diet, Protein-Restricted/
121	diet therapy.fs.
122	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
123	or/117-122
124	Cannabis/
125	exp Cannabinoids/
126	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
127	or/124-126
128	exp Electric Stimulation Therapy/
129	Electromagnetic Fields/
130	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
131	(TTField* or TTF or NovoTTF).tw.
132	or/128-131
133	Watchful Waiting/
134	Observation/
135	(watch* adj2 wait*).tw.
136	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
137	(best supportive care or BSC).tw.
138	supportive care.tw.
139	or/133-138
140	or/24,31,104,107,116,123,127,132,139
141	13 and 140
142	limit 141 to english language
143	limit 142 to yr="1977 -Current"
144	Letter/

#	Searches
145	Editorial/
146	News/
147	exp Historical Article/
148	Anecdotes as Topic/
149	Comment/
150	Case Report/
151	(letter or comment* or abstracts).ti.
152	or/144-151
153	Randomized Controlled Trial/ or random*.ti,ab.
154	152 not 153
155	Animals/ not Humans/
156	exp Animals, Laboratory/
157	exp Animal Experimentation/
158	exp Models, Animal/
159	exp Rodentia/
160	(rat or rats or mouse or mice).ti.
161	or/154-160
162	143 not 161
163	randomized controlled trial.pt.
164	controlled clinical trial.pt.
165	pragmatic clinical trial.pt.
166	randomi#ed.ab.
167	placebo.ab.
168	drug therapy.fs.
169	randomly.ab.
170	trial.ab.
171	groups.ab.
172	or/163-171
173	Clinical Trials as topic.sh.
174	trial.ti.
175	or/163-167,169,173-174
176	162 and 175

Randomised controlled trials

Date of initial search: 24/11/2016

Database: Embase 1974 to 2016 Week 48

Date of re-run: 07/09/2017
Database: Embase 1980 to 2016 Week 35

#	Searches
1	exp glioma/
2	exp astrocytoma/
3	1 or 2
4	anaplastic carcinoma/
5	tumor recurrence/ or "oncogenesis and malignant transformation"/
6	exp "oncogenesis and malignant transformation"/
7	exp Glioma/ or exp Astrocytoma/
8	anaplastic carcinoma/
9	exp "oncogenesis and malignant transformation"/
10	8 or 9
11	7 and 10
12	glioblastoma/
13	11 or 12
14	(glioblastoma* or GBM).tw.

#	Searches
15	gliosarcoma*.tw.
16	((grade* 4 or four or IV) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
17	((grade* 3 or three or III) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
18	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) adj3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*)).tw.
19	or/13-18
20	exp neurosurgery/
21	exp cancer surgery/
22	surgery.fs.
23	exp stereotactic procedure/
24	tumor ablation/
25	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*)).tw.
26	(neurosurg* or craniotom* or craniectom*).tw.
27	(ventriculostom* or ventriculocisternostom*).tw.
28	(intra?operat* adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
29	or/20-28
30	exp radiotherapy/
31	radiotherapy.fs.
32	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron).tw.
33	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT).tw.
34	(chemo?radiotherap* or chemo?radiat* or chemo?irradiat* or radio?chemotherap*).tw.
35	or/30-34
36	exp antineoplastic agent/
37	multimodality cancer therapy/
38	exp combination drug therapy/
39	((combin* or concomitant or concurrent) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
40	CCRT.tw.
41	stupp.tw.
42	exp chemotherapy/
43	exp monoclonal antibody/
44	oncolytic virotherapy/
45	exp antivirus agent/
46	exp cancer vaccine/
47	cancer gene therapy/
48	exp angiogenesis inhibitor/
49	vasculotropin/
50	exp cancer immunotherapy/
51	target cell destruction/
52	drug therapy.fs.
53	chemotherap*.tw.
54	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
55	(virotherap* or anti?viral*).tw.
56	((virus or viral or anti?virus or anti?viral) adj2 (therap* or treatment* or regimen* or protocol* or agent* or drug*)).tw.
57	(anti?angiogenic or (angiogenesis and inhibit*)).tw.
58	vascular endothelial growth factor*.tw.
59	(VEGF or VEGFR or VEGF-R).tw.
60	bevacizumab/
61	(bevacizumab or avastin or altusan).tw.
62	exp Bleomycin/
63	(blanoxan or blenoxane or bleo?cell or bleolem or bleomycin* or peplomycin or phleomycin*).tw.
64	carboplatin/
65	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.

#	Searches
66	carmustine/
67	biodegradable implant/
68	drug implant/
69	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitros?urea* or nitrumon).tw.
70	cilengitide/
71	(cilcane or cilengitide or impetreve).tw.
72	cisplatin/
73	(biocisplatinum or cddp or cisplatin or cis?diamminedichloroplatinum or cis?platinum or dichlorodiammineplatinum or platidiam or platino* or platinum).tw.
74	cyclophosphamide/
75	(cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc?26271 or neosar or procytox or sendoxan).tw.
76	cytarabine/
77	(ara?c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*).tw.
78	dacarbazine/
79	(biocarbazine or carboxamide or dtic or dticdome or d?carbazine or deticene or icdt or nsc?45388).tw.
80	dactinomycin/
81	(actinomycin or cosmegan or dactinomycin or meractinomycin).tw.
82	dendritic cell vaccine/
83	(DCVAX or (dentri* cell? adj (vaccin* or immnuotherap*))).tw.
84	etoposide/
85	(celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc?141540 or onkoposid or riboposid or toposar or vp?16?213 or vepesid).tw.
86	ganciclovir/
87	(biolf?62 or bw?759 or cytovene or ganc?clovir or rs?21592 or virgan).tw.
88	(valganc?clovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt*1 or valixa).tw.
89	ifosfamide/
90	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
91	ipilimumab/
92	(Ipilimumab or yervoy).tw.
93	irinotecan/
94	(Irinotecan or campto*).tw.
95	lomustine/
96	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
97	methotrexate/
98	(amethopterin or methotrexate or mexate).tw.
99	nimustine/
100	(acnu or nimustine or nsc?245382).tw.
101	nivolumab/
102	(Nivolumab or opdivo).tw.
103	procarbazine/
104	(matulan or natulan or procarbazine).tw.
105	rindopepimut/
106	(rindopepimut or rintega).tw.
107	sitimagene ceradenovec/
108	(sitimagene ceradenovec or cerepro).tw.
109	tamoxifen/
110	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
111	temozolomide/
112	(temozolomide or temodal or temodar).tw.
113	teniposide/
114	(nsc?122819 or ten?poside or vm?26 or vumon).tw.
115	vinblastine/
116	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
117	vincristine/
118	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
119	or/36-118
120	metformin/
121	(dimethylbiguandine or glucophage or metformin).tw.

#	Searches
122	120 or 121
123	exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
124	(hmg?coa reductase inhibitor* or statin* or (hydroxymethlglutaryl adj2 inhibitor*)).tw.
125	(atorvastatin or lipitor or liptonorm or ci?981).tw.
126	(lovastatin or 6?methylcompactin or mk?803 or mevacor or mevinolin or monacolin).tw.
127	(meglutol or methylglutar* acid).tw.
128	(pravastatin or bristacol or cs?514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravac?ol or pravasin or rms?431 or sq?31000 or selektine or vasten).tw.
129	(rosuvastatin or crestor or zd?4522).tw.
130	(simvastatin or mk?733 or synvinolin or zocor).tw.
131	or/123-130
132	ketogenic diet/
133	caloric restriction/
134	low calory diet/
135	low carbohydrate diet/
136	protein restriction/
137	diet therapy.fs.
138	((calor* or carbohydrate* or protein*) adj2 (low or restrict* or diet*)).tw.
139	or/132-138
140	exp cannabinoid/
141	(cannabi* or hashish* or hemp* or mari?uana* or sativex).tw.
142	140 or 141
143	exp electrotherapy/
144	electromagnetic field/
145	((electr* or tumo* treat*) adj2 (field* or therap* or treatment*)).tw.
146	(TTField* or TTF or NovoTTF).tw.
147	or/143-146
148	watchful waiting/
149	conservative treatment/
150	clinical observation/
151	(watch* adj2 wait*).tw.
152	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
153	(best supportive care or BSC).tw.
154	supportive care.tw.
155	or/148-154
156	or/29,35,119,122,131,139,142,147,155
157	19 and 156
158	limit 157 to english language
159	limit 158 to yr="1977 -Current"
160	letter.pt. or letter/
161	note.pt.
162	editorial.pt.
163	case report/ or case study/
164	(letter or comment*).ti.
165	or/160-164
166	randomized controlled trial/ or random*.ti,ab.
167	165 not 166
168	animal/ not human/
169	nonhuman/
170	exp Animal Experiment/
171	exp Experimental Animal/
172	animal model/
173	exp Rodent/
174	(rat or rats or mouse or mice).ti.
175	or/167-174
176	159 not 175
177	random*.ti,ab.
178	factorial*.ti,ab.
179	(crossover* or cross over*).ti,ab.
180	((doubl* or singl*) adj blind*).ti,ab.

#	Searches
181	(assign* or allocat* or volunteer* or placebo*).ti,ab.
182	crossover procedure/
183	single blind procedure/
184	randomized controlled trial/
185	double blind procedure/
186	or/177-185
187	176 and 186

Date of initial search: 29/11/2016

Database: The Cochrane Library, Issue 11 of 12, November 2016

Date of re-run: 07/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	MeSH descriptor: [Astrocytoma] explode all trees
#3	Oligodendroglioma
#4	{or #1-#3}
#5	MeSH descriptor: [Anaplasia] explode all trees
#6	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#7	#5 or #6
#8	#4 and #7
#9	MeSH descriptor: [Glioblastoma] explode all trees
#10	(glioblastoma* or GBM)
#11	gliosarcoma*
#12	((grade* 4 or four or IV) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*))
#13	((grade* 3 or three or III) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligo?astrocytoma*))
#14	((high-grade or malignant or invasive or anaplas* or recurr* or transform*) near/3 (glioma* or astrocytoma* or oligodendrogli* or oligodendroblastoma* or oligoastrocytoma*))
#15	{or #8-#14}
#16	MeSH descriptor: [Neurosurgery] explode all trees
#17	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#18	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#19	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#20	MeSH descriptor: [Neuroendoscopy] this term only
#21	Any MeSH descriptor with qualifier(s): [Surgery - SU]
#22	((brain or neuro* or intracereb* or intracrani* or crani* or cereb*) near/2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops* or aspirat* or shunt*))
#23	(neurosurg* or craniotom* or craniectom* or ventriculostom* or ventriculocisternostom*)
#24	(intraoperat* near/3 (technolog* or modalit* or procedur* or technique* or method*))
#25	{or #16-#24}
#26	MeSH descriptor: [Radiotherapy] explode all trees
#27	Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#28	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap* or proton beam or carbon ion or boron neutron)
#29	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or IGRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT or BNCT)
#30	(chemoradiotherap* or chemoradiat* or chemoirradiat* or radiochemotherap*)
#31	{or #26-#30}
#32	MeSH descriptor: [Antineoplastic Agents] explode all trees
#33	MeSH descriptor: [Combined Modality Therapy] explode all trees
#34	MeSH descriptor: [Antineoplastic Protocols] explode all trees

ID	Search
#35	MeSH descriptor: [Drug Therapy, Combination] explode all trees
#36	((combin* or concomitant or concurrent) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#37	(CCRT or stupp)
#38	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#39	MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#40	MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees
#41	MeSH descriptor: [Cancer Vaccines] explode all trees
#42	MeSH descriptor: [Immunotherapy] explode all trees
#43	MeSH descriptor: [Oncolytic Virotherapy] explode all trees
#44	MeSH descriptor: [Antiviral Agents] explode all trees
#45	(virotherap* or anti-viral*)
#46	((virus or viral or anti-virus or anti-viral) near/2 (therap* or treatment* or regimen* or protocol* or agent* or drug*))
#47	(anti-angiogenic or (angiogenesis and inhibit*))
#48	(vascular endothelial growth factor* or VEGF or VEGFR or VEGF-R)
#49	Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#50	MeSH descriptor: [Absorbable Implants] explode all trees
#51	chemotherap*
#52	((anti?cancer or systemic or anti?neoplas* or cytotoxi*) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#53	(bevacizumab or altusan or avastin or blanoxan or blenoxane or bleo cell or bleolem or bleomycin* or peplomycin or phleomycin* or blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo)
#54	MeSH descriptor: [Drug Implants] explode all trees
#55	MeSH descriptor: [Absorbable Implants] explode all trees
#56	(bcnu or bicnu or carmustine or fivb or gliadel wafer* or nitrosourea* or nitrosourea or nitrumon or cilcane or cilengitide or impetreve or biocisplatinum or cddp or cisplatin or cisdiamminedichloroplatinum or cisplatinum or dichlorodiammineplatinum or platidiam or platino* or platinum or cyclophosphamide or cyclophosphan* or cytoxan or endoxan or nsc-26271 or neosar or procytox or sendoxan or ara-c or arabinofuranosylcytosine or arabinoside or arabinosylcytosine or aracytidine or aracytine or cytarabine or cytonal or cytosar*)
#57	(biocarbazine or carboxamide or dtic or dticdome or dacarbazine or deticene or icdt or nsc-45388 or actinomycin or cosmegan or dactinomycin or meractinomycin or celltop or eposide or eposin or etomodac or etopos* or exitop or lastet or nsc-141540 or onkoposid or riboposid or toposar or vp-16-213 or vepesid)
#58	(biolf-62 or bw-759 or cytovene or gangciclovir or gancyclovir or rs-21592 or virgan or valganciclovir or valgancyclovir or cymeval or darilin or patheon or rovalcyte or syntex or valcyt* or valixa)
#59	(holoxan or ifosfamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide or ipilimumab or yervoy or irinotecan or campto* or belustine or ccnu or cecenu or ceenu or lomustine or nsc-79037 or amethopterin or methotrexate or mexate or acnu or nimustine or nsc-245382 or nivolumab or opdivo)
#60	(matulan or natulan or procarbazine or rindopepimut or rintega or sitimagene ceradenovec or cerepro or nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium or temozolomide or temodal or temodar or nsc-122819 or teniposide or vm-26 or vumon or lemblastine or velban or velbe or vinblastin* or vincaleukoblastin* or citomid or farmistin or leucocristine or oncovin* or onkocristin or pcv or vincasar or vincristin* or vincrisul or vintec)
#61	(dimethylbiguandine or glucophage or metformin)
#62	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#63	(hmg-coa reductase inhibitor* or statin* or (hydroxymethlyglutaryl near/2 inhibitor*))
#64	(atorvastatin or lipitor or liptonorm or ci-981 or lovastatin or 6-methylcompactin or mk-803 or mevacor or mevinolin or monacolin or meglutol or methylglutar* acid or pravastatin or bristacol or cs-514 or elisor or eptastatin or lipemol or liplat or lipostat or mevalotin or prareduct or pravacol or pravasin or rms-431 or sq-31000 or selektine or vasten or rosuvastatin or crestor or zd-4522 or simvastatin or mk-733 or synvinolin or zocor)
#65	MeSH descriptor: [Ketogenic Diet] explode all trees
#66	MeSH descriptor: [Diet Therapy] explode all trees
#67	((calor* or carbohydrate* or protein*) near/2 (low or restrict* or diet*))
#68	MeSH descriptor: [Cannabinoids] explode all trees
#69	MeSH descriptor: [Cannabis] explode all trees
#70	(cannabi* or hashish* or hemp* or mari?uana* or sativex)
#71	MeSH descriptor: [Electric Stimulation Therapy] explode all trees
#72	MeSH descriptor: [Electromagnetic Fields] explode all trees
#73	((electr* or tumo* treat*) near/2 (field* or therap* or treatment*))
#74	(TTField* or TTF or NovoTTF)
#75	{or #32-#74}
#76	MeSH descriptor: [Watchful Waiting] explode all trees
#77	(watch* near/2 wait*)

ID	Search
#78	((active or expect* or symptom* or watch*) near/2 (manag* or monitor* or surveill* or observ* or control*))
#79	supportive care
#80	{or #76-#79}
#81	#25 or #31 or #75 or #80
#82	#15 and #81 Publication Year from 1977 to 2016

Literature search strategy for review 2b – resection of glioma

Systematic reviews and RCTs

Date of initial search: 04/05/2017 Database: Embase 1947 to 2017 May 03, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run:12/09/2017
Database: Embase 1947 to 2017 May 03, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp glioma/ or exp astrocytoma/ or oligodendroglioma/
2	exp Glioblastoma/
3	1 or 2 use ppez
4	exp glioma/ use emczd or exp astrocytoma/ use emczd
5	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
6	or/1-5
7	Surgery, Computer-Assisted/ use ppez
8	computer assisted surgery/ use emczd
9	7 or 8
10	6 and 9
11	Brain Neoplasms/dg use ppez and Brain Neoplasms/su use ppez
12	exp brain radiography/ use emczd and brain tumor/su use emczd
13	11 or 12
14	Neurosurgery/ use ppez
15	neurosurgery/ use emczd
16	Neurosurgical Procedures/ use ppez
17	Craniotomy/ use ppez
18	craniotomy/ use emczd
19	(craniotom* or craniectom*).tw.
20	(ablat* or biops* or cytoreduc* or debulk* or excis* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*).tw.
21	or/14-20
22	6 and 21
23	10 or 13 or 22
24	Neuronavigation/ use ppez
25	neuronavigation/ use emczd
26	Monitoring, Intraoperative/ use ppez
27	exp intraoperative monitoring/ use emczd
28	((intra-operative or intraoperative or peri-operative or perioperative or perisurg* or peri-surg*) adj3 (tech* or modalit* or monitor* or navigat*)).tw.
29	(neuronavigat* or neuro-navigat* or neuroimag* or neuro-imag* or neuromonitor* or neuro-monitor*).tw.
30	((brain or neuro* or intracereb* or intra-cereb* or intracrani* or intra-crani* or crani*) adj2 navigat*).tw.
31	(frameless stereota* or imag* guid*).tw.
32	Aminolevulinic Acid/ use ppez
33	aminolevulinic acid/ use emczd

#	Searches
34	(5ALA or 5-ALA or 5-aminol?evulin* or aminolevulinic acid or amino levulinic acid or gliolan or levulan).tw.
35	Fluorescence/ use ppez
36	exp fluorescence/ use emczd
37	fluorescen*.tw.
38	or/24-37
39	Craniotomy/ use ppez
40	Wakefulness/ use ppez or Stereotaxic Techniques/ use ppez
41	39 and 40
42	craniotomy/ use emczd
43	wakefulness/ use emczd or stereotactic procedure/ use emczd
44	42 and 43
45	((awake or wakeful* or stereota*) adj2 (craniotom* or craniectom* or biops* or cytoreduc* or debult* or microsurg* or neurosurg* or operat* or procedure* or resect* or surg*)).tw.
46	or/38,41,44-45
47	exp Neuroimaging/ use ppez
48	exp neuroimaging/ use emczd
49	brain mapping/ use emczd
50	Electric Stimulation/ use ppez
51	electrostimulation/ use emczd
52	Deep Brain Stimulation/ use ppez
53	brain depth stimulation/ use emczd
54	exp Electroencephalography/ use ppez
55	exp electroencephalography/ use emczd
56	((electric* or electro* or brain or cereb* or cortex or cortical or neuro* or subcortex or subcortical or bipolar or bi-polar or monopolar or mono-polar) adj3 (mapping or stimulat*)).tw.
57	(electrocorticogra* or ECoG).tw.
58	(electrosubcorticogra* or ESubCoG).tw.
59	(((intracranial or intra-cranial) adj3 electroencephalogra*) or iEEG).tw.
60	Ultrasonography/ use ppez
61	Imaging, Three-Dimensional/ use ppez
62	3D.tw.
63	exp echography/ use emczd
64	three dimensional imaging/ use emczd
65	((intraoperat* or intra-operat* or operative) adj2 (ultraso* or sonogra* or echogra*)).tw.
66	exp Magnetic Resonance Imaging/ use ppez
67	exp nuclear magnetic resonance imaging/ use emczd
68	((intraoperat* or intra-operat* or operative) adj2 (MR*1 or fMRI or magnetic resonance or DTI or imag* or tractogra*)).tw.
69	(iMRI or ioMRI).tw.
70	or/46-69
71	23 and 70
72	limit 71 to english language
73	Letter/ use ppez
74	letter.pt. or letter/ use emczd
75	note.pt.
76	editorial.pt.
77	Editorial/ use ppez
78	News/ use ppez
79	exp Historical Article/ use ppez
80	Anecdotes as Topic/ use ppez
81	Comment/ use ppez
82	Case Report/ use ppez
83	case report/ or case study/ use emczd
84	(letter or comment*).ti.
85	or/73-84
86	randomized controlled trial/ use ppez
87	randomized controlled trial/ use emczd
88	random*.ti,ab.
89	or/86-88
90	85 not 89

#	Searches
91	animals/ not humans/ use ppez
92	animal/ not human/ use emczd
93	nonhuman/ use emczd
94	exp Animals, Laboratory/ use ppez
95	exp Animal Experimentation/ use ppez
96	exp Animal Experiment/ use emczd
97	exp Experimental Animal/ use emczd
98	exp Models, Animal/ use ppez
99	animal model/ use emczd
100	exp Rodentia/ use ppez
101	exp Rodent/ use emczd
102	(rat or rats or mouse or mice).ti.
103	or/90-102
104	72 not 103
105	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
106	105 use ppez
107	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
108	107 use ppez
109	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
110	109 use emczd
111	106 or 108
112	110 or 111
113	Meta-Analysis/
114	Meta-Analysis as Topic/
115	systematic review/
116	meta-analysis/
117	(meta analy* or metanaly* or metaanaly*).ti,ab.
118	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
119	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
120	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
121	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
122	(search* adj4 literature).ab.
123	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
124	cochrane.jw.
125	((pool* or combined) adj2 (data or trials or studies or results)).ab.
126	or/113-114,117,119-124 use ppez
127	or/112-115,117-122 use emczd
128	or/126-127
129	112 or 128
130	104 and 129
131	remove duplicates from 130

Observational studies

Date of initial search: 04/05/2017

Database: Embase 1947 to 2017 May 03, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 12/09/2017

Database: Embase 1947 to 2017 May 03, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp glioma/ or exp astrocytoma/ or oligodendroglioma/
2	exp Glioblastoma/
3	1 or 2 use ppez
4	exp glioma/ use emczd or exp astrocytoma/ use emczd
5	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
6	or/1-5
7	Surgery, Computer-Assisted/ use ppez
8	computer assisted surgery/ use emczd
9	7 or 8
10	6 and 9
11	Brain Neoplasms/dg use ppez and Brain Neoplasms/su use ppez
12	exp brain radiography/ use emczd and brain tumor/su use emczd
13	11 or 12
14	Neurosurgery/ use ppez
15	neurosurgery/ use emczd
16	Neurosurgical Procedures/ use ppez
17	Craniotomy/ use ppez
18	craniotomy/ use emczd
19	(craniotom* or craniectom*).tw.
20	(ablat* or biops* or cytoreduc* or debulk* or excis* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*).tw.
21	or/14-20
22	6 and 21
23	10 or 13 or 22
24	Neuronavigation/ use ppez
25	neuronavigation/ use emczd
26	Monitoring, Intraoperative/ use ppez
27	exp intraoperative monitoring/ use emczd
28	((intra-operative or intraoperative or peri-operative or perioperative or perisurg* or peri-surg*) adj3 (tech* or modalit* or monitor* or navigat*)).tw.
29	(neuronavigat* or neuro-navigat* or neuroimag* or neuro-imag* or neuromonitor* or neuro-monitor*).tw.
30	((brain or neuro* or intracereb* or intra-cereb* or intracrani* or intra-crani* or crani*) adj2 navigat*).tw.
31	(frameless stereota* or imag* guid*).tw.
32	Aminolevulinic Acid/ use ppez
33	aminolevulinic acid/ use emczd
34	(5ALA or 5-ALA or 5-aminol?evulin* or aminolevulinic acid or amino levulinic acid or gliolan or levulan).tw.
35	Fluorescence/ use ppez
36	exp fluorescence/ use emczd
37	fluorescen*.tw.
38	or/24-37
39	Craniotomy/ use ppez
40	Wakefulness/ use ppez or Stereotaxic Techniques/ use ppez
41	39 and 40
42	craniotomy/ use emczd
43	wakefulness/ use emczd or stereotactic procedure/ use emczd
44	42 and 43
45	((awake or wakeful* or stereota*) adj2 (craniotom* or craniectom* or biops* or cytoreduc* or debult* or microsurg* or neurosurg* or operat* or procedure* or resect* or surg*)).tw.
46	or/38,41,44-45
47	exp Neuroimaging/ use ppez
48	exp neuroimaging/ use emczd
49	brain mapping/ use emczd
50	Electric Stimulation/ use ppez
51	electrostimulation/ use emczd

#	Searches
52	Deep Brain Stimulation/ use ppez
53	brain depth stimulation/ use emczd
54	exp Electroencephalography/ use ppez
55	exp electroencephalography/ use emczd
56	((electric* or electro* or brain or cereb* or cortex or cortical or neuro* or subcortex or subcortical or bipolar or bi-polar or monopolar or mono-polar) adj3 (mapping or stimulat*)).tw.
57	(electrocorticogra* or ECoG).tw.
58	(electrosubcorticogra* or ESubCoG).tw.
59	(((intracranial or intra-cranial) adj3 electroencephalogra*) or iEEG).tw.
60	Ultrasonography/ use ppez
61	Imaging, Three-Dimensional/ use ppez
62	3D.tw.
63	exp echography/ use emczd
64	three dimensional imaging/ use emczd
65	((intraoperat* or intra-operat* or operative) adj2 (ultraso* or sonogra* or echogra*)).tw.
66	exp Magnetic Resonance Imaging/ use ppez
67	exp nuclear magnetic resonance imaging/ use emczd
68	((intraoperat* or intra-operat* or operative) adj2 (MR*1 or fMRI or magnetic resonance or DTI or imag* or tractogra*)).tw.
69	(iMRI or ioMRI).tw.
70	or/46-69
71	23 and 70
72	limit 71 to english language
73	Letter/ use ppez
74	letter.pt. or letter/ use emczd
75	note.pt.
76	editorial.pt.
77	Editorial/ use ppez
78	News/ use ppez
79	exp Historical Article/ use ppez
80	Anecdotes as Topic/ use ppez
81	Comment/ use ppez
82	Case Report/ use ppez
83	case report/ or case study/ use emczd
84	(letter or comment*).ti.
85	or/73-84
86	randomized controlled trial/ use ppez
87	randomized controlled trial/ use emczd
88	random*.ti,ab.
89	or/86-88
90	85 not 89
91	animals/ not humans/ use ppez
92	animal/ not human/ use emczd
93	nonhuman/ use emczd
94	exp Animals, Laboratory/ use ppez
95	exp Animal Experimentation/ use ppez
96	exp Animal Experiment/ use emczd
97	exp Experimental Animal/ use emczd
98	exp Models, Animal/ use ppez
99	animal model/ use emczd
100	exp Rodentia/ use ppez
101	exp Rodent/ use emczd
102	(rat or rats or mouse or mice).ti.
103	or/90-102
104	72 not 103
105	Epidemiologic Studies/
106	Case Control Studies/
107	Retrospective Studies/
108	Cohort Studies/
109	Longitudinal Studies/

#	Searches
110	Follow-Up Studies/
111	Prospective Studies/
112	Cross-Sectional Studies/
113	or/105-112 use ppez
114	clinical study/
115	case control study/
116	family study/
117	longitudinal study/
118	retrospective study/
119	prospective study/
120	cohort analysis/
121	or/114-120 use emczd
122	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
123	113 or 121 or 122
124	104 and 123
125	remove duplicates from 124

Other studies:

Date of initial search: 04/05/2017

Database: Cochrane Library, Issue 5 of 12, May 2017

Date of re-run: 12/09/2017
Database: Cochrane Library, Issue 9 of 12, September 2017 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	MeSH descriptor: [Astrocytoma] explode all trees
#3	MeSH descriptor: [Oligodendroglioma] explode all trees
#4	MeSH descriptor: [Glioblastoma] explode all trees
#5	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*)
#6	{or #1-#5}
#7	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees
#8	#6 and #7
#9	MeSH descriptor: [Neurosurgery] explode all trees
#10	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#11	(craniotom* or craniectom*)
#12	(ablat* or biops* or cytoreduc* or debulk* or microsur* or neurosurg* or operat* or procedure* or resect* or surg*)
#13	{or #9-#12}
#14	#6 and #13
#15	#8 or #14
#16	MeSH descriptor: [Neuronavigation] explode all trees
#17	MeSH descriptor: [Monitoring, Intraoperative] explode all trees
#18	((intra-operative or intraoperative or peri-operative or perioperative or perisurg* or peri-surg*) near/5 (tech* or modalit* or monitor* or navigat*))
#19	(neuronavigat* or neuro-navigat* or neuroimag* or neuro-imag* or neuromonitor* or neuro-monitor*)
#20	((brain or neuro* or intracereb* or intra-cereb* or intracrani* or intra-crani* or crani*) near/3 navigat*)
#21	(frameless stereota* or imag* guid*)
#22	MeSH descriptor: [Aminolevulinic Acid] explode all trees
#23	(5ALA or 5-ALA or 5-aminol?evulin* or aminolevulinic acid or amino levulinic acid or gliolan or levulan)
#24	MeSH descriptor: [Fluorescence] explode all trees
#25	fluorescen*
#26	((awake or wakeful* or stereota*) near/3 (craniotom* or craniectom* or biops* or cytoreduc* or debult* or excis* or microsurg* or neurosurg* or operat* or procedure* or resect* or surg*))
#27	MeSH descriptor: [Neuroimaging] explode all trees

ID	Search
#28	MeSH descriptor: [Electric Stimulation] explode all trees
#29	MeSH descriptor: [Deep Brain Stimulation] explode all trees
#30	MeSH descriptor: [Electroencephalography] explode all trees
#31	((electric* or electro* or brain or cereb* or cortex or cortical or neuro* or subcortex or subcortical or bipolar or bi-polar or monopolar or mono-polar) near/3 (mapping or stimulat*))
#32	(electrocorticogra* or ECoG)
#33	(electrosubcorticogra* or ESubCoG)
#34	(((intracranial or intra-cranial) near/3 electroencephalogra*) or iEEG)
#35	MeSH descriptor: [Ultrasonography] explode all trees
#36	MeSH descriptor: [Imaging, Three-Dimensional] explode all trees
#37	3D
#38	((intraoperat* or intra-operat* or operative) near/3 (ultraso* or sonogra* or echogra*))
#39	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#40	((intraoperat* or intra-operat* or operative) near/3 (MR* or fMR* or magnetic resonance or DTI or imag* or tractogra*))
#41	(iMRI or ioMRI)
#42	{or #16-#41}
#43	#15 and #42

Literature search strategy for review 5a – follow-up for glioma

Date of initial search: 22/03/2017

Database: Embase 1974 to 2017 March 21, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database: Embase 1980 to 2017 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/ use ppez
2	exp Glioma/ use oemezd
3	exp Astrocytoma/ use ppez
4	exp Astrocytoma/ use oemezd
5	Oligodendroglioma/ use ppez
6	exp Glioblastoma/ use ppez
7	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
8	or/1-7
9	Meningioma/ use ppez
10	Meningeal Neoplasms/ use ppez
11	exp Meningioma/ use oemezd
12	meningioma*.tw.
13	(mening* adj3 (neoplas* or cancer* or carcin* or tumo* or malign* or h?emangiopericytoma* or h?emangioblastoma*)).tw.
14	or/9-13
15	exp Brain Neoplasms/ use ppez
16	exp Brain Tumor/ use oemezd
17	exp Cerebral Cortex/ use ppez
18	exp Brain Cortex/ use oemezd
19	exp Brain/ use ppez
20	exp Brain/ use oemezd

#	Searches
21	exp Meninges/ use ppez
22	Meninx/ use oemezd
23	or/15-22
24	exp Neoplasm Metastasis/ use ppez
25	metastasis/ use oemezd
26	24 or 25
27	23 and 26
28	exp Brain Neoplasms/sc use ppez
29	Brain Metastasis/ use oemezd
30	Meningeal Metastasis/ use oemezd
31	or/28-30
32	27 or 31
33	((brain or cereb* or intracranial or mening* or brainstem*) adj3 (metasta* or micrometa* or macrometa* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
34	32 or 33
35	8 or 14 or 34
36	exp Recurrence/ use ppez
37	Neoplasm Recurrence, Local/ use ppez
38	Disease Progression/ use ppez
39	cancer recurrence/ use oemezd
40	recurrent disease/ use oemezd
41	tumor recurrence/ use oemezd
42	recurr*.ti.
43	or/36-42
44	35 and 43
45	exp Aftercare/ use ppez
46	exp aftercare/ use oemezd
47	(aftercare or "after care" or after-care or follow-up or "follow up" or followup or surveillance).tw.
48	(after treatment or after-treatment or posttreatment or post treatment or post-treatment or post-therap* or post therap*).ti,ab.
49	((post-surg* or post surg* or post-operat* or postoperat* or post operat*) adj1 (evaluat* or monitor* or care)).tw.
50	(post-hospital* or post hospital* or posthospital* or after hospital* or follow* hospital*).ti,ab.
51	disease surveillance/ use oemezd
52	periodic medical examination/ use oemezd
53	"medical record review"/ use oemezd
54	exp patient monitoring/ use oemezd
55	(re-examin* or reexamin or monitor* or periodic examin* or regular examin* or checkup* or check-up* or check up*).ti,ab.
56	follow*.ti.
57	or/45-56
58	44 and 57
59	limit 58 to english language
60	limit 59 to yr="1990 -Current"
61	Letter/ use ppez
62	letter.pt. or letter/ use oemezd
63	note.pt.
64	editorial.pt.
65	Editorial/ use ppez
66	News/ use ppez
67	exp Historical Article/ use ppez
68	Anecdotes as Topic/ use ppez
69	Comment/ use ppez
70	Case Report/ use ppez
71	case report/ or case study/ use oemezd
72	(letter or comment*).ti.
73	or/61-72
74	randomized controlled trial/ use ppez
75	randomized controlled trial/ use oemezd
76	random*.ti,ab.
77	or/74-76

#	Searches
78	73 not 77
79	animals/ not humans/ use ppez
80	animal/ not human/ use oemezd
81	nonhuman/ use oemezd
82	exp Animals, Laboratory/ use ppez
83	exp Animal Experimentation/ use ppez
84	exp Animal Experiment/ use oemezd
85	exp Experimental Animal/ use oemezd
86	exp Models, Animal/ use ppez
87	animal model/ use oemezd
88	exp Rodentia/ use ppez
89	exp Rodent/ use oemezd
90	(rat or rats or mouse or mice).ti.
91	or/78-90
92	60 not 91
93	Meta-Analysis/
94	Meta-Analysis as Topic/
95	systematic review/
96	meta-analysis/
97	(meta analy* or metanaly* or metaanaly*).ti,ab.
98	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
99	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
100	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
101	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
102	(search* adj4 literature).ab.
103	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
104	cochrane.jw.
105	((pool* or combined) adj2 (data or trials or studies or results)).ab.
106	or/93-94,97,99-104 use ppez
107	or/95-98,100-105 use oemezd
108	or/106-107
109	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
110	109 use ppez
111	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
112	111 use ppez
113	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
114	113 use oemezd
115	110 or 112
116	112 or 114
117	Cohort Studies/ or Longitudinal Studies/ or Follow-Up Studies/ or Prospective Studies/ or Comparative Study/
118	117 use ppez
119	cohort analysis/ or longitudinal study/ or follow up/ or prospective study/ or comparative study/
120	119 use oemezd
121	((cohort* or follow-up or follow?up or inciden* or longitudinal or prospective) adj1 (stud* or research or analys*)).tw.
122	118 or 120 or 121
123	108 or 115 or 122
124	92 and 123
125	remove duplicates from 124

Date of initial search: 22/03/2017

Database: The Cochrane Library, Issue 3 of 12, March 2017

Date of re-run: 07/09/2017

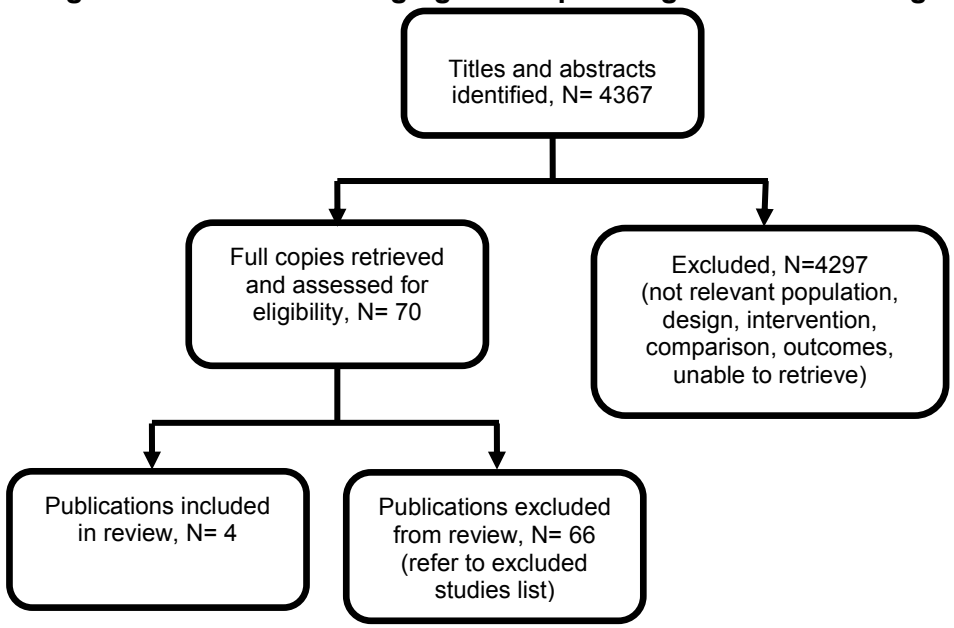
Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	(glioma* or glioblastoma* or gliosarcoma* or astrocytoma* or astroblastoma* or oligodendroglioma* or oligodendrocytoma* or oligoastrocytoma* or GBM)
#3	(glial near/3 (neoplas* or cancer* or tumo* or carcin* or malign* or metasta*))
#4	{or #1-#3}
#5	MeSH descriptor: [Meningioma] explode all trees
#6	MeSH descriptor: [Meningeal Neoplasms] explode all trees
#7	meningioma*
#8	(mening* near/3 (neoplas* or cancer* or carcin* or tumo* or malign* or metasta*))
#9	{or #5-#8}
#10	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#11	MeSH descriptor: [Brain Neoplasms] explode all trees
#12	MeSH descriptor: [Brain] explode all trees
#13	#11 or #12
#14	#10 and #13
#15	((brain or cereb* or intracranial or mening*) near/3 (metasta* or micometasta* or spread* or involvement or carcinosis or secondar*))
#16	#14 or #15
#17	#4 or #9 or #16
#18	MeSH descriptor: [Recurrence] explode all trees
#19	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#20	recurr*
#21	{or #18-#20}
#22	#17 and #21
#23	MeSH descriptor: [Aftercare] explode all trees
#24	(aftercare or "after care" or after-care or follow-up or "follow up" or followup or surveillance)
#25	("after treatment*" or after-treatment* or posttreatment* or "post treatment*" or post-treatment* or post-therap* or "post therap*")
#26	((post-surg* or "post surg*" or post-operat* or postoperat* or "post operat*") adj1 (evaluat* or monitor* or care))
#27	(post-hospital* or "post hospital*" or posthospital* or "after hospital*" or "follow* hospital*")
#28	{or #23-#27}
#29	#22 and #28 Publication Year from 1990 to 2017

Appendix C – Clinical evidence study selection

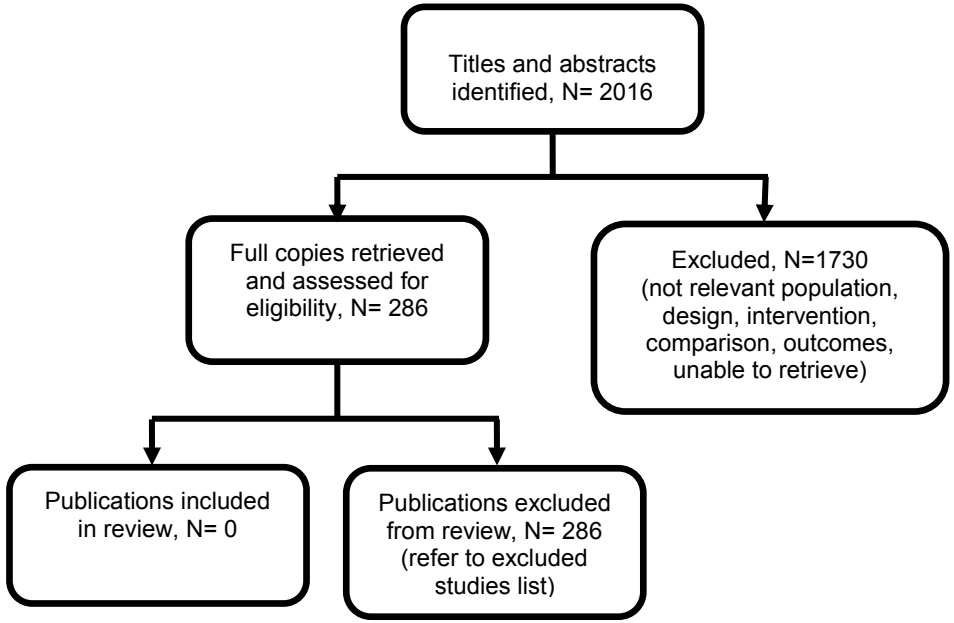
PRISMA flowchart for review 1a - imaging for suspected glioma and meningioma

Figure 2: Flow diagram of review 1a - imaging for suspected glioma and meningioma



PRISMA flowchart for review 1d – molecular markers to inform prognosis / guide treatment

Figure 3: Flow diagram of clinical article selection for review 1d – molecular markers to inform prognosis / guide treatment



PRISMA flowchart for review 1c – timing and extend of initial surgery for low-grade glioma

Figure 4: Flow diagram of clinical article selection for review 1c – timing and extend of initial surgery for low-grade glioma

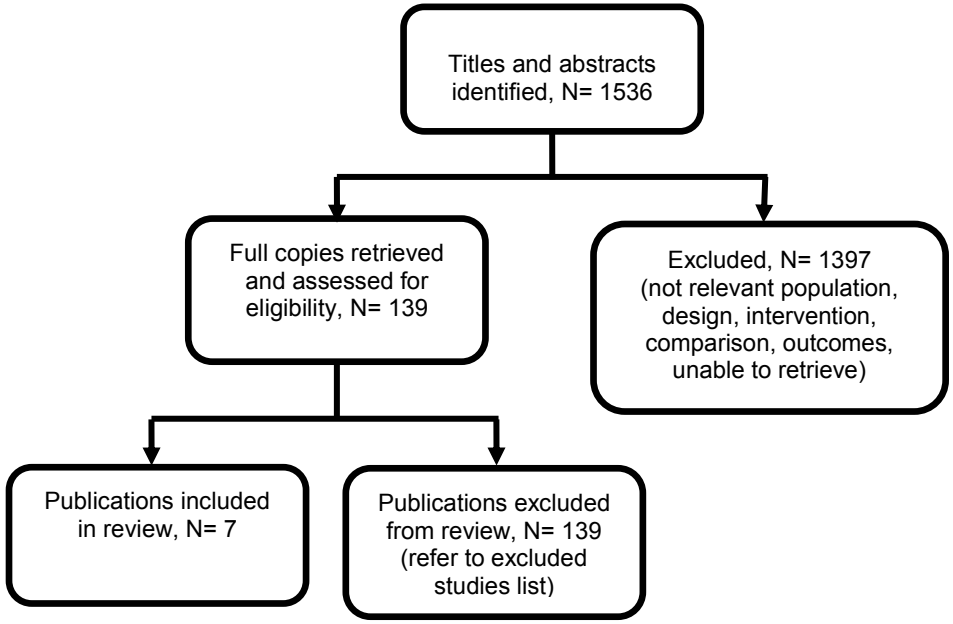
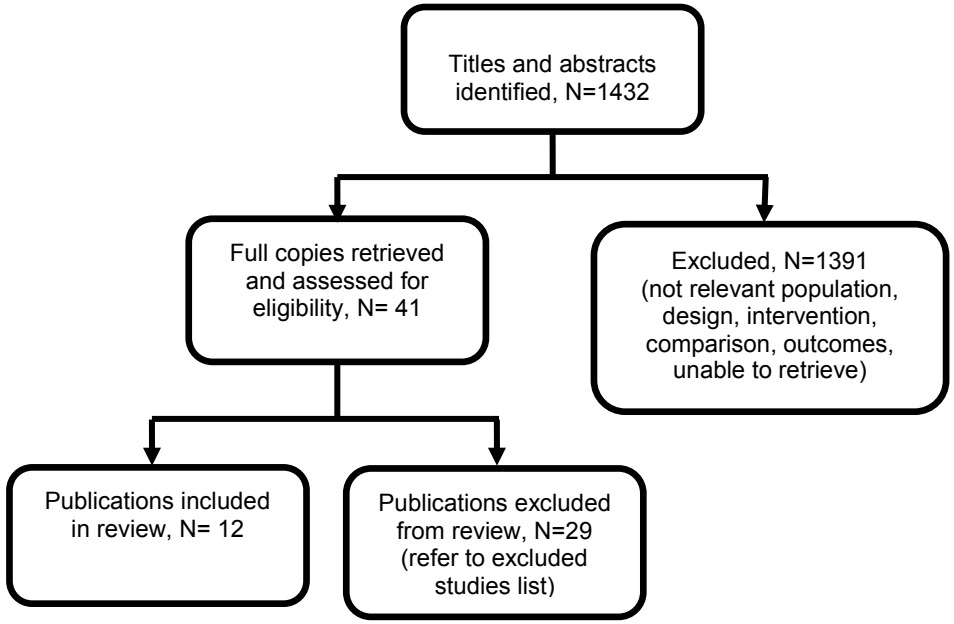
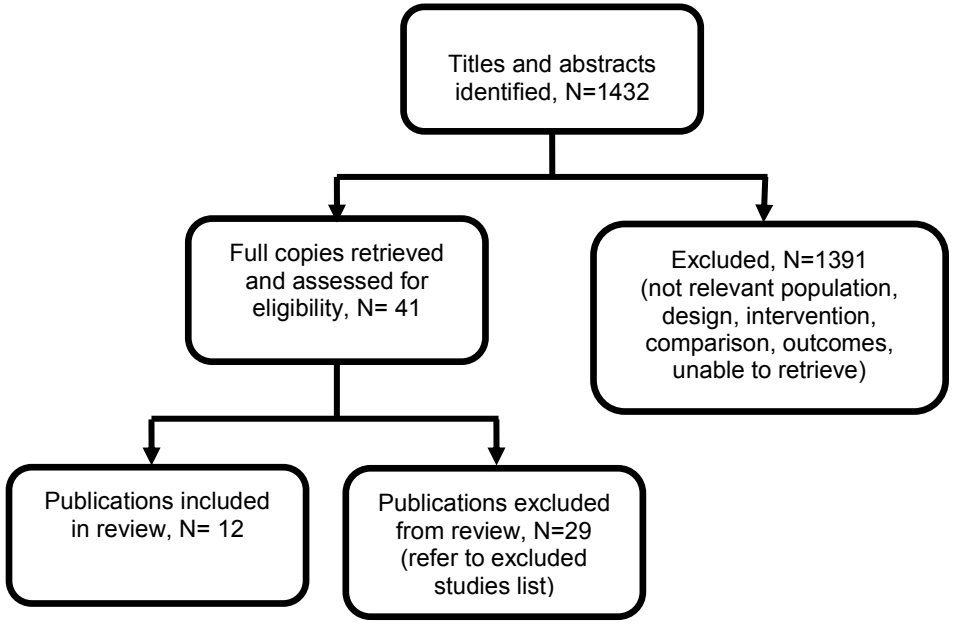


Figure 5: Flow diagram of clinical article selection for review 1c – Timing and extend of initial surgery for low-grade glioma



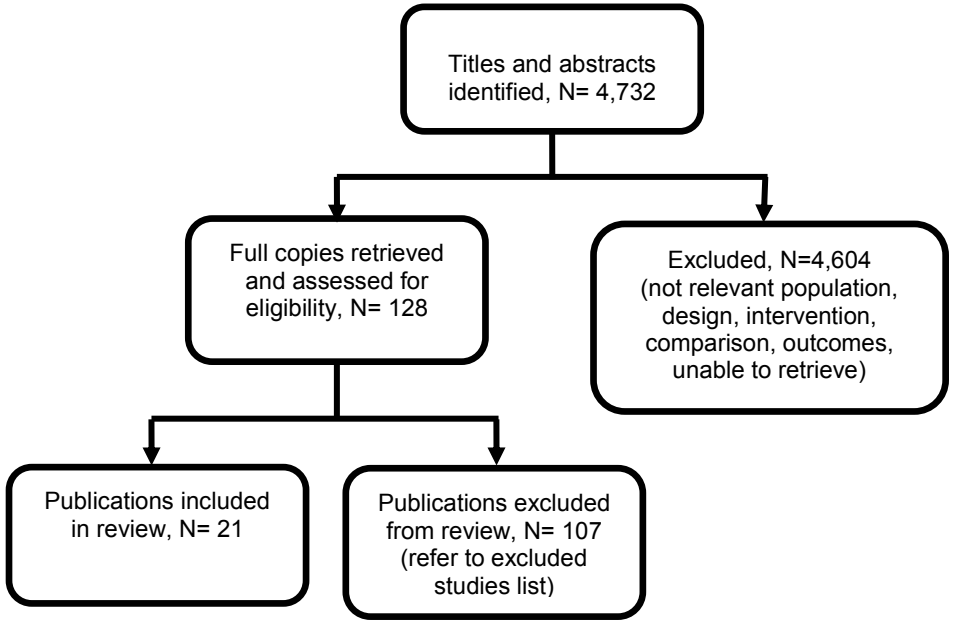
PRISMA flowchart for review 2a – further management of low-grade glioma

Figure 6: Flow diagram of clinical article selection for review 2a – further management of low-grade glioma



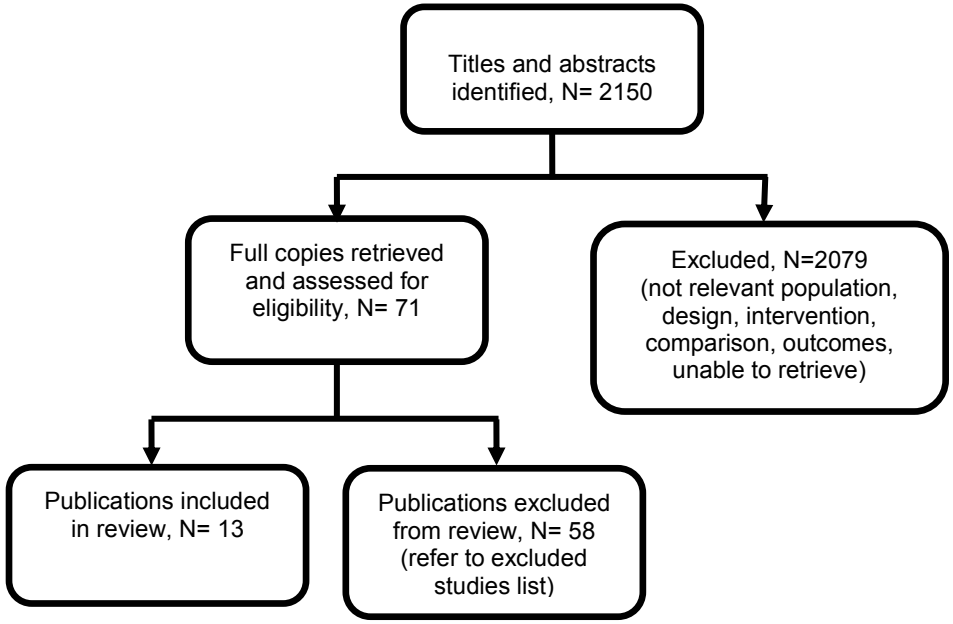
PRISMA flowchart for review 2c – initial management of high-grade glioma

Figure 7: Flow diagram of clinical article selection for review 2c – initial management of high-grade glioma



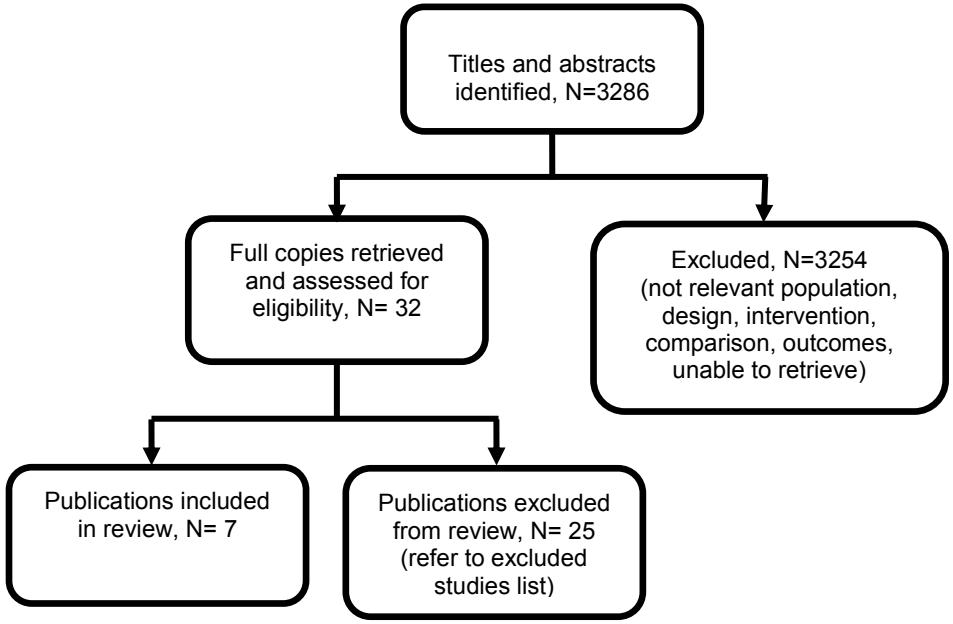
PRISMA flowchart for review 2d – management of recurrent high-grade glioma

Figure 8: Flow diagram of clinical article selection for review 2d – management of recurrent high-grade glioma



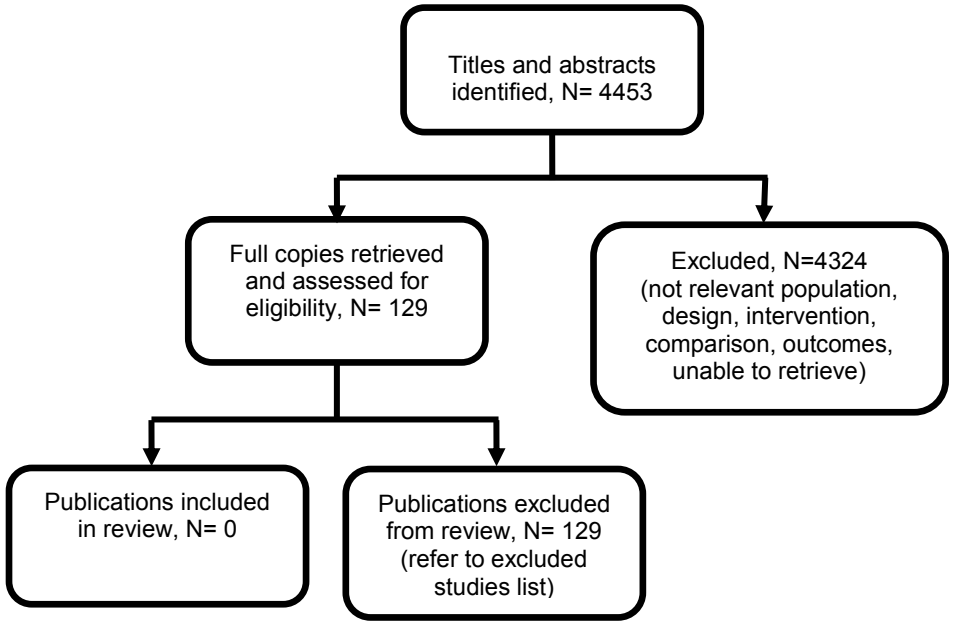
PRISMA flowchart for review 2b – resection of glioma

Figure 9: Flow diagram of clinical article selection for review 2b – resection of glioma



PRISMA flowchart for review 5a – follow-up for glioma

Figure 10: Flow diagram of clinical article selection for follow up after treatment for glioma, meningioma and brain metastases reviews (the searches for all three reviews were conducted as one search)



Appendix D – Clinical evidence tables

See Supplementary Material D.

Appendix E – Forest plots

Forest plots for review 1a - imaging for suspected glioma and meningioma

Not applicable – identified evidence was not suitable for meta-analysis.

Forest plots for review 1d – molecular markers to inform prognosis / guide treatment

Not applicable - no evidence was identified.

Forest plots for review 1c – timing and extend of initial surgery for low-grade glioma

Not applicable – identified evidence was not suitable for meta-analysis.

Forest plots for review 2a – further management of low-grade glioma

Figure 11: RT + PCV versus RT: overall survival – subgroup differences by histological subtype in WHO grade I/II glioma

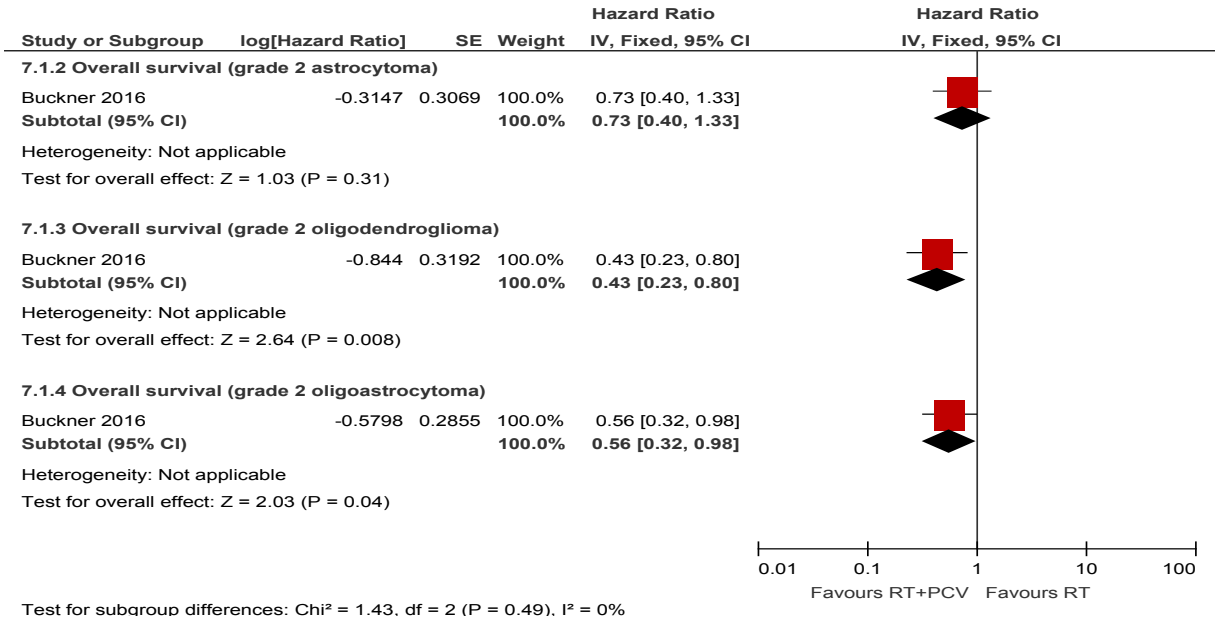


Figure 12: RT + PCV versus RT: progression free survival – subgroup differences by histological subtype in WHO grade I/II glioma

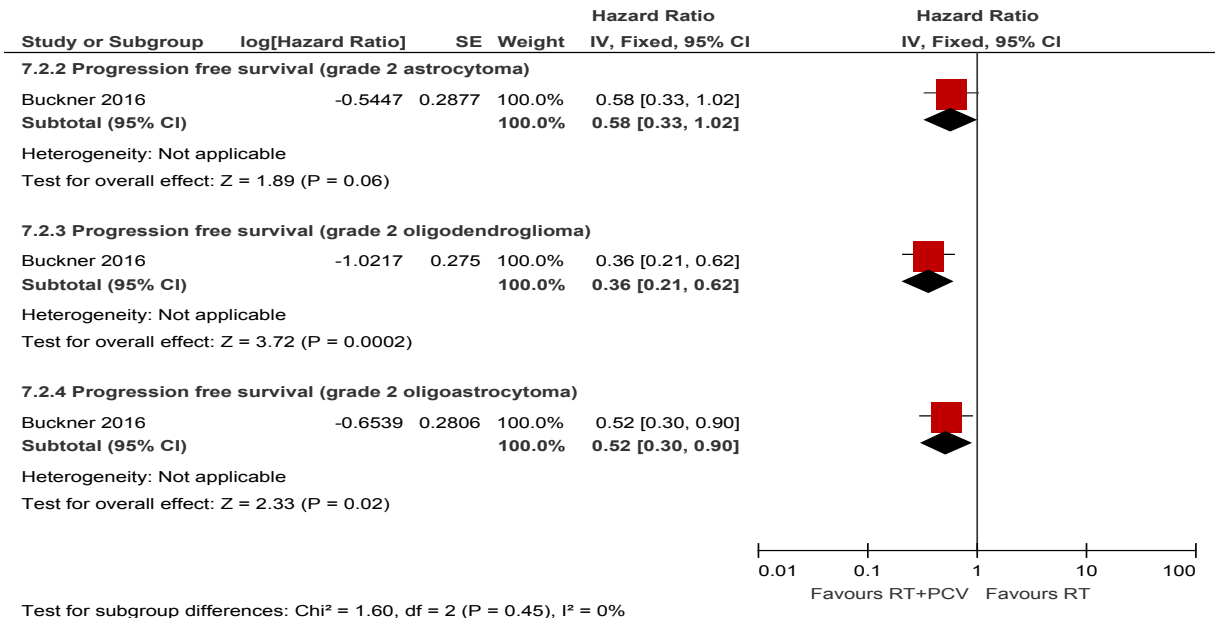
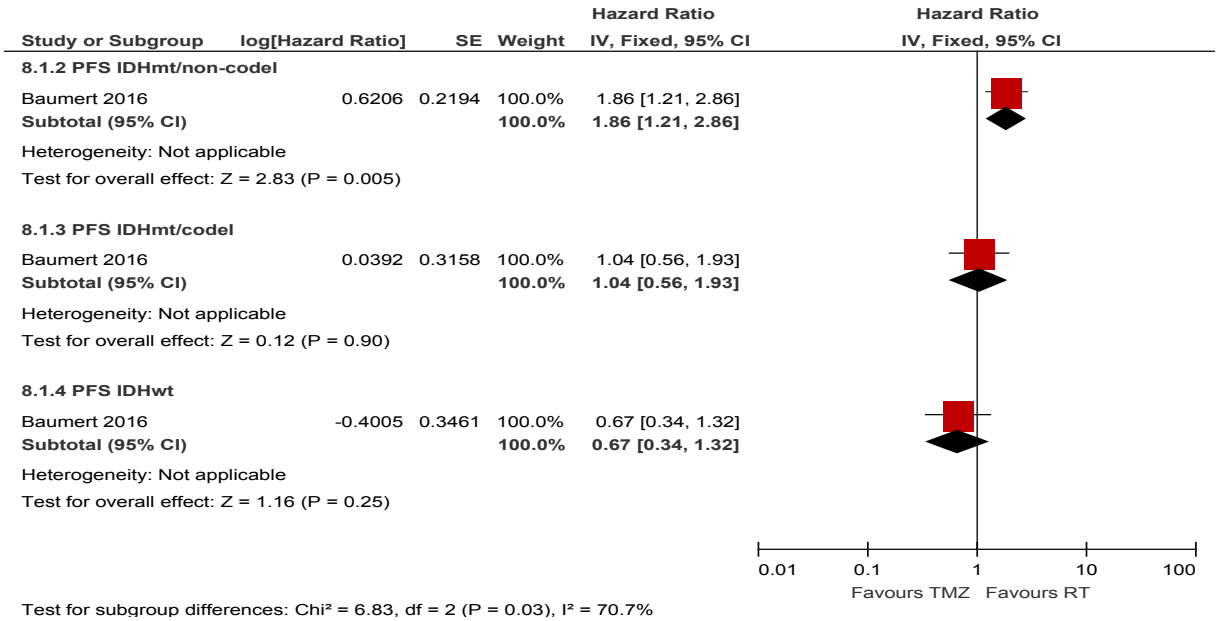


Figure 13: TMZ versus RT: progression free survival – subgroup differences by IDH mutation in WHO grade I/II glioma



Forest plots for review 2c – initial management of high-grade glioma

Figure 14: Bevacuzimab plus TMZ + RT versus TMZ + RT: overall survival in WHO grade IV glioma

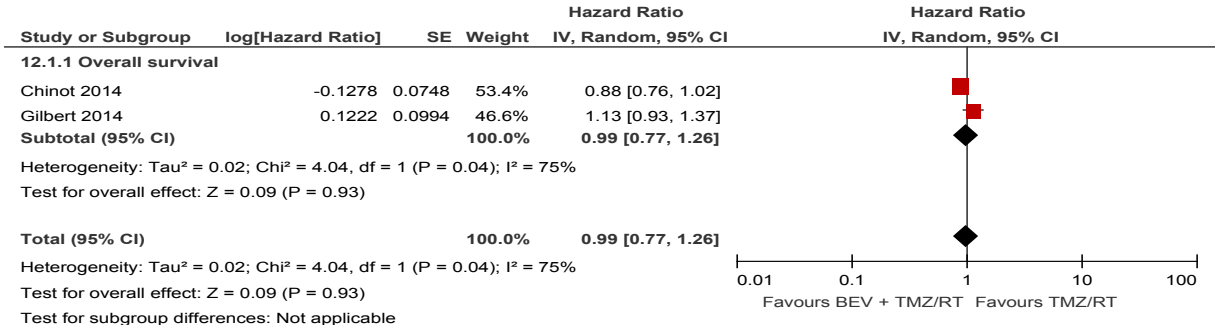


Figure 15: Bevacuzimab plus TMZ + RT versus TMZ + RT: overall survival – subgroup differences by MGMT methylation in WHO grade IV glioma

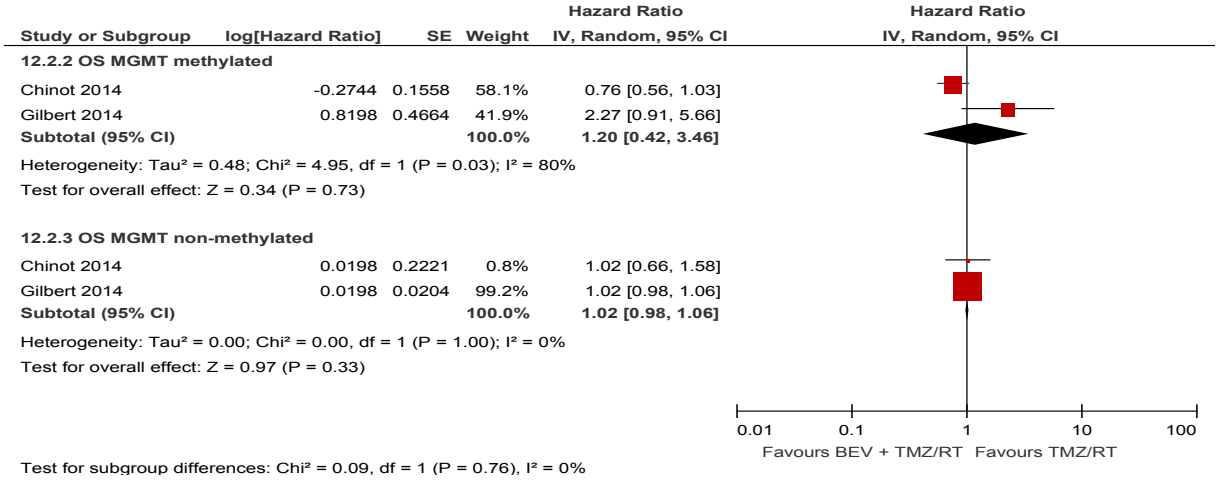


Figure 16: Bevacuzimab plus TMZ + RT versus TMZ + RT: overall survival – subgroup differences by RPA class in WHO grade IV glioma

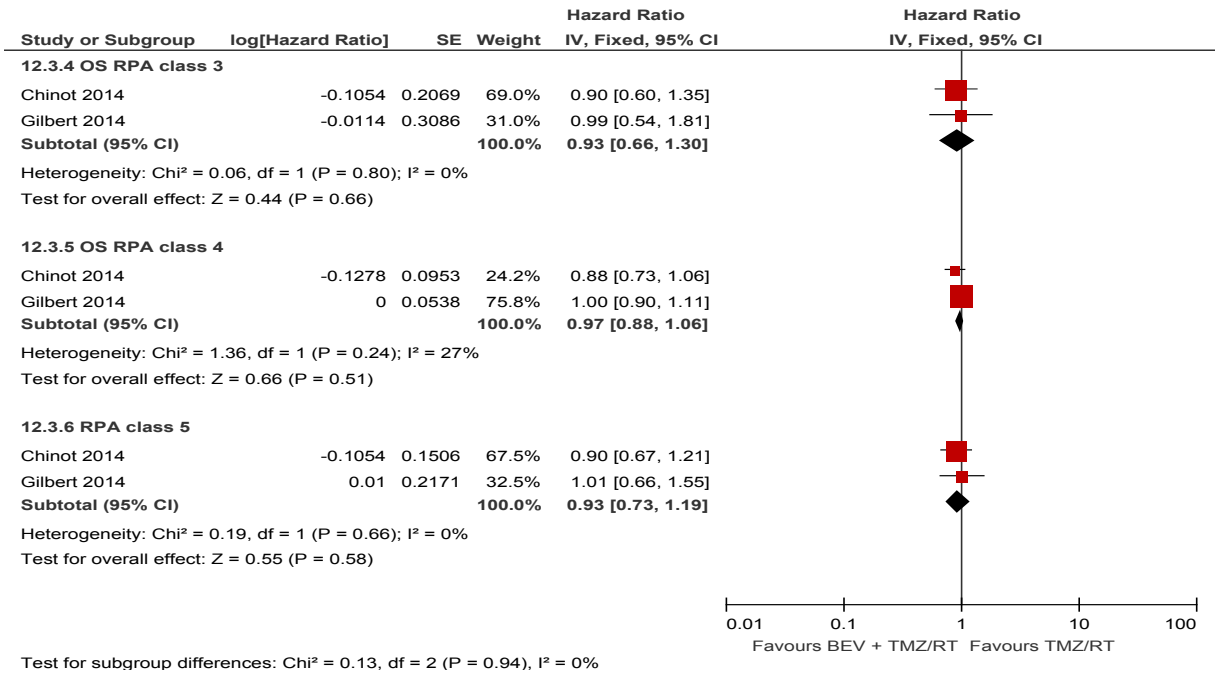


Figure 17: Bevacuzimab plus TMZ + RT versus TMZ + RT: progression free survival in WHO grade IV glioma

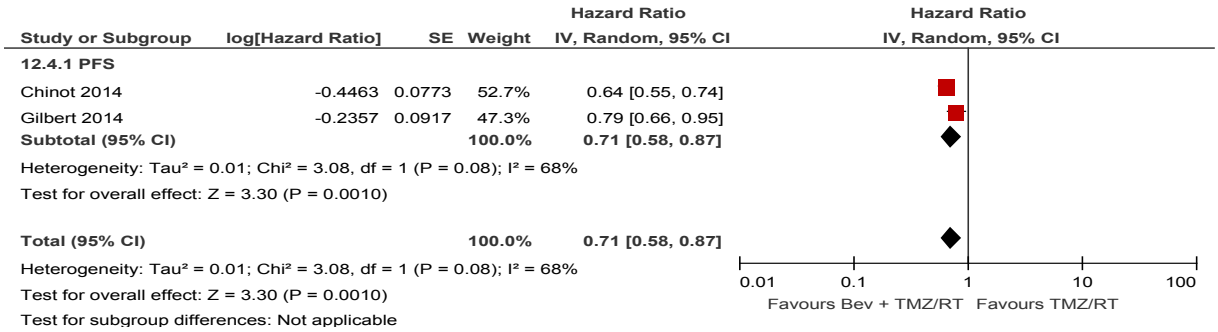


Figure 18: Bevacuzimab plus TMZ + RT versus TMZ + RT: progression free survival – subgroup differences by MGMT methylation status in WHO grade IV glioma

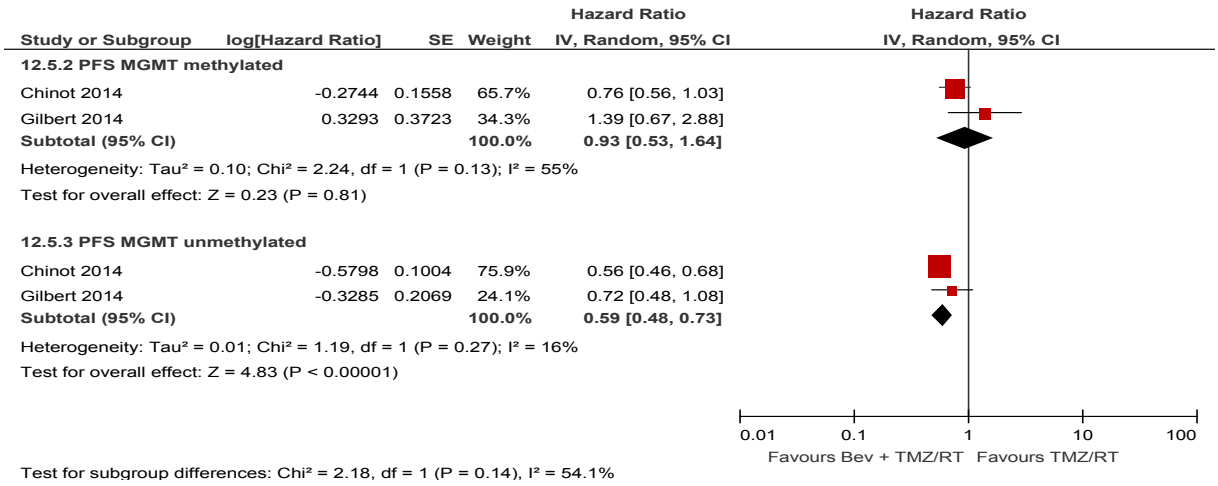


Figure 19: Bevacuzimab plus TMZ + RT versus TMZ + RT: progression free survival – subgroup difference by RPA class in WHO grade IV glioma

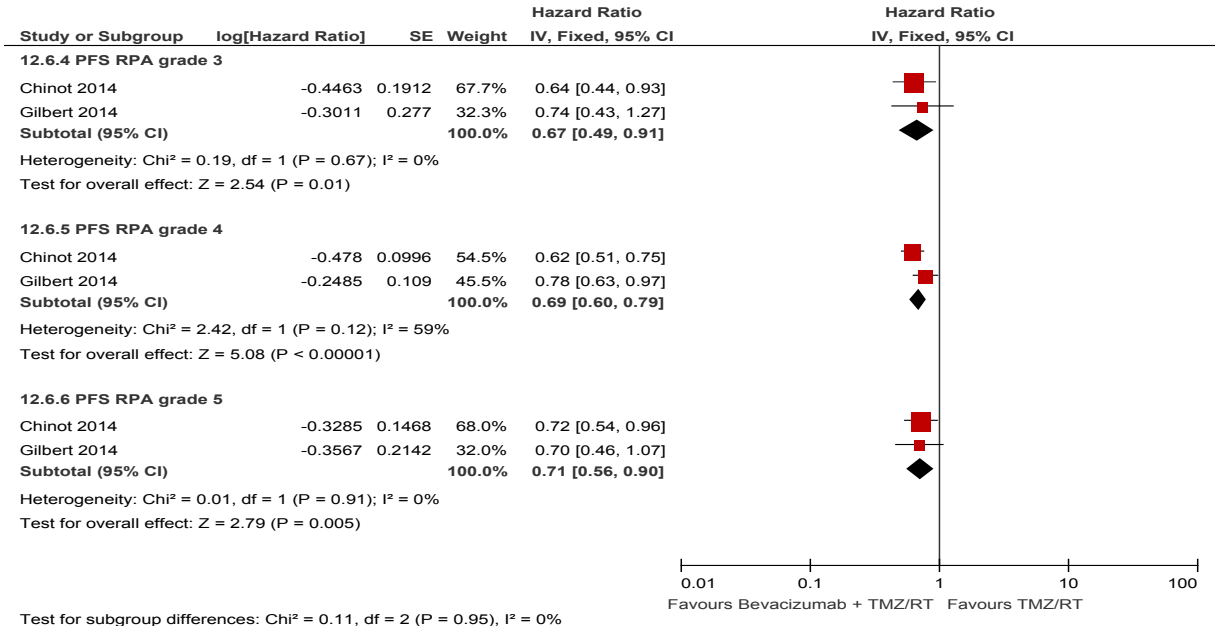


Figure 20: Bevacuzimab plus TMZ + RT versus TMZ + RT: wound complications in WHO grade IV glioma

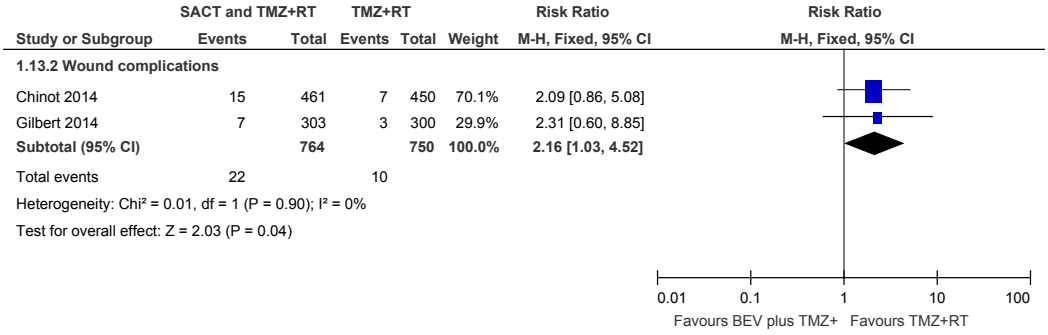


Figure 21: Nimotuzumab plus TMZ+RT versus TMZ+RT: overall survival – subgroup differences by MGMT methylation status in grade IV glioma

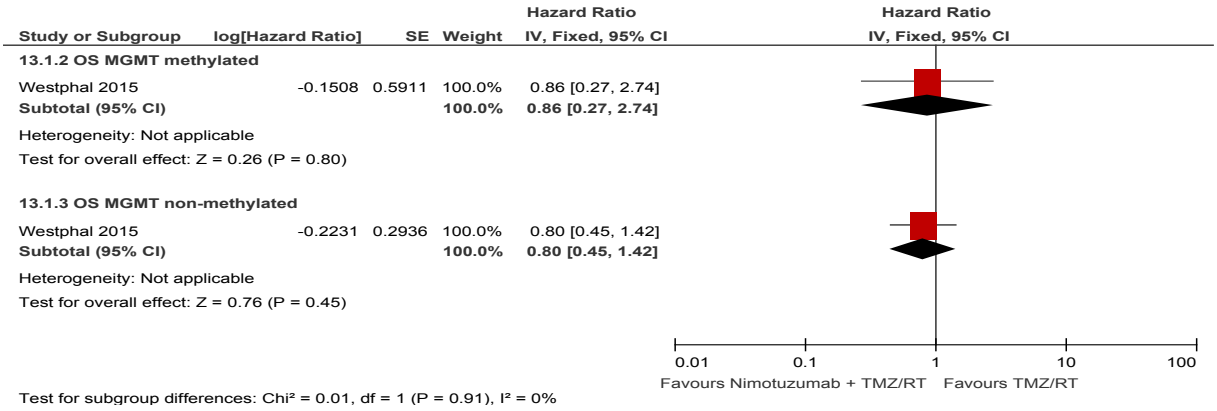


Table 91: Cilengitide plus TMZ+RT versus TMZ+RT. Overall survival – subgroup differences by RPA grade in WHO grade IV glioma

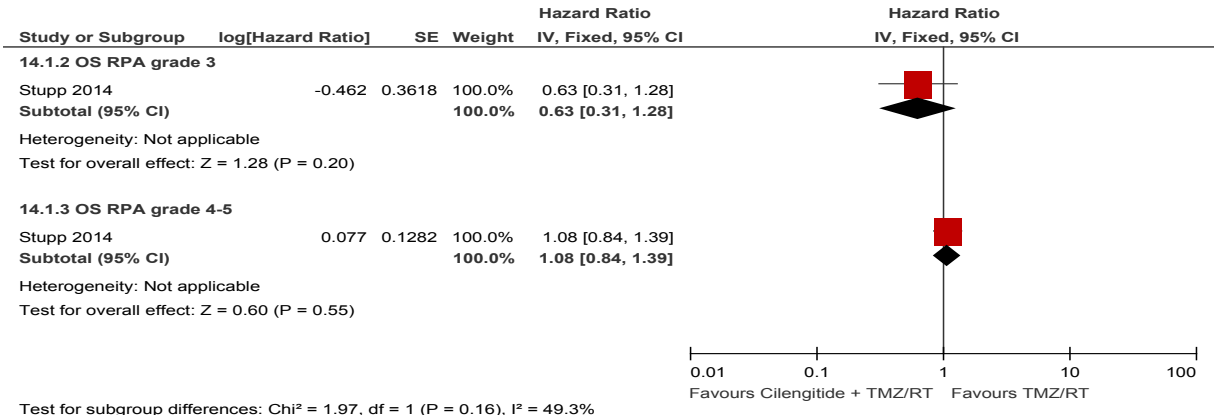


Figure 22: TMZ+RT and dose dense TMZ versus TMZ+RT and standard TMZ: overall survival – subgroup differences by MGMT status in grade IV glioma

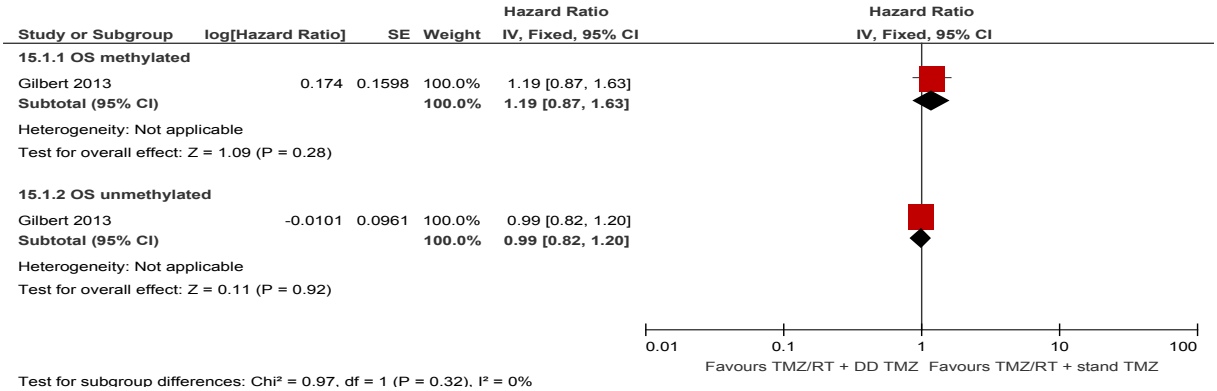


Figure 23: TMZ+RT and dose dense TMZ versus TMZ+RT and standard TMZ: progression free survival – subgroup differences by MGMT status in grade IV glioma

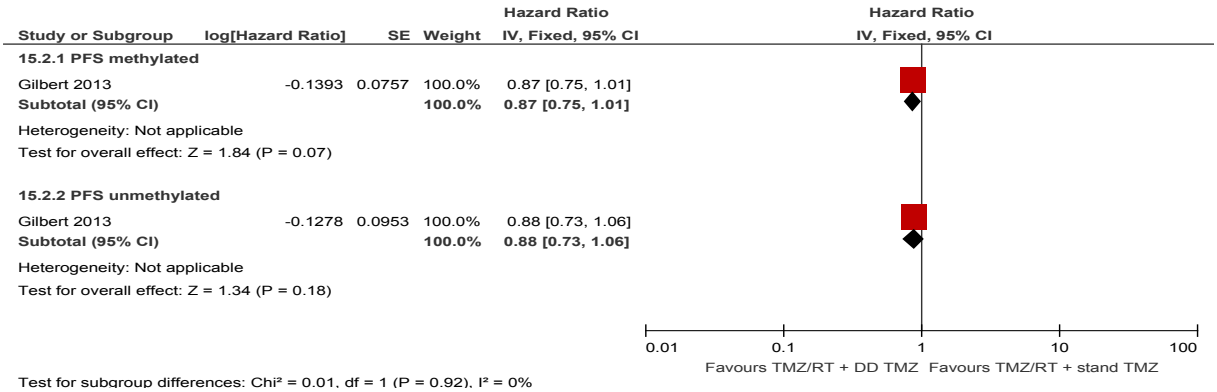


Figure 24: TMZ versus standard RT in older people: overall survival in WHO grade IV glioma

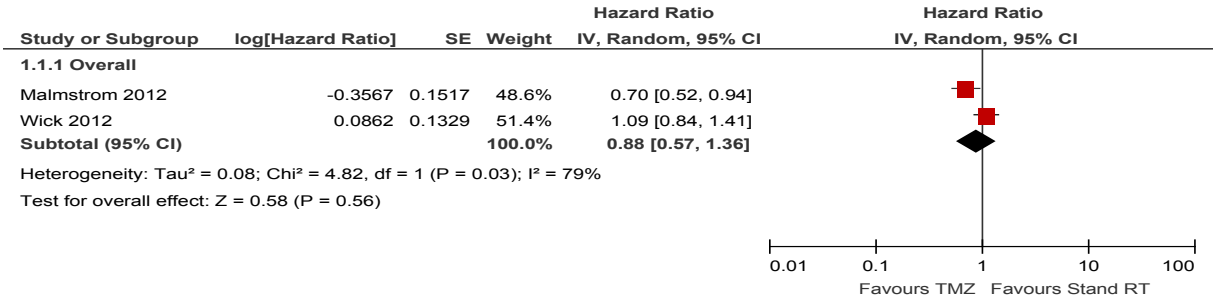
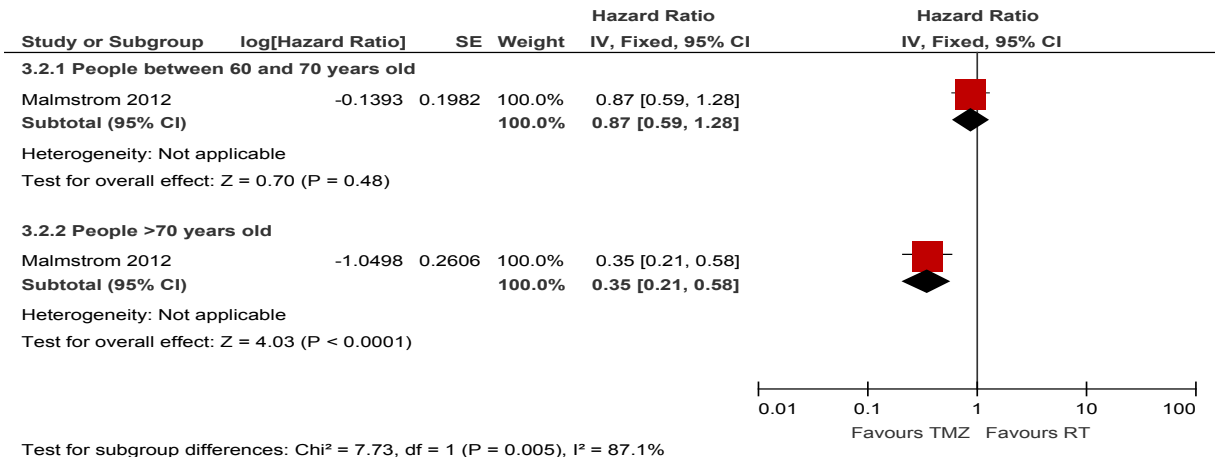


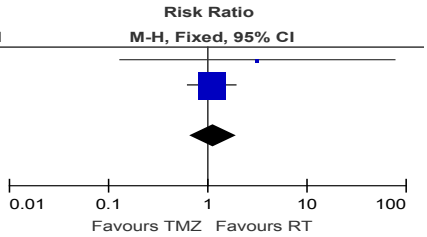
Figure 25: TMZ versus standard RT in older people: overall survival – subgroup differences by age in WHO grade IV glioma



Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
3.2.1 People between 60 and 70 years old				
Malmstrom 2012	-0.1393	0.1982	100.0%	0.87 [0.59, 1.28]
Subtotal (95% CI)			**100.0%**	**0.87 [0.59, 1.28]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.70 (P = 0.48)				
3.2.2 People >70 years old				
Malmstrom 2012	-1.0498	0.2606	100.0%	0.35 [0.21, 0.58]
Subtotal (95% CI)			**100.0%**	**0.35 [0.21, 0.58]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.03 (P < 0.0001)				

Test for subgroup differences: Chi² = 7.73, df = 1 (P = 0.005), I² = 87.1%

Figure 26: TMZ versus standard RT in older people: Grade 3-4 fatigue for WHO grade IV glioma



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malmstrom 2012	1	90	0	95	2.3%	3.16 [0.13, 76.70]
Wick 2012	24	195	20	178	97.7%	1.10 [0.63, 1.91]
Total (95% CI)		**285**		**273**	**100.0%**	**1.14 [0.66, 1.97]**
Total events	25		20			
Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						

Figure 27: RT with concomitant and adjuvant TMZ versus RT alone: overall survival – subgroup differences by age in WHO grade IV glioma

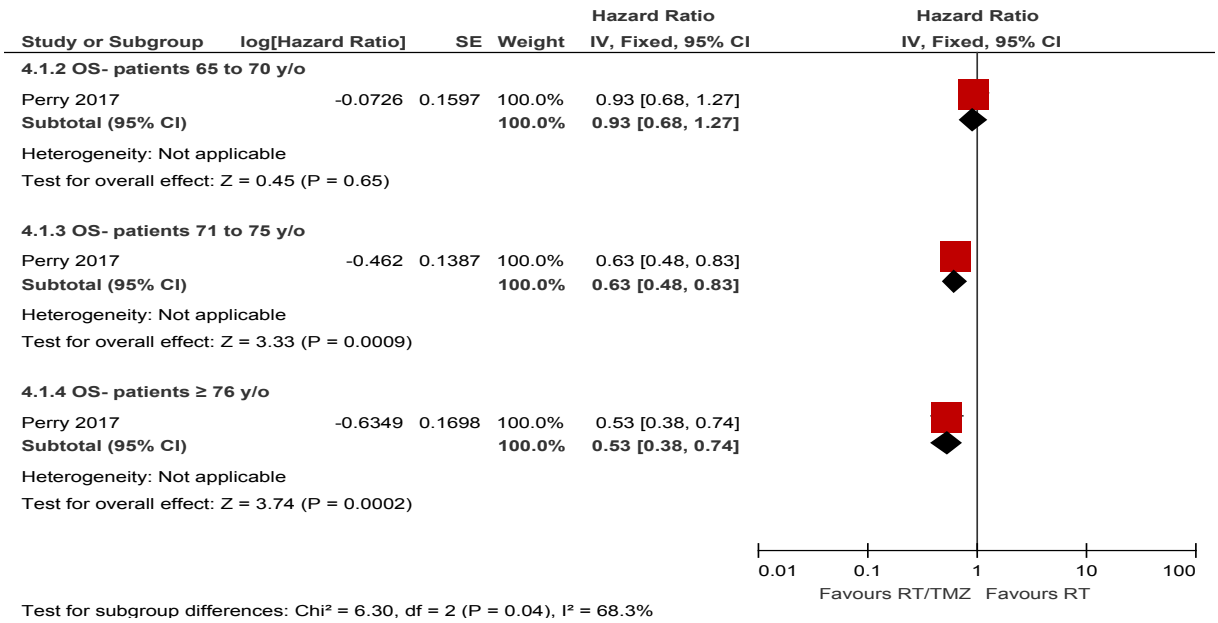


Figure 28: RT with concomitant and adjuvant TMZ versus RT alone: overall survival – subgroup differences by MGMT methylation status in WHO grade IV glioma

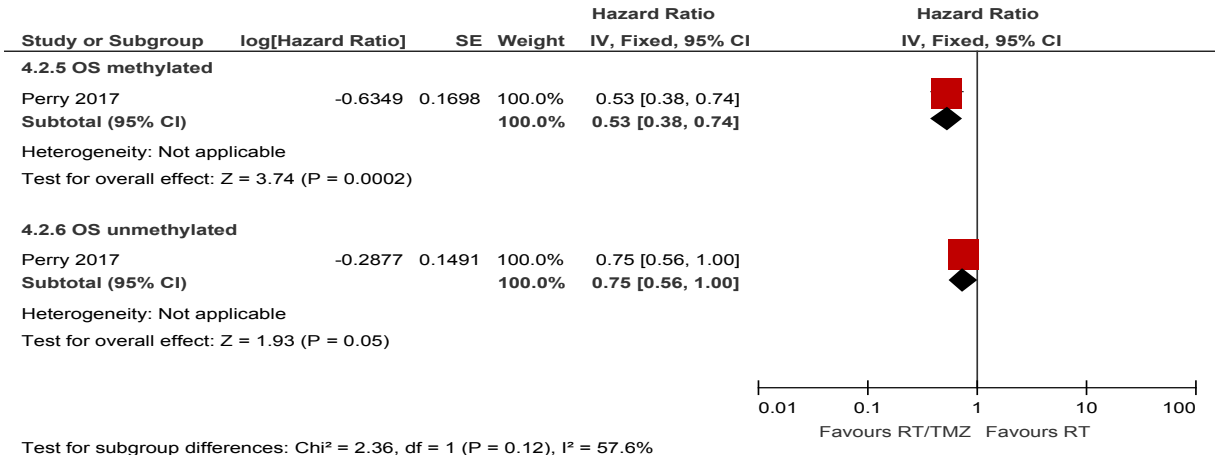


Figure 29: RT with concomitant and adjuvant TMZ versus RT alone: progression free survival – subgroup differences by age in WHO grade IV glioma

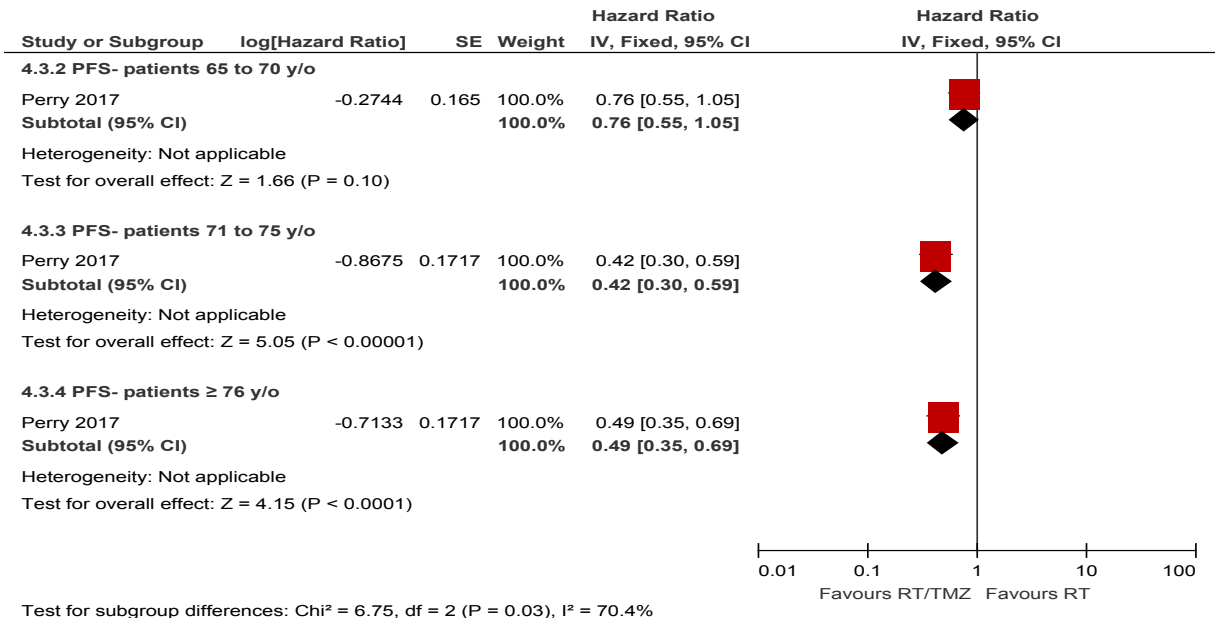


Figure 30: RT with concomitant and adjuvant TMZ versus RT alone: overall survival – subgroup differences by MGMT methylation status in WHO grade IV glioma

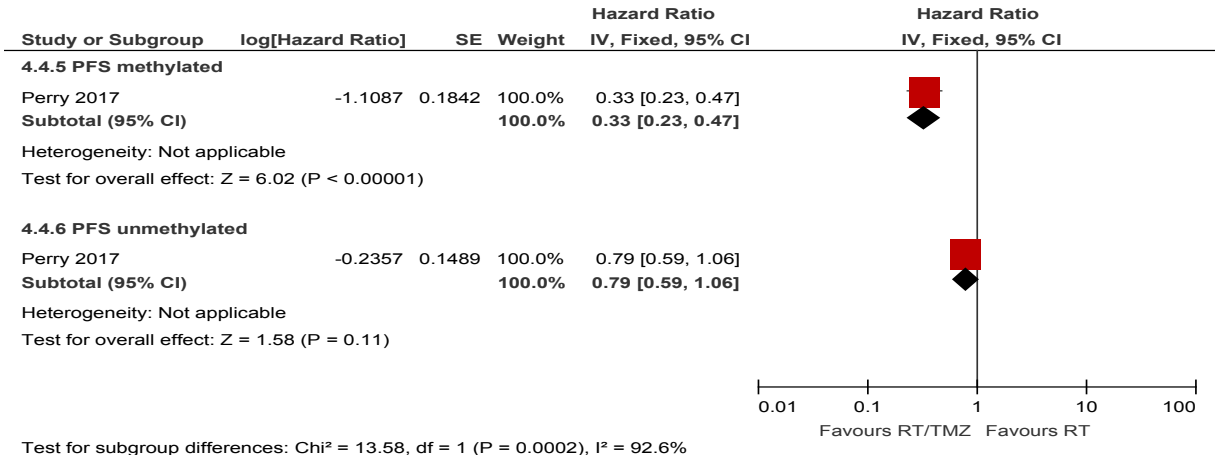


Figure 31: RT + PCV versus RT: overall survival in WHO III glioma

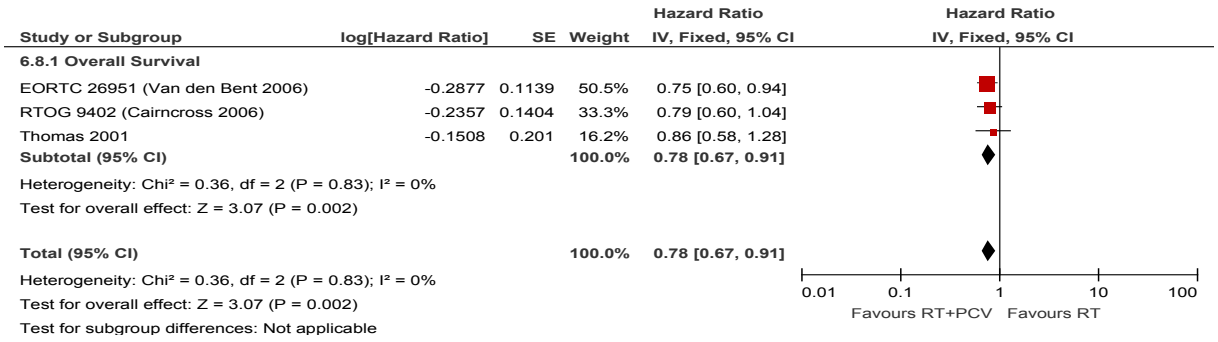


Figure 32: RT + PCV versus RT: overall survival - subgroup differences by codeletion of chromosomes 1p/19q in WHO III glioma

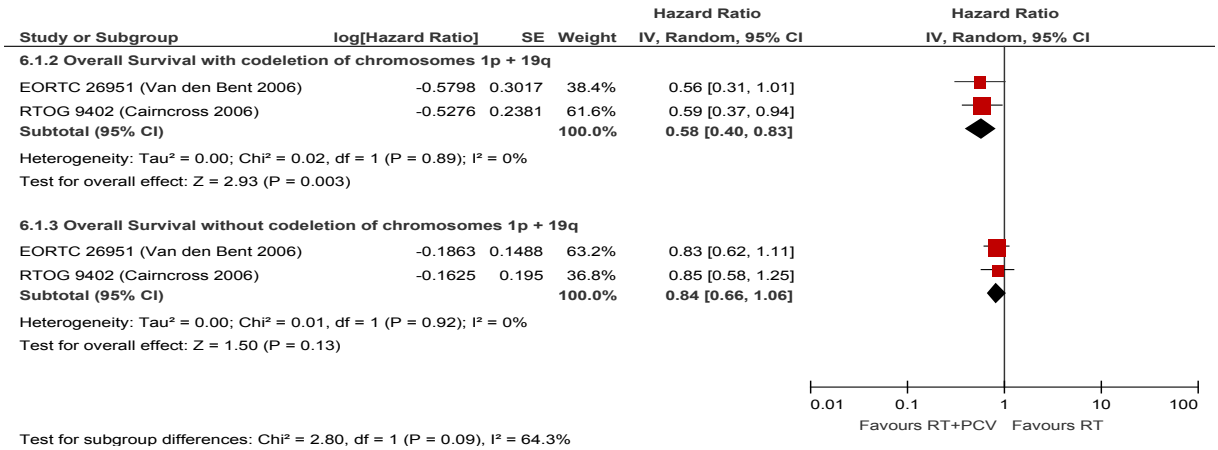


Figure 33: RT + PCV versus RT: overall survival – subgroup differences by MGMT methylation in WHO III glioma

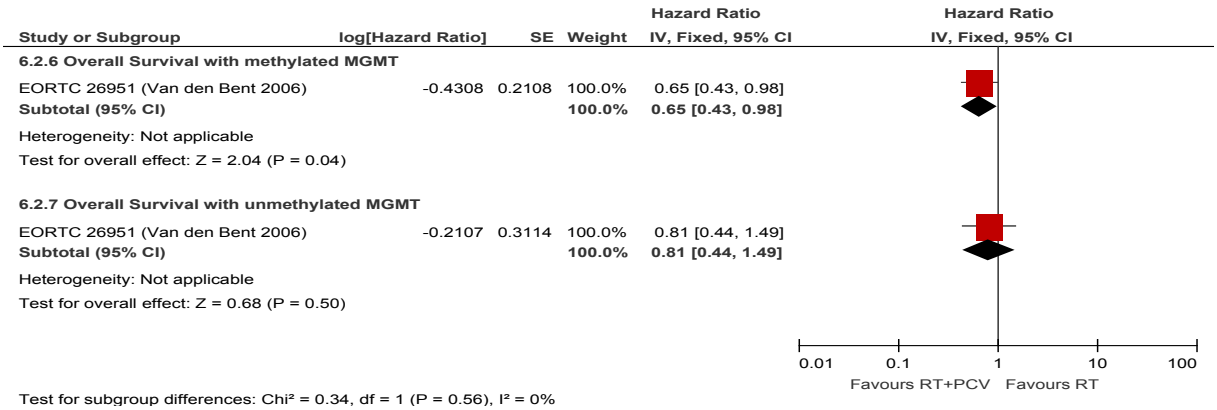


Figure 34: RT + PCV versus RT: overall survival – subgroup differences by IDH-1 mutation in WHO III glioma

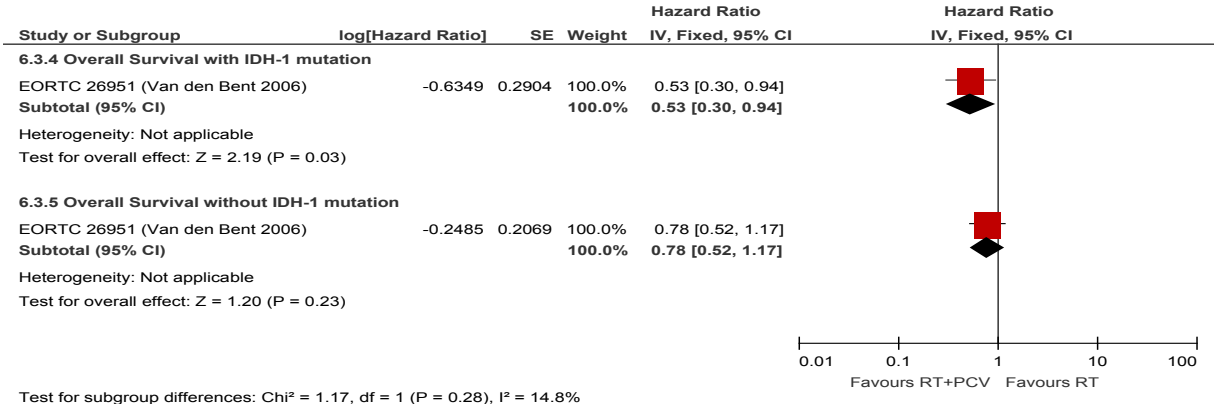


Figure 35: RT + PCV versus RT: overall survival – subgroup differences by IDH-1 or 2 mutations in WHO III glioma

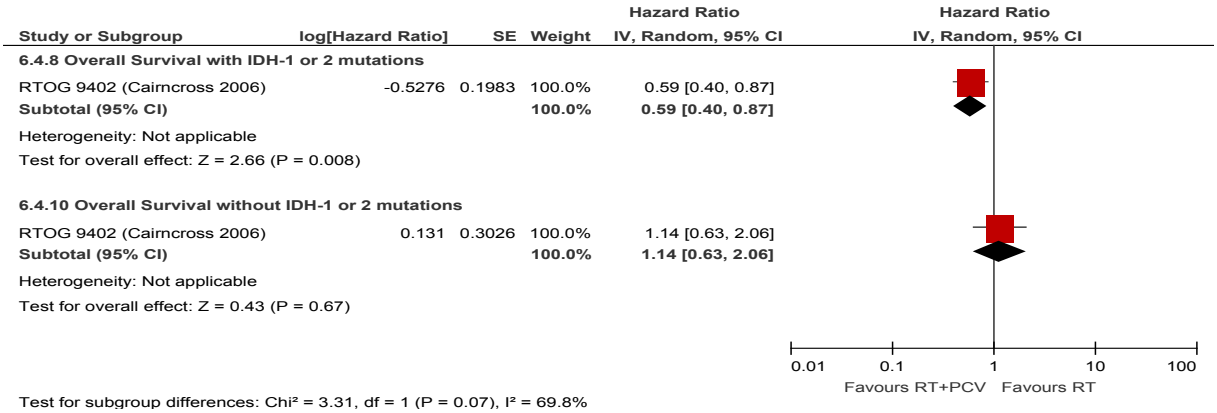


Figure 36: RT + PCV versus RT: progression free survival in WHO III glioma

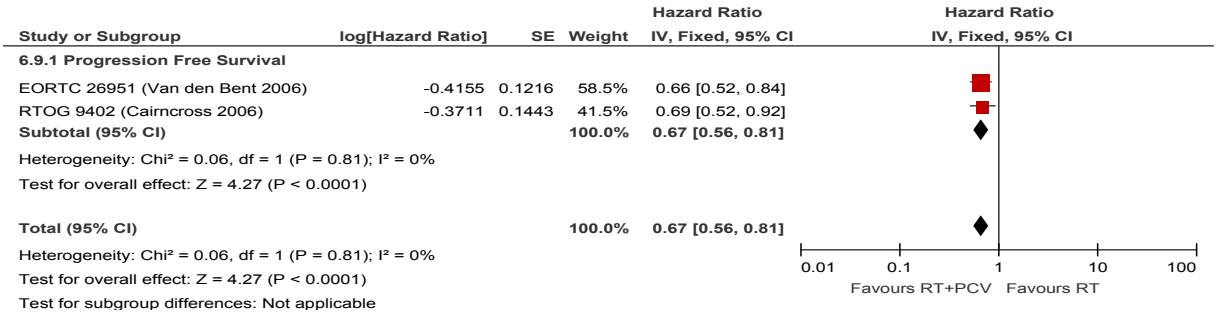


Figure 37: RT + PCV versus RT: progression free survival – subgroup differences by codeletion of chromosomes 1p/19q in WHO III glioma

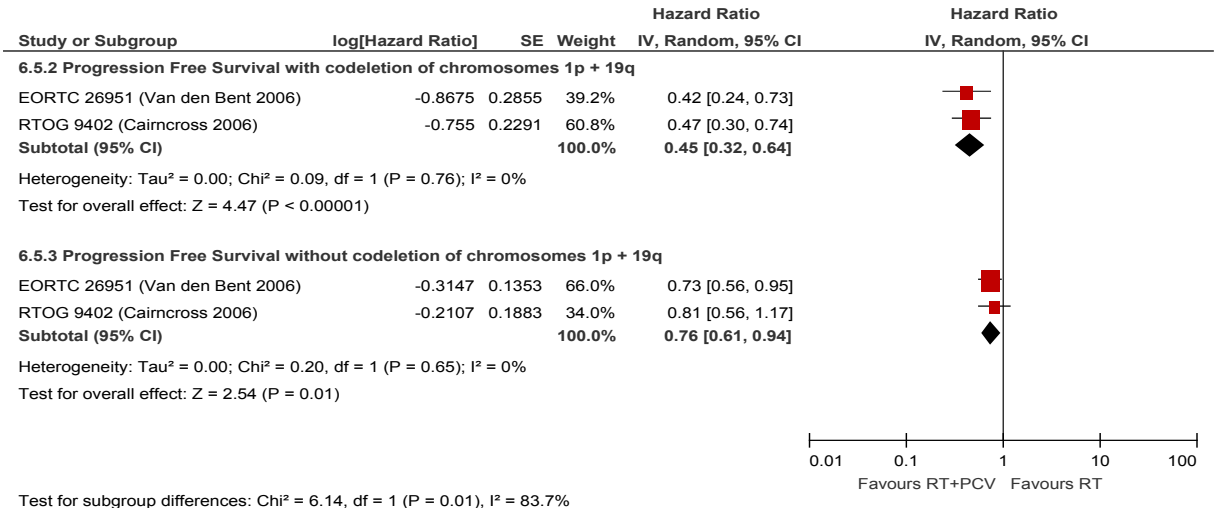


Figure 38: RT + PCV versus RT: progression free survival – subgroup differences by IDH-1 mutation in WHO III glioma

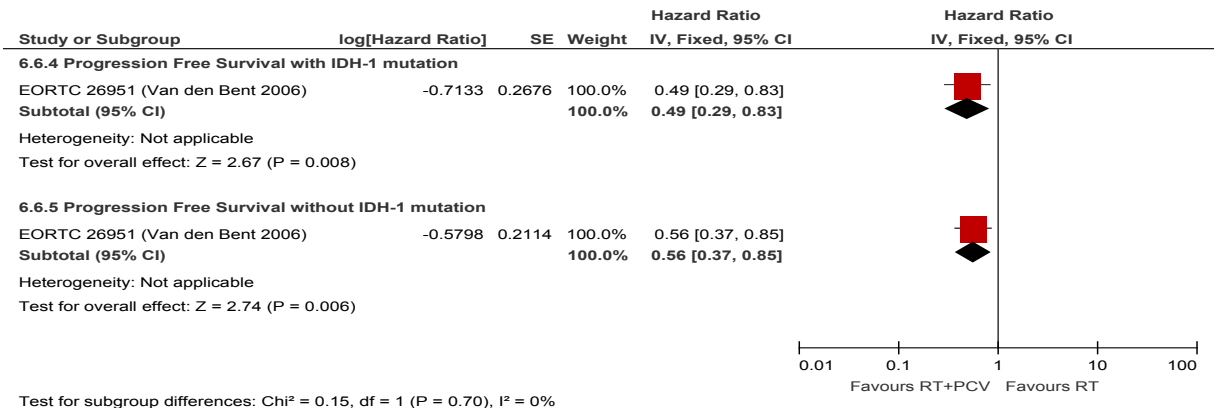
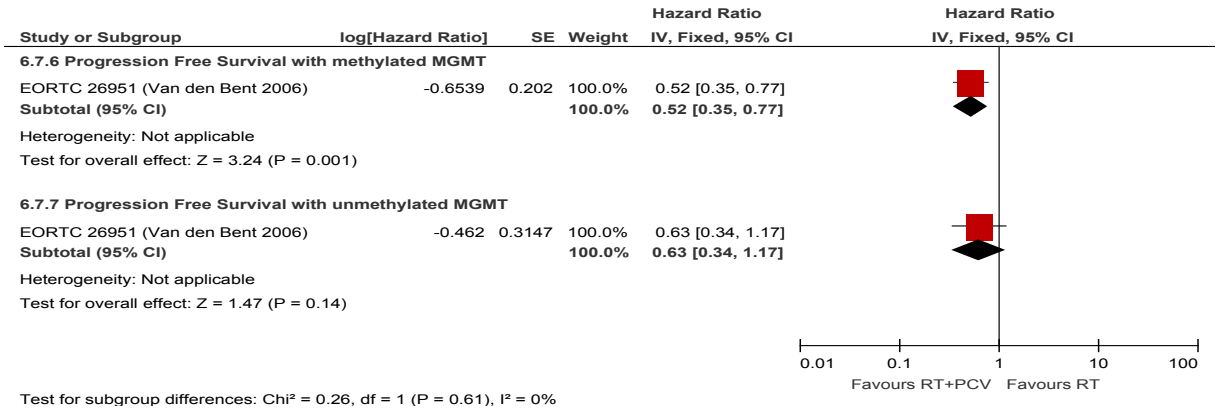


Figure 39: RT + PCV versus RT: progression free survival – subgroup differences by MGMT methylation status in WHO III glioma



Forest plots for review 2d – management of recurrent high-grade glioma

Not applicable – identified evidence was not suitable for meta-analysis.

Forest plots for review 2b – resection of glioma

Not applicable – identified evidence was not suitable for meta-analysis.

Forest plots for review 5a – follow-up for glioma

Not applicable - no evidence was identified.

Appendix F – GRADE tables

GRADE tables for review 1a - imaging for suspected glioma and meningioma

Table 92: Clinical evidence profile: colour map images derived from PWI, MRS and the following cut-off data: 1.75 rCBV, 1.5 for Choline, 1.5 Cho/NAA (semi quantitative analysis from Caulo 2014)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
PWI and MRS	1	81.6% (71 to 90%)	50% (32 to 68%)	110	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval
1 Unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive rest was not pre-specified but determined post-hoc after assessing the data

Table 93: Clinical evidence profile: conventional MRI sequences (qualitative analysis from Caulo 2014)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI	1	83% (73 to 91%)	61% (42 to 77%)	110	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval
1 Interval between index test and reference standard unclear; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 94: Clinical evidence profile: DWI (ADC maps generated), DTI, MRS (Cho/Cr, NAA/Cr, Cho/NAA, lactate/Cr, and lipids/Cr) and PWI (blood volume and mean transit maps were generated) with a cut-off value of -0.3096 (quantitative analysis from Caulo 2014)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
DWI, DTI, MRS and WPI	1	84% (74 to 92%)	100% (89 to 100%)	110	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

ADC apparent diffusion coefficient; CI confidence interval
1 unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive rest was not pre-specified but determined post-hoc after assessing the data.

Table 95: Clinical evidence profile: DWI (ADC maps generated), DTI, MRS (Cho/Cr, NAA/Cr, Cho/NAA, lactate/Cr, and lipids/Cr) and PWI (blood volume and mean transit maps were generated) with a cut-off value of -0.3096 without including oligodendroglioma (ODG) (identification of high- versus low-grade glioma) (quantitative analysis from Caulo 2014)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
DWI, DTI, MRS and WPI	1	88% (78 to 94%)	92% (75 to 99%)	110	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

ADC apparent diffusion coefficient; CI confidence interval
1 unclear whether index test results were interpreted without knowledge of the results of the reference standard; unclear interval between index test and reference standard; unclear whether the study was free of commercial funding; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data.

Table 96: Summary clinical evidence profile: conventional MRI (Law 2003)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI	1	72% (64 to 80%)	65% (48 to 79%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval
1 unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 97: Clinical evidence profile: perfusion MRI (Law 2003)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Perfusion MRI – threshold values for rCBV with minimum C2 error	1	95% (89 to 98%)	57% (41 to 73%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold values for rCBV with minimum C1 error	1	72% (64 to 80%)	88% (73 to 96%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold values for same	1	72% (64 to 80%)	88% (73 to 96%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
sensitivity as cMRI									
Perfusion MRI – threshold values for same specificity as cMRI	1	88% (80 to 93%)	65% (48 to 79%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval; cMRI conventional magnetic resonance imaging; rCBV relative cerebral blood volume
1 unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 98: Clinical evidence profile: threshold values for Cho/Cr from perfusion MRS (Law 2003)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Perfusion MRI – threshold values for Cho/Cr with minimum C2 error	1	97% (93 to 99%)	13% (0.4 to 27%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold values for Cho/Cr with minimum C1 error	1	76% (67 to 83%)	47% (32 to 64%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold values for same	1	72% (64 to 80%)	50% (34 to 66%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
sensitivity as cMRI									
Perfusion MRI – threshold values for same specificity as cMRI	1	55% (46 to 64%)	65% (48 to 79%)	160	very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval, rCBV relative cerebral blood volume, Cho/Cr choline [Cho] / creatine [Cr]; cMRI conventional magnetic resonance imaging;
1 unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 99: Clinical evidence profile: thresholds for Cho/NAA from perfusion MRI (Law 2003)

Index test	Number of studies	N	Sensitivity (95%CI)	Specificity (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Perfusion MRI – threshold values for Cho/NAA with minimum C2 error	1	160	97% (92 to 99%)	10% (0.3 to 24%)	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold values for Cho/NAA with minimum C1 error	1	160	74% (65 to 82%)	63% (46 to 77%)	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Perfusion MRI – threshold	1	160	72% (64 to 80%)	63% (46 to 77%)	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Very low

Index test	Number of studies	N	Sensitivity (95%CI)	Specificity (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
values for same sensitivity as cMRI									
Perfusion MRI – threshold values for same specificity as cMRI	1	160	68% (58 to 76%)	65% (48 to 79%)	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Cho/NAA Cho/N-acetylaspartate [NAA], MRS magnetic resonance spectroscopy, CI confidence interval; cMRI conventional magnetic resonance imaging;
1 unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
2 The difference between the upper and lower 95% CI for sensitivity was >0.25

Table 100: Clinical evidence profile: threshold values for rCBV and Cho/NAA ratio together (Law 2003)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Threshold values for rCBV and Cho/NAA ratio together with minimum C2 error	1	93% (87 to 97%)	60% (43 to 75%)	160	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Threshold values for rCBV and Cho/NAA ratio together	1	71% (62 to 79%)	93% (80 to 98%)	160	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
with minimum C1 error									
Threshold values for rCBV and Cho/NAA ratio together – threshold values for same sensitivity as cMRI	1	72% (64 to 80%)	88% (73 to 96%)	160	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Threshold values for rCBV and Cho/NAA ratio together – threshold values for same specificity as cMRI	1	89% (82 to 94%)	65% (48 to 79%)	160	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Cho/NAA Cho/N-acetylaspartate [NAA], MRS magnetic resonance spectroscopy, CI confidence interval; cMRI conventional magnetic resonance imaging; rCBV relative cerebral blood volume

1 unclear interval between index test and reference test; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 101: Clinical evidence profile: conventional MRI (Zou 2011)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI	1	72%	67%	30	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Very low

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
		(47 to 90%)	(35 to 90%)						

CI confidence interval; MRI magnetic resonance imaging
1 Unclear whether the results of the index test were interpreted without prior knowledge of the reference standard; the conduct or interpretation of the index test could have introduced bias; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data
2 The difference between upper and lower 95% CI was >0.25 for sensitivity

Table 102: Clinical evidence profile: combination of apparent diffusion coefficient (ADC) and N-acetylaspartate/choline ratio (NAA/Cho) (Zou 2011)

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI	1	83% (59 to 96%)	100% (74 to 100%)	30	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

ADC apparent diffusion coefficient; CI confidence interval; MRI magnetic resonance imaging
1 Unclear whether the results of the index test were interpreted without prior knowledge of the reference standard; the conduct or interpretation of the index test could have introduced bias; data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data

Table 103: Clinical evidence profile: T2 WI - FLAIR GLCM Cluster Shade

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI (T2 WI - FLAIR GLCM Cluster Shade)	1	75% (59 to 87%)	84.6% (65 to 96%)	66	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	Very low

ADC apparent diffusion coefficient; CI confidence interval; MRI magnetic resonance imaging
1 data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding
2 The difference between upper and lower 95% CI was >0.25 for sensitivity

Table 104: Clinical evidence profile: T1W1-CE GLCM Entropy on the T1W1-CE sequence

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Conventional MRI (T1W1-CE GLCM Entropy on the T1W1-CE sequence)	1	97.5% (87 to 100%)	80.8% (61 to 93%)	66	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

CI confidence interval; GLCM Gray level co-occurrence matrix; MRI magnetic resonance imaging
1 data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding

Table 105: Clinical evidence profile for ADC homogeneity on the ADC map

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ADC GLCM homogeneity	1	97.5% (87 to 100%)	80.8% (61 to 93%)	66	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

1 data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding

Table 106: Clinical evidence profile: Summary clinical evidence profile for combined features of conventional MRI, DWI and ADC

Index test	Number of studies	Sensitivity (95%CI)	Specificity (95% CI)	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Combined features of conventional MRI (T1W1-CE GLCM Entropy on the T1W1-CE sequence) and DWI (ADC homogeneity on the ADC map)	1	90% (76 to 97%)	89% (70 to 98%)	63	Very serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Low

ADC apparent diffusion coefficient; CI confidence interval; MRI magnetic resonance imaging
[1] data driven study: the threshold for a positive test was not pre-specified but determined post-hoc after assessing the data; unclear whether patient flow could have introduced bias; unclear whether the study was free of commercial funding

GRADE tables for review 1d – molecular markers to inform prognosis / guide treatment

Not applicable - no evidence was identified.

GRADE tables for review 1c – timing and extend of initial surgery for low-grade glioma

Table 99: Clinical evidence profile: Local excision/biopsy versus no surgery (active monitoring)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No surgery (active monitoring)	Local excision/biopsy	Relative (95% CI)	Absolute	**Quality**	**Importance**
Overall survival (follow up not reported)												
1 (Alattar 2017)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious imprecision[3]	none	0/438 (0%)[4]	0/550 (0%)[4]	HR 1.69 (1.15 to 2.48)	Not estimable[3]	⊕OOO VERY LOW	IMPORTANT

[1] Uncontrolled confounders
[2] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[3] 95% CI crosses the upper threshold for appreciable benefit (i.e., 1.2 as per the review protocol).
[4] Event rate not reported

Table 100: Clinical evidence profile: Subtotal resection versus no surgery (active monitoring)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No surgery (active monitoring)	Subtotal resection	Relative (95% CI)	Absolute	**Quality**	**Importance**
Overall survival (follow up min 120 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No surgery (active monitoring)	Subtotal resection	Relative (95% CI)	Absolute		
1 (Schupper 2017)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious imprecision[3]	none	0/1487 (0%)[4]	0/1710 (0%)[4]	HR 1.32 (1.14 to 1.53)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT

[1] Uncontrolled confounders
[2] N = 528 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[3] 95% CI crosses the upper threshold for appreciable benefit (i.e., 1.2 as per the review protocol).
[4] Event rate not reported

Table 101: Clinical evidence profile: Local excision/biopsy versus subtotal resection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subtotal resection	Local excision / biopsy	Relative (95% CI)	Absolute		
Overall survival (follow up NR)												
1 (Alattar 2017)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/557 (0%)[4]	0/550 (0%)[4]	HR 1.21 (0.83 to 1.76)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT
Progression-free survival (follow-up median 59 months)												
1 (Gousias 2014)	observational studies	serious[5]	serious[6]	serious[7]	very serious[8]	none	0/75 (0%)[4]	0/11 (0%)[4]	HR 0.23 (0.11 to 0.49) and	Not estimable[4]	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subtotal resection	Local excision / biopsy	Relative (95% CI)	Absolute		
									0.87 (0.31 to 2.42)			
Malignant progression-free survival (follow-up 59-82 months)												
2 (Gousias 2014; Pallud 2014)	observational studies	serious[9]	no serious inconsistency	serious[7]	serious imprecision[10]	none	0/388 (0%)[4]	0/630 (0%)[4]	HR 0.35 (0.15 to 0.82) and 0.43 (0.35 to 0.53)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT

[1] Uncontrolled confounders
[2] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[3] The confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm (i.e., 1.2 as per the review protocol).
[4] Event rate not reported
[5] Unclear how much missing data in the study
[6] The authors performed 2 multivariate analyses in which they varied the levels of 1 of the covariates (eloquence of location), having 2 levels in 1 of the analyses and 3 levels in the other. The former multivariate analysis returned a HR of 0.865 (95% CI 0.308-2.421), p = 0.78 for STR (v biopsy), whereas the latter analysis returned a HR of 0.234 (95% CI 0.111-0.493), p < 0.001 for STR (v biopsy),
[7] Population had confirmed, not suspected, low-grade glioma
[8] For 1 of the 2 estimates, the confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm and the lower threshold for appreciable benefit (i.e., 1.2 and 0.8, respectively, as per the review protocol).
[9] Unclear how much missing data in 1 of the studies
[10] For 1 of the 2 estimates, the confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol).

Table 102: Clinical evidence profile: Local excision/biopsy versus gross total resection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gross total re-section	Local excision / biopsy	Relative (95% CI)	Absolute		
Overall survival (follow up NR)												
1 (Alattar 2017)	observational studies	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/833 (0%)[4]	0/550 (0%)[4]	HR 1.06 (0.73 to 1.54)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT
Progression-free survival (follow-up median 59 months)												
1 (Gousias 2014)	observational studies	serious[5]	no serious inconsistency[6]	serious[7]	no serious imprecision	none	0/62 (0%)[4]	0/11 (0%)[4]	HR 0.04 (0.02 to 0.1) and 0.22 (0.07 to 0.72)	Not estimable[4]	⊕OOO VERY LOW	CRITICAL
Malignant progression-free survival (follow-up 59-82 months)												
2 (Gousias 2014; Pallud 2014)	observational studies	serious[8]	no serious inconsistency	serious[7]	no serious imprecision	none	0/212 (0%)[4]	0/630 (0%)[4]	HR 0.05 (0.02 to 0.15) and 0.22 (0.16 to 0.32)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT

[1] Uncontrolled confounders
[2] N = 146 were aged < 18 years; population had confirmed, not suspected, low-grade glioma.
[3] The confidence interval includes 0 (no effect) and crosses the upper threshold for appreciable harm and the lower threshold for appreciable benefit (i.e., 1.2 and 0.8, respectively, as per the review protocol).
[4] Event rate not reported
[5] Unclear how much missing data in the study
[6] The authors performed 2 multivariate analyses in which they varied the levels of 1 of the covariates (eloquence of location), having 2 levels in 1 of the analyses and 3 levels in the other. The former multivariate analysis returned a HR of 0.221 (95% CI 0.067-0.723), p = 0.013 for GTR (v biopsy), whereas the latter analysis returned a HR of 0.039 (95% CI 0.016-0.096), p < 0.001 for GTR (v biopsy),
[7] Population had confirmed, not suspected, low-grade glioma.
[8] Unclear how much missing data in 1 of the studies

Table 103: Clinical evidence profile: Gross total resection versus subtotal resection

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gross total re-section	Sub total resection	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (follow up NR-min 120 months)												
2 (Schupper 2017; Yang 2013)	observational studies	serious[1]	no serious inconsistency[9]	serious[2]	serious[3]	none	0/1273 (0%)[4]	0/2067 (0%)[4]	HR 0.72 (0.6 to 0.85) and 0.78 (0.53 to 1.16)	Not estimable[4]	⊕OOO VERY LOW	IMPORTANT
Progression-free survival (follow-up mean 52 months)												
2 (Coburger 2016; Yang 2013)	observational studies	serious[5]	serious[6]	serious[2]	serious[7]	none	0/495 (0%)[4]	0/579 (0%)[4]	HR 0.44 (0.27 to 0.72) and 0.93 (0.75 to 1.15)	Not estimable[4]	⊕OOO VERY LOW	CRITICAL
New neurological deficit (follow-up mean 52 months)												
1 (Coburger 2016)	observational studies	no serious risk of bias	no serious inconsistency	serious[2]	serious[8]	none	13/138 (9.4%)	21/105 (20%)	RR 0.47 (0.25 to 0.9)	106 fewer per 1000 (from 20 fewer to 150 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Uncontrolled confounders in both studies and missing data in 1 of the studies
[2] Population had confirmed, not suspected, low-grade glioma in both studies; in 1 of the studies N = 528 aged < 18 years
[3] The confidence interval includes 0 (no effect) and crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol) in 1 of the studies.
[4] Event rate not reported
[5] Uncontrolled confounders and missing data in 1 of the studies
[6] One of the studies reports a HR of 0.44 (95% CI 0.27-0.72), whereas the other study reports a HR of 0.93 (95% CI 0.74-1.15)

[7] The confidence interval includes 0 (no effect) and crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol) in 1 of the studies
[8] The confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol)
[9] Although the HR of 1 of the studies is significant, while the HR of the other study is not, the direction of the effect is the same and the confidence intervals overlap.

Table 104: Clinical evidence profile: Biopsy versus partial resection

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Partial re-section	Biopsy	Relative (95% CI)	Absolute	Quality	Importance
Malignant progression-free survival (follow-up mean 82 months)												
1 (Pallud 2014)	observational studies	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	0/427 (0%)[2]	0/619 (0%)[2]	HR 0.68 (0.58 to 0.80)	Not estimable[2]	⊕OOO VERY LOW	IMPORTANT

[1] Population had confirmed, not suspected low-grade glioma
[2] Event rate not reported

Table 105: Clinical evidence profile: Gross total excision/radical subtotal excision (GTR/rSTR) versus subtotal excision/biopsy (STR/Bx)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GTR/rSTR	STR/Bx	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (follow-up median 8.7 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GTR/rSTR	STR/Bx	Relative (95% CI)	Absolute		
1 (Youland 2013)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious imprecision[3]	none	0/231 (0%)[4]	0/340 (0%)[4]	RR 0.61 (0.43 to 0.87)	Not estimable[3]	⊕OOO VERY LOW	IMPORTANT
Progression-free survival (follow-up median 8.7 years)												
1 (Youland 2013)	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/231 (0%)[3]	0/340 (0%)[3]	RR 0.45 (0.35 to 0.58)	Not estimable[3]	⊕OOO VERY LOW	CRITICAL

[1] Uncontrolled confounder(s)
[2] Population had confirmed, not suspected, low-grade glioma
[3] The confidence interval crosses the lower threshold for appreciable benefit (i.e., 0.80 as per the review protocol).
[4] Event rate not reported

GRADE tables for review 2a – further management of low-grade glioma

Table 107: RT + CCNU versus RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT**	**RT + CCNU**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS (follow-up median 76 months)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT	RT + CCNU	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	Very serious [1]	no serious inconsistency	no serious indirectness	Very serious[2]	None	27	27	Not estimable	Not estimable	VERY LOW	CRITICAL

1 No details were given about randomisation and allocation concealment methods
2 Only descriptive data without p-values was reported, insufficient details given to assess the MID thresholds and imprecision

Table 108: Clinical evidence profile: Low dose (45 Gy) versus high dose (59.4 Gy)

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose (45 Gy)	High dose (69.4 Gy)	Relative (95% CI)	Absolute	Quality	Importance
OS (follow-up median 76 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	None	64/171 (37.4%)	59/172 (31.4%)	RR 1.19 (0.89 to 1.60)	60 more per 1000 (from 35 fewer to 188 more)	LOW	CRITICAL
PFS (follow-up median 76 months)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	None	79/171 (46.2%)	70/172 (40.7%)	RR 1.14 (0.89 to 1.45)	57 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low dose (45 Gy)**	**High dose (69.4 Gy)**	**Relative (95% CI)**	**Absolute**		
										45 fewer to 183 more)		
Adverse events (fatigue, insomnia)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	None	Total=171	Total=172	-	-	VERY LOW	IMPORTANT
Quality of life (leisure activity and emotional functioning)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	None	Total=171	Total=172	Not estimable	Not estimable	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed and concealed.
2 95% CI crossed 1 default MID (1.25)
3 Unclear how randomisation was performed and concealed; unclear whether participants and assessors were blinded to treatment allocation
4 Only descriptive data without p-values was reported, insufficient details given to assess the MID thresholds and imprecision

Table 109: Clinical evidence profile: Low dose (50.4 Gy) versus high dose (64.8 Gy)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low dose (50.4 Gy)**	**High dose (64.8 Gy)**	**Relative (95% CI)**	**Absolute**		
OS (follow-up median 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/101 (6.9%)	19/102 (18.6%)	RR 0.37 (0.16 to 0.85)	117 fewer per 1000 (from 28 fewer to 156 fewer)	LOW	CRITICAL
OS (follow-up median 5 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Low dose (50.4 Gy)**	**High dose (64.8 Gy)**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/101 (40.6%)	48/102 (47.1%)	RR 0.86 (0.63 to 1.18)	66 fewer per 1000 (from 174 fewer to 85 more)	LOW	CRITICAL
PFS (follow-up median 2 years)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	19/101 (18.8%)	32/102 (31.4%)	RR 0.60 (0.36 to 0.99)	125 fewer per 1000 (from 3 fewer to 201 fewer)	VERY LOW	IMPORTANT
PFS (follow-up median 5 years)												
1	randomised trials	serious[1,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	44/101 (43.6%)	40/102 (39.2%)	RR 1.11 (0.80 to 1.54)	43 more per 1000 (from 78 fewer to 212 more)	VERY LOW	IMPORTANT
Toxicity (grade 3, 4, and 5) at 5 years follow-up (follow-up median 6.4 years)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	42/101 (41.6%)	54/102 (52.9%)	RR 0.79 (0.58 to 1.05)	111 fewer per 1000 (from 222 fewer to 26 more)	VERY LOW	IMPORTANT
MMSE scores												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[5]	none	-	-	-	Not estimable	VERY LOW	IMPORTANT
Cognitive function												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[6]	none	10	10	-	Not estimable	VERY LOW	IMPORTANT

1 Unclear how randomisation was concealed
2 95% CI crossed 1 default MID (0.80)

3 unclear whether patients and assessors were blinded
4 95% CI crossed 2 default MIDs (0.80 and 1.25)
5 Data reported narratively, with insufficient details given to assess the MID thresholds and imprecision. Data reported overall and not per treatment arm (76%, 89% and 89% of adults presented with a stable MMSE score at year 1, 2 and 5 respectively. Adults with an abnormal score at baseline were more likely to have an improvement in cognitive abilities after radiotherapy)
6 Data reported narratively, with insufficient details given to assess the MID thresholds and imprecision. Analyses of these battery tests suggested a stable cognitive function amongst those adults who received low-dose (50.4-Gy) radiotherapy and those who received high-dose radiotherapy (64.8-Gy), although results have not been reported by treatment arm.

Table 110: Clinical evidence profile: Early RT versus deferred RT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early RT[a]**	**Deferred RT[b]**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Time to progression (follow-up median 5 years[1])												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.71 (0.52 to 0.97)	-	LOW	IMPORTANT
Time to progression (follow-up median 7.8 years[4])												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.59 (0.45 to 0.77)	-	MODERATE	IMPORTANT
Overall survival (follow-up median 5 years[1])												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	-	-	HR 1.04 (0.61 to 1.77)	-	VERY LOW	CRITICAL
Overall survival (follow-up median 7.8 years[4])												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	none	-	-	HR 0.97 (0.71 to 1.33)	-	VERY LOW	CRITICAL

1 Karim 2002
2 Unclear how randomisation was concealed
3 95% CI crossed 1 default MID (0.80)
4 van den Bent 2005

5 95% CI crossed 2 default MIDs (0.80 and 1.25)
a N=154
b N=157

Table 111: Clinical evidence profile: RT + PCV versus RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT + PCV	RT	Relative (95% CI)	Absolute		
Overall survival (total) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.59 (0.42 to 0.83)	-	LOW	CRITICAL
Overall survival (grade 2 astrocytoma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.73 (0.40 to 1.33)	-	VERY LOW	CRITICAL
Overall survival (grade 2 oligodendroglioma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.43 (0.23 to 0.80)	-	LOW	CRITICAL
Overall survival (grade 2 oligoastrocytoma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.56 (0.32 to 0.98)	-	LOW	CRITICAL
Overall survival amongst those with IDH1 R132H Mutation (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.42 (0.20 to 0.88)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT + PCV**	**RT**	**Relative (95% CI)**	**Absolute**		
Progression free survival (total) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.50 (0.36 to 0.69)	-	MODERATE	IMPORTANT
Progression free survival (grade 2 astrocytoma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.58 (0.33 to 1.02)	-	LOW	IMPORTANT
Progression free survival (grade 2 oligodendroglioma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.36 (0.21 to 0.62)	-	MODERATE	IMPORTANT
Progression free survival (grade 2 oligoastrocytoma) (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.52 (0.30 to 0.90)	-	LOW	IMPORTANT
Progression free survival among those with IDH1 R132H Mutation (follow-up median 11.9 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.32 (0.17 to 0.60)	-	MODERATE	IMPORTANT
MMSE decline year 1												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/51 (3.9 %)	5/74 (6.8 %)	RR 0.58 (0.12 to 2.88)	28 fewer per 1000 (from 59 fewer to 127 more)	VERY LOW	IMPORTANT
MMSE decline year 2												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT + PCV	RT	Relative (95% CI)	Absolute		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/50 (0%)	1/60 (1.7%)	RR 0.40 (0.02 to 9.58)	10 fewer per 1000 (from 16 fewer to 143 more)	VERY LOW	IMPORTANT
MMSE decline year 3												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/43 (0%)	1/48 (2.1%)	RR 0.37 (0.02 to 8.88)	13 fewer per 1000 (from 20 fewer to 164 more)	VERY LOW	IMPORTANT
MMSE decline year 5												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/25 (8%)	0/22 (0%)	RR 4.42 (0.22 to 87.44)	-	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed and how it was concealed
2 95% CI crossed 1 default MID (0.80)
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 112: Clinical evidence profile: TMZ versus RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ	RT	Relative (95% CI)	Absolute		
Progression free survival – PFS (total)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMZ**	**RT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none			HR 1.16 (0.9 to 1.5)	-	LOW	IMPORTANT
Progression free survival - PFS IDHmt/codel (follow-up median 48 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 1.04 (0.56 to 1.93)	-	VERY LOW	IMPORTANT
Progression free survival - PFS IDHmt/non-codel (follow-up median 48 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.86 (1.21 to 2.86)	-	LOW	IMPORTANT
Progression free survival - PFS IDHwt (follow-up median 48 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.67 (0.34 to 1.32)	-	VERY LOW	IMPORTANT
Global health-related quality of life - 3 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196	173	-	MD 6 higher (5.8 to 6.2 higher)[4]	MODERATE	IMPORTANT
Global health-related quality of life - 6 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182	158	-	MD 2.5 lower (2.71 to 2.29 lower)[4]	MODERATE	IMPORTANT
Global health-related quality of life - 24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	100	-	MD 1.6 lower (1.87 to 1.33 lower)[4]	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ	RT	Relative (95% CI)	Absolute		
Global health-related quality of life - 36 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	63	-	MD 0.2 lower (0.56 lower to 0.16 higher)[4]	MODERATE	IMPORTANT
MMSE - 3 months (Better indicated by lower values)												
1	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196	173	-	MD 2.8 lower (2.82 to 2.78 lower)[5]	LOW	IMPORTANT
MMSE - 6 months (Better indicated by lower values)												
1	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182	158	-	MD 3 lower (3.02 to 2.98 lower)[5]	LOW	IMPORTANT
MMSE - 24 months (Better indicated by lower values)												
1	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	100	-	MD 2.9 lower (2.93 to 2.87 lower)[5]	LOW	IMPORTANT
MMSE - 36 months (Better indicated by lower values)												
1	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	63	-	MD 2.9 lower (2.93 to 2.87 lower)[5]	LOW	IMPORTANT

1 Unclear how randomisation was concealed; open label trial
2 95% CI crossed 1 default MID (1.25)

3 95% CI crossed 2 default MIDs (0.80 and 1.25)
4 Figures represent mean differences between both treatment groups (TMZ versus RT) for global quality of life. Changes between 5 to 10 represent a small difference and between 10 and 20 represent a moderate difference (>10 points considered as clinically relevant)
5 Figures represent mean different between both treatment groups (TMZ versus RT) for MMSE scores. Changes >3 are considered to be clinically significant

GRADE tables for review 2c – initial management of high-grade glioma

Grade IV Glioma

Table 113: Bevacizumab plus TMZ+RT versus TMZ+RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab plus TMZ+RT	TMZ+RT	Relative (95% CI)	Absolute		
OS												
2	randomised trials	serious[1]	very serious inconsistency[2]	no serious indirectness	serious imprecision[3]	none	-	-	HR 0.99 (0.77 to 1.26)	-	VERY LOW	CRITICAL
OS - MGMT methylated												
2	randomised trials	serious[1]	very serious inconsistency[2]	no serious indirectness	very serious[6]	none	-	-	HR 1.20 (0.42 to 3.46)	-	VERY LOW	CRITICAL
OS -MGMT non-methylated												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious	none	-	-	HR 1.02 (0.98 to 1.06)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab plus TMZ+RT	TMZ+RT	Relative (95% CI)	Absolute		
					imprecision							
OS -RPA class 3												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 0.93 (0.66 to 1.30)	-	LOW	CRITICAL
OS -RPA class 4												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.97 (0.88 to 1.06)	-	MODERATE	CRITICAL
OS RPA class 5												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 0.93 (0.73 to 1.19)	-	LOW	CRITICAL
Progression free survival												
2	randomised trials	serious[1]	serious[5]	no serious indirectness	serious [3]	none	-	-	HR 0.71 (0.58 to 0.87)	-	VERY LOW	CRITICAL
Progression free survival MGMT methylated												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab plus TMZ+RT**	**TMZ+RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
2	randomised trials	serious[1]	serious[5]	no serious indirectness	very serious[6]	none	-	-	HR 0.93 (0.53 to 1.64)	-	VERY LOW	CRITICAL
Progression free survival - PFS MGMT non-methylated												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.59 (0.49 to 0.70)	-	MODERATE	CRITICAL
Progression free survival - PFS RPA grade 3												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.67(0.49 to 0.91)	-	LOW	CRITICAL
Progression free survival - PFS RPA grade 4												
2	randomised trials	serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	-	-	HR 0.69 (0.60 to 0.79)	-	LOW	CRITICAL
Progression free survival - PFS RPA grade 5												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab plus TMZ+RT**	**TMZ+RT**	**Relative (95% CI)**	**Absolute**		
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.71 (0.56 to 0.90)	-	LOW	CRITICAL
Adverse events overall - Grade ≥3												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	150/461 (32.5%)	71/450 (15.8%)	RR 2.06 (1.60 to 2.65)	167more per 1000 (from 95 more to 260 more)	MODERATE	IMPORTANT
Wound complications												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	18/764 (2.4%)	8/750 (1.1%)	RR 2.16 (1.03 to 4.52)	12 more per 1000 (from 95 more to 38 more)	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab plus TMZ+RT**	**TMZ+RT**	**Relative (95% CI)**	**Absolute**		
Fatigue – Fatigue												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	34/303 (11.2%)	21/300 (7%)	RR 1.60 (0.95 to 2.70)	42 more per 1000 (from 4 fewer to 119 more)	LOW	IMPORTANT

1 Unclear how allocation concealment was performed
2 I-square ≥75%
3 95% CI crossed 1 default MID (0.80)
4 95% CI crossed 1 MID (1.25)
5 I-square between 50 and 74.99%
6 95% CI crossed 2 default MIDs (0.8 and 1.25)

Table 114: Nimotuzumab plus TMZ+RT versus TMZ+RT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimotuzumab plus TMZ+ RT**	**TMZ + RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.86 (0.57 to 1.31)	-	VERY LOW	CRITICAL
OS - MGMT methylated												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.86 (0.27 to 2.74)	-	VERY LOW	CRITICAL
OS - MGMT non-methylated												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.80 (0.45 to 1.42)	-	VERY LOW	CRITICAL
PFS												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.95 (0.93 to 1.14)	-	LOW	CRITICAL
PFS - MGMT methylated												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	-	-	HR 0.93 (0.76 to 1.14)	-	VERY LOW	CRITICAL
Grade 3/4 adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nimotuzumab plus TMZ+ RT**	**TMZ + RT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/71 (31%)	6/71 (8.5 %)	RR 3.67 (1.58 to 8.50)	226 more per 1000 (from 49 more to 634 more)	LOW	IMPORTANT
Fatigue												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious[4]	none	39/142 (27.5%)	31/71 (43.7 %)	RR 1.26 (0.90 to 1.76)	162 fewer per 1000 (from 35 fewer to 249 fewer)	VERY LOW	IMPORTANT
Memory impairment												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	4/142 (2.8%)	8/71 (11.3 %)	RR 0.50 (0.16 to 1.59)	85 fewer per 1000 (from 23 fewer to 104 fewer)	VERY LOW	IMPORTANT

1 Unclear how randomisation was done, only randomisation by fax was described. High risk of performance bias
2 95% CI crossed 2 default MID (0.80 and 1.25)
3 Open label study
4 95% CI crossed 1 default MID (1.25)

Table 115: Cilengitide pluz TMZ+RT versus TMZ+RT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cilengitide plus TMZ + RT**	**TMZ+RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 1.02 (0.81 to 1.28)	-	MODERATE	CRITICAL
OS - OS RPA grade 3												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.63 (0.31 to 1.28)	-	LOW	CRITICAL
OS - OS RPA grade 4-5												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 1.08 (0.84 to 1.39)	-	MODERATE	CRITICAL
PFS												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cilengitide plus TMZ + RT**	**TMZ+RT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.92 (0.75 to 1.13)	-	LOW	CRITICAL
Grade 3 and 4 toxicity												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	169/272 (62.1%)	158/273 (57.9%)	RR 1.07 (0.94 to 1.23)	41 more per 1000 (from 35 fewer to 133 more)	MODERATE	IMPORTANT
Fatigue												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/263 (5.3%)	8/258 (3.1%)	RR 1.72 (0.73 to 4.02)	22 more per 1000 (from 8 fewer to 94 more)	VERY LOW	IMPORTANT
Memory impairment												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/263 (0.38%)	1/258 (0.39%)	RR 0.98 (0.06 to 14.91)	0 fewer per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cilengitide plus TMZ + RT	TMZ+RT	Relative (95% CI)	Absolute		
										(from 4 fewer to 54 more)		

1 95% CI crossed 1 default MID (1.25)
2 95% CI crossed 2 default MID (0.80 and 1.25)
3 Open label study

Table 116: Clinical evidence profile for comparison of TMZ+RT plus DD TMZ (150-200 mg/m^2) versus TMZ+RT plus standard TMZ (75-100mg/m^2)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ+RT plus DD TMZ (150-200 mg/m^2)	TMZ+RT plus stand TMZ (75-100mg/m^2)	Relative (95% CI)	Absolute		
Overall survival												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1.03 (0.88 to 1.21)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMZ+RT plus DD TMZ (150-200 mg/m²)**	**TMZ+RT plus stand TMZ (75-100mg/m²)**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS for patients with MGMT methylated status												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	-	-	HR 1.19 (0.87 to 1.63)	-	LOW	CRITICAL
OS for patients with MGMT non-methylated status												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.99 (0.82 to 1.20)	-	MODERATE	CRITICAL
Progression free survival												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	-	-	HR 0.87 (0.75 to 1.01)	-	VERY LOW	CRITICAL
Progression free survival for patients with MGMT methylated status												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	-	-	HR 0.87 (0.66 to 1.15)	-	VERY LOW	CRITICAL
Progression free survival for patients with MGMT non-methylated status												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMZ+RT plus DD TMZ (150-200 mg/m^2)**	**TMZ+RT plus stand TMZ (75-100mg/m^2)**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	-	-	HR 0.88 (0.73 to 1.06)	-	VERY LOW	CRITICAL
Grade 3-4 toxicity												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	194/369 (52.6%)	120/351 (34.2%)	RR 1.54 (1.29 to 1.83)	185 more per 1000 (from 99 more to 284 more)	LOW	IMPORTANT
Fatigue												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMZ+RT plus DD TMZ (150-200 mg/m^2)**	**TMZ+RT plus stand TMZ (75-100mg/m^2)**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/369 (8.9%)	12/351 (3.4%)	RR 2.62 (1.37 to 4.98)	55 more per 1000 (from 13 more to 136 more)	LOW	IMPORTANT

1 Unclear allocation concealment
2 95% CI crossed 1 MID (1.25)
3 Not blinded
4 95% CI crossed 1 MID (0.80)

Table 117: Clinical evidence profile for comparison of ceradenovec followed by ganciclovir and TMZ+RT versus TMZ+RT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceradenovec + ganciclovir plus TMZ+ RT	TMZ+ RT	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.18 (0.86 to 1.62)	-	LOW	CRITICAL
OS for patients with MGMT non-methylated status												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.40 (0.92 to 2.13)	-	LOW	CRITICAL
Adverse events (grade 3 and 4)												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	72/124 (58.1%)	47/126 (37.3 %)	RR 1.56 (1.19 to 2.04)	209 more per 1000 (from 71 more to 388 more)	VERY LOW	CRITICAL

1 Incomplete outcome data, insufficient detail regarding randomisation process
2 95% CI crossed 1 MID (1.25)
3 unclear whether outcomes assessors were blinded to treatment allocation

Table 118: Clinical evidence profile for comparison of ACNU-CDDP and TMZ/ RT versus TMZ/ RT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACNU-CDDP ± Standard of care	TMZ+RT	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.59 (0.33 to 1.05)	-	LOW	CRITICAL
Progression free survival												
1	randomised trials	very serious[1, 4]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.76 (0.43 to 1.34)	-	VERY LOW	CRITICAL
Adverse events grade >=3												
1	randomised trials	very serious[1, 4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/38 (68.4 %)	6/38 (15.8 %)	RR 4.33 (2.64 to 5.49)	526 more per 1000 (from 259 more to 709 more)	LOW	IMPORTANT

1 No details on actual randomisation process; no details reported on whether any form of allocation concealment was used
2 95% crossed 1 MID (0.80)
3 95% crossed 2 MIDs (0.80 and 1.25)
4 no blinding of outcome assessors

Table 119: Clinical evidence profile for comparison of TTFields + TMZ versus TMZ

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TTFields + TMZ**	**TMZ**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.74 (0.56 to 0.98)	-	MODERATE	CRITICAL
Progression free survival												
1	randomised trials	serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.62 (0.43 to 0.89)	-	LOW	CRITICAL
Fatigue												
1	randomised trials	serious risk	no serious inconsistency	no serious indirectness	very serious[3]	none	4/203 (2%)	4/101 (4%)	RR 1.00 (0.31 to 3.23)	0 fewer per 1000	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TTFields + TMZ	TMZ	Relative (95% CI)	Absolute		
		of bias[2]								(from 27 fewer to 88 more)		

1 95% CI crossed 1 MID (0.80)
2 Open label study
3 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 120: Clinical evidence profile for comparison of TMZ versus standard RT in older people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ	Standard RT	Relative (95% CI)	Absolute		
OS - Overall												
2	randomised trials	no serious	serious[1]	serious[2]	very serious[5]	none	-	-	HR 0.88 (0.57 to 1.36)	-	VERY LOW	CRITICAL
OS- people 60 to 70 years old												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**TMZ**	**Standard RT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious	no serious inconsistency	serious[2]	very serious[5]	none	-	-	HR 0.87 (0.59 to 1.28)	-	VERY LOW	CRITICAL
OS - People >70 years old												
1	randomised trials	no serious	no serious inconsistency	serious[2]	no serious imprecision	none	-	-	HR 0.35 (0.21 to 0.58)	-	MODERATE	CRITICAL
OS - People with MGMT methylated status versus non-methylated												
1	randomised trials	no serious	no serious inconsistency	serious[2]	serious[3]	none	-	-	HR 0.62 (0.42 To 0.91)	-	LOW	CRITICAL
Grade 3- 4 Fatigue												
2	randomised trials	serious[4]	no serious inconsistency	serious[2]	very serious[5]	none	-	-	RR 1.14 (0.66 to 1.97)	-	VERY LOW	IMPORTANT
Grade 3-4 neurological symptoms												
1	randomised trials	serious[4]	no serious inconsistency	serious[2]	serious[6]	none	-	-	RR 1.31 (0.82 to 2.1)	-	VERY LOW	IMPORTANT

1 I^2>75%
2 some of the patients presented with de-novo anaplastic astrocytoma
3 95% CI crossed 1 default MID (0.80)
4 No blinding of outcome assessors

5 95% CI crossed 2 default MIDs (0.80 and 1.25)
6 95% CI crossed 1 default MID (1.25)

Table 121: Clinical evidence profile for comparison of hypofractionated RT versus standard RT in those aged 60 years and over

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hypofractionated RT**	**RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS - Overall												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.85 (0.64 to 1.13)	-	MODERATE	CRITICAL
OS - People > 70 years old												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.59 (0.37 to 0.94)	-	MODERATE	CRITICAL
Grade 3 and 4 fatigue												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/95 (2.1%)	0/95 (0%)	RR 5 (0.24 to 102.78)	-	VERY LOW	IMPORTANT

1 95% CI crossed 1 default MID (0.80)
2 No blinding of outcome assessors
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 122: Clinical evidence profile for comparison of RT schedules in older people [60-Gy versus 40-Gy]

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	60-Gy	40-Gy	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 0.90 (0.60 to 1.35)	-	LOW	CRITICAL

1 95% CI crossed 2 MIDs (0.80 and 1.25)

Table 123: Clinical evidence profile for comparison of RT schedules in older/frail people [40-Gy versus 25-Gy]

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40-Gy	25-Gy	Relative (95% CI)	Absolute	Quality	Importance
Overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	48	50	HR 0.95 (0.75 to 1.2)	-	LOW	CRITICAL
Progression free survival												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	48	50	HR 0.99 (0.80 to 1.23)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40-Gy	25-Gy	Relative (95% CI)	Absolute		
Quality of life (Better indicated by higher values)												
1	randomised trials	very serious [1,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	48	50	-	MD 3.6 lower (17.17 lower to 9.97 higher)	VERY LOW	IMPORTANT

1 Insufficient details on allocation concealment
2 95% CI crossed 1 default MID (0.80)
3 unclear whether outcome assessors were blinded to treatment allocation
4 95% CI crossed 2 default MIDs (±17.6 x ± 0.5= ± 8.08)

Table 124: Clinical evidence profile for subanalysis of RT schedules in older/frail people [40-Gy versus 25-Gy]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course RT	Commonly used RT	Relative (95% CI)	Absolute		
Median OS (Better indicated by higher values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	26	35	-	Not estimable[5]	VER	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Short course RT**	**Commonly used RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
											Y LOW	
Median PFS - short course RT (Better indicated by higher values)												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[2]	none	26	35	-	Not estimable[6]	VERY LOW	CRITICAL
QoL - 4 wks after treatment - older people (Better indicated by higher values)												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[4]	none	26	35	-	MD 6.5 higher (0.81 lower to 13.81 higher)	VERY LOW	IMPORTANT
QoL - 8 wks after treatment - older people (Better indicated by higher values)												
1	randomised trials	very serious 3	no serious inconsistency	no serious indirectness	serious4	none	26	35	-	MD 3.1 higher (4.21 lower to 10.41 higher)	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed

2 Only descriptive data reported, insufficient details given to assess the MID threshold and imprecision
3 Unclear how randomisation was performed and concealed; unclear whether outcome assessors and participants were blinded to treatment allocation
4 95% CI crossed 1 default MID (8.6 [17.2 x ± 0.5 = ± 8.6])
5 Not calculable as only medians have been reported. The median OS in the short course RT arm = 6.8 months (95% CI 4.5-9.1 months) and the median OS in the commonly used RT = 6.2 months (95% CI, 4.7-7.7 months)
6 Not calculable as only medians have been reported. The median PFS in the short course RT arm = 4.3 months (95% CI 2.6- 5.9 months) and the median PFS in the commonly used RT= 3.2 months (95% CI 0.1-6.3 months)

Table 125: Clinical evidence profile for comparison of RT and supportive care versus supportive care

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT +supportive care**	**Supportive care**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	No serious imprecision	none	-	-	HR 0.47 (0.29 to 0.76)	-	MODERATE	
Progression free survival												
1	randomised trials	very serious [1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.28 (0.17 to 0.46)	-	LOW	CRITICAL
Quality of life (QLQ-C30)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT +supportive care	Supportive care	Relative (95% CI)	Absolute		
1	Randomised trials	very serious [1,2]	no serious inconsistency	no serious indirectness	no serious imprecision		39	42	-	MD 10.50 higher (9.37 to 11.63 higher)	LOW	IMPORTANT

1 No details on how randomisation was performed or how randomisation concealment was used
2 Outcome assessors were aware of treatment allocation

Table 126: TMZ followed by RT versus RT alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ followed by RT	RT alone	Relative (95% CI)	Absolute		
Overall survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ followed by RT	RT alone	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 1.40 (0.93 to 2.09)	-	MODERATE	CRITICAL

1 95% CI crossed 1 default MID (1.25)

Table 127: RT with concomitant and adjuvant TMZ versus RT alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT with concomitant and adjuvant TMZ**	**RT alone**	**Relative (95% CI)**	**Absolute**		
OS RT with concomitant and adjuvant TMZ versus RT alone - OS overall												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.67 (0.56 to 0.80)	-	HIGH	CRITICAL
OS RT with concomitant and adjuvant TMZ versus RT alone - OS- patients 65 to 70 y/o												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	very serious1	none	-	-	HR 0.93 (0.68 to 1.27)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT with concomitant and adjuvant TMZ	RT alone	Relative (95% CI)	Absolute		
		risk of bias										
OS RT with concomitant and adjuvant TMZ versus RT alone - OS- patients 71 to 75 y/o												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.63 (0.48 to 0.83)	-	MODERATE	CRITICAL
OS RT with concomitant and adjuvant TMZ versus RT alone - OS- patients ≥ 76 y/o												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.53 (0.38 to 0.74)	-	HIGH	CRITICAL
OS RT with concomitant and adjuvant TMZ versus RT alone - OS MGMT methylated												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.53 (0.38 to 0.74)	-	HIGH	CRITICAL
OS RT with concomitant and adjuvant TMZ versus RT alone - OS MGMT non-methylated												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.75 (0.56 to 1)	-	MODERATE	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS overall												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT with concomitant and adjuvant TMZ	RT alone	Relative (95% CI)	Absolute		
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.5 (0.41 to 0.61)	-	MODERATE	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS- patients 65 to 70 y/o												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious [2]	none	-	-	HR 0.76 (0.55 to 1.05)	-	LOW	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS- patients 71 to 75 y/o												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.42 (0.30 to 0.59)	-	MODERATE	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS- patients ≥ 76 y/o												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.49 (0.35 to 0.69)	-	MODERATE	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS methylated												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.33 (0.23 to 0.47)	-	MODERATE	CRITICAL
PFS RT with concomitant and adjuvant TMZ versus RT alone - PFS non-methylated												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious [2]	none	-	-	HR 0.79 (0.59 to 1.06)	-	LOW	CRITICAL

Time to quality of life deterioration - Emotional												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.86 (0.69 to 1.07)	-	LOW	IMPORTANT
Time to quality of life deterioration - Role												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.94 (0.76 to 1.16)	-	LOW	IMPORTANT
Time to quality of life deterioration - Social												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.94 (0.76 to 1.16)	-	LOW	IMPORTANT
Time to quality of life deterioration - Cognitive												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.84 (0.68 to 1.04)	-	LOW	IMPORTANT
Time to quality of life deterioration - Constipation												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.11 (0.88 to 1.40)	-	LOW	IMPORTANT
Time to quality of life deterioration - Nausea and vomiting												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 1 (0.79 to 1.27)	-	VERY LOW	IMPORTANT
Time to quality of life deterioration - Fatigue												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.90 (0.73 to 1.11)	-	LOW	IMPORTANT

1 95% CI crossed 2 default MIDs (0.80 and 1.25)
2 95% CI crossed 1 default MID (0.80)
3 Not blinded

Grade III glioma

Table 128: Clinical evidence profile: RT + TMZ versus RT + a nitrosourea (NU)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + TMZ**	**Surgery/Biopsy + RT + NU**	**Relative (95% CI)**	**Absolute**		
Overall Survival (univariate analysis) (follow-up median 3.6 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	65/97 (67%)	65/99 (65.7%)	HR 0.94 (0.67 to 1.32)	23 fewer per 1000 (from 145 fewer to 99 more)	LOW	CRITICAL
Progression-free survival (univariate analyses)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + TMZ**	**Surgery/Biopsy + RT + NU**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	71/97 (73.2%)	75/99 (75.8%)	HR 0.85 (0.61 to 1.18)	57 fewer per 1000 (from 179 fewer to 55 more)	LOW	CRITICAL
Overall Toxicity (> Grade 3)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	46/96 (47.9%)	75/99 (75.8%)	RR 0.63 (0.5 to 0.80)	280 fewer per 1000 (from 152 fewer to 379 fewer)	LOW	IMPORTANT

[1] *CI crosses 2 MID (0.80 and 1.25)*
[2] *CI crosses 1 MID (0.80)*
[3] *Unclear if blinding of participants, personnel, and outcome assessors*

Table 129: Clinical evidence profile: RT + PCV versus RT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute	Quality	Importance
Overall Survival												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.78 (0.67 to 0.91)	-	MODERATE	CRITICAL
Overall Survival with codeletion of chromosomes 1p + 19q												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.58 (0.40 to 0.83)	-	MODERATE	CRITICAL
Overall Survival without codeletion of chromosomes 1p + 19q												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.84 (0.66 to 1.06)	-	MODERATE	CRITICAL
Overall Survival with IDH-1 mutation												
1	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.53 (0.30 to 0.94)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute	Quality	Importance
		of bias										
Overall Survival without IDH-1 mutation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.78 (0.52 to 1.17)	-	MODERATE	CRITICAL
Overall Survival with methylated MGMT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.65 (0.43 to 0.98)	-	MODERATE	CRITICAL
Overall Survival with non-methylated MGMT												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious2	none	-	-	HR 0.81 (0.44 to 1.49)	-	LOW	CRITICAL
Overall Survival with IDH-1 or 2 mutations												
1	randomised trials	no serious risk	no serious inconsistency	no serious	serious1	none	-	-	HR 0.59 (0.40 to 0.87)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute		
		of bias		indirectness								
Overall Survival without codeletion of chromosomes but with IDH-1 or 2												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.56 (0.32 to 0.98)	-	MODERATE	CRITICAL
Overall Survival without IDH-1 or 2 mutations												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious2	none	-	-	HR 1.14 (0.63 to 2.06)	-	LOW	CRITICAL
Progression Free Survival												
2	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.67 (0.56 to 0.81)	-	LOW	CRITICAL
Progression Free Survival with codeletion of chromosomes 1p + 19q												
2	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.45 (0.32 to 0.64)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute		
Progression Free Survival without codeletion of chromosomes 1p + 19q												
2	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.76 (0.61 to 0.94)	-	LOW	CRITICAL
Progression Free Survival with IDH-1 mutation												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.49 (0.29 to 0.83)	-	LOW	CRITICAL
Progression Free Survival without IDH-1 mutation												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	serious1	none	-	-	HR 0.56 (0.37 to 0.85)	-	LOW	CRITICAL
Progression Free Survival with methylated MGMT												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.52 (0.35 to 0.77)	-	MODERATE	CRITICAL
Progression Free Survival with non-methylated MGMT												
1	randomised trials	serious3	no serious inconsistency	no serious	serious1	none	-	-	HR 0.63 (0.34 to 1.17)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute		
				indirectness								
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (end of RT) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	128	129	-	MD 0.9 lower (4.93 lower to 3.13 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (end of RT + 1 year) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	63	-	MD 0.5 higher (3.51 lower to 4.51 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Fatigue HRQoL scale (end of RT + 2.5 years) (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + PCV**	**Surgery/Biopsy + RT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	39	-	MD 2 lower (6.01 lower to 2.01 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (end of RT) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	128	129	-	MD 2.3 higher (0.29 to 4.31 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (end of RT + 1 year) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	63	-	MD 1.8 higher (0.2 lower to 3.8	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute	Quality	Importance
										higher)		
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Nausea and Vomiting HRQoL scale (end of RT + 2.5 years) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	39	-	MD 0.7 lower (2.71 lower to 1.31 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	128	129	-	MD 8.5 higher (4.06 to 12.94 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT + 1 year) (Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + PCV**	**Surgery/Biopsy + RT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	63	-	MD 2.5 higher (2.01 lower to 7.01 higher)	MODERATE	IMPORTANT
Health Related Quality of Life - QLQ-C30 + QLQ-BN20 - Physical Functioning HRQoL scale (end of RT + 2.5 years) (Better indicated by lower values)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	39	-	MD 2.2 higher (2.3 lower to 6.7 higher)	MODERATE	IMPORTANT
Toxicity - Overall Toxicity (Grade 3 or 4)												
1	randomised trials	serious3	no serious inconsistency	no serious indirectness	no serious imprecision	none	94/146 (64.4%)	7/141 (5%)	RR 12.97 (6.24 to 26.97)	594 more per 1000 (from	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + RT + PCV	Surgery/Biopsy + RT	Relative (95% CI)	Absolute	Quality	Importance
										260 more to 1000 more)		

[1] *95% CI crossed 1 default MID (0.80)*
[2] *95% CI crossed 2 default MIDs (0.80 and 1.25)*
[3] *Unclear blinding of participants, personnel and outcome assessors*

Table 130: Clinical evidence profile: estramustine + RT versus RT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/Biopsy + Estramustine + RT	Control	Relative (95% CI)	Absolute	Quality	Importance
Overall Survival for Grade III Astrocytoma												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.99 (0.92 to 1.07)	-	MODERATE	CRITICAL
Toxicity - Grade III + IV Nausea/vomiting												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + Estramustine + RT**	**Control**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1, 2]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/59 (3.4%)	3/68 (4.4%)	RR 0.77 (0.13 to 4.44)	10 fewer per 1000 (from 38 fewer to 152 more)	VERY LOW	IMPORTANT
Health Related Quality of Life - QLQ-30 - Global QoL (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1, 2]	no serious inconsistency	serious[4]	very serious imprecision	none	28	38	-	MD 2.1 higher (0 to 0 higher)	VERY LOW	CRITICAL

1 Randomisation process nor allocation concealment not described in methods
2 Unblinded to participants, personnel, and assessors
3 95% CI crossed 2 default MIDs (0.80 and 1.25)
4 Grade III and IV Astrocytoma analysed together, not stratified per grade
5 No SDs were reported to assess the MID thresholds or imprecision

Table 131: Clinical evidence profile: PCV or TMZ + RT on progression versus RT + PCV or TMZ on progression

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + chemo on progression**	**Surgery/Biopsy + chemo + RT on progression**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall Survival (Long-term analysis, median follow-up time 9.5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	67/139 (48.2%)	72/135 (53.3%)	HR 1.11 (0.80 to 1.54)	38 more per 1000 (from 77 fewer to 157 more)	LOW	CRITICAL
Progression Free-Survival (Long-term analysis, median follow-up 9.5 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + chemo on progression**	**Surgery/Biopsy + chemo + RT on progression**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	109/139 (78.4%)	107/135 (79.3%)	HR 0.97 (0.74 to 1.27)	10 fewer per 1000 (from 105 fewer to 72 more)	VERY LOW	CRITICAL
Time to treatment failure (long-term follow-up, 9.5 years)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	92/139 (66.2%)	90/135 (66.7%)	HR 0.99 (0.75 to 1.31)	4 fewer per 1000 (from 105 fewer to 96 more)	VERY LOW	CRITICAL
Differential treatment outcomes in IDH mutant + 1p/19q co-deleted - Progression-Free Survival (follow-up median 9.5 years)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/Biopsy + RT + chemo on progression**	**Surgery/Biopsy + chemo + RT on progression**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	33	35	HR 1.3 (0.7 to 2.41)		VERY LOW	CRITICAL
Differential treatment outcomes in IDH mutant + 1p/19q co-deleted - Time-to-Treatment Failure (Follow-up: median 9.5 years)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[3]	none	33	35	HR 1.35 (0.68 to 2.68)		VERY LOW	CRITICAL
Differential treatment outcomes in IDH mutant + 1p/19q co-deleted - Overall Survival (Follow-up: median 9.5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	33	35	HR 0.46 (0.04 to 5.56)		VERY LOW	CRITICAL

1 Unclear risk of allocation concealment and no mention of loss to follow-up
2 95% CI crossed 1 default MID (1.25)
3 95% CI crosses 2 MIDs (0.80 and 1.25)
4 Unclear risk of allocation concealment, no mention of loss to follow-up, un-blinded

Table 132: TMZ followed by RT versus standard RT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMZ followed by RT	RT alone	Relative (95% CI)	Absolute		
OS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.40 (0.79 to 0.84)	-	MODERATE	CRITICAL

195% CI crossed 1 default MID (0.80)

Table 133: RT with adjuvant TMZ versus RT without adjuvant therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT with concurrent/adjuvant TMZ	RT without adjuvant therapy	Relative (95% CI)	Absolute		
OS												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RT with concurrent/adjuvant TMZ**	**RT without adjuvant therapy**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.65 (0.45 to 0.94)	-	MODERATE	CRITICAL
PFS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.58 (0.47 to 0.72)	-	HIGH	CRITICAL
Adjusted analyses for adjuvant TMZ only - Age (>50 y/o versus ≤ 50 y/o)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 4.04 (2.78 to 5.87)	-	HIGH	CRITICAL
Adjusted analyses for adjuvant TMZ only - WHO performance status score (>0 versus 0)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RT with concurrent/adjuvant TMZ	RT without adjuvant therapy	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.36 (0.94 to 1.97)	-	MODERATE	CRITICAL
Adjusted analyses for adjuvant TMZ only - 1p loss of heterozygosity (yes versus no)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.56 (0.84 to 2.90)	-	MODERATE	CRITICAL
Adjusted analyses for adjuvant TMZ only - Methylated versus non-methylated MGMT status												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 1.81 (1.44 to 2.27)	-	HIGH	CRITICAL

[1] *95% CI crossed 1 default MID (0.80)*
[2] *95% CI crossed 1 default MID (1.25)*

GRADE tables for review 2d – management of recurrent high-grade glioma

Table 134: Clinical evidence profile: Erlotinib versus TMZ or BCNU

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCNU/TMZ	Erlotinib	Relative (95% CI)	Absolute	**Quality**	**Importance**
PFS (Erlotinib)												
1	randomised trials	very serious [1,2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	-	-	Not estimable [4]	-	VERY LOW	CRITICAL
PFS (BCNU/TMZ)												
1	randomised trials	very serious [1,2]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	-	-	Not estimable [4]	-	VERY LOW	CRITICAL
OS (Erlotinib)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	-	-	Not estimable [4]	-	LOW	CRITICAL
OS (BCNU/TMZ)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BCNU/TMZ	Erlotinib	Relative (95% CI)	Absolute		
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	-	-	Not estimable [4]	-	LOW	CRITICAL

1 Selective reporting of outcomes
2 Unclear blinding
3 Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
4 Not calculated as SDs or IQr of the outcomes were not reported. Median overall survival in the control group = 7.7 months; median progression free survival = 1.8 months; median overall survival in the BCNU/TMZ arm= 7.3 months and median progression free survival= 2.4 months

Table 135: Clinical evidence profile: Cediranib alone versus Cediranib + lomustine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib alone	Cediranib + lomustine	Relative (95% CI)	Absolute		
OS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 1.43 (0.96 to 2.13)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib alone	Cediranib + lomustine	Relative (95% CI)	Absolute	Quality	Importance
PFS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 1.05 (0.74 to 1.49)	-	LOW	CRITICAL
Adverse events												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	78/128 (60.9%)	98/123 (79.7%)	RR 0.76 (0.65 to 0.9)	191 fewer per 1000 (from 80 fewer to 279 fewer)	MODERATE	IMPORTANT
Fatigue												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	21/131 (16%)	19/129 (14.7%)	RR 0.20 (0.13 to 0.3)	118 fewer per 1000 (from 103	HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib alone	Cediranib + lomustine	Relative (95% CI)	Absolute		
										fewer to 128 fewer)		

1 95% CI crossed 1 default MID (1.25)
2 95% CI crossed 2 default MIDs (0.80 and 1.25)
3 95% CI crossed 1 default MID (0.80)

Table 136: Clinical evidence profile: Cediranib + lomustine versus lomustine + placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib + lomustine	Lomustine + placebo	Relative (95% CI)	Absolute		
OS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 1.15 (0.77 to 1.71)	-	LOW	CRITICAL
PFS												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib + lomustine	Lomustine + placebo	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.76 (0.53 to 1.08)	-	MODERATE	CRITICAL
Fatigue												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/129 (14.7%)	6/64 (9.4%)	RR 1.57 (0.66 to 3.74)	53 more per 1000 (from 32 fewer to 257 more)	MODERATE	IMPORTANT
Adverse events												
1	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[3]	none	98/129 (76%)	39/65 (60%)	RR 1.27 (1.02 to 1.58)	162 more per 1000 (from 12	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cediranib + lomustine	Lomustine + placebo	Relative (95% CI)	Absolute		
		of bias								more to 348 more)		

1 95% CI crossed 2 default MIDs (0.80 and 1.25)
2 95% CI crossed 1 default MID (0.80)
3 95%CI crossed 1 default MID (1.25)

Table 137: Clinical evidence profile: Bevacizumab versus Bevacizumab + irinotecan

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BEV	BEV + irinotecan	Relative (95% CI)	Absolute		
OS												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.04 (0.85 to 1.28)	-	LOW	CRITICAL
PFS												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.01 (0.83 to 1.22)	-	LOW	CRITICAL
Wound healing complications												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BEV	BEV + irinotecan	Relative (95% CI)	Absolute		
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/84 (2.4 %)	1/79 (1.3%)	RR 1.88 (0.17 to 20.3)	11 more per 1000 (from 11 fewer to 244 more)	VERY LOW	IMPORTANT
Aphasia												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/84 (3.6 %)	6/79 (7.6%)	RR 0.47 (0.12 to 1.8)	40 fewer per 1000 (from 67 fewer to 61 more)	VERY LOW	IMPORTANT
Fatigue												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/84 (3.6 %)	7/79 (8.9%)	RR 0.40 (0.12 to 1.5)	53 fewer per 1000 (from 78 fewer to 44 more)	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed
2 95% CI crossed 1 default MID (1.25)
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 138: Clinical evidence profile: Bevacizumab / lomustine 90 versus lomustine

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab / Lom 90**	**Lomustine**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
OS												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.68 (0.42 to 1.10)	-	MODERATE	CRITICAL
PFS												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.58 (0.37 to 0.90)	-	LOW	
Fatigue												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/44 (18.2%)	3/46 (6.5%)	RR 2.79 (0.79 to 9.84)	117 more per 1000 (from 14	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Bevacizumab / Lom 90**	**Lomustine**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
										fewer to 577 more)		

1 95% CI crossed 1 default MID (0.80)
2 Outcome assessors not blinded
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 139: Clinical evidence profile: Bevacizumab / lomustine 90 versus Bevacizumab

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab / Lom 90	Lomustine	Relative (95% CI)	Absolute	**Quality**	**Importance**
OS												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.64 (0.40 to 1.02)	-	MODERATE	CRITICAL
PFS												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab / Lom 90	Lomustine	Relative (95% CI)	Absolute		
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.60 (0.38 to 0.95)	-	LOW	CRITICAL
Fatigue												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/44 (18.2%)	3/46 (6.5%)	RR 4.55 (1.02 to 20.28)	117 more per 1000 (from 14 fewer to 577 more)	LOW	IMPORTANT

1 95% CI crossed 1 default MID (0.80)
2 Outcome assessors not blinded
3 95% CI crossed 1 default MID (1.25)

Table 140: Clinical evidence profile: HRQOL for Bevacizumab or lomustine versus a combination of bevacizumab + lomustine

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab / Lom 90	Bevacizumab or Lomustine	Relative (95% CI)	Absolute	**Quality**	**Importance**
Lomustine												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	-	Total=27	Not estimable	Not estimable	VERY LOW	IMPORTANT
Bevacizumab												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	-	Total=36	Not estimable	-	VERY LOW	IMPORTANT
Lomustine + bevacizumab												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	Total=44	-	Not estimable	Not estimable	VERY LOW	IMPORTANT

5 Not blinded
6 Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision

Table 141: Clinical evidence profile: Bevacizumab + carboplatin versus bevacizumab

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab + carboplatin	Bevacizumab monotherapy	Relative (95% CI)	Absolute	Quality	Importance
PFS												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.92 (0.63 to 1.32)	-	VERY LOW	CRITICAL
OS												
1	randomised trials	serious[1]	serious	no serious indirectness	serious[4]	none	-	-	HR 1.18 (0.82 to 1.69)	-	LOW	CRITICAL
Adverse events grade >= 3												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[4]	none	37/58 (63.8%)	36/62 (58.1%)	RR 1.10 (0.82 to 1.46)	58 more per 1000 (from 105 fewer to 267 more)	VERY LOW	IMPORTANT
Wound healing complications												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab + carboplatin	Bevacizumab monotherapy	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	not estimable	none	0/58 (0%)	0/62 (0%)	-	-	LOW	IMPORTANT
Fatigue												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/58 (8.6%)	4/62 (6.5%)	RR 1.34 (0.38 to 4.73)	22 more per 1000 (from 40 fewer to 241 more)	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed; outcome assessors not blinded
2 95% CI crossed 1 default MID (1.25)
3 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 142: Clinical evidence profile: Bevacizumab + irinotecan versus bevacizumab + DD TMZ

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab + irinotecan	Bevacizumab + DD TMZ	Relative (95% CI)	Absolute	Quality	Importance
OS												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.86 (0.64 to 1.15)	-	LOW	CRITICAL
PFS												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 1.03 (0.81 to 1.30)	-	VERY LOW	CRITICAL
Neurologic adverse events												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	6/60 (10%)	3/57 (5.3%)	RR 1.90 (0.5 to 7.24)	47 more per 1000 (from 26 fewer to 328 more)	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed

2 95% CI crossed 1 default MID (0.80)
3 Unclear how randomisation was done; outcome assessors not blinded
4 95% CI crossed 1 default MID (1.25)
5 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 143: Clinical evidence profile: Low dose bevacizumab + CCNU versus standard dose bevacizumab monotherapy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab + CCNU	BEV	Relative (95% CI)	Absolute	Quality	Importance
PFS (patients at 1st and 2nd recurrence)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	-	-	HR 0.71 (0.43 to 1.17)	-	LOW	CRITICAL
PFS (patients at 1st recurrence only)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 0.58 (0.31 to 1.08)	-	LOW	CRITICAL
Median OS in patients at 1st recurrence												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	-	-	Not estimable[7]	-	VERY LOW	CRITICAL
Adverse events (grade ≥3)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab + CCNU	BEV	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/21 (4.8%)	4/35 (11.4%)	RR 0.27 (0.03 to 2.25)	83 fewer per 1000 (from 111 fewer to 143 more)	VERY LOW	IMPORTANT

1 Selective reporting of outcomes
2 Not blinded
3 95% CI crossed 1 default MID (0.80)
4 Only descriptive data have been reported, insufficient details given to assess the MID threshold and imprecision
5 95% crossed 2 default MIDs (0.80 and 1.25)
7 Not calculable as only medians have been reported. Median OS in the low dose bevacizumab + lomustine 90 arm= 13.05 months (7.08 to 17.82) and median OS in the bevacizumab monotherapy group= 8.8 (6.42 to 20.22)

Table 144: Clinical evidence profile: NovoTTF-100A versus active control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TTF	Active control	Relative (95% CI)	Absolute		
OS												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.86 (0.60 to 1.23)	-	LOW	CRITICAL
PFS												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.81 (0.60 to 1.09)	-	VERY LOW	CRITICAL
Cognitive disorder (grade ≥2)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[4]	none	2/117 (1.7%)	2/120 (1.6%)	RR 0.78 (0.11 to 5.46)	-	VERY LOW	IMPORTANT

1 Unclear method of allocation; high risk of attrition bias
2 95% CI crossed 1 default MID (0.80)
3 not blinded
4 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 145: Clinical evidence profile: post-hoc analysis[a] of NOVO-TTF-100A + second line chemotherapy versus second line chemotherapy alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	**TTF + second line chemotherapy**	**Second line chemotherapy alone**	**Relative (95% CI)**	**Absolute**		
OS –overall												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.70 (0.48 to 1.02)	-	LOW	CRITICAL
OS- patients treated with bevacizumab only												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.61 (0.37 to 1.01)	-	LOW	CRITICAL
Grade 3/4 adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	70/144 (48.6%)	20/60 (33.3%)	RR 1.46 (0.98 to 2.17)	153 more per 1000 (from 7	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	**TTF + second line chemotherapy**	**Second line chemotherapy alone**	**Relative (95% CI)**	**Absolute**		
										fewer to 390 more)		

aThis is a post-hoc analysis of Stupp 2015 and comprises those patients who presented with tumour progression after the initial treatment.
1 Unclear how randomisation was concealed
2 95% CI crossed 1 default MID (0.80)
3 95% CI crossed 1 default MID (1.25)

Table 146: Clinical evidence profile: Active treatment (TMZ, surgery, surgery + TMZ, surgery + RT, RT only) versus BSC in older and/or frail people

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active treatment	BSC	Relative (95% CI)	Absolute		
Overall survival												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.31 (0.17 to 0.56)		MODERATE	CRITICAL
OS - Age <65 versus ≥ 65 years												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Active treatment	BSC	Relative (95% CI)	Absolute		
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.91 (0.54 to 1.53)		LOW	CRITICAL
OS - KPS at relapse ≤50% versus ≥60%												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[3]	none	-	-	HR 1.60 (0.93 to 2.73)		LOW	CRITICAL
PPS												
1	randomised trials	very serious risk of bias[1,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.34 (0.19 to 0.60)		LOW	CRITICAL
PPS - Age <65 versus ≥ 65 years												
1	randomised trials	very serious risk of bias[1,4]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	HR 0.75(0.45 to 1.24)		VERY LOW	CRITICAL
PPS - KPS at relapse ≤50% versus ≥60%												
1	randomised trials	very serious risk of bias[1,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.31 (0.17 to 0.57)		LOW	

1 Selection criteria for treatment modalities were not consistent- the decision was left to the discretion of doctors
2 95% CI crossed 2 default MIDs (0.80 and 1.25)
3 95% CI crossed 1 default MID (1.25)
4 Not blinded
5 95% CI crossed 1 default MID (0.80)

Table 147: Carmustine polymer versus placebo polymer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Carmustine polymer**	**Placebo polymer**	**Relative (95% CI)**	**Absolute**		
OS- overall												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.83 (0.63 to 1.09)	-	MODERATE	CRITICAL
OS - KPS ≥70 versus KPS≤ 70												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.53 (0.40 to 0.70)	-	HIGH	CRITICAL
OS - AA versus GBM												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Carmustine polymer**	**Placebo polymer**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.60 (0.40 to 0.90)	-	MODERATE	CRITICAL
OS - Oligodendroglioma versus glioblastoma												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.39 (0.26 to 0.59)	-	HIGH	CRITICAL

1 95% CI crossed 1 default MID (0.80)

GRADE tables for review 2b – resection of glioma

Table 148: Clinical evidence profile: 5-ALA versus white light microsurgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5ALA	WL microsurgery	Relative (95% CI)	Absolute		
Complete tumour resection												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90/130 (69.2%)	47/131 (35.9%)	RR 1.80 (1.39 to 2.34)	-	LOW	CRITICAL
PFS												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.73 (0.57 to 0.93)	-	VERY LOW	CRITICAL
OS - Age ≤55												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	-	-	HR 1.04 (0.64 to 1.70)	-	VERY LOW	CRITICAL
OS - Age >55												
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.73 (0.53 to 1.01)	-	LOW	CRITICAL
OS- combined												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**5ALA**	**WL microsurgery**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.82 (0.62 to 1.08)	-	LOW	CRTITICAL
Convulsions												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	3/139 (2.2%)	1/131 (0.76%)	RR 2.83 (0.30 to 26.84)	-	VERY LOW	NOT IMPORTANT
Grade 3/4 neurological AEs												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[4]	none	10/139 (7.2%)	7/131 (5.3%)	RR 1.35 (0.53 to 3.43)	-	VERY LOW	IMPORTANT

1 Outcome assessors not blinded; participants excluded due to major violations of MRI inclusion criteria and due to histological criteria. High selective reporting of outcomes.
2 95% CI crossed 1 default MID (0.80)
3 Participants excluded due to major violations of MRI inclusion criteria and due to histological criteria. High selective reporting of outcomes.
4 95% CI crossed 2 default MIDs (0.80 and 1.25)

Table 149: Clinical evidence profile: iMRI versus neuronavigation[a]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMRI	Neuronavigation	Relative (95% CI)	Absolute		
Complete tumour resection												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/24 (95.8 %)	17/25 (68%)	RR 1.14 (1.06 to 1.87)	279 fewer per 1000 (from 41 more to 592 fewer)	VERY LOW	CRITICAL
PFS												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/24 (33.3 %)	16/25 (64%)	RR 1.85 (1.02 to 3.36)	544 more per 1000 (from 13 more to 1000 more)	VERY LOW	CRITICAL
New or aggravated language deficits												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMRI	Neuronavigation	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/24 (12.5 %)	2/25 (8%)	RR 1.56 (0.29 to 8.55)	45 more per 1000 (from 57 fewer to 604 more)	VERY LOW	IMPORTANT

1 Not blinded; unclear risk of attrition bias; study stopped early due to an interim analysis resulting in a reduced sample size.
2 95% CI crossed 1 default MID (0.80)
3 95% CI crossed 1 default MID (1.25)
a Senft 2011

Table 150: Clinical evidence profile: iMRI versus neuronavigation[b]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	iMRI	Neuronavigation	Relative (95% CI)	Absolute		
Rate of gross total resection												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**iMRI**	**Neuronavigation**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/58 (75.9%)	43/56 (76.8 %)	RR 0.99 (0.81 to 1.21)	-	MODERATE	CRITICAL
Progression												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 1 (0.96 to 1.04)	-	MODERATE	CRITICAL
New or aggravated language deficits												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[1]	none	6/58 (10.3%)	13/56 (23.2 %)	RR 0.45 (0.18 to 1.09)	-	LOW	IMPORTANT

1 Unclear whether all the pre-determined outcomes have been reported
2 95% CI crossed 1 default MID (0.80)
b Wu 2014

Table 151: Clinical evidence profile: DTI based functional neuronavigation versus routine neuronavigation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DTI based functional neuronavigation**	**Routine neuronavigation**	**Relative (95% CI)**	**Absolute**		
Complete tumour resection HGG												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/42 (76.2%)	14/43 (32.6%)	RR 2.34 (1.47 to 3.72)	436 more per 1000 (from 153 more to 886 more)	LOW	CRITICAL
Complete tumour resection LGG												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/61 (65.6%)	42/68 (61.8%)	RR 1.06 (0.82 to 1.38)	37 more per 1000 (from 111 fewer to 235 more)	VERY LOW	CRITICAL
OS												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DTI based functional neuronavigation**	**Routine neuronavigation**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 0.57 (0.33 to 1)	-	LOW	CRITICAL
KPS												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	MD 12 (5.37 to 18.63)	-	VERY LOW	IMPORTANT
Postoperative motor function deterioration												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/118 (15.3%)	39/120 (32.5%)	RR 0.47 (0.29 to 0.77)	-	LOW	IMPORTANT

1 High risk of selection bias and incomplete outcome data. Outcome assessors not blinded to intervention
2 95% CI crossed 1 default MID (1.25)
3 High risk of selection bias and incomplete outcome data
4 95% CI crossed 1 default MID (0.80)
5 95% CI crossed 1 default MID (+14) (±0.5 x ±28=±14)

Table 152: Clinical evidence profile: surgery with neuronavigation versus standard surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery with neuronavigation	Standard surgery	Relative (95% CI)	Absolute		
Complete tumour resection												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[3]	none	20/23 (86.9%)	17/22 (77.2 %)	RR 1.13 (0.85 to 1.48)	100 more per 1000 (from 116 fewer to 371 more)	VERY LOW	CRITICAL

1 Selective reporting of outcomes; trial significantly underpowered and terminated prematurely; perioperative evaluations and postoperative motor function and surgical complications conducted by the resident neurosurgeon and operating neurosurgeon who were not blinded.
2 15% of patients presented with cerebral metastasis
3 95% CI crossed 1 default MID (1.25)

Table 153: Clinical evidence profile: awake craniotomy versus surgery under general anaesthesia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awake craniotomy**	**Surgery under general anaesthesia**	**Relative (95% CI)**	**Absolute**		
Deteriorated speech area lesion - Immediate postoperatively												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[4]	none	4/26 (15.4%)	2/27 (7.4%)	RR 2.08 (0.42 to 10.32)	80 more per 1000 (from 43 fewer to 696 more)	VERY LOW	IMPORTANT
Deteriorated speech area lesion - At 3-month follow up												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[4]	none	3/26 (11.5%)	2/27 (7.4%)	RR 1.82 (0.57 to 5.84)	61 more per 1000 (from 32 fewer to 359 more)	VERY LOW	IMPORTANT
Deteriorate motor cortex lesions - Immediate postoperatively												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	very serious[3]	none	7/26 (26.9%)	2/27 (7.4%)	RR 3.64 (0.87 to 8.97)	196 more per	VER	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awake craniotomy**	**Surgery under general anaesthesia**	**Relative (95% CI)**	**Absolute**		
										1000 (from 10 fewer to 590 more)	Y LOW	
Deteriorate motor cortex lesions - At 3-month follow up												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[4]	none	10/26 (38.5%)	9/27 (33.3%)	RR 1.15 (0.51 to 1.98)	50 more per 1000 (from 163 fewer to 327 more)	VERY LOW	IMPORTANT
Residual tumour												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[4]	none	11/21 (52.4%)	7/19 (36.8%)	RR 1.42 (0.64 to 2.16)	155 more per 1000 (from 133 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Awake craniotomy**	**Surgery under general anaesthesia**	**Relative (95% CI)**	**Absolute**		
										427 more)		
KPS score (better indicated by higher values)												
1	randomised trials	very serious [1]	no serious inconsistency	serious[2]	serious[5]	none	-	-	The mean KPS score in the intervention arm was 7.80 lower (from 13.25 to 2.35 lower)	-	VERY LOW	IMPORTANT

1 Drop outs not accounted for; no data regarding survival or adverse events has been reported. Outcome assessors not blinded to intervention
2 One patient presented with a metastatic lesion
3 95% CI crossed 1 default MID (1.25)
4 95% CI crossed 2 default MIDs (0.80 and 1.25)
5 95% CI crossed 1 default MID (-4.15) (±8.3 x ±0.5=±4.15)

GRADE tables for review 5a – follow-up for glioma

Not applicable - no evidence was identified.

Appendix G – Economic evidence study selection

Economic evidence study selection for review 1a - imaging for suspected glioma and meningioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 1d – molecular markers to inform prognosis / guide treatment

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 1c – timing and extend of initial surgery for low-grade glioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 2a – further management of low-grade glioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 2c – initial management of high-grade glioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 2d – management of recurrent high-grade glioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 2b – resection of glioma

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 5a – follow-up for glioma

Economic study selection flowcharts are in Supplementary Material D.

Appendix H – Economic evidence tables

Economic evidence table for review 1a - imaging for suspected glioma and meningioma

Not applicable – no economic evidence was identified.

Economic evidence table for review 1d – molecular markers to inform prognosis / guide treatment

Not applicable – no economic evidence was identified.

Economic evidence table for review 1c – timing and extend of initial surgery for low-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence table for review 2a – further management of low-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence table for review 2c – initial management of high-grade glioma

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Kovic Year: 2015 Country:	Type of analysis: Cost utility Model structure: Markov Model Cycle length:	Base-case (population): Hypothetical cohort was identical to that in the AVAglio trial. In short the	1.Standard of Care (SOC) 2.Bevacizumab +SOC	Effectiveness (QALYs): SOC Bevacizumab + SOC Total costs (per patient): SOC	 0.83 0.96 CA$17,000	Funding: No specific funding declared

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Canada	3 month Time horizon: 2 years, (sensitivity analysis of 8 years). Perspective: Canadian public healthcare payer. Source of base-line data: Base line data reported is identical to those reported in the AVAglio trial discussed in detail in the clinical evidence review. (Chinot 2014) Source of effectiveness data: Effectiveness data were taken from the AVAglio trial discussed in detail in the clinical evidence review. (Chinot 2014) Where parameters had not been reported in the trial model calibration was used until effectiveness matched that reported in the AVAglio trial.	population consisted of adults with newly diagnosed GBM after biopsy or resection with a WHO performance status between 0 and 2, adequate healing of craniotomy or cranial biopsy site, adequate hematologic, hepatic, and renal function and acceptable blood coagulation levels. No population demographics were reported. Subgroup analysis: None performed		Bevacizumab + SOC ICER (cost per QALY): Bevacizumab + SOC versus SOC 95% Confidence Interval Uncertainty: Deterministic Sensitivity Analysis (cost per Life Year) Sensitivity analyses considering discount rate of 0%-6%, ±20% on costs, ±20% progression free survival utility, ±50% on QALY detriment with progression, hazard ratios varied between their 95% CI. Alternate analysis: 1st line bevacizumab+SOC versus bevacizumab 2nd line Probabilistic Sensitivity Analysis ICER 8 Year time horizon Base-case:Cost per QALY threshold for probability bevacizumab preferred option>0%	CA$80,000 CA$607,966 CA$305,000-CA$2,550,000 All analyses >CA$350,000 1st Line use dominated CA$439,764(95% CI CA$235,000-1,520,000 $210,000	for this study. Author FX received honoraria, had a consulting or advisory role and received travel, accommodation and expenses from GlaxoSmithKline Canada Comments

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of utility data: Utility values were obtained from 1 previous study which used a standard gamble to elicit preferences for GBM health states from a general UK population. Source of cost data: Resource use for treatment was largely taken from the AVAglio trial with the majority of costs for treatment being taken from a previous economic evaluation of temozolomide in GBM from a Canadian healthcare payer perspective. The costs for bevacizumab was taken from a previous economic evaluation of the drug in colorectal cancer. Adverse event costs and drug administration costs were taken from the publicly available costing			8 year time horizon cost per QALY threshold for probability bevacizumab preferred option>0% Value of Information Expected Value of perfect Information cost per QALY threshold= $607,966/QALY Expected Value of perfect information cost per QALY threshold= $100,000/QALY	CA$170,000 CA$33,000,000 CA$0	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	tariffs for the Ontario region of Canada. Currency unit: Canadian Dollar(CA$) Cost year: 2014 Discounting: Cost: 5% per annum QALYs: 5% per annum					
Study 2						
Author: Bernard-Arnoux Year: 2016 Country: France	Type of analysis: Cost Effectiveness Model structure: Markov Model Cycle length: 1 month Time horizon: Lifetime Perspective: French Health Insurance	Base-case (population): The hypothetical cohort for the model was populated using the characteristics reported in the EF-14 trial.	1.Standard chemotherapy and radiotherapy (SC) 2.Standard chemotherapy and radiotherapy with the addition of TTF (TTF)	Effectiveness (Life Months)f: SC TTF Total costs (per patient): SC TTF ICER (cost per Life Year): TTF versus SC 95% Confidence Interval	 18.00 22.08 €57,665 €243,131 €596,411	Funding: None declared Comments.

[f] The assumptions of the model mean that effectiveness outcomes are identical for Analysis 1 and Analysis 2

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of base-line data: Base-line data were taken from the EF-14 trial comparing TTF therapy in addition to standard chemotherapy and radiotherapy to standard chemotherapy and radiotherapy alone. The trial is discussed in detail in the accompanying clinical evidence review. (Stupp 2015) Source of effectiveness data: Effectiveness data were populated from the EF-14 trial discussed in the accompanying clinical evidence review. (Stupp 2015) Source of utility data: N/A outcomes reported in terms of costs per life year gained. No quality of life	Briefly the hypothetical cohort consisted of patients with newly diagnosed grade IV astrocytoma and a Karnofsky performance status≥70. The cohort were assumed to have stable disease and have previously undergone radiotherapy plus temozolomide. Subgroup analysis: None performed		Uncertainty: Deterministic Sensitivity Analysis (cost per Life Year) TTF therapy reduced to €10,000 month TTF therapy reduced to €3,000 month TTF therapy reduced to €2,000 month Sensitivity analyses considering ±50% on discount rate, ±20% on costs and ±2 weeks for survival parameters were performed. Probabilistic Sensitivity Analysis Probability TTF cost effective at a cost per LY threshold of €100,000 Costper LY threshold required year for probability TTF to be the preferred option >50%	€447,017-€745,805 €292,353 €98,862 €71,220 All above €450,000 0% €600,000	

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	adjusted measures were used for survival. Source of cost data: Costs were derived from a literature search covering the period 2010 to 2015 focussing on GBM in a French setting. The direct costs of newly diagnosed GBM was taken from 1 observational study, in a French setting, estimating the French Health Insurance costs for a cohort receiving chemotherapy and radiotherapy similar to that of the base-case cohort. TTF costs were taken from a company reported value of €21,000 per month including additional support. Currency unit: Euro(€)					

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Cost year: Not reported Discounting: Cost: 4% per annum QALYs: 4% per annum					

Economic evidence table for review 2d – management of recurrent high-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence table for review 2b – resection of glioma

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Slof Year: 2015 Country: Spain	Type of analysis: Cost-Utility Model structure: Post-Hoc economic evaluation of trial. Cycle length:	Base-case (population): People with Grade III and Grade IV glioma. No further patient characteristics were reported	(1) Fluorescent-guided resection with 5-ALA (2)Conventional resection under White Light	Incremental Effectiveness (QALY): 5-ALA versus White Light Incremental Cost 5-ALA versus White Light ICER (cost per QALY): 5-ALA versus White Light	0.11 €1010 €9,021	Funding: Laboratorios Gebro Pharma, S.A. Comments Only incremental

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	N/A Time horizon: Lifetime Perspective: Spanish Healthcare payer perspective Source of base-line data: See below Source of effectiveness data: Base-case data were taken from a retrospective, observational database of 251 patients comparing 5-ALA to white light surgery after July 2008. A sensitivity analysis was performed using data from one RCT (Stummer 2006). Stummer 2006 was a RCT comparing the resection of	Subgroup analysis: None Performed		Uncertainty: Deterministic sensitivity analysis (Incremental Cost per QALY) Stummer 2006 data used 5-ALA 40% more effective 5-ALA 40% less effective Adapting microscope cost included Adapting microscope, most expensive Combination least favourable assumptions for 5-ALA use Probabilistic sensitivity analysis (Incremental Cost per QALY) None performed	 €9,111 €6,444 €15,036 €9,950 €11,533 €19,222	values reported for interventions . No probabilistic sensitivity analysis performed.

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	glioma guided by 5-ALA to resection alone in 270 patients in a German healthcare setting. Source of utility data: Utility values were taken from one UK cost utility analysis comparing intracranial implantation of carmustine wafers as an adjunct to resection to resection and radiotherapy alone in patients with high-grade glioma. This study used a general population sample of 93 people of which 36 responded to this health state elicitation exercise. Hypothetical health states were developed using the EORTC QLQ-30 alongside the brain cancer module BC20 and standard gamble techniques used to estimate quality of life weights.					

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Source of cost data: Costs were taken from a public database maintained by the Spanish General Council of Official Pharmacists' Association Currency unit: Euro(€) Cost year: Not reported Discounting: Costs: All incurred first year so no discounting applied Outcomes: No Discounting applied					
Study 2						
Author: Eseonu Year: 2017 Country:	Type of analysis: Cost utility Model structure:	Base-case (population): Adults with WHO grade II, III and IV glioma in the perirolandic motor	(1)Awake Craniotomy (2) Surgery under general anaesthesia	Effectiveness (QALY): Awake Craniotomy Surgery under general anaesthesia Total Costs Awake Craniotomy	 0.97 0.47	Funding: Author was grant holder for Fundacio La Caixa

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
USA	Economic evaluation of retrospective observational data. Cycle length: N/A Time horizon: Life time Perspective: US Healthcare Payer Source of base-line data: See below Source of effectiveness data: Retrospective case-control study of 40 patients undergoing either awake craniotomy or surgery under general anaesthesiafor glioma in the perirolandic, motor area by one surgeon at one	area location. All people received the operation as an elective procedure and had no major comorbidities. Subgroup analysis: None performed		Surgery under general anaesthesia ICER (cost per QALY): Awake Craniotomy versus Surgery Under General Anaesthesia Uncertainty: No sensitivity analyses performed	 $34,804 $46,798 Dominant	Comments No sensitivity analysis performed

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	institution between December 2005 and March 2015. Source of utility data: Utility weights were calculated by dividing the reported Karnofsky performance status of patients by 100. Source of cost data: All costs were taken from the hospital database of one institution. The analysis included all inpatient costs. Currency unit: US Dollars ($) Cost year: Not reported Discounting: Not reported.					
Study 3						

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author: Martino Year: 2013 Country: Spain	Type of analysis: Cost Utility Model structure: Economic evaluation of retrospective observational data. Cycle length: N/A Time horizon: Lifetime Perspective: Spanish Healtchcare Payer (Direct),	Base case (population): Adults with WHO grade II glioma involving an eloquent area. Patients with significant comorbidities were excluded. The patient group only included individuals in active employment. Subgroup analysis: None performed	(1) Surgery under general anaesthesia/Awake/Surgery under general anaesthesia (AC) (2) Surgery under general anaesthesia (GA).	Effectiveness (QALYs): AC GA Total Costs Direct AC GA Indirect AC GA ICER (cost per QALY): Direct (AC vs GA) Indirect (AC vs GA)	 4.8 2.9 $38,663 $32,116 $49,302 $80.921 $3,500 Dominant	Funding: None reported Comments

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	Spanish Societal Perspective (Indirect) Source of base-line data: See below Source of effectiveness data: Patients receiving awake/sleep/awake craniotomy were taken from 11 consecutive patient records at one Spanish hospital between July 2009 and September 2011. These were matched with 11 patients from a retrospective cohort of 23 patients at the same hospital receiving			Uncertainty: No sensitivity analyses performed		

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	craniotomy under general anaesthetic. Source of utility data: Utility weights were calculated by dividing the reported Karnofsky Performance Score of patients by 100. Source of cost data: Healthcare unit costs from one Spanish Research Centre's database. All healthcare resource use was costed. Societal costs were based on lost wages as self-reported by people in the study. Currency unit:					

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
	US Dollars ($) Cost year: 2011 Discounting: Costs: Not reported Outcomes:3%					

Economic evidence table for review 5a – follow-up for glioma

Not applicable – no economic evidence was identified.

Appendix I – Health economic profiles

Economic evidence profiles for review 1a - imaging for suspected glioma and meningioma

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 1d – molecular markers to inform prognosis / guide treatment

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 1c – timing and extend of initial surgery for low-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 2a – further management of low-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 2c – initial management of high-grade glioma

See evidence review for initial management of high-grade glioma for health economic evidence profiles.

Economic evidence profiles for review 2d – management of recurrent high-grade glioma

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 2b – resection of gliomaSee evidence review for resection of glioma for health economic evidence profiles.

Economic evidence profiles for review 5a – follow-up for glioma

Not applicable – no economic evidence was identified.

Appendix J – Health economic analysis

Health economic analysis for review 2b – resection of glioma

Background

High-grade gliomas are intrinsic tumours of the central nervous system which are rapidly growing infiltrative malignancies. Neurosurgical resection is utilised as the initial treatment for many patients with high-grade gliomas to reduce intra-cranial pressure, facilitate molecular diagnosis and achieve cytoreduction. It is recognised that high-grade gliomas extensively involve the brain, making surgical cure impossible, but benefits for complete or near-complete (>95%) recovery have been described.

Traditional surgical resective techniques rely on visual assessment by the operating surgeon, with image guidance using neuro-navigation based on pre-operative radiological imaging. Resection can be limited by difficulty in discerning tumour from normal brain tissue and by intra-operative shift of structures as surgery progresses. Adjuncts to surgery have been introduced to attempt to help maximise the extent and safety of tumour resection, including 5-Amino-Levulinic Acid (5-ALA) fluorescence. 5-ALA is taken orally by the patient prior to resection. Then through overcoming the blood-brain barrier and surrounding glioma tumour cells it allows the glioma to be viewed fluorescently through specially adapted surgical microscopes. This allows for a greater probability of achieving maximal safe resection and potentially leading to greater overall survival, progression-free survival and higher quality of life. The addition of 5-ALA to traditional surgical resective techniques is associated with additional costs through both the cost of the 5-ALA vial and where necessary the large capital costs of the relevant module to allow the surgical microscope to view the fluorescence.

Intra-operative ultrasound and intra-operative MR are other adjuncts which can be added to traditional surgical resective techniques to allow intra-operative imaging of the glioma again increasing the probability of maximal safe resection. Both of these interventions are associated with large capital costs particularly in adapting or building suitable surgical theatres to allow their use.

This analysis compares the cost effectiveness of traditional surgical techniques with the addition of 5-ALA compared to traditional surgical techniques alone.. Intra-operative Ultrasound and Intra-operative MRI were not considered by the economic model. The accompanying clinical evidence review for this topic identified only 1 RCT of intra-operative ultrasound and 1 RCT of intraoperative MRI as part of a Cochrane Systematic Review (Barone 2014). Both studies only provided evidence around the extent of resection with too little evidence to evaluate overall survival, progression-free survival or quality of life. Both these interventions also have large capital costs, especially intra-operative MRI, with cost effectiveness likely to be dependent on the number of patients utilising the technology. As the throughput is likely to differ widely by centre the cost effectiveness is also likely to differ. Given the large uncertainty around the effectiveness of these interventions and the accompanying large uncertainty around costs, any cost effectiveness analysis would be unlikely to produce any helpful output for informing recommendations. A full discussion around the issues of intra-operative ultrasound and intra-operative MRI, particularly the issues of the large capital cost, is presented in the ‘Cost effectiveness and resource use’ section of the question about ‘techniques for resection of glioma’.

Awake craniotomy was not considered by this analysis as this is usually only performed in a subsection of the considered patient group for which the tumour is situated in an eloquent area of the brain and would only be relevant for a subgroup of this patient population. Cost effectiveness evidence was also identified around awake craniotomy during the review of

published economic evidence and discussed in the 'Economic evidence' section of the question about 'techniques for resection of glioma. Type of brain stimulation, MRI ablation, BrainPath and endoscopic resection were also not considered in the economic analysis, despite being included in interventions listed in the PICO table as either the clinical evidence review identified too little evidence for it to be included appropriately or the intervention was only appropriate for a subgroup of the patient population considered by this topic.

Methods

Interventions considered

The base-case analysis considered 2 potential interventions:

- traditional surgical resective techniques with the addition of 5-ALA (5-ALA)
- traditional surgical resective techniques under white light with no adjuncts (resection alone)

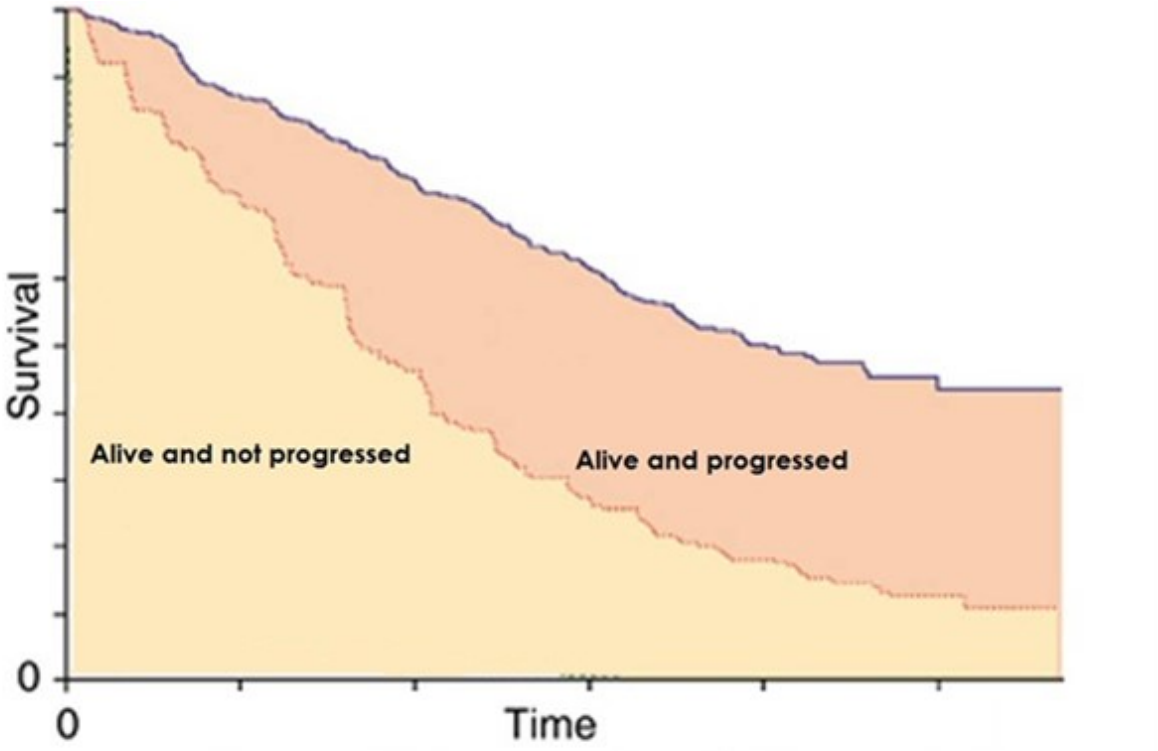
Model structure

A partitioned survival analysis was developed to estimate the expected life time quality adjusted life years (QALYs) and costs associated with the 2 interventions considered for this analysis. A partitioned survival analysis divides the model cohort between different health states based on survival curves derived for overall survival (OS) and progression-free survival (PFS) derived from the accompanying clinical evidence review. The expected OS and PFS are then calculated from the area under the respective curves. For our model, 3 mutually exclusive health states were derived for the cohort to be partitioned into:

- alive without progressed disease (equal to the area under the PFS curve)
- alive with progressed disease (equal to the area between the PFS curve and the OS curve)
- death (area above the OS curve).

An illustrative example of the structure of the partitioned survival analysis is shown in Figure 40.

Figure 40: Illustrative example of partitioned survival analysis



A partitioned survival analysis approach was chosen over other modelling approaches, for example, a state transition model as only 1 relevant study (Stummer 2006) was identified in the accompanying clinical evidence review and consequently all clinical evidence, including OS and PFS were taken from the outcomes and Kaplan Meier curves reported in that paper. As all evidence was taken from this 1 study and there was very limited extrapolation beyond the time horizon used in the Stummer trial there would only be small differences in model results from using this approach compared to a more traditional state transition model. How this evidence was used to inform the OS and PFS curves for the economic model is discussed in detail below. This approach is widely used in models of the cost effectiveness of oncology interventions. A review of recent oncology NICE Technology Appraisals found that this approach was used in 73% of submissions (Woods 2017).

While not a consideration in choosing the most appropriate modelling approach, a partitioned survival analysis is a more intuitive modelling approach for brain metastases than state transition models. Evidence from trials and observational studies where survival is a key outcome are almost exclusively reported as median overall and progression-free survival with accompanying hazard ratio and Kaplan Meier survival curves. As these are the primary inputs for partitioned survival analysis the inputs can be easily compared with those observed in the included trials and other external sources.

A partitioned survival analysis was performed for both interventions considered in the economic evaluation and total time spent in each health state for the model cohort was

calculated. Each health state was assigned a quality of life weighting so that survival could be adjusted to QALYs.

The economic component of the model was built and run in Microsoft Excel 2013. The model had a cycle length of 0.75 months. This was chosen over a more standard 1 month cycle length as it provided a better fit to the observed data from the Stummer trial without being excessively short and adding unnecessary computational requirements to the model. The model had a time horizon of 5 years, the longest duration of follow up identified in the accompanying clinical evidence review. The study (Stummer 2006).suggested that over 95% of the cohort would be dead at this time horizon and that in over 95% of people disease progression would have occurred by 15 months

Population

Given that only Stummer 2006 (described in detail below) was the only identified clinical evidence in the accompanying clinical evidence review, the hypothetical patient population of the economic model was chosen to match the population of the published trial as closely as possible to maximise the validity of any inputs. The hypothetical cohort consisted of adults with WHO grade IV glioma (96% of patients in Stummer 2006) with a Karnofsky performance status (KPF) greater than 70. None of the patients had received any previous surgical treatment for their tumour. All patients were clinically indicated as suitable for surgery and the tumour was not located in either the midline, basal ganglia, cerebellum or brain stem.

Model Parameters

Progression-free survival

Stummer 2006, the only identified evidence in the clinical evidence review, was a randomised controlled trial comparing the resection of glioma guided by 5-ALA to resection alone. The study involved 322 patients and reported interim results from 270 patients with 131 and 139 patients randomised to 5-ALA and conventional resection, respectively. The study was terminated following the interim analysis in line with the trial protocol which allowed premature termination after 270 patients if a difference in PFS was observed such that it could be identified with a power of 80%. Median follow up was 35.4 months.

PFS in the trial was higher throughout for the 5-ALA group, with 41% of people having not experienced disease progression or died at 6 months compared to 21% in the resection alone group. The Kaplan Meier survival curves presented in the report were extracted using an image digitising program (WebPlotDigitisier) and incorporated directly as the PFS curves in the model as both interventions mapped exactly to those considered in the guideline economic analysis. During the probabilistic sensitivity analysis (PSA) PFS for 5-ALA was estimated using the hazard ratio reported in the Stummer trial (0.73 [95%CI 0.57 to 0.93]) relative to resection alone following the usual proportional hazard assumptions. While the Kaplan Meier curves reported by Stummer cross, in a departure from proportional hazards, the committee could suggest no clinical reason why that would be the case and their opinion was that 5-ALA would have higher PFS throughout the first 15 months. This crossing of the curves was therefore assumed to be down to statistical variance within the two treatment cohorts. The crossing of the curves only occurred before 3 months after which 5-ALA had greater PFS throughout until the 15 months after which it is assumed, in the model, all disease progresses. While parametric alternatives to the proportional hazards assumptions exist there was not enough evidence reported to fit these without making large assumptions. Therefore, despite these violations, the assumption that the crossing was down to statistical variation meant that using the proportional hazard assumptions would reasonably capture uncertainty in the PSA.

Overall survival

Overall survival for the model was informed by Stummer 2006. Median overall survival in the study was 15.2 months for the 5-ALA group and 13.5 months for resection alone. Kaplan Meier curves were not reported for overall survival and were assumed to follow an exponential function with a constant hazard assumed. Where PFS was greater than OS, OS was assumed to be equal to PFS to avoid any logical anomalies. The OS curve was then fitted so that it gave a median overall survival identical to that reported by Stummer 2006. It may be expected that interventions which delay disease progression in cancer also lead to an increase in overall survival. There is evidence in glioma of a positive correlation between better PFS and OS from 11 Phase II trials of 1348 glioma patients (Ballman 2007) although there was not enough evidence identified to estimate this relationship empirically. The committee was of the opinion that this assumption had clinical validity. Median overall survival was varied along a log normal distribution during PSA and the curves adjusted accordingly. As a difference in OS was not statistically significant between the two interventions a deterministic sensitivity analysis was undertaken where median OS was assumed to be 14 months for both interventions.

Extrapolation of overall and progression-free survival

Progression-free survival was only reported up to 15 months. As the time horizon of the model (5 years, or 60 months) exceeds that time, 45 months of extrapolation beyond the published 15 month follow-up time point was needed. At this time point, 94% of the 5-ALA cohort and 97% of the cohort who received resection alone had disease progression or had died. After 15 months PFS was assumed to be zero in both groups. Given the nature of glioma, and the inability to remove all of a tumour (only achieve the maximal resection) all people with the disease will either experience disease progression or die with or from the disease. The committee felt that PFS after 15 months was likely to negligible. The committee also considered that patients with disease that had not progressed after 24 months were very rare. Given the very small number of people for which PFS has been extrapolated for, alternate assumptions around PFS extrapolation would be unlikely to change any model conclusions. This assumption was therefore not varied during either the PSA or any deterministic sensitivity analysis.

Overall survival was extrapolated beyond the 15 months it was matched to PFS using an exponential function which gave an overall survival of less than 95% at 60 months. This was consistent with 5 year survival rates reported for WHO grade IV glioma in the accompanying clinical evidence review.

Health related quality of life

The accompanying clinical evidence review looked for studies considering quality of life amongst those that met the inclusion criteria. No evidence around quality of life for patients receiving either 5-ALA or resection alone for high-grade glioma was identified. The search for evidence of quality of life was then expended to searching the CEA (Cost-Effectiveness Analysis) registry website, excluded studies from the evidence review and through discussion with the committee. This again identified no quality of life evidence for people receiving these 2 interventions. Previous economic evaluations, discussed above, were therefore searched and in conjunction with the committee the most appropriate estimate of quality of life was used to inform quality of life in the economic model.

Informed by 1 previous economic evaluation (Slof 2015), quality of life evidence was taken from Rogers 2008. Rogers 2008 was a cost utility study analysis comparing intracranial implantation of carmustine wafers as an adjunct to resection and radiotherapy alone in patients with high-grade glioma. This study used a general population sample of 93 people of which 36 responded to this health state elicitation exercise. Hypothetical health states were developed using the EORTC QLQ-30 alongside the brain cancer module BC20 and standard

gamble techniques used to estimate quality of life weights.

Two disease states were used from Rogers 2008 to inform the economic model. ‘Not progressed’ disease was valued from the stable disease scenario define as ‘patients stable post-surgery without receiving any further treatment’. Progressed disease was informed by the progressive disease state defined as ‘patients with general symptomatic deterioration’. From this the quality of life weights used in the economic model for ‘Not progressed’ and progressed disease were 0.8772 and 0.7314 respectively

It should be noted that standardising the quality of life impact of high-grade glioma is difficult given that different locations of the tumour (leading to differing symptoms) can lead to differing symptoms from the disease. There would likely be large variation in any quality of life weights between different people with high-grade glioma it would not be possible to account for this in our model as we did not identify clinical or quality of life evidence which differentiated between different locations of the tumour. Given this and other validity issues described above with using these values in the model a range of deterministic sensitivity analyses were carried out around these values. They were also varied along their reported range during PSA using a normal distribution bound to be less than or equal to 1. The 95% confidence intervals for both ‘Not Progressed’ and ‘Progressed’ disease’ overlap each other. This may be reflecting the large variation in quality of life of patients with glioma discussed above or possibly a consequence of collecting these quality of life weights from a small population sample or some function of both. As it was not clear why this was the case, or whether it was reasonable to assume that ‘Not Progressed’ disease always has a higher quality of life weight than ‘Progressed Disease’ this potential counterintuitive input was not adjusted for in the PSA.

Costs and resource use

Resource use

The base-case model explicitly assumes that the only difference in resource use between the 5-ALA and the resection alone cohort will be that of the vial of 5-ALA and the additional follow-up appointments and MRI scans following any difference in overall survival. In a subsequent analysis the impact of including the cost of the potential purchase of the relevant module for the surgical microscope to see the fluorescents will also be explored.

In Stummer 2006, additional treatment following both 5-ALA and resection alone were explored. Stummer 2006 found no statistically significant difference between either group in terms of radiotherapy and chemotherapy following treatment but before disease progression and no difference between the groups in terms of chemotherapy following surgery. This matched with the committee’s clinical experience and highlighted that chemotherapy following surgery but before radiological progression was very rarely given in this patient cohort in the NHS and this was most likely as a result of different clinical practice in Germany where the trial was conducted. Stummer 2006 did report a statistically significant difference in the number of patients receiving resection following disease progression with 30% of 5-ALA patients and 37% of resection alone patients receiving repeat surgery. Therefore as part of a deterministic sensitivity analysis an additional cost of the above patients receiving a further resection following disease progression. It was assumed that the surgery would be received in the first year following initial treatment and that both groups would receive resection alone regardless of their initial treatment. These additional resections were only added upon the cost side of the model and as any clinical impact for them would have been accounted for in the results of the Stummer trial.

All other future costs were assumed to be identical between the 2 groups and would cancel each other out during incremental analysis. For ease of modelling any other future resource use was not included in the economic model.

5-ALA

It was assumed that all patients who received 5-ALA as an adjunct to their resection would take 1 vial (1.5g) of 5-ALA hydrochloride approximately 3 hours before anaesthetic for resection. While in the Stummer 2006 patients received 20mg per kilogram of body mass which would allow 1 vial to be used for per patient under 75kg (approximately 12 stone) assuming that vial splitting did not take place. If the Stummer protocol was to be followed exactly and again no vial splitting then a sizeable proportion of the population would receive 2 vials before anaesthetic. No evidence was identified for the average weight of patients with high-grade glioma but if it is similar to the UK general population, where the median female and male weighed 70.2kg and 83.6kg (ONS 2016) respectively then it is likely that over half of patients would be required to receive 2 vials of 5-ALA. It is common practice in the UK when administering 5-ALA vials to only give 1 per patient regardless of their body mass. Vial sharing is also very uncommon given the effective life of 5-ALA post production and the relative low prevalence of high-grade glioma. Therefore, in the base-case all patients were assumed only to receive 1 vial of 5-ALA prior to surgery. As part of a deterministic sensitivity analysis patients were assumed to receive 1.5 vials, reflecting a scenario where 50% of treated patients would require a second vial, and a sensitivity analysis where patients would receive 2 vials representing an absolute upper estimate of total vials received by this patient group. The number of vials received was not varied during the PSA but some of this uncertainty would be picked up by the variation around costs described below.

No costs were reported for a vial of 5-ALA in either the BNF or the Drugs and Pharmaceutical Electronic Market Information (eMit). Papers identified in the search for previous economic evidence, including those which had been rejected for this or other topics, were searched to try and inform this cost. No UK pricings were identified for 5-ALA vials. One Spanish costing was identified which priced a vial of 5-ALA at €980 at 2015 prices. This was converted to UK 2016 prices using the IMF Purchasing Power Parities for Healthcare and inflation indices reported by Curtis 2016. This gave a base-case estimate of £1016.44 per vial of 5-ALA. This value was very similar to committee estimates around the price of 5-ALA vial of about £900. Given the uncertainty around this value and the likelihood that different centres may be negotiating their own purchasing price for 5-ALA the value was given a wide range of ±50% during PSA and varied across a uniform distribution.

Cost of resection

The cost of resection in this model was costed from NHS Reference Costs and assumed to be £7,032. Given the assumptions of the model where all patients receive a resection either with or without the adjunct of 5-ALA the cost of resection would make no difference to the base-case analysis where future treatment is assumed identical. In both these analyses both set of patients will receive an identical number of resections and therefore the cost of resection will zero out during any incremental analysis. In the further surgery deterministic scenario analysis future resections were costed identically to initial treatment. It was assumed that 5-ALA would not be used in subsequent resections.

Cost of follow-up

Patients were assumed to receive a 3 monthly MRI scan and consultant led follow up for every 3 months they are alive in the model. Follow-up was costed as 1 non-admitted face to face follow up in neurosurgery and 1 MRI scan of the brain. The combined cost of 1 follow-up session was £333. The costs were varied using a gamma distribution during the PSA using their reported ranges.

Cost of module

To be able to see the fluorescent results of the 5-ALA vial, surgical microscopes need to be fitted with the relevant module. Many of the recent models of surgical microscope will already have this fitted or may have already been purchased by the centre if already using 5-ALA.

Other centres with older surgical microscopes or those that do not use 5-ALA may not already have this module and there will be significant fixed capital costs with purchasing it. Therefore, to be able to use 5-ALA as an adjunct to resection some centres may incur large capital costs while others will not. Two scenarios were therefore explored as part of this economic model.

The first scenario ignored any cost of the module and assumed that the surgical microscopes would already have this installed. In this scenario the surgical costs excluding the 5-ALA vial were identical between the 2 groups. A second scenario assumed 3 potential costs for the module based on the range of costs estimated by Slof 2015. €37,500 was assumed as our base-case estimate and took the extreme of the ranges as the low and high estimate. These were converted to UK Sterling 2016 costs using identical methodology as that described for the 5-ALA vial costs above to give values of £31,595, £39,493 and £47,392. These costs were assumed to include maintenance and repair and that there would be no future costs associated with the use of the machine. The effective life span of the module was assumed to be 8 years after which time it would need to be replaced again based on length of depreciation reported by Slof 2015.

As these costs are reported per module and outcomes of this economic model are reported as cost and QALY per patient we tried to convert this capital cost into a cost per patient. We attempted to estimate this by calculating the throughput of 1 centre over the 8th year effective life span and dividing the total module costs by this figure. The model would then add that to the cost of the 5-ALA group. It was difficult to estimate the throughput of the centre for 2 reasons. Firstly, there was likely to be large variation across the NHS in England in regards to the size of centres and the number of high-grade gliomas they treat surgically each year leading to large variations in cost per patient. Secondly, the module would potentially not be used solely in high-grade glioma with 5-ALA also potentially used for surgery in other cancers. It is unclear in which areas 5-ALA is already being used and how, the availability of the required module would increase uptake of 5-ALA and consequently throughput from increased patient numbers.

It was therefore suggested that we look at what throughputs would be needed for 5-ALA to remain cost effective, if it is cost effective in the base-case analysis, at both the £20,000 and £50,000 cost per QALY thresholds discussed below.

Training costs

Currently surgeons attend a 2 day course before using 5-ALA. The costs of this are currently paid for by the manufacturer of 5-ALA although there is potentially an opportunity cost to the NHS, from surgeons being away their centres. This could potentially be estimated using the surgeons wage rate and other employment costs over those 2 days. It is also not clear if the manufacturer of 5-ALA would cover the costs of training if the use of 5-ALA was to become routine.

Typically training costs are not included in NICE economic analyses as healthcare professionals are allocated time for training and continued professional development and this is already built into other reference costs through staff wage costs. Also when interventions become routine and there is a training need there for all relevant healthcare professionals these will get built into the training syllabuses for the relevant Royal College. Training costs were therefore not considered as part of this economic evaluation.

Cost year

All costs were inflated to 2016 prices and converted to pound sterling where necessary. All other costs in the model were taken from 2015-2016 NHS Reference Costs the latest year available and consequently it was not necessary to perform any inflation of costs for these values.

Discounting

All health and cost outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual. This was not varied during sensitivity analyses.

Cost per QALY threshold

For our analysis the cost per QALY thresholds were assumed to be both £20,000, the cost per QALY below which NICE conventionally recommends interventions and £50,000, a higher cost per QALY, which NICE consider for interventions which increase life expectancy by at least 3 months in people in their final 24 months of life relative to current treatment. Stummer 2006 reported a median overall survival in the 5-ALA group of 15.2 months and an increase in median overall survival between the 2 groups of 1.7 months with a 95% upper confidence interval of 4.0 months increased survival. As there is some uncertainty around whether the interventions in this analysis meet the criteria for the higher cost per QALY threshold both from the results of this 1 trial and through a lack of other supporting evidence to this survival gain both thresholds were considered when assessing cost effectiveness for this economic analysis.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base-case are replaced with values drawn randomly from the distributions around the mean values. This is done over 10,000 iterations and the different outcomes of these iterations presented both diagrammatically and in terms of mean results to reflect the uncertainty around the outcomes of the model. The distributions used are presented in Table 154.

Table 154 List of parameters used in the economic model and PSA distribution

	Value	Source	PSA Distribution
Overall Survival (Months)			
Resection Alone	13.5	Stummer 2006	Log Normal(2.60,0.08)
5-ALA	15.2	Stummer 2006	Log Normal(2.72,0.05)
Progression-Free Survival			
Resection Alone	Fitted report Kaplan Meier Curve	Stummer 2006	N/A
5-ALA	Fitted report Kaplan Meier Curve	Stummer 2006	N/A
Hazard Ratio (PSA) 5-ALA versus Resection ALone	0.57	Stummer 2006	Log Normal(0.31,0.12)
Quality of Life			
Not progressed Disease	0.8872	Rogers 2008	Normal(0.89,0.13)
Progressed Disease	0.7314	Rogers 2008	Normal(0.73,0.21)
Death	0		Not Varied
Costs			
5-ALA Vial	£1,032	Slof 2015	Uniform(516,1548)
Surgical Resection	£7,032	NHS Reference Costs 15-16	Gamma(7,032,18.51)
Follow-Up Appointment	£188	NHS Reference Costs 15-16	Gamma(188,5.15)
MRI Scan	£145	NHS Reference Costs 15-16	Gamma(145,10.55)

	Value	Source	PSA Distribution
Total Cost Module	£39,493	Slof 2015	N/A
Effective Life of Module (years)	8	Slof 2015	Not Varied
Discount Rate (per annum)			
Costs	3.5%	NICE 2016	Not varied
QALYs	3.5%	NICE 2016	Not varied

Results

Base-case results

Table 155 shows the base-case deterministic results for 5-ALA compared to resection alone. The model estimated an increase in overall survival of just over 2 months and 0.1398 additional QALYs when 5-ALA is used. 5-ALA leads to an increase in costs compared to resection alone of £1,257, taking account of the increased follow up costs from increased survival and the initial one off cost of the 5-ALA vial. This equates to a cost per additional QALY of £8,991 below the £20,000 and significantly below £50,000 thresholds discussed above.

Table 155: Base-case Analysis Results

Intervention	Life Months	QALY	Disc. QALY	Cost	Disc Cost	Inc. QALY	Inc. COST	ICER
Resection Only	18.58	1.1872	1.1504	£1,947	£1,874	Ref	Ref	
5-ALA	20.75	1.3353	1.2903	£3,220	£3,131	0.1398	£1257	£8,991

These results are almost identical to the stochastic results where the mean of the PSA iterations are used to estimate outcomes of the model. In this case overall QALYs are marginally lower for each intervention with broadly similar costs. In this analysis 5-ALA leads to higher incremental costs and QALYs compared to the deterministic results but the difference are very small (0.0069 QALYs, £7). The resulting ICER is also marginally less favourable to 5-ALA than the deterministic base-case results although both are well below £20,000 per QALY.

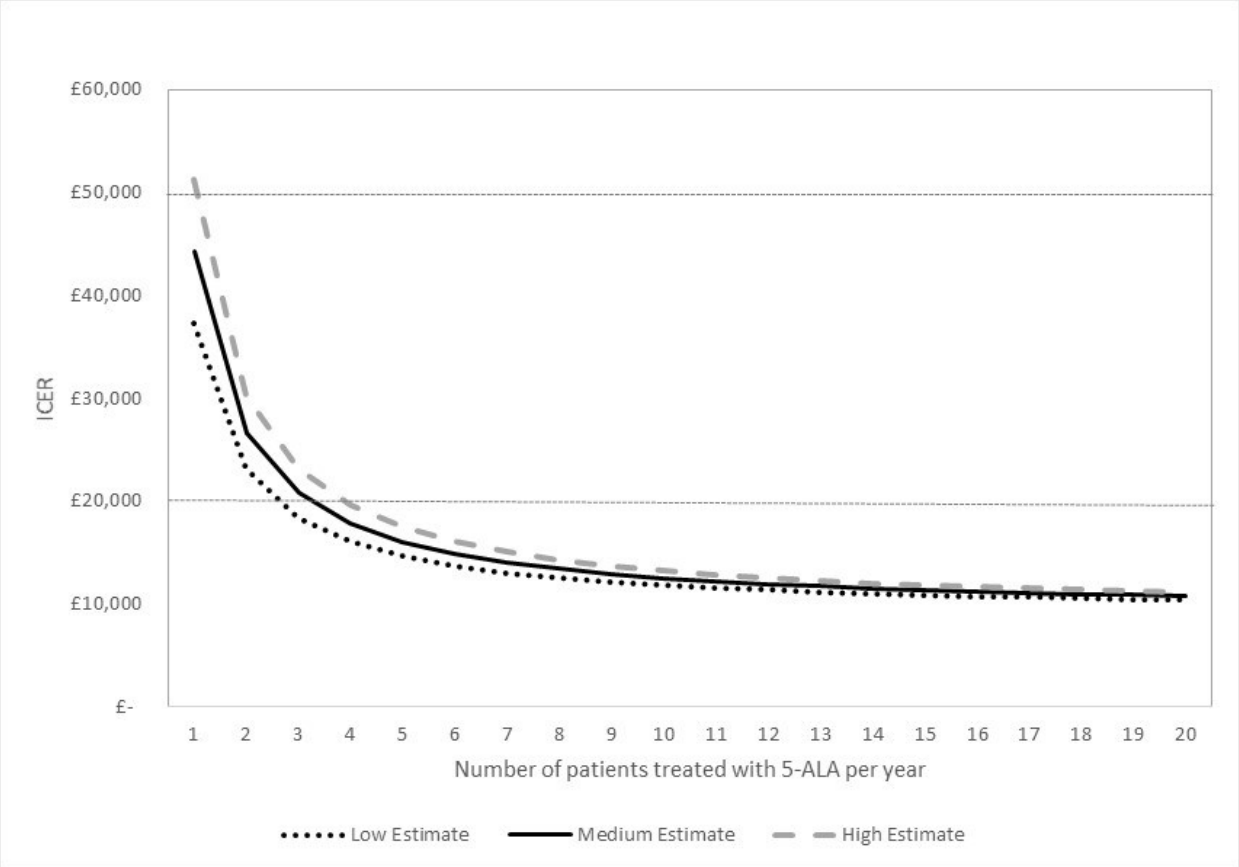
Table 156: Stochastic Base-case Analysis Results

Intervention	Disc QALY	Disc Cost	I.QALY	I.COST	ICER
Resection Only	1.1355	£ 1,875	Ref	Ref	
5-ALA	1.2684	£ 3,139	0.1329	£1,264	£9,509

Base-case analysis including module costs

Figure 41 shows the relationship of between the ICER and annual throughput at a centre for all 3 estimates of the cost of the addition of the relevant module to the surgical microscope when this cost is included in the model. Even at the highest estimate of module costs and assuming the lower threshold of £20,000 per QALY a centre would only need to treat 5 people per year with 5-ALA (for any condition) for it to remain cost effective. This is reduced to 4 people per year when the middle or lower estimates are considered. When the higher £50,000 threshold is assumed only 1 patient is needed to be treated per year for all but the highest cost estimate of module cost.

Figure 41: Relationship between patient throughput and the ICER



Deterministic sensitivity analysis

Table 157 shows the results of the deterministic sensitivity analysis results. Changing the inputs to the extremes of their estimated values only resulted in 5-ALA not being the preferred option in 2 scenarios for the £20,000 threshold and in only 1 scenario (where the lower estimate of overall survival is assumed for 5-ALA) for the £50,000 threshold. The ICER did not appear sensitive to the cost of health resources other than for the 5-ALA vial costs. This is unsurprising given that the non 5-ALA resource use was largely consistent between the 2 interventions. 5-ALA remained the preferred option for both considered thresholds when an average of 1.5 and 2 vials per patient were used in contrast to many centres limiting of 5-ALA to 1 vial per patient.

Despite poor quality evidence around quality of life the conclusions seemed robust to differing assumptions. Even when no difference was assumed between progressed and unprogressed health states, an assumption that would strongly bias against 5-ALA, it still remains the preferred option.

Table 157: Deterministic sensitivity analyses

Parameter	Value	ICER (versus Resection Alone)/Per Additional QALY
Overall Survival 5-ALA	L95=12.9 months	Dominated
	U95=17.5 months	£5,637

Parameter	Value	ICER (versus Resection Alone)/Per Additional QALY
Overall Survival Resection Alone	L95=12.0 months	£6,096
	U95=14.7 months	£16,834
Overall Survival	Both interventions=14.0 months	£27,361
Progression-Free Survival Hazard Ratio	L95=0.57	£7,608
	U95=0.93	£11.169
5-ALA Vial	1.5 vials per patient	£12,681
	2.0 vials per patient	£16,371
Follow-Up app cost	IQRL=£127	£8,694
	IQRU=£238	£9,233
MRI Cost	IQRL=£113	£8,835
	IQRU=£173	£9,130
Additional resections assumed		£8,232
Quality of Life	All non-dead health states=1	£7,421
	Values reduced 25%	£11,988
	Values States reduced 50%	£17,982
	Difference progressed and not progressed halved	£8,666
L95=Lower 95% Confidence Interval, U95=Upper 95% Confidence Interval, IQRL=Lower Interquartile Range, IQRU=Upper Interquartile Range		

Probabilistic sensitivity analysis

Figure 42 shows the difference in cost and QALYs for 5-ALA compared to resection alone for all iterations of the PSA. 5-ALA is cost increasing for all iterations of the PSA. 84% of iterations fall below the £20,000 per QALY line indicating cost effectiveness at this threshold. When the £50,000 per QALY threshold is assumed 92% iterations of the PSA are cost effective.

Figure 42: Cost effectiveness plane 5-ALA versus resection alone

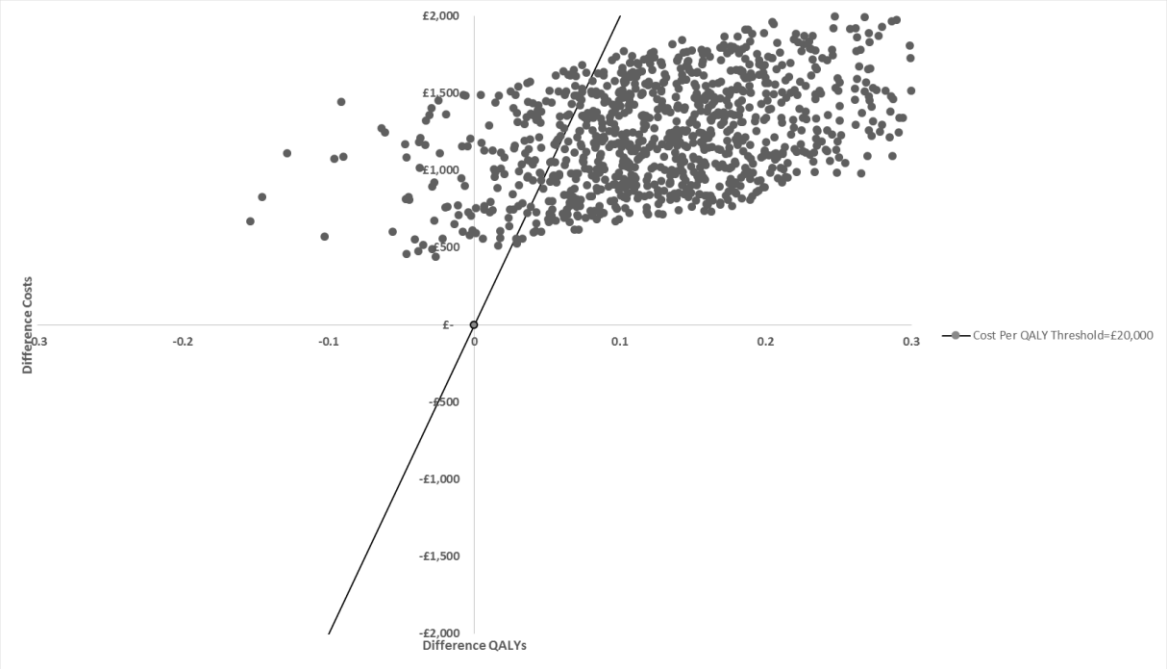
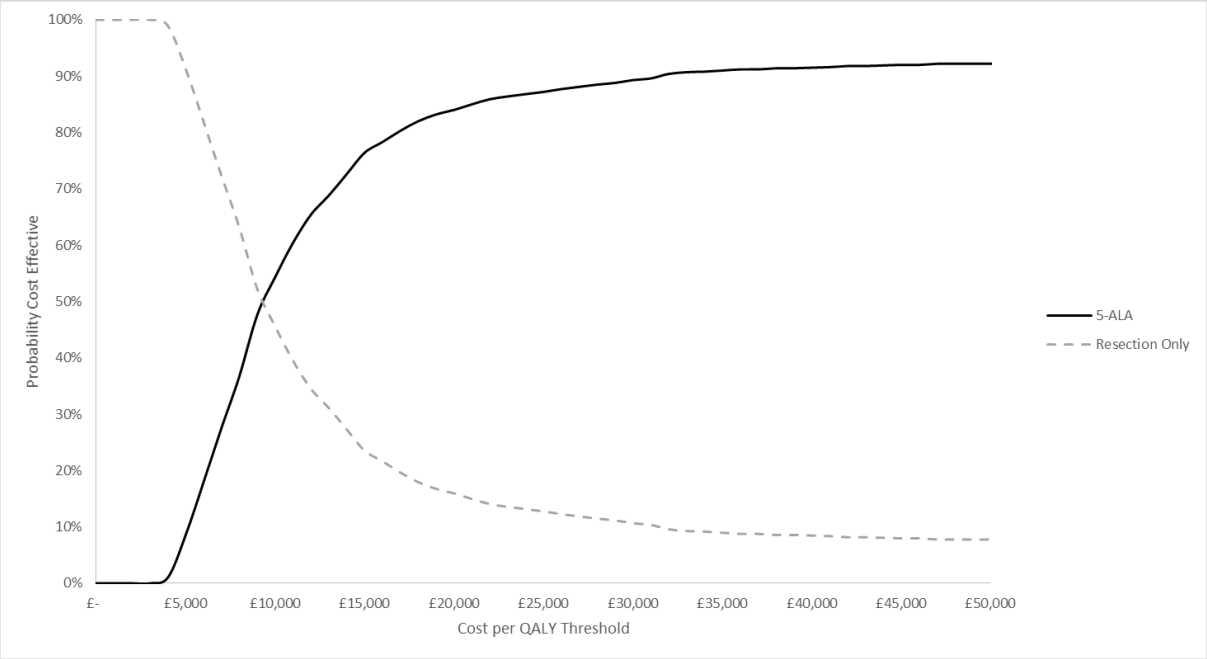


Figure 43 plots the cost per QALY thrshold against the probability of either 5-ALA or resection alone being the preferred intervention.At a threshold of £0 there is a 0% probability of 5-ALA being cost effective or, as the least costly option is always preferred at this threshold a 0% probability of 5-ALA being cost saving. As the £20,000 and £50,000 thresholds the probability of 5-ALA being the preferred option are 84% and 92% respectively. 5-ALA has a greater that 50% probability of being cost effective for all cost per QALY thresholds above £9,000.

Figure 43: Cost effectiveness acceptability curve



Discussion

Using 5-ALA as an adjunct to surgery appears to be a cost effective use of NHS resources. In the base-case the economic model estimated a cost per QALY of £8,991 well below thresholds at which NICE typically allow new technologies. When the additional costs of purchasing the necessary module for addition to the surgical microscope only a small number of patients need to be treated per year for 5-ALA to remain cost effective. For the middle estimate of module cost only four patients, across all disease areas not just high-grade glioma, need to use 5-ALA a year for it to remain cost effective at a £20,000 per QALY threshold. Even small centres should be able to comfortably achieve that level of throughput. 5-ALA remained the preferred option under deterministic and probabilistic sensitivity analyses with 5-ALA always being more costly with 84% of those iterations being cost effective the £20,000 per QALY threshold.

This clinical parameters economic model was based on 1 RCT (Stummer 2006) the only evidence for this comparison identified by the accompanying clinical evidence review. The quality of this evidence was either low or very low as rated by GRADE in the clinical evidence review. The main sources of bias were the way in which participants were excluded from the study, selective reporting of outcomes and imprecision around estimates. Despite these limitations the committee were persuaded by this evidence and their own clinical experience that 5-ALA was likely to lead to greater percentage of resected glioma and consequently greater PFS and OS in line with that reported by the trial. No high quality evidence around quality of life was identified for the economic model despite a comprehensive search and therefore estimates had to be taken from sources other than the cohort considered by this model. Despite this the conclusions of the model were robust to a large range of alternative assumptions around quality of life. This suggests that the addition of better quality of life evidence would not have changed the conclusions of the model.

Our conclusions were in line with 1 previous economic evaluation of the use of 5-ALA as an adjunct to resection alone from the perspective of the Spanish healthcare system (Slof 2015); this study concluded that the addition of 5-ALA to resection alone would lead to an increase in QALYs and costs of €1010 and 0.11 QALYs. This is almost identical to the incremental QALYs estimated in our analysis of 0.13 which is unsurprising given the identical sources for both quality of life and clinical inputs. Probabilistic sensitivity analysis was not performed in this analysis but all deterministic sensitivity analyses, varying the parameters between the most and least plausible estimates resulted in 5-ALA remaining cost increasing, health improving and cost effective again concurring with the conclusions of our bespoke economic model.

Appendix K – Excluded studies

Excluded studies for review 1a - imaging for suspected glioma and meningioma

Clinical studies

Excluded studies - 6. On top of standard MRI, would having additional sequences of advanced MRI or MRI/CT help to better characterise radiologically suspected glioma and meningioma?	
Study	**Reason for Exclusion**
Ahmad, N., Shaukat, A., Rehan, A., Rashid, S., Diagnostic Accuracy of Perfusion Computed Tomography in Cerebral Glioma Grading, Jcpsp, Journal of the College of Physicians & Surgeons - PakistanJ Coll Physicians Surg Pak, 26, 562-5, 2016	Standard MRI was not used
Bell, C., Dowson, N., Puttick, S., Gal, Y., Thomas, P., Fay, M., Smith, J., Rose, S., Increasing feasibility and utility of (18)F-FDOPA PET for the management of glioma, Nuclear Medicine & BiologyNucl Med Biol, 42, 788-95, 2015	Narrative review
Bulakbasi, N., Guvenc, I., Onguru, O., Erdogan, E., Tayfun, C., Ucoz, T., The added value of the apparent diffusion coefficient calculation to magnetic resonance imaging in the differentiation and grading of malignant brain tumors, J Comput Assist TomogrJournal of computer assisted tomography, 28, 735-46, 2004	Study did not provide the results of conventional MRI alone
Chawalparit, O., Sangruchi, T., Witthiwej, T., Sathornsumetee, S., Tritrakarn, S., Piyapittayanan, S., Chaicharoen, P., Direksunthorn, T., Charnchaowanish, P., Diagnostic performance of advanced MRI in differentiating high-grade from low-grade gliomas in a setting of routine service, Journal of the Medical Association of Thailand, 96, 1365-73, 2013	Study unavailable
Chen, Z., Ma, L., Lou, X., Zhou, Z., Diagnostic value of minimum apparent diffusion coefficient values in prediction of neuroepithelial tumor grading, Journal of Magnetic Resonance ImagingJ Magn Reson Imaging, 31, 1331-1338, 2010	Only advanced techniques were used
Collet, S., Valable, S., Constans, J. M., Lechapt-Zalcman, E., Roussel, S., Delcroix, N., Abbas, A., Ibazizene, M., Bernaudin, M., Barre, L., Derlon, J. M., Guillamo, J. S., [¹⁸F]-fluoro-l-thymidine PET and advanced MRI for preoperative grading of gliomas, NeuroImage: Clinical, 8, 448-454, 2015	No relevant outcomes were reported
Darwiesh, A. M. N., Maboud, N. M. A. E., Khalil, A. M. R., ElSharkawy, A. M., Role of magnetic resonance spectroscopy & diffusion weighted imaging in differentiation of supratentorial brain tumors, Egyptian Journal of Radiology and Nuclear Medicine, 47, 1037-1042, 2016	Sensitivity and specificity have not been provided and no other figures were given in the article to calculate these

Excluded studies - 6. On top of standard MRI, would having additional sequences of advanced MRI or MRI/CT help to better characterise radiologically suspected glioma and meningioma?	
De Fatima Vasco Aragao, M., Law, M., Batista De Almeida, D., Fatterpekar, G., Delman, B., Bader, A. S., Pelaez, M., Fowkes, M., Vieira De Mello, R., Moraes Valenca, M., Comparison of perfusion, diffusion, and MR spectroscopy between low-grade enhancing pilocytic astrocytomas and high-grade astrocytomas, American Journal of Neuroradiology, 35, 1495-1502, 2014	Study did not provide the results of conventional MRI alone
Delgado, A. F., Delgado, A. F., Discrimination between Glioma Grades II and III Using Dynamic Susceptibility Perfusion MRI: A Meta-Analysis, Ajnr: American Journal of NeuroradiologyAJNR Am J Neuroradiol, 38, 1348-1355, 2017	Conventional MRI was not used as a comparison
Direksunthorn, T., Chawalparit, O., Sangruchi, T., Witthiwej, T., Tritrakarn, S. O., Piyapittayanan, S., Charnchaowanish, P., Pornpunyawut, P., Sathornsumetee, S., Diagnostic performance of perfusion MRI in differentiating low-grade and high-grade gliomas: advanced MRI in glioma, A Siriraj project, Journal of the Medical Association of Thailand, 96, 1183-90, 2013	Study unavailable
Dunet, V., Prior, J. O., Diagnostic accuracy of F-18-fluoroethyltyrosine PET and PET/CT in patients with brain tumor, Clinical and Translational Imaging, 1, 135-144, 2013	Index test not in protocol
Dunet, V., Rossier, C., Buck, A., Stupp, R., Prior, J. O., Performance of 18F-fluoro-ethyl-tyrosine (18F-FET) PET for the differential diagnosis of primary brain tumor: a systematic review and Metaanalysis, Journal of Nuclear MedicineJ Nucl Med, 53, 207-14, 2012	Index test not in protocol
Ellika, S. K., Jain, R., Patel, S. C., Scarpace, L., Schultz, L. R., Rock, J. P., Mikkelsen, T., Role of perfusion CT in glioma grading and comparison with conventional MR imaging features, 28, 1981-7, 2007	Index test not in protocol; small number of participants
El-Serougy, L., Abdel Razek, A. A., Ezzat, A., Eldawoody, H., El-Morsy, A., Assessment of diffusion tensor imaging metrics in differentiating low-grade from high-grade gliomas, Neuroradiology JournalNeuroradiol, 29, 400-7, 2016	Only advanced techniques were used
Falk, A., Fahlstrom, M., Rostrup, E., Berntsson, S., Zetterling, M., Morell, A., Larsson, H. B., Smits, A., Larsson, E. M., Discrimination between glioma grades II and III in suspected low-grade gliomas using dynamic contrast-enhanced and dynamic susceptibility contrast perfusion MR imaging: a histogram analysis approach, NeuroradiologyNeuroradiology, 56, 1031-8, 2014	Index test not in protocol
Ferda, J., Kastner, J., Mukensnabl, P., Choc, M., Horemuzova, J., Ferdova, E., Kreuzberg, B., Diffusion tensor magnetic resonance imaging of glial brain tumors, Eur J RadiolEuropean journal of radiology, 74, 428-436, 2010	Only advanced techniques have been reported
Floeth, F. W., Pauleit, D., Wittsack, H. J., Langen, K. J., Reifenberger, G., Hamacher, K., Messing-Junger, M., Zilles, K., Weber, F., Stummer, W., Steiger, H. J., Woebker, G., Muller, H. W., Coenen, H., Sabel, M.,	Index test not in PICO

Excluded studies - 6. On top of standard MRI, would having additional sequences of advanced MRI or MRI/CT help to better characterise radiologically suspected glioma and meningioma?	
Multimodal metabolic imaging of cerebral gliomas: positron emission tomography with [18F]fluoroethyl-L-tyrosine and magnetic resonance spectroscopy, J NeurosurgJournal of neurosurgery, 102, 318-27, 2005	
Fouke, S. J., Benzinger, T., Gibson, D., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of imaging in the management of adults with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-Oncology, 125, 457-479, 2015	Only advanced techniques were used
Garibotto, V., Forster, S., Haller, S., Vargas, M. I., Drzezga, A., Molecular neuroimaging with PET/MRI, Clinical and Translational Imaging, 1, 53-63, 2013	Narrative review
Hakyemez, B., Erdogan, C., Ercan, I., Ergin, N., Uysal, S., Atahan, S., High-grade and low-grade gliomas: differentiation by using perfusion MR imaging, Clinical RadiologyClin Radiol, 60, 493-502, 2005	Study did not provide the results of conventional MRI alone
Hatakeyama, T., Kawai, N., Nishiyama, Y., Yamamoto, Y., Sasakawa, Y., Ichikawa, T., Tamiya, T., ¹¹C-methionine (MET) and ¹⁸F-fluorothymidine (FLT) PET in patients with newly diagnosed glioma, Eur J Nucl Med Mol ImagingEuropean journal of nuclear medicine and molecular imaging, 35, 2009-2017, 2008	Index test not in protocol
Hilario, A., Ramos, A., Perez-Nunez, A., Salvador, E., Millan, J. M., Lagares, A., Sepulveda, J. M., Gonzalez-Leon, P., Hernandez-Lain, A., Ricoy, J. R., The added value of apparent diffusion coefficient to cerebral blood volume in the preoperative grading of diffuse gliomas, 33, 701-7, 2012	Only advanced techniques were used
Hollingworth, W., Medina, L. S., Lenkinski, R. E., Shibata, D. K., Bernal, B., Zurakowski, D., Comstock, B., Jarvik, J. G., A systematic literature review of magnetic resonance spectroscopy for the characterization of brain tumors, American Journal of Neuroradiology, 27, 1404-1411, 2006	Only advanced techniques have been reported
Hutterer, M., Nowosielski, M., Putzer, D., Jansen, N. L., Seiz, M., Schocke, M., McCoy, M., Gobel, G., la Fougere, C., Virgolini, I. J., Trinka, E., Jacobs, A. H., Stockhammer, G., [18F]-fluoro-ethyl-L-tyrosine PET: a valuable diagnostic tool in neuro-oncology, but not all that glitters is glioma, Neuro OncolNeuro-oncology, 15, 341-51, 2013	Index test not in protocol
Jansen, N. L., Graute, V., Armbruster, L., Suchorska, B., Lutz, J., Eigenbrod, S., Cumming, P., Bartenstein, P., Tonn, J. C., Kreth, F. W., La Fougere, C., MRI-suspected low-grade glioma: Is there a need to perform dynamic FET PET?, Eur J Nucl Med Mol ImagingEuropean journal of nuclear medicine and molecular imaging, 39, 1021-1029, 2012	Index test not in protocol
Kim, H. S., Goh, M. J., Kim, N., Choi, C. G., Kim, S. J., Kim, J. H., Which combination of MR imaging modalities is best for predicting recurrent glioblastoma? Study of diagnostic accuracy and reproducibility, RadiologyRadiology, 273, 831-43, 2014	Recurrent glioblastoma is not part of the population of interest

Excluded studies - 6. On top of standard MRI, would having additional sequences of advanced MRI or MRI/CT help to better characterise radiologically suspected glioma and meningioma?	
Liang, R., Wang, X., Li, M., Yang, Y., Luo, J., Mao, Q., Liu, Y., Potential role of fractional anisotropy derived from diffusion tensor imaging in differentiating high-grade gliomas from low-grade gliomas: A meta-analysis, International journal of clinical and experimental medicineInt J Clin Exp Med, 7, 3647-3653, 2014	Only advanced techniques have been reported
Nguyen, T. B., Cron, G. O., Perdrizet, K., Bezzina, K., Torres, C. H., Chakraborty, S., Woulfe, J., Jansen, G. H., Sinclair, J., Thornhill, R. E., Foottit, C., Zanette, B., Cameron, I. G., Comparison of the diagnostic accuracy of DSC- and dynamic contrast-enhanced MRI in the preoperative grading of astrocytomas, American Journal of Neuroradiology, 36, 2017-2022, 2015	The study looked at the different types of perfusion imaging and did not compare the results with conventional MRI
Pauleit, D., Floeth, F., Hamacher, K., Riemenschneider, M. J., Reifenberger, G., Muller, H. W., Zilles, K., Coenen, H. H., Langen, K. J., O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas, BrainBrain, 128, 678-87, 2005	Index test not in protocol
Rapp, M., Heinzel, A., Galldiks, N., Stoffels, G., Felsberg, J., Ewelt, C., Sabel, M., Steiger, H. J., Reifenberger, G., Beez, T., Coenen, H. H., Floeth, F. W., Langen, K. J., Diagnostic performance of 18F-FET PET in newly diagnosed cerebral lesions suggestive of glioma, Journal of Nuclear MedicineJ Nucl Med, 54, 229-35, 2013	Index test not in protocol
Sahoo, P., Gupta, R. K., Gupta, P. K., Awasthi, A., Pandey, C. M., Gupta, M., Patir, R., Vaishya, S., Ahlawat, S., Saha, I., Diagnostic accuracy of automatic normalization of CBV in glioma grading using T1- weighted DCE-MRI, Magnetic Resonance ImagingMagn Reson Imaging, 44, 32-37, 2017	Index test (region of interest placement) not in protocol
Saito, T., Yamasaki, F., Kajiwara, Y., Abe, N., Akiyama, Y., Kakuda, T., Takeshima, Y., Sugiyama, K., Okada, Y., Kurisu, K., Role of perfusion-weighted imaging at 3 T in the histopathological differentiation between astrocytic and oligodendroglial tumors, Eur J RadiolEuropean journal of radiology, 81, 1863-1869, 2012	Only advanced techniques were used
Server, A., Graff, B. A., Orheim, T. E. D., Schellhorn, T., Josefsen, R., Gadmar, O. B., Nakstad, P. H., Measurements of diagnostic examination performance and correlation analysis using microvascular leakage, cerebral blood volume, and blood flow derived from 3T dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in glial tumor grading, NeuroradiologyNeuroradiology, 53, 435-447, 2011	Only advanced techniques were used
Song, Pj, Lu, Qy, Li, My, Li, X, Shen, F, Comparison of effects of 18F-FDG PET-CT and MRI in identifying and grading gliomas, J Biol Regul Homeost AgentsJournal of biological regulators and homeostatic agents, 30, 833-838, 2017	Index tests were not compared to histology
Sui, Y., Xiong, Y., Jiang, J., Karaman, M. M., Xie, K. L., Zhu, W., Zhou, X. J., Differentiation of Low- and High-Grade Gliomas Using High b-Value Diffusion Imaging with a Non-Gaussian Diffusion Model, 37, 1643-9, 2016	Only advanced techniques were used
Testart Dardel, N., Gomez-Rio, M., Trivino-Ibanez, E., Llamas-Elvira, J. M., Clinical applications of PET using C-11/F-18-choline in brain tumours: a systematic review, Clinical and Translational Imaging, 5, 101-119, 2017	Only advanced techniques were used

Excluded studies - 6. On top of standard MRI, would having additional sequences of advanced MRI or MRI/CT help to better characterise radiologically suspected glioma and meningioma?	
Tomura, N., Mizuno, Y., Saginoya, T., PET/CT findings for tumors in the base of the skull: Comparison of 18 F-FDG with 11 C-methionine, Acta RadiologicaActa Radiol, 57, 325-332, 2016	Sensitivity and specificity have not been provided and no other figures were given in the article to calculate these
Tong, T., Yang, Z., Chen, J. W., Zhu, J., Yao, Z., Dynamic ¹H-MRS assessment of brain tumors: A novel approach for differential diagnosis of glioma, OncotargetOncotarget, 6, 32257-32265, 2015	Only advanced techniques were used
van den Bent, M. J., Wefel, J. S., Schiff, D., Taphoorn, M. J., Jaeckle, K., Junck, L., Armstrong, T., Choucair, A., Waldman, A. D., Gorlia, T., Chamberlain, M., Baumert, B. G., Vogelbaum, M. A., Macdonald, D. R., Reardon, D. A., Wen, P. Y., Chang, S. M., Jacobs, A. H., Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas, Lancet OncologyLancet Oncol, 12, 583-93, 2011	Did not provide any analysis or study related with the added value of an imaging strategy over standard MRI
Verburg, N., Hoefnagels, F. W. A., Barkhof, F., Boellaard, R., Goldman, S., Guo, J., Heimans, J. J., Hoekstra, O. S., Jain, R., Kinoshita, M., Pouwels, P. J. W., Price, S. J., Reijneveld, J. C., Stadlbauer, A., Vandertop, W. P., Wesseling, P., Zwinderman, A. H., De Witt Hamer, P. C., Diagnostic Accuracy of Neuroimaging to Delineate Diffuse Gliomas within the Brain: A Meta-Analysis, American Journal of Neuroradiology, 2017	Advanced MRI techniques were not used in combination with conventional MRI
Wakabayashi, T., Iuchi, T., Tsuyuguchi, N., Nishikawa, R., Arakawa, Y., Sasayama, T., Miyake, K., Nariai, T., Narita, Y., Hashimoto, N., Okuda, O., Matsuda, H., Kubota, K., Ito, K., Nakazato, Y., Kubomura, K., Diagnostic Performance and Safety of Positron Emission Tomography Using ¹⁸F-Fluciclovine in Patients with Clinically Suspected High- or Low-grade Gliomas: A Multicenter Phase IIb Trial, Asia Oceania Journal of Nuclear Medicine & BiologyAsia ocean, 5, 10-21, 2017	The outcome was to locate the presence versus absence of (any) tumour grade
Wang, Q., Zhang, H., Zhang, J., Wu, C., Zhu, W., Li, F., Chen, X., Xu, B., The diagnostic performance of magnetic resonance spectroscopy in differentiating high-from low-grade gliomas: A systematic review and meta-analysis, European Radiology, 26, 2670-84, 2016	Only advanced techniques have been reported
Zikou, A., Alexiou, G. A., Goussia, A., Kosta, P., Xydis, V., Voulgaris, S., Kyritsis, A. P., Argyropoulou, M. I., The role of diffusion tensor imaging and dynamic susceptibility perfusion MRI in the evaluation of meningioma grade and subtype, Clinical Neurology and Neurosurgery, 146, 109-115, 2016	Only advanced techniques were used
Zonari, P., Baraldi, P., Crisi, G., Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging, Neuroradiology, 49, 795-803, 2007	Study did not provide the results of conventional MRI alone

Economic studies

Not applicable – no economic evidence was identified.

Excluded studies for review 1d – molecular markers to inform prognosis / guide treatment

Clinical studies

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Study	**Reason for Exclusion**
Abudumijiti, A., Chan, A. K., Shi, Z., Li, Y., Zhang, R., Yang, R., Li, K. K., Chung, N. Y., Yao, Y., Zhou, L., Wu, J., Chen, H., Ng, H. K., Adult IDH Wild-type Lower-grade Gliomas Should Be Further Stratified, Neuro OncologyNeuro-oncol, 27, 27, 2017	Analyses not in PICO
Akyerli, C. B., Yuksel, S., Can, O., Erson-Omay, E. Z., Oktay, Y., Cosgun, E., Ulgen, E., Erdemgil, Y., Sav, A., von Deimling, A., Gunel, M., Yakicier, M. C., Pamir, M. N., Ozduman, K., Use of telomerase promoter mutations to mark specific molecular subsets with reciprocal clinical behavior in IDH mutant and IDH wild-type diffuse gliomas, Journal of Neurosurgery, 1-13, 2017	Analyses not in PICO (no mention of 1p19Q)
Alentorn, A., Carpentier, C., Labreche, K., Ducray, F., Dehais, C., Mokhtari, K., Uro-Coste, E., Figarella-Branger, D., Delattre, J., Idbaih, A., TERT promoter mutation is an independent prognostic factor in 1P/19Q co-deleted oligodendrogliomas: A pola network study, Neuro-OncologyNeuro-oncol, 18, iv32-iv33, 2016	Abstract only, not enough information can be extracted to ascertain relevance. Analyses do not appear to be adjusted for IDH mutation status
Alentorn, A., Gleize, V., Gleize, M., Marie, Y., Delattre, J. Y., Idbaih, A., Hoang-Xuan, K., Sanson, M., Recursive partitioning analysis of WHO grade II, III and IV gliomas using 3121 samples, European Journal of Neurology, 22, 70, 2015	Abstract only, not enough information can be extracted to ascertain relevance
Alentorn, A., Marie, Y., Carpentier, C., Boisselier, B., Giry, M., Labussiere, M., Mokhtari, K., Hoang-Xuan, K., Sanson, M., Delattre, J. Y., Idbaih, A., Prevalence, clinico-pathological value, and co-occurrence of PDGFRA abnormalities in diffuse gliomas, Neuro-OncologyNeuro-oncol, 14, 1393-1403, 2012	Analyses not in PICO (not controlled for grade, no target biomarkers)

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Alqudah, M. A., Agarwal, S., Al-Keilani, M. S., Sibenaller, Z. A., Ryken, T. C., Assem, M., NOTCH3 is a prognostic factor that promotes glioma cell proliferation, migration and invasion via activation of CCND1 and EGFR, 8, e77299, 2013	Analyses not in PICO (no multivariate analyses; no target biomarkers)
Ambroise, M. M., Khosla, C., Ghosh, M., Mallikarjuna, V. S., Annapurneswari, S., The role of immunohistochemistry in predicting behavior of astrocytic tumors, Asian Pacific Journal of Cancer Prevention: ApjcpAsian Pac J Cancer Prev, 11, 1079-84, 2010	Analyses not in PICO (no multivariate analyses; no null univariate analyses with target outcomes)
Andersson, U., Osterman, P., Sjostrom, S., Johansen, C., Henriksson, R., Brannstrom, T., Broholm, H., Christensen, H. C., Ahlbom, A., Auvinen, A., Feychting, M., Lonn, S., Kiuru, A., Swerdlow, A., Schoemaker, M., Roos, G., Malmer, B., MNS16A minisatellite genotypes in relation to risk of glioma and meningioma and to glioblastoma outcome, International Journal of CancerInt J Cancer, 125, 968-972, 2009	Analyses not in PICO
Andersson, U., Scwartzbaum, J., Wiklund, F., Sjostrom, S., Liu, Y., Tsavachidis, S., Ahlbom, A., Auvinen, A., Collatz-Laier, H., Feychting, M., Johansen, C., Kiuru, A., Lonn, S., Schoemaker, M. J., Swerdlow, A. J., Henriksson, R., Bondy, M., Melin, B., A comprehensive study of the association between the EGFR and ERBB2 genes and glioma risk, Neuro-OncologyNeuro-oncol, 12, iii17, 2010	Published as abstract only, not enough information to ascertain relevance
Andrade, C. V., Sao Martinho, A. L., Rodrigues, A. M., Fonseca, E. C., Silva, L. E., Silvestre, P. A. F., Hahn, M. D., Prognostic significance of P53, Ki-67, EGFR, MDM2 and MGMT immunostaining in Brazilian series of low-grade astrocytoma who grade II, anaplastic astrocytoma grade III, and glioblastoma, HistopathologyHistopathology, 57, 203, 2010	Abstract only, not enough information can be extracted to ascertain relevance
Andrade, C. V., Sao Martinho, A. L., Rodrigues, A. M., Fonseca, E. C., Silva, L. E., Silvestre, P. A. F., Hahn, M. D., Analysis of EGFR gene amplification in Brazilian patients lowgrade astrocytoma who grade II, anaplastic astrocytoma grade III, and glioblastoma, HistopathologyHistopathology, 57, 203, 2010	Abstract only, not enough information can be extracted to ascertain relevance
Ang, C., Guiot, M. C., Ramanakumar, A. V., Roberge, D., Kavan, P., Clinical significance of molecular biomarkers in glioblastoma, Canadian Journal of Neurological SciencesCan J Neurol Sci, 37, 625-30, 2010	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Appin, C. L., Gao, J., Chisolm, C., Torian, M., Alexis, D., Vincentelli, C., Schniederjan, M. J., Hadjipanayis, C., Olson, J. J., Hunter, S., Hao, C., Brat, D. J., Glioblastoma with oligodendroglioma component (GBM-O): Molecular genetic and clinical characteristics, Brain PathologyBrain Pathol, 23, 454-461, 2013	Unclear which variables included in analyses
Arai, H., Ikota, H., Sugawara, K. i, Nobusawa, S., Hirato, J., Nakazato, Y., Nestin expression in brain tumors: Its utility for pathological diagnosis and correlation with the prognosis of high-grade gliomas, Brain Tumor PathologyBrain Tumor Pathol, 29, 160-167, 2012	Analyses not in PICO in terms of target biomarkers and outcomes
Arimappamagan, A., Somasundaram, K., Thennarasu, K., Peddagangannagari, S., Srinivasan, H., Shailaja, B. C., Samuel, C., Patric, I. R. P., Shukla, S., Thota, B., Prasanna, K. V., Pandey, P., Balasubramaniam, A., Santosh, V., Chandramouli, B. A., Hegde, A. S., Kondaiah, P., Sathyanarayana Rao, M. R., A Fourteen Gene GBM Prognostic Signature Identifies Association of Immune Response Pathway and Mesenchymal Subtype with High Risk Group, PLoS ONE [Electronic Resource]PLoS ONE, 8 (4) (no pagination), 2013	Analysis not in PICO
Arita, H., Yamasaki, K., Matsushita, Y., Nakamura, T., Shimokawa, A., Takami, H., Tanaka, S., Mukasa, A., Shirahata, M., Shimizu, S., Suzuki, K., Saito, K., Kobayashi, K., Higuchi, F., Uzuka, T., Otani, R., Tamura, K., Sumita, K., Ohno, M., Miyakita, Y., Kagawa, N., Hashimoto, N., Hatae, R., Yoshimoto, K., Shinojima, N., Nakamura, H., Kanemura, Y., Okita, Y., Kinoshita, M., Ishibashi, K., Shofuda, T., Kodama, Y., Mori, K., Tomogane, Y., Fukai, J., Fujita, K., Terakawa, Y., Tsuyuguchi, N., Moriuchi, S., Nonaka, M., Suzuki, H., Shibuya, M., Maehara, T., Saito, N., Nagane, M., Kawahara, N., Ueki, K., Yoshimine, T., Miyaoka, E., Nishikawa, R., Komori, T., Narita, Y., Ichimura, K., A combination of TERT promoter mutation and MGMT methylation status predicts clinically relevant subgroups of newly diagnosed glioblastomas, Acta Neuropathologica CommunicationsActa Neuropathol Commun, 4, 79, 2016	Analyses not in PICO (and Cohort 2 not in PICO [only IDH wild-type])
Arita, H., Yamasaki, K., Matsushita, Y., Nakamura, T., Shirahata, M., Tamura, K., Terakawa, Y., Fukai, J., Mukasa, A., Suzuki, H., Shibuya, M., Kanemura, Y., Yoshimine, T., Saito, N., Nagane, M., Ueki, K., Komori, T., Nishikawa, R., Narita, Y., Ichimura, K., Molecular classification based on IDH1/2 and TERT promoter well-defines subgroups with different outcome in adult diffuse gliomas: A report from glioma molecular classification consortium, Neuro-OncologyNeuro-oncol, 17, v138, 2015	Published as abstract only, not enough information to ascertain relevance

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Arita, H., Yamasaki, K., Nakamura, T., Shirahata, M., Kobayashi, K., Tamura, K., Fukai, J., Terakawa, Y., Mori, K., Nakamura, H., Yoshimoto, K., Kanemura, Y., Mukasa, A., Nagane, M., Ueki, K., Komori, T., Nishikawa, R., Narita, Y., Ichimura, K., TERT promoter mutation is a poor prognostic marker for GBMs and interacts with MGMT methylation status, Neuro-OncologyNeuro-oncol, 18, vi108, 2016	Published as abstract only, not enough information to ascertain relevance
Bach, F., Westphal, M., Current status of a phase III trial of nimotuzumab (ti-EGF-R) in newly diagnosed glioblastoma, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Published as abstract only, not enough information to ascertain relevance
Balvers, R. K., Kloezeman, J. J., Heijsman, D., Kremer, A., French, P. J., Dirven, C. M., Leenstra, S., Lamfers, M. L., Genotypic profiling of serum-free primary malignant glioma cultures reveals EGFR/PTEN aberrations as a prerequisite for successful propagation, Neuro-OncologyNeuro-oncol, 13, iii166, 2011	Published as abstract only, not enough information to ascertain relevance
Barbosa, K. C., Oba-Shinjo, S. M., Uno, M., Carvalho, P. O., Rosemberg, S., Aguiar, P. H. P., Carlotti, C. G., Malheiros, S. M. F., Toledo, S., Lotufo, P., Marie, S. K. N., Association of EGFRc.2073A>T polymorphism with decreased risk of diffusely infiltrating astrocytoma in a Brazilian case-control study, International Journal of Biological Markers, 23, 140-146, 2008	Unavailable
Batchelor, T. T., Mulholland, P., Neyns, B., Nabors, L. B., Campone, M., Wick, A., Mason, W., Mikkelsen, T., Phuphanich, S., Ashby, L. S., Degroot, J., Gattamaneni, R., Cher, L., Rosenthal, M., Payer, F., Jurgensmeier, J. M., Jain, R. K., Sorensen, A. G., Xu, J., Liu, Q., van den Bent, M., Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma, Journal of Clinical OncologyJ Clin Oncol, 31, 3212-8, 2013	Recurrent glioma not in PICO
Batchelor, Tt, Mulholland, P, Neyns, B, Nabors, Lb, Campone, M, Wick, A, Mason, W, Mikkelsen, T, Phuphanich, S, Ashby, Ls, Degroot, J, Gattamaneni, R, Cher, L, Rosenthal, M, Payer, F, Jürgensmeier, Jm, Jain, Rk, Sorensen, Ag, Xu, J, Liu, Q, Bent, M, Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 3212-8, 2013	Recurrent glioma not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Batista, R., Cruvinel-Carloni, A., Vinagre, J., Peixoto, J., Catarino, T. A., Campanella, N. C., Menezes, W., Becker, A. P., De Almeida, G. C., Matsushita, M. M., Clara, C., Neder, L., Viana-Pereira, M., Honavar, M., Castro, L., Lopes, J. M., Carvalho, B., Vaz, R. M., Maximo, V., Soares, P., Sobrinho-Simoes, M., Reis, R. M., Lima, J., The prognostic impact of TERT promoter mutations in glioblastomas is modified by the rs2853669 single nucleotide polymorphism, International Journal of CancerInt J Cancer, 139, 414-423, 2016	Analyses not in PICO
Bell, E. H., McElroy, J. P., Fleming, J., Timmers, C. D., Chakraborty, A. R., Salavaggione, A. L., Chang, S. M., Aldape, K. D., Brachman, D., Shih, H. A., Zhang, P., Mehta, M. P., Chakravarti, A., Comprehensive mutation analysis in NRG Oncology/RTOG 9813: A phase III trial of RT + TMZ versus RT + nu for anaplastic astrocytoma and mixed anaplastic oligoastrocytoma (Astrocytoma Dominant), Journal of Clinical Oncology. Conference, 34, 2016	Published as abstract only, not enough information to ascertain relevance
Bell, E. H., McElroy, J. P., Fleming, J., Timmers, C. D., Chakraborty, A. R., Salavaggione, A. L., Shaw, E. G., Aldape, K. D., Brachman, D., Murtha, A. D., Won, M., Mehta, M. P., Chakravarti, A., Comprehensive mutation analysis in NRG Oncology/RTOG 9802: A phase III study of RT versus RT + PCV in high-risk lowgrade gliomas (LGGs), Journal of Clinical Oncology. Conference, 34, 2016	Published as abstract only, not enough information to ascertain relevance
Bent, Mj, Brandes, Aa, Rampling, R, Kouwenhoven, Mc, Kros, Jm, Carpentier, Af, Clement, Pm, Frenay, M, Campone, M, Baurain, Jf, Armand, Jp, Taphoorn, Mj, Tosoni, A, Kletzl, H, Klughammer, B, Lacombe, D, Gorlia, T, Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27, 1268-74, 2009	Recurrent glioma not in PICO
Bent, Mj, Dubbink, Hj, Marie, Y, Brandes, Aa, Taphoorn, Mj, Wesseling, P, Frenay, M, Tijssen, Cc, Lacombe, D, Idbaih, A, Marion, R, Kros, Jm, Dinjens, Wn, Gorlia, T, Sanson, M, IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendroglial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group, Clinical cancer research : an official journal of the American Association for Cancer Research, 16, 1597-604, 2010	Analyses not in PICO
Bienkowski, M., Piaskowski, S., Stoczynska-Fidelus, E., Szybka, M., Banaszczyk, M., Witusik-Perkowska, M., Jesien-Lewandowicz, E., Jaskolski, D. J., Radomiak-Zaluska, A., Jesionek-Kupnicka, D., Sikorska, B.,	N < 100

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Papierz, W., Rieske, P., Liberski, P. P., Screening for EGFR amplifications with a novel method and their significance for the outcome of glioblastoma patients, 8, e65444, 2013	
Binder, Z., Bakas, S., Paul Wileyto, E., Akbari, H., Rathore, S., Rozycki, M., Morrissette, J. J. D., Martinez-Lage, M., Dahmane, N., Davatzikos, C., O'Rourke, D., Extracellular EGFR289 activating mutations confer poorer survival and suggest enhanced motility in primary GBMs, Neuro OncolNeuro-oncology, 18, vi105-vi106, 2016	Published as abstract only, not enough information to ascertain relevance
Birner, P., Toumangelova-Uzeir, K., Natchev, S., Guentchev, M., Expression of mutated isocitrate dehydrogenase-1 in gliomas is associated with p53 and EGFR expression, Folia NeuropathologicaFolia Neuropathol, 49, 88-93, 2011	Analyses not in PICO
Brada, M., Collins, V. P., Ichimura, K., Thompson, L. C., Gabe, R., Stenning, S. P., Prognostic and predictive markers in recurrent high-grade glioma (HGG): Results from the BR12 randomized trial, Journal of Clinical Oncology. Conference, 28, 2010	Published as abstract only, not enough information to ascertain relevance, but recurrent glioma
Brandes, A. A., Carpentier, A. F., Kesari, S., Sepulveda-Sanchez, J. M., Wheeler, H. R., Chinot, O., Cher, L., Steinbach, J. P., Capper, D., Specenier, P., Rodon, J., Cleverly, A., Smith, C., Gueorguieva, I., Miles, C., Guba, S. C., Desaiah, D., Lahn, M. M., Wick, W., A Phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma, Neuro-OncologyNeuro-oncol, 18, 1146-56, 2016	Recurrent glioma not in PICO
Brat, D. J., Update on the morphologic and molecular features of adult brain tumors, Brain PathologyBrain Pathol, 24, 17, 2014	Published as abstract only, not enough information to ascertain relevance
Bredel, M., Renfrow, J., Yadav, A., Alvarez, A., Lin, D., Scholtens, D., He, X., Chandler, J., Scheck, A., Harsh, G., Role of IB as a negative regulator of EGFR and a molecular determinant of prognosis in glioblastoma multiforme, Journal of Clinical OncologyJ Clin Oncol, 1), 2028, 2009	Published as abstract only, not enough information to ascertain relevance
Bredel, M., Scholtens, D. M., Yadav, A. K., Alvarez, A. A., Renfrow, J. J., Chandler, J. P., Yu, I. L. Y., Carro, M. S., Dai, F., Tagge, M. J., Ferrarese, R., Bredel, C., Phillips, H. S., Lukac, P. J., Robe, P. A., Weyerbrock,	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
A., Vogel, H., Dubner, S., Mobley, B., He, X., Scheck, A. C., Sikic, B. I., Aldape, K. D., Chakravarti, A., Harsh, Iv G. R., NFKBIA deletion in glioblastomas, New England Journal of Medicine, 364, 627-637, 2011	
Bredel, M., Yadav, A., Renfrow, J., Alvarez, A. A., Scholtens, D., Lin, D., He, X., Chandler, J. P., Bredel, C., Phillips, H. S., Vogel, H., Robe, P., Mobley, B., Scheck, A. C., Sikic, B. I., Aldape, K. D., Chakravarti, A., Harsh, G. R., Ikba is an EGFR-regulating tumor suppressor in glioblastomas, Neuro-OncologyNeuro-oncol, 11 (5), 575, 2009	Published as abstract only, not enough information to ascertain relevance
Bredel, M., Yadav, A., Renfrow, J., Scholtens, D., Bredel, C., Chandler, J., Scheck, A., Aldape, K. D., Chakravarti, A., Harsh, G., Deletion of NFKBIA in malignant gliomas, Journal of Clinical Oncology. Conference, 28, 2010	Published as abstract only, not enough information to ascertain relevance
Bredel, M., Yadav, A., Renfrow, J., Scholtens, D., Bredel, C., Chandler, J., Tagge, M., Lukac, P., Robe, P., Vogel, H., Scheck, A., Aldape, K., Chakravarti, A., Harsh, G. R., NFKBIA deletion in glioblastoma multiforme, Journal of NeurosurgeryJ Neurosurg, 113 (2), A430, 2010	Published as abstract only, not enough information to ascertain relevance
Bredel, M., Yadav, A., Renfrow, J., Scholtens, D., Chandler, J., Bredel, C., Tagge, M., Lukac, P., Robe, P., Vogel, H., Scheck, A., Aldape, K., Chakravarti, A., Harsh, G., NFKBIA deletion in malignant gliomas, Cancer Research. Conference: 101st Annual Meeting of the American Association for Cancer Research, AACR, 70, 2010	Published as abstract only, not enough information to ascertain relevance
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Jha, P., Suri, V., Jain, A., Sharma, M. C., Pathak, P., Jha, P., Srivastava, A., Suri, A., Gupta, D., Chosdol, K., Chattopadhyay, P., Sarkar, C., O6-methylguanine DNA methyltransferase gene promoter methylation status in gliomas and its correlation with other molecular alterations: first Indian report with review of challenges for use in customized treatment, NeurosurgeryNeurosurgery, 67, 1681-91, 2010	Analyses not in PICO
Jha, P., Suri, V., Sharma, V., Singh, G., Sharma, M. C., Pathak, P., Chosdol, K., Jha, P., Suri, A., Mahapatra, A. K., Kale, S. S., Sarkar, C., IDH1 mutations in gliomas: first series from a tertiary care centre in India with comprehensive review of literature, Experimental & Molecular PathologyExp Mol Pathol, 91, 385-93, 2011	Analyses not in PICO
Jin, G., Gao, J., Wong, S. T. C., Activated signaling mechanism of glioblastoma recurrence derived from genetics, epigenetics, and genomics abnormalities, Cancer Research. Conference: 103rd Annual Meeting of the American Association for Cancer Research, AACR, 72, 2012	Published as abstract only, not enough information to ascertain relevance
Kalita, O., Hajduch, M., Trojanec, R., Megova, M., Vaverka, M., Hrabalek, L., Zlevorova, M., Drabek, J., Tuckova, L., Vrbkova, J., Prognostic and predictive factors in primary glioblastoma multiforme who grade IV patients with resection: A single-institution study, Neuro-OncologyNeuro-oncol, 18, iv58, 2016	Published as abstract only, not enough information to ascertain relevance
Kapoor, G. S., Gocke, T. A., Chawla, S., Whitmore, R. G., Nabavizadeh, A., Krejza, J., Lopinto, J., Plaum, J., Maloney-Wilensky, E., Poptani, H., Melhem, E. R., Judy, K. D., O'Rourke, D. M., Magnetic resonance perfusion-weighted imaging defines angiogenic subtypes of oligodendroglioma according to 1p19q and EGFR status, Journal of Neuro-OncologyJ Neurooncol, 92, 373-386, 2009	N < 100

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Kavan, P., Guiot, M., Dion, B., Tecu, A., Dinu, C., Roberge, D., Clinical utility of biological markers in patients with glioblastoma multiforme, Annals of OncologyAnn Oncol, 19 (S8), viii249, 2008	Published as abstract only, not enough information to ascertain relevance
Killela, P. J., Pirozzi, C. J., Healy, P., Reitman, Z. J., Lipp, E., Rasheed, B. A., Yang, R., Diplas, B. H., Wang, Z., Greer, P. K., Zhu, H., Wang, C. Y., Carpenter, A. B., Friedman, H., Friedman, A. H., Keir, S. T., He, J., He, Y., McLendon, R. E., Herndon, Ii J. E., Yan, H., Bigner, D. D., Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas, OncotargetOncotarget, 5, 1515-1525, 2014	Analyses not in PICO
Kim, B., Myung, J. K., Seo, J. H., Park, C. K., Paek, S. H., Kim, D. G., Jung, H. W., Park, S. H., The clinicopathologic values of the molecules associated with the main pathogenesis of the glioblastoma, Journal of the Neurological Sciences, 294, 112-8, 2010	Unclear which covariates are included in the uni- and multivariate analyses
Kim, Y. H., Nonoguchi, N., Paulus, W., Brokinkel, B., Keyvani, K., Sure, U., Wrede, K., Mariani, L., Giangaspero, F., Tanaka, Y., Nakazato, Y., Vital, A., Mittelbronn, M., Perry, A., Ohgaki, H., Frequent BRAF gain in low-grade diffuse gliomas with 1p/19q loss, Brain PathologyBrain Pathol, 22, 634-640, 2012	Analyses not in PICO
Kloosterhof, N. K., De Rooi, J. J., Kros, M., Eilers, P. H. C., Smitt, P. A. E. S., Van den Bent, M. J., French, P. J., Molecular subtypes of glioma identified by genome-wide methylation profiling, Genes Chromosomes and Cancer, 52, 665-674, 2013	Analyses not in PICO
Kouwenhoven, M. C. M., Gorlia, T., Kros, J. M., Ibdaih, A., Brandes, A. A., Bromberg, J. E. C., Mokhtari, K., Van Duinen, S. G., Teepen, J. L., Wesseling, P., Vandenbos, F., Grisold, W., Sipos, L., Mirimanoff, R., Vecht, C. J., Allgeier, A., Lacombe, D., Van Den Bent, M. J., Molecular analysis of anaplastic oligodendroglial tumors in a prospective randomized study: A report from EORTC study 26951, Neuro-Oncology, 11, 737-746, 2009	Analyses not in PICO (used backward selection but did not control for chemotherapy and radiotherapy received)
Kros, J. M., French, P., Van Den Bent, M. J., Gorlia, T., Construction of an integrated diagnostic algorithm consisting of consensus histologic and molecular parameters of two eortc trials on anaplastic glioma, Neuro-OncologyNeuro-oncol, 16, v16, 2014	Published as abstract only, not enough information to ascertain relevance
Kuczynski, E. A., Patten, S. G., Coomber, B. L., VEGFR2 expression and TGF-beta signaling in initial and recurrent high-grade human glioma, Oncology, 81, 126-134, 2011	N < 100

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Kuncova, K., Janda, A., Kasal, P., Zamecnik, J., Immunohistochemical prognostic markers in intracranial ependymomas: Systematic review and meta-analysis, Pathology and Oncology Research, 15, 605-614, 2009	Analyses not in PICO
Labussiere, M., Boisselier, B., Mokhtari, K., Di Stefano, A. L., Rahimian, A., Rossetto, M., Ciccarino, P., Saulnier, O., Paterra, R., Marie, Y., Finocchiaro, G., Sanson, M., Combined analysis of TERT, EGFR, and IDH status defines distinct prognostic glioblastoma classes, NeurologyNeurology, 83, 1200-1206, 2014	Analyses not in PICO (no mention of 1p19Q)
Labussiere, M., Boisselier, B., Mokhtari, K., Rahimian, A., Saulnier, O., Marie, Y., Sanson, M., Combined analysis of TERT, EGFR and IDH status define distinct prognostic classes of GBM, Cancer Research. Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR, 74, 2014	Published as abstract only, not enough information to ascertain relevance
Labussiere, M., Di Stefano, A. L., Gleize, V., Boisselier, B., Giry, M., Mangesius, S., Bruno, A., Paterra, R., Marie, Y., Rahimian, A., Finocchiaro, G., Houlston, R. S., Hoang-Xuan, K., Idbaih, A., Delattre, J. Y., Mokhtari, K., Sanson, M., TERT promoter mutations in gliomas, genetic associations and clinico-pathological correlations, British Journal of Cancer, 111, 2024-32, 2014	Analyses not in PICO (histological subtype missing)
Le Mercier, M., Hastir, D., Moles Lopez, X., De Neve, N., Maris, C., Trepant, A. L., Rorive, S., Decaestecker, C., Salmon, I., A simplified approach for the molecular classification of glioblastomas, 7, e45475, 2012	N < 100
Lee, E. Q., Batchelor, T. T., Lassman, A. B., Schiff, D. S., Kaley, T. J., Wong, E. T., Mikkelsen, T., Purow, B. W., Drappatz, J., Norden, A. D., Beroukhim, R., Weiss, S., Alexander, B. M., Sceppa, C., Gerard, M., Hallisey, S. D., Bochacki, C. A., Smith, K. H., Muzikansky, A. M., Wen, P. Y., Preliminary data from a multicenter, phase II, randomized, noncomparative clinical trial of radiation therapy and temozolomide with or without vandetanib in newly-diagnosed glioblastoma, Neuro-OncologyNeuro-oncol, 13, iii86, 2011	Published as abstract only, not enough information to ascertain relevance
Lee, E. Q., Kaley, T. J., Duda, D. G., Schiff, D., Lassman, A. B., Wong, E. T., Mikkelsen, T., Purow, B. W., Muzikansky, A., Ancukiewicz, M., Huse, J. T., Ramkissoon, S., Drappatz, J., Norden, A. D., Beroukhim, R., Weiss, S. E., Alexander, B. M., McCluskey, C. S., Gerard, M., Smith, K. H., Jain, R. K., Batchelor, T. T., Ligon, K. L., Wen, P. Y., A Multicenter, Phase II, Randomized, Noncomparative Clinical Trial of Radiation and Temozolomide with or without Vandetanib in Newly Diagnosed Glioblastoma Patients, Clinical Cancer ResearchClin Cancer Res, 21, 3610-8, 2015	N < 100 (106 were enrolled, but 7 withdrew consent)

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Lee, Eq, Kaley, Tj, Duda, Dg, Schiff, D, Lassman, Ab, Wong, Et, Mikkelsen, T, Purow, Bw, Muzikansky, A, Ancukiewicz, M, Huse, Jt, Ramkissoon, S, Drappatz, J, Norden, Ad, Beroukhim, R, Weiss, Se, Alexander, Bm, McCluskey, Cs, Gerard, M, Smith, Kh, Jain, Rk, Batchelor, Tt, Ligon, Kl, Wen, Py, A Multicenter, Phase II, Randomized, Noncomparative Clinical Trial of Radiation and Temozolomide with or without Vandetanib in Newly Diagnosed Glioblastoma Patients, Clinical cancer research : an official journal of the American Association for Cancer Research, 21, 3610-8, 2015	Duplicate
Lee, Y., Koh, J., Kim, S. I., Won, J. K., Park, C. K., Choi, S. H., Park, S. H., The frequency and prognostic effect of TERT promoter mutation in diffuse gliomas, Acta Neuropathologica CommunicationsActa Neuropathol Commun, 5, 62, 2017	Analyses not in PICO
Li, B., Zhao, W., Li, J., Yan, M., Xie, Z., Zhu, Y., Chen, C., Jin, T., Effect of epidermal growth factor receptor gene polymorphisms on prognosis in glioma patients, OncotargetOncotarget, 7, 63054-63064, 2016	Analyses not in PICO
Li, J., Li, H., Liu, J., Feng, B., Feng, M., Lv, B., Cheng, S., Yang, X., The Clinical Implications of Human Telomerase Reverse Transcriptase Expression in Grade and Prognosis of Gliomas: a Systematic Review and Meta-analysis, Molecular Neurobiology, 53, 2887-2893, 2016	Article retracted
Li, J., Li, H., Liu, J., Feng, B., Feng, M., Lv, B., Cheng, S., Yang, X., Retraction Note to: The Clinical Implications of Human Telomerase Reverse Transcriptase Expression in Grade and Prognosis of Gliomas: a Systematic Review and Meta-analysis.[Retraction of Mol Neurobiol. 2016 Jul;53(5):2887-93; PMID: 25895660], Molecular Neurobiology, 12, 12, 2017	Retraction notice
Li, L., Quang, T. S., Gracely, E. J., Kim, J. H., Emrich, J. G., Yaeger, T. E., Jenrette, J. M., Cohen, S. C., Black, P., Brady, L. W., A Phase II study of anti-epidermal growth factor receptor radioimmunotherapy in the treatment of glioblastoma multiforme, Journal of Neurosurgery, 113, 192-8, 2010	Analyses not in PICO
Li, R., Qian, J., Wang, Y. Y., Zhang, J. X., You, Y. P., Long Noncoding RNA Profiles Reveal Three Molecular Subtypes in Glioma, CNS Neuroscience and Therapeutics, 20, 339-343, 2014	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Li, Y. X., Shi, Z., Aibaidula, A., Chen, H., Tang, Q., Li, K. K. W., Chung, N. Y. F., Chan, D. T. M., Poon, W. S., Mao, Y., Wu, J., Zhou, L., Chan, A. K. Y., Ng, H. K., Not all 1p/19q non-codeleted oligodendroglial tumors are astrocytic, OncotargetOncotarget, 7, 64615-64630, 2016	Analyses not in PICO (not adjusted for treatment)
Lin, N., Yan, W., Gao, K., Wang, Y., Zhang, J., You, Y., Prevalence and clinicopathologic characteristics of the molecular subtypes in malignant glioma: A multi-institutional analysis of 941 cases, PLoS ONE, 9 (4) (no pagination), 2014	Analyses not in PICO
Lotsch, D., Ghanim, B., Laaber, M., Wurm, G., Weis, S., Lenz, S., Webersinke, G., Pichler, J., Berger, W., Spiegl-Kreinecker, S., Prognostic significance of telomeraseassociated parameters in glioblastoma: Effect of patient age, Neuro-Oncology, 15, 423-432, 2013	Analyses not in PICO
Lotsch, D., Ghanim, B., Laaber, M., Wurm, G., Weis, S., Lenz, S., Webersinke, G., Pichler, J., Berger, W., Spiegl-Kreinecker, S., Prognostic significance of telomerase-associated parameters in glioblastoma: effect of patient age, Neuro-OncologyNeuro-oncol, 15, 423-32, 2013	Duplicate
Manda, S. V., Kataria, Y., Tatireddy, B. R., Ramakrishnan, B., Ratnam, B. G., Lath, R., Ranjan, A., Ray, A., Exosomes as a biomarker platform for detecting epidermal growth factor receptor-positive high-grade gliomas, Journal of Neurosurgery, 1-11, 2017	N < 100
Martinez-Saez, E., Peg, V., Ortega-Aznar, A., Martinez-Ricarte, F., Camacho, J., Hernandez-Losa, J., Ferreres Pinas, J. C., Ramon y Cajal, S., peIF4E as an independent prognostic factor and a potential therapeutic target in diffuse infiltrating astrocytomas, Cancer Medicine, 5, 2501-2512, 2016	Analyses not in PICO
Martinho, O., Longatto-Filho, A., Lambros, M. B. K., Martins, A., Pinheiro, C., Silva, A., Pardal, F., Amorim, J., MacKay, A., Milanezi, F., Tamber, N., Fenwick, K., Ashworth, A., Reis-Filho, J. S., Lopes, J. M., Reis, R. M., Expression, mutation and copy number analysis of platelet-derived growth factor receptor A (PDGFRA) and its ligand PDGFA in gliomas, British Journal of CancerBr J Cancer, 101, 973-982, 2009	Analyses not in PICO
McDonald, K. L., McDonnell, J., Muntoni, A., Henson, J. D., Hegi, M. E., von Deimling, A., Wheeler, H. R., Cook, R. J., Biggs, M. T., Little, N. S., Robinson, B. G., Reddel, R. R., Royds, J. A., Presence of alternative lengthening of telomeres mechanism in patients with glioblastoma identifies a less aggressive tumor type with	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
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Mellai, M., Monzeglio, O., Piazzi, A., Caldera, V., Annovazzi, L., Cassoni, P., Valente, G., Cordera, S., Mocellini, C., Schiffer, D., MGMT promoter hypermethylation and its associations with genetic alterations in a series of 350 brain tumors, Journal of Neuro-OncologyJ Neurooncol, 107, 617-631, 2012	Analyses not in PICO
Mellai, M., Piazzi, A., Caldera, V., Annovazzi, L., Monzeglio, O., Senetta, R., Cassoni, P., Schiffer, D., Promoter hypermethylation of the EMP3 gene in a series of 229 human gliomas, BioMed Research InternationalBiomed Res Int, 2013 (no pagination), 2013	Analyses not in PICO
Mellai, M., Piazzi, A., Caldera, V., Monzeglio, O., Cassoni, P., Valente, G., Schiffer, D., IDH1 and IDH2 mutations, immunohistochemistry and associations in a series of brain tumors, Journal of Neuro-OncologyJ Neurooncol, 105, 345-357, 2011	Analyses not in PICO
Meng, D., Chen, Y., Zhao, Y., Wang, J., Yun, D., Yang, S., Chen, J., Chen, H., Lu, D., Expression and prognostic significance of TCTN1 in human glioblastoma, Journal of Translational MedicineJ, 12, 288, 2014	Analyses not in PICO
Meyronet, D., Esteban-Mader, M., Bonnet, C., Joly, M. O., Uro-Coste, E., Amiel-Benouaich, A., Forest, F., Rousselot-Denis, C., Burel-Vandenbos, F., Bourg, V., Guyotat, J., Fenouil, T., Jouvet, A., Honnorat, J., Ducray, F., Characteristics of H3 K27M-mutant gliomas in adults, Neuro OncologyNeuro-oncol, 13, 13, 2017	Analyses not in PICO
Michaelsen, S. R., Christensen, I. J., Grunnet, K., Stockhausen, M. T., Broholm, H., Kosteljanetz, M., Poulsen, H. S., Clinical variables serve as prognostic factors in a model for survival from glioblastoma multiforme: an observational study of a cohort of consecutive non-selected patients from a single institution, BMC Cancer, 13, 402, 2013	Analyses not in PICO
Mock, A., Warta, R., Geisenberger, C., Bischoff, R., Schulte, A., Lamszus, K., Stadler, V., Felgenhauer, T., Schichor, C., Schwartz, C., Matschke, J., Jungk, C., Ahmadi, R., Sahm, F., Capper, D., Glass, R., Tonn, J. C., Westpha, M., Von Deimling, A., Unterberg, A., Bermejo, J. L., Herold-Mende, C., Printed peptide arrays identify prognostic TNC serumantibodies in glioblastoma patients, OncotargetOncotarget, 6, 13579-13590, 2015	Analyses not in PICO

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Mosrati, M. A., Malmstrom, A., Lysiak, M., Krysztofiak, A., Hallbeck, M., Milos, P., Hallbeck, A. L., Bratthall, C., Strandeus, M., Stenmark-Askmalm, M., Soderkvist, P., TERT promoter mutations and polymorphisms as prognostic factors in primary glioblastoma, OncotargetOncotarget, 6, 16663-16673, 2015	Analyses not in PICO
Motomura, K., Mittelbronn, M., Paulus, W., Brokinkel, B., Keyvani, K., Sure, U., Wrede, K., Nakazato, Y., Tanaka, Y., Nonoguchi, N., Pierscianek, D., Kim, Y. H., Mariani, L., Vital, A., Perry, A., Ohgaki, H., PDGFRA gain in low-grade diffuse gliomas, Journal of Neuropathology and Experimental Neurology, 72, 61-66, 2013	Analyses not in PICO
Mott, R. T., Turner, K. C., Bigner, D. D., McLendon, R. E., Utility of EGFR and PTEN numerical aberrations in the evaluation of diffusely infiltrating astrocytomas Laboratory investigation, Journal of NeurosurgeryJ Neurosurg, 108, 330-335, 2008	Analyses not in PICO (used backward elimination, but for logistic regression and not for any outcomes in PICO)
Myung, J. K., Cho, H. J., Kim, H., Park, C. K., Lee, S. H., Choi, S. H., Park, P., Yoon, J. M., Park, S. H., Prognosis of Glioblastoma With Oligodendroglioma Component is Associated With the IDH1 Mutation and MGMT Methylation Status, Translational OncologyTransl Oncol, 7, 712-9, 2014	Analyses not in PICO
Myung, J. K., Cho, H. J., Park, C. K., Kim, S. K., Phi, J. I. H., Park, S. H., IDH1 mutation of gliomas with long-term survival analysis, Oncology ReportsOncol Rep, 28, 1639-1644, 2012	Analyses not in PICO
Myung, J. K., Cho, H., Park, C. K., Kim, S. K., Lee, S. H., Park, S. H., Analysis of the BRAF(V600E) Mutation in Central Nervous System Tumors, Translational Oncology, 5, 430-6, 2012	Analyses not in PICO
Navarro, L., Gil-Benso, R., Megias, J., Munoz-Hidalgo, L., San-Miguel, T., Callaghan, R. C., Gonzalez-Darder, J. M., Lopez-Gines, C., Cerda-Nicolas, M. J., Alteration of major vault protein in human glioblastoma and its relation with EGFR and PTEN status, Neuroscience, 297, 243-251, 2015	Analyses not in PICO
Nencha, U., Rahimian, A., Giry, M., Sechi, A., Mokhtari, K., Polivka, M., Schmitt, Y., Di Stefano, A. L., Alentorn, A., Labussiere, M., Sanson, M., TERT promoter mutations and rs2853669 polymorphism: prognostic impact and interactions with common alterations in glioblastomas, Journal of Neuro-OncologyJ Neurooncol, 126, 441-446, 2016	Analyses not in PICO (no mention of 1p19Q)

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Nguyen, H. N., Lie, A., Li, T., Chowdhury, R., Liu, F., Ozer, B., Wei, B., Green, R. M., Ellingson, B. M., Wang, H. J., Elashoff, R., Liau, L. M., Yong, W. H., Nghiemphu, P. L., Cloughesy, T., Lai, A., Human TERT promoter mutation enables survival advantage from MGMT promoter methylation in IDH1 wild-type primary glioblastoma treated by standard chemoradiotherapy, Neuro-OncologyNeuro-oncol, 19, 394-404, 2017	Analyses not in PICO (no mention of 1p19Q)
Nguyen, H. T. N., Li, T., Lie, A., Ozer, B. H., Chowdhury, R., Liu, F., Wei, B., Wang, H. J., Elashoff, R. M., Liau, L. M., Yong, W. H., Ellingson, B. M., Nghiemphu, P. L., Cloughesy, T. F., Lai, A., Benefit of MGMT methylation in glioblastoma in relation to hTERT promoter mutation, Journal of Clinical Oncology. Conference, 34, 2016	Abstract of Nguyen 2017
Nobusawa, S., Watanabe, T., Kleihues, P., Ohgaki, H., IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas, Clinical Cancer ResearchClin Cancer Res, 15, 6002-6007, 2009	Analyses not in PICO
Nonoguchi, N., Ohta, T., Oh, J. E., Kim, Y. H., Kleihues, P., Ohgaki, H., TERT promoter mutations in primary and secondary glioblastomas, Acta NeuropathologicaActa Neuropathol (Berl), 126, 931-937, 2013	Analyses not in PICO (no mention of 1p19Q)
Nordfors, K., Haapasalo, J., Makela, K., Granberg, K. J., Nykter, M., Korja, M., Paavonen, T., Haapasalo, H., Soini, Y., Twist predicts poor outcome of patients with astrocytic glioma, Journal of Clinical PathologyJ Clin Pathol, 68, 905-912, 2015	Analyses not in PICO
Noushmehr, H., Decoding gliomas using 'omics' data, a TCGA project, Brain PathologyBrain Pathol, 24, 26, 2014	Published as abstract only, not enough information available to ascertain relevance
Ohashi, R., Matsuda, Y., Ishiwata, T., Naito, Z., Downregulation of fibroblast growth factor receptor 2 and its isoforms correlates with a high proliferation rate and poor prognosis in high-grade glioma, Oncology ReportsOncol Rep, 32, 1163-1169, 2014	N < 100
Ohgaki, H., Watanabe, T., Nobusawa, S., Kleihues, P., IDH1 mutations in gliomas, Virchows Archiv, 455, S21, 2009	Published as abstract only, not enough information available to ascertain relevance

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Ozduman, K., Akyerli, C., Yuksel, S., Can, O., Oktay, Y., Nanni, P., Selevsek, N., Grossmann, J., Ozpinar, A., Sav, A., Yakicier, C., Pamir, M. N., An analysis for the role of telomerase (HTERT) promoter mutations in gliomagenesis, Journal of NeurosurgeryJ Neurosurg, 122 (6), A1563-A1564, 2015	Published as abstract only, not enough information to ascertain relevance
Pal, S., Zhang, Z. F., Gupta, R., Bi, Y., Fetting, H. H., O'Rourke, D. M., Davuluri, R. V., Molecular subtyping of glioblastoma based on isoform level network modeling, Cancer Research. Conference: 103rd Annual Meeting of the American Association for Cancer Research, AACR, 72, 2012	Published as abstract only, not enough information available to ascertain relevance, but does not appear to be in PICO
Pandey, J. P., Kistner-Griffin, E., Radwan, F. F., Kaur, N., Namboodiri, A. M., Black, L., Butler, M. A., Carreon, T., Ruder, A. M., Endogenous antibody responsiveness to epidermal growth factor receptor is associated with immunoglobulin allotypes and overall survival of patients with glioblastoma, Neuro-OncologyNeuro-oncol, 17, 678-684, 2015	Analyses not in PICO
Patil, C. G., Nuno, M., Elramsisy, A., Mukherjee, D., Carico, C., Dantis, J., Hu, J., Yu, J. S., Fan, X., Black, K. L., Bannykh, S. I., High levels of phosphorylated MAP kinase are associated with poor survival among patients with glioblastoma during the temozolomide era, Neuro-oncology, 15, 104-11, 2013	Analyses not in PICO
Pedeutour-Braccini, Z., Burel-Vandenbos, F., Goze, C., Roger, C., Bazin, A., Costes-Martineau, V., Duffau, H., Rigau, V., Microfoci of malignant progression in diffuse low-grade gliomas: towards the creation of an intermediate grade in glioma classification?, Virchows Archiv, 466, 433-444, 2015	N < 100
Peereboom, D. M., Ahluwalia, M. S., Ye, X., Supko, J. G., Hilderbrand, S. L., Phuphanich, S., Nabors, L. B., Rosenfeld, M. R., Mikkelsen, T., Grossman, S. A., NABTT 0502: A phase II and pharmacokinetic study of erlotinib and sorafenib for patients with progressive or recurrent glioblastoma multiforme, Neuro-OncologyNeuro-oncol, 15, 490-496, 2013	N < 100
Pekmezci, M., Rice, T., Molinaro, A. M., Walsh, K. M., Decker, P. A., Hansen, H., Sicotte, H., Kollmeyer, T. M., McCoy, L. S., Sarkar, G., Perry, A., Giannini, C., Tihan, T., Berger, M. S., Wiemels, J. L., Bracci, P. M., Eckel-Passow, J. E., Lachance, D. H., Clarke, J., Taylor, J. W., Luks, T., Wiencke, J. K., Jenkins, R. B.,	Analyses not in PICO

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Wrensch, M. R., Adult infiltrating gliomas with WHO 2016 integrated diagnosis: additional prognostic roles of ATRX and TERT, Acta Neuropathologica, 133, 1001-1016, 2017	
Ping, Y., Zhang, H., Deng, Y., Wang, L., Zhao, H., Pang, L., Fan, H., Xu, C., Li, F., Zhang, Y., Gong, Y., Xiao, Y., Li, X., IndividualizedPath: identifying genetic alterations contributing to the dysfunctional pathways in glioblastoma individuals, Molecular BiosystemsMol Biosyst, 10, 2031-42, 2014	Analyses not in PICO
Pinto, G. R., Yoshioka, F. K. N., Clara, C. A., Santos, M. J., Almeida, J. R. W., Burbano, R. R., Rey, J. A., Casartelli, C., Association study of an epidermal growth factor gene functional polymorphism with the risk and prognosis of gliomas in Brazil, International Journal of Biological Markers, 24, 277-281, 2009	Unavailable
Poukka, M. J., Haapasalo, H., Rilla, K. J., Tyynela-Korhonen, K., Soini, Y., Pasonen-Seppanen, S. M., Elevated expression of hyaluronan synthase 2 associates with poor prognosis in diffusely infiltrating astrocytomas, Cancer Research. Conference: 107th Annual Meeting of the American Association for Cancer Research, AACR, 76, 2016	Published as abstract only, not enough information available to ascertain relevance
Purkait, S., Mallick, S., Sharma, V., Kumar, A., Pathak, P., Jha, P., Biswas, A., Julka, P. K., Gupta, D., Suri, A., Upadhyay, A. D., Suri, V., Sharma, M. C., Sarkar, C., Prognostic stratification of gbms using combinatorial assessment of IDH1 mutation, MGMT promoter methylation, and tert mutation status: Experience from a tertiary care center in India, Translational Oncology, 9, 371-376, 2016	N < 100
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Garzia, L., Dubuc, A. M., Zhukova, N., Vanner, R., Kros, J. M., French, P. J., Van Meir, E. G., Vibhakar, R., Zitterbart, K., Chan, J. A., Bognar, L., Klekner, A., Lach, B., Jung, S., Saad, A. G., Liau, L. M., Albrecht, S., Zollo, M., Cooper, M. K., Thompson, R. C., Delattre, O. O., Bourdeaut, F., Doz, F. F., Garami, M., Hauser, P., Carlotti, C. G., Van Meter, T. E., Massimi, L., Fults, D., Pomeroy, S. L., Kumabe, T., Ra, Y. S., Leonard, J. R., Elbabaa, S. K., Mora, J., Rubin, J. B., Cho, Y. J., McLendon, R. E., Bigner, D. D., Eberhart, C. G., Fouladi, M., Wechsler-Reya, R. J., Faria, C. C., Croul, S. E., Huang, A., Bouffet, E., Hawkins, C. E., Dirks, P. B., Weiss, W. A., Schuller, U., Pollack, I. F., Rutkowski, S., Meyronet, D., Jouvet, A., Fevre-Montange, M., Jabado, N., Perek-Polnik, M., Grajkowska, W. A., Kim, S. K., Rutka, J. T., Malkin, D., Tabori, U., Pfister, S. M., Korshunov, A., von Deimling, A., Taylor, M. D., TERT promoter mutations are highly recurrent in SHH subgroup medulloblastoma, Acta Neuropathologica, 126, 917-29, 2013	
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Suh, J. H., Park, C. K., Park, S. H., Alpha internexin expression related with molecular characteristics in adult glioblastoma and oligodendroglioma, Journal of Korean medical science, 28, 593-601, 2013	Analyses not in PICO
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Vuong, H. G., Altibi, A. M. A., Duong, U. N. P., Ngo, H. T. T., Pham, T. Q., Fung, K. M., Hassell, L., BRAF Mutation is Associated with an Improved Survival in Glioma-a Systematic Review and Meta-analysis, Molecular Neurobiology, 1-7, 2017	Analyses not in PICO

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Weller, M., Felsberg, J., Hartmann, C., Berger, H., Steinbach, J. P., Schramm, J., Westphal, M., Schackert, G., Simon, M., Tonn, J. C., Heese, O., Krex, D., Nikkhah, G., Pietsch, T., Wiestler, O., Reifenberger, G., Von Deimling, A., Loeffler, M., Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: A prospective translational study of the German Glioma Network, Journal of Clinical OncologyJ Clin Oncol, 27, 5743-5750, 2009	Analyses not in PICO
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Yan, W., Liu, Y., Yang, P., Wang, Z., You, Y., Jiang, T., MicroRNA profiling of Chinese primary glioblastoma reveals a temozolomide-chemoresistant subtype, OncotargetOncotarget, 6, 11676-11682, 2015	Analyses not in PICO
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Yang, P., Cai, J., Yan, W., Zhang, W., Wang, Y., Chen, B., Li, G., Li, S., Wu, C., Yao, K., Li, W., Peng, X., You, Y., Chen, L., Jiang, C., Qiu, X., Jiang, T., Classification based on mutations of TERT promoter and IDH characterizes subtypes in grade II/III gliomas, Neuro-OncologyNeuro-oncol, 18, 1099-1108, 2016	Analyses not in PICO
Yang, P., Liang, T., Zhang, C., Cai, J., Zhang, W., Chen, B., Qiu, X., Yao, K., Li, G., Wang, H., Jiang, C., You, G., Jiang, T., Clinicopathological factors predictive of postoperative seizures in patients with gliomas, SeizureSeizure, 35, 93-99, 2016	Analyses not in PICO
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Yang, X, Lv, S, Liu, Y, Li, D, Shi, R, Tang, Z, Fan, J, Xu, Z, The clinical utility of matrix metalloproteinase 9 in evaluating pathological grade and prognosis of glioma patients: a meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, epub, 2014	Retracted article
Youland, R. S., Kreofsky, C. R., Schomas, D. A., Brown, P. D., Buckner, J. C., Laack, N. N., The impact of adjuvant therapy for patients with high-risk diffuse WHO grade II glioma, Journal of Neuro-Oncology, 1-9, 2017	N < 100 with relevant data
Yuan, P., Cao, J. L., Abuduwufuer, A., Wang, L. M., Yuan, X. S., Lv, W., Hu, J., Clinical characteristics and prognostic significance of TERT promoter mutations in cancer: A cohort study and a meta-analysis, PLoS ONE, 11 (1) (no pagination), 2016	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Yuan, Y., Qi, C., Maling, G., Xiang, W., Yanhui, L., Ruofei, L., Yunhe, M., Jiewen, L., Qing, M., TERT mutation in glioma: Frequency, prognosis and risk, Journal of Clinical Neuroscience, 26, 57-62, 2016	Analyses not in PICO
Yung, W. K. A., Vredenburgh, J. J., Cloughesy, T. F., Nghiemphu, P., Klencke, B., Gilbert, M. R., Reardon, D. A., Prados, M. D., Safety and efficacy of erlotinib in first-relapse glioblastoma: A phase II open-label study, Neuro-OncologyNeuro-oncol, 12, 1061-1070, 2010	N < 100
Yunhe, M., Yuan, Y., Xiang, W., Yanhui, L., Qing, M., Mapping seizure foci and tumor genetic factors in glioma associated seizure patients, Journal of Neurosurgical SciencesJ Neurosurg Sci, 11, 11, 2017	Unavailable
Zacharia, B. E., DiStefano, N., Mader, M. M., Chohan, M. O., Ogilvie, S., Brennan, C., Gutin, P., Tabar, V., Prior malignancies in patients harboring glioblastoma: an institutional case-study of 2164 patients, Journal of Neuro-OncologyJ Neurooncol, 1-7, 2017	Analyses not in PICO
Zhang, J. X., Han, L., Bao, Z. S., Wang, Y. Y., Chen, L. Y., Yan, W., Yu, S. Z., Pu, P. Y., Liu, N., You, Y. P., Jiang, T., Kang, C. S., HOTAIR, a cell cycle-associated long noncoding RNA and a strong predictor of survival, is preferentially expressed in classical and mesenchymal glioma, Neuro-OncologyNeuro-oncol, 15, 1595-1603, 2013	Analyses not in PICO
Zhang, R. Q., Shi, Z., Chen, H., Chung, N. Y. F., Yin, Z., Li, K. K. W., Chan, D. T. M., Poon, W. S., Wu, J., Zhou, L., Chan, A. K. Y., Mao, Y., Ng, H. K., Biomarker-based prognostic stratifi cation of young adult glioblastoma, Oncotarget, 7, 5030-5041, 2016	Analyses not in PICO
Zhang, X., Yang, H., Gong, B., Jiang, C., Yang, L., Combined gene expression and protein interaction analysis of dynamic modularity in glioma prognosis, Journal of Neuro-OncologyJ Neurooncol, 107, 281-288, 2012	Analyses not in PICO
Zhang, Y. A., Zhou, Y., Luo, X., Song, K., Ma, X., Sathe, A., Girard, L., Xiao, G., Gazdar, A. F., SHOX2 is a Potent Independent Biomarker to Predict Survival of WHO Grade II-III Diffuse Gliomas, EBioMedicine, 13, 80-89, 2016	Analyses not in PICO

Excluded studies: - What are the most useful molecular markers to determine prognosis/guide treatment for gliomas?	
Zhang, Z. Y., Chan, A. K. Y., Ding, X. J., Qin, Z. Y., Hong, C. S., Chen, L. C., Zhang, X., Zhao, F. P., Wang, Y., Zhou, L. F., Zhuang, Z., Ng, H. K., Yan, H., Yao, Y., Mao, Y., TERT promoter mutations contribute to IDH mutations in predicting differential responses to adjuvant therapies in WHO grade II and III diffuse gliomas, OncotargetOncotarget, 6, 24871-24883, 2015	Analyses not in PICO
Zhao, L. L., Xu, K. L., Wang, S. W., Hu, B. L., Chen, L. R., Pathological significance of epidermal growth factor receptor expression and amplification in human gliomas, HistopathologyHistopathology, 61, 726-736, 2012	Analyses not in PICO
Zhou, Y. H., Hess, K. R., Raj, V. R., Yu, L., Liu, L., Yung, A. W. K., Linskey, M. E., Establishment of prognostic models for astrocytic and oligodendroglial brain tumors with standardized quantification of marker gene expression and clinical variables, Biomarker Insights, 2010, 153-158, 2010	Analyses not in PICO

Economic studies

Not applicable – no economic evidence was identified.

Excluded studies for review 1c – timing and extend of initial surgery for low-grade glioma

Clinical studies

Clinical studies from the search for RCTs and systematic reviews

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Study	**Reason for Exclusion**

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Abudumijiti, A., Chan, A. K., Shi, Z., Li, Y., Zhang, R., Yang, R., Li, K. K., Chung, N. Y., Yao, Y., Zhou, L., Wu, J., Chen, H., Ng, H. K., Adult IDH Wild-type Lower-grade Gliomas Should Be Further Stratified, Neuro OncologyNeuro-oncol, 27, 27, 2017	N < 100 / population not in PICO ("lower grade" = grade II (N = 81) and grade III (N = 85)
Afra, D., Osztie, E., Sipos, L., Vitanovics, D., Preoperative history and postoperative survival of supratentorial low-grade astrocytomas, British Journal of NeurosurgeryBr J Neurosurg, 13, 299-305, 1999	N < 100
Aghi, M. K., Nahed, B. V., Sloan, A. E., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of surgery in the management of patients with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-OncologyJ Neurooncol, 125, 503-30, 2015	Systematic review without meta-analysis, different inclusion criteria compared to the guideline review; included studies checked for relevance
Ahmadi, R., Dictus, C., Hartmann, C., Zurn, O., Edler, L., Hartmann, M., Combs, S., Herold-Mende, C., Wirtz, C. R., Unterberg, A., Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients., Acta Neurochirurgica, 151, 1359-65, 2009	N < 50 in all apart from 1 of the treatment groups
Anderson, M., Leary, S., Presentation and outcome of metastatic low-grade astrocytoma, Neuro-Oncology, 16, i65, 2014	Abstract only, not enough information to ascertain relevance
Barone, D. G., Lawrie, T. A., Hart, M. G., Image guided surgery for the resection of brain tumours, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 1, CD009685, 2014	Analyses not in PICO
Bauman, G., Fisher, B., Watling, C., Cairncross, J. G., Macdonald, D., Adult Supratentorial Low-Grade Glioma: Long-Term Experience at a Single Institution, International Journal of Radiation Oncology Biology Physics, 75, 1401-1407, 2009	N < 50 in all apart from 1 of the treatment groups
Bonney, P. A., Boettcher, L. B., Burks, J. D., Baker, C., Conner, A. K., Fujii, T., Mehta, V. A., Briggs, R. G., Sughrue, M. E., Rates of Seizure Freedom after Surgical Resection of Diffuse Low-Grade Gliomas, World NeurosurgeryWorld Neurosurg, 30, 30, 2017	Systematic review without meta-analysis; checked for relevant included studies
Chen, C., Alattar, A., Schupper, A., Brandel, M., Padwal, J., Hirshman, B., Carter, B., Personalizing the decision gross total resection (GTR) in neuro-oncology, Neuro-Oncology, 18, vi196-vi197, 2016	Abstract only, not enough information to ascertain relevance
Chen, X., Meng, X., Zhang, J., Li, F., Li, J., Xu, B. N., Low-grade insular glioma resection with 1.5t intra-operative MRI: Preliminary results of a prospective randomized trial, J NeurosurgJournal of neurosurgery, 117 (2), A406-A407, 2012	Abstract only, not enough information to ascertain relevance

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Chen, X., Meng, X., Zhang, J., Wang, F., Zhao, Y., Xu, B. N., Low-grade insular glioma resection with 1.5T intra-operative MRI: Preliminary results of a prospective randomized trial, Neuro OncolNeuro-oncology, 13, iii157, 2011	Abstract only, not enough information to ascertain relevance
Claus, E. B., Black, P. M., Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: data from the SEER program, 1973-2001, Cancer, 106, 1358-63, 2006	Analyses not in PICO
Claus, E. B., Horlacher, A., Hsu, L., Schwartz, R. B., Dello-Iacono, D., Talos, F., Jolesz, F. A., Black, P. M., Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance, CancerCancer, 103, 1227-33, 2005	N = 28 and 39 of 156 patients also received RT or CT, respectively. Analyses not reported separately for interventions in PICO and not adjusted for adjuvant treatments
Constantini, S., Miller, D. C., Allen, J. C., Rorke, L. B., Freed, D., Epstein, F. J., Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults, Journal of Neurosurgery, 93, 183-93, 2000	Population not in PICO ("One hundred sixty-four consecutive patients ranging in age from 6 months to 21 years (median 10.4 /- 0.5 years)"); N < 50 in all apart from one of the treatment groups
Donahue, B., Scott, C. B., Nelson, J. S., Rotman, M., Murray, K. J., Nelson, D. F., Banker, F. L., Earle, J. D., Fischbach, J. A., Asbell, S. O., Gaspar, L. E., Markoe, A. M., Curran, W., Influence of an oligodendroglial component on the survival of patients with anaplastic astrocytomas: A report of Radiation Therapy Oncology Group 83-02, International Journal of Radiation Oncology Biology Physics, 38, 911-914, 1997	Interventions not in PICO (surgery RT)
Dorward, N L, Paleologos, T S, Alberti, O, Thomas, D G, The advantages of frameless stereotactic biopsy over frame-based biopsy (Structured abstract), British Journal of NeurosurgeryBr J Neurosurg, 16, 110-118, 2002	Intervention not in PICO (biopsy versus biopsy); 99 high-grade gliomas/19 low-grade gliomas
Duffau, H., A new philosophy in surgery for diffuse low-grade glioma (DLGG): oncological and functional outcomes, Neuro-ChirurgieNeurochirurgie, 59, 2-8, 2013	Narrative review
Duffau, H., Lopes, M., Arthuis, F., Bitar, A., Sichez, J. P., Van Effenterre, R., Capelle, L., Contribution of intraoperative electrical stimulations in surgery of low-grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution, Journal of Neurology, Neurosurgery & PsychiatryJ Neurol Neurosurg Psychiatry, 76, 845-51, 2005	N < 50 in all apart from one of the treatment groups
Englot, D. J., Berger, M. S., Barbaro, N. M., Chang, E. F., Predictors of seizure freedom after resection of supratentorial low-grade gliomas: A review, Journal of NeurosurgeryJ Neurosurg, 115, 240-244, 2011	Mixed population (>12% of total population aged below 18 years); unclear how many

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
	patients aged below 18 years in relevant analyses (which includes a total of 635 patients)
Englot, D. J., Han, S. J., Berger, M. S., Barbaro, N. M., Chang, E. F., Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors, Neurosurgery, 70, 921-927, 2012	Mixed population (>29% of total population aged below 18 years); unclear how many patients aged below 18 years in relevant analyses (which includes a total of 580 patients)
Escalona, Lopez S, Reza, Goyanes M, Blasco, Amaro Ja, Linertova, R, Garcia, Perez L, Serrano, Aguilar P, Surgery guided by imaging assessment: efficacy, safety and economic impact of Intraoperative Magnetic Resonance Imaging (Structured abstract), Health Technology Assessment Database, 2008	In Spanish with English abstract; does not appear to be in PICO (examines “Surgery guided by imaging assessment: efficacy, safety and economic impact of Intraoperative and Open Magnetic Resonance Imaging.”)
Fouke, S. J., Benzinger, T., Gibson, D., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of imaging in the management of adults with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-Oncology, 125, 457-479, 2015	Interventions/analyses not in PICO
Gnekow, A. K., Falkenstein, F., Walker, D., Perilongo, G., Picton, S., Grill, J., Kortmann, R. D., Stokland, T., Van Meeteren, A. S., Slavc, I., Faldum, A., De Salvo, G. L., SIOP-LGG 2004-cohort description of a comprehensive treatment strategy for low-grade glioma in children and adolescents including a randomised chemotherapy trial and a radiotherapy trial, Neuro-OncologyNeuro-oncol, 14, i74, 2012	Abstract only, not enough information to ascertain relevance.
Gousias, K., Schramm, J., Simon, M., Extent of resection and survival in supratentorial infiltrative low-grade gliomas: Analysis of and adjustment for treatment bias, Acta NeurochirurgicaActa Neurochir (Wien), 156, 327-337, 2014	Duplicate
Grossman, R., Nossek, E., Sitt, R., Hayat, D., Shahar, T., Barzilai, O., Gonen, T., Korn, A., Sela, G., Ram, Z., Outcome of elderly patients undergoing awake-craniotomy for tumor resection, Annals of Surgical OncologyAnn Surg Oncol, 20, 1722-8, 2013	N with LGG < 100
Hervey-Jumper, S. L., Berger, M. S., Technical nuances of awake brain tumor surgery and the role of maximum safe resection, Journal of Neurosurgical SciencesJ Neurosurg Sci, 59, 351-60, 2015	Narrative review

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Huang, C., Chi, X. S., Hu, X., Chen, N., Zhou, Q., Zhou, D., Li, J. M., Predictors and mechanisms of epilepsy occurrence in cerebral gliomas: What to look for in clinicopathology, Experimental and Molecular Pathology, 102, 115-122, 2017	Analyses not in PICO
Incekara, F., Olubiyi, O., Ozdemir, A., Lee, T., Rigolo, L., Golby, A., The Value of Pre- and Intraoperative Adjuncts on the Extent of Resection of Hemispheric Low-Grade Gliomas: A Retrospective Analysis, Journal of Neurological SurgeryJ Neurol Surg A Cent Eur Neurosurg, 77, 79-87, 2016	Analyses not in PICO/N not ≥ 50 in at least 2 treatment groups
Jakola, A. S., Myrmel, K. S., Kloster, R., Torp, S. H., Lindal, S., Unsgard, G., Solheim, O., Comparison of a strategy favoring early surgical resection versus a strategy favoring watchful waiting in low-grade gliomas, JAMAJama, 308, 1881-8, 2012	Analyses not in PICO (not adjusting for adjuvant treatment)
Jiang, Bowen, Chaichana, Kaisorn, Veeravagu, Anand, Chang, Steven D, Black, Keith L, Patil, Chirag G, Biopsy versus resection for the management of low-grade gliomas, Cochrane Database of Systematic Reviews, 2017	Cochrane review with no included studies as there are no RCTs comparing biopsy to resection in LGG
Johannesen, T. B., Langmark, F., Lote, K., Progress in long-term survival in adult patients with supratentorial low-grade gliomas: a population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993, J Neurosurg, 99, 854-62, 2003	Analyses or comparisons not in PICO: patients received resection or biopsy with or without RT or CT; no analyses just for resection groups or adjusted for adjuvant treatment
Kaloshi, G., Psimaras, D., Mokhtari, K., Dehais, C., Houillier, C., Marie, Y., Laigle-Donadey, F., Taillibert, S., Guillevin, R., Martin-Duverneuil, N., Sanson, M., Hoang-Xuan, K., Delattre, J. Y., Supratentorial low-grade gliomas in older patients, NeurologyNeurology, 73, 2093-8, 2009	Analyses not in PICO and/or N not ≥ 50 in at least 2 treatment groups
Karim, A. B., Maat, B., Hatlevoll, R., Menten, J., Rutten, E. H., Thomas, D. G., Mascarenhas, F., Horiot, J. C., Parvinen, L. M., van Reijn, M., Jager, J. J., Fabrini, M. G., van Alphen, A. M., Hamers, H. P., Gaspar, L., Noordman, E., Pierart, M., van Glabbeke, M., A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844, Int J Radiat Oncol Biol Phys, 36, 549-56, 1996	Analyses not in PICO (no adjustment for RT dose)
Keles, G. E., Lamborn, K. R., Berger, M. S., Low-grade hemispheric gliomas in adults: A critical review of extent of resection as a factor influencing outcome, Journal of Neurosurgery, 95, 735-745, 2001	Narrative review (all included studies checked for relevance)

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Kurwale, N. S., Suri, V., Suri, A., Sarkar, C., Gupta, D. K., Sharma, B. S., Mahapatra, A. K., Predictive factors for early symptomatic recurrence in pilocytic astrocytoma: does angiogenesis have a role to play?, Journal of Clinical Neuroscience, 18, 472-7, 2011	N < 100 (> 15 years old)
Leighton, C., Fisher, B., Bauman, G., Depiero, S., Stitt, L., MacDonald, D., Cairncross, G. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol. 1997 15 p.1294-301	Interventions not in PICO: all patients had RT after surgery, either immediately after or deferred; it is therefore not possible to adjust for receipt of radiotherapy, only timing of radiotherapy
Lopci, E., Riva, M., Olivari, L., Raneri, F., Soffietti, R., Piccardo, A., Bizzi, A., Navarria, P., Ascolese, A. M., Ruda, R., Fernandes, B., Pessina, F., Grimaldi, M., Simonelli, M., Rossi, M., Alfieri, T., Zucali, P. A., Scorsetti, M., Bello, L., Chiti, A., Prognostic value of molecular and imaging biomarkers in patients with supratentorial glioma, 21, 21, 2017	N < 100 LGG
Lote, K., Egeland, T., Hager, B., Stenwig, B., Skullerud, K., Berg-Johnsen, J., Storm-Mathisen, I., Hirschberg, H., Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients, J Clin Oncol, 15, 3129-40, 1997	Analyses not in PICO (not adjusted for RT, chemotherapy or age [N = 41 aged 0-19 years])
Martino, J., Gomez, E., Bilbao, J. L., Duenas, J. C., Vazquez-Barquero, A., Cost-utility of maximal safe resection of WHO grade II gliomas within eloquent areas, Acta NeurochirurgicaActa Neurochir (Wien), 155, 41-50, 2013	N < 100 LGG
Mathew, R., Spink, S., O'Hara, D., Loughrey, C., Wright, E., Chakrabarty, A., Patankar, T., MacMullen-Price, J., Goodden, J., Chumas, P., The leeds low-grade glioma service 2010-13, Neuro-OncologyNeuro-oncol, 16, ii19, 2014	Abstract only, not enough information to ascertain relevance, but seems N not ≥ 50 in at least 2 treatment groups
Nitta, M., Muragaki, Y., Maruyama, T., Iseki, H., Ikuta, S., Konishi, Y., Saito, T., Tamura, M., Chernov, M., Watanabe, A., Okamoto, S., Maebayashi, K., Mitsuhashi, N., Okada, Y., Updated therapeutic strategy for adult low-grade glioma stratified by resection and tumor subtype, Neurologia Medico-ChirurgicaNeurol Med Chir (Tokyo), 53, 447-54, 2013	Analyses not in PICO (not adjusted for adjuvant treatment)
Olson, J. J., Kalkanis, S. N., Ryken, T. C., Evidence-based clinical practice parameter guidelines for the treatment of adults with diffuse low-grade glioma: introduction and methods, J NeurooncolJournal of neuro-oncology, 125, 449-456, 2015	Methods section describing development of a guideline

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Pignatti, F., van den Bent, M., Curran, D., Debruyne, C., Sylvester, R., Therasse, P., Afra, D., Cornu, P., Bolla, M., Vecht, C., Karim, A. B., European Organization for, Research, Treatment of Cancer Brain Tumor Cooperative, Group, European Organization for, Research, Treatment of Cancer Radiotherapy Cooperative, Group, Prognostic factors for survival in adult patients with cerebral low-grade glioma, Journal of Clinical Oncology, 20, 2076-84, 2002	Analyses not in PICO (not adjusted for RT)
Qaddoumi, I., Sultan, I., Gajjar, A., Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology, and End Results database, Cancer, 115, 5761-70, 2009	Population aged 0-20 years with grade I-IV glioma; no subgroup analyses for patients aged > 15 years with LGG
Raval, S., Momyer, V., Murray, K., Raval, R., Advances in management of low-grade gliomas, Neuro-oncology, 18, vi14, 2016	Abstract only, not enough information to ascertain relevance
Rezvan, A., Christine, D., Christian, H., Olga, Z., Lutz, E., Marius, H., Stephanie, C., Christel, H. M., Rainer, W. C., Andreas, U., Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients, Acta NeurochirurgicaActa Neurochir (Wien), 151, 1359-1365, 2009	N not ≥ 50 in at least 2 treatment groups
Riva, M., Bello, L., Low-grade glioma management: A contemporary surgical approach, Current Opinion in Oncology, 26, 615-621, 2014	Narrative review
Roelz, R., Strohmaier, D., Jabbarli, R., Kraeutle, R., Egger, K., Coenen, V. A., Weyerbrock, A., Reinacher, P. C., Residual Tumor Volume as Best Outcome Predictor in Low-grade Glioma - A Nine-Years Near-Randomized Survey of Surgery vs. Biopsy, Scientific ReportsSci, 6, 32286, 2016	N not ≥ 50 in at least 2 treatment groups
Sanai, N., Berger, M. S., Glioma extent of resection and its impact on patient outcome, NeurosurgeryNeurosurgery, 62, 753-64; discussion 264-6, 2008	Narrative review
Sankar, T., Moore, N. Z., Johnson, J., Ashby, L. S., Scheck, A. C., Shapiro, W. R., Smith, K. A., Spetzler, R. F., Preul, M. C., Magnetic resonance imaging volumetric assessment of the extent of contrast enhancement and resection in oligodendroglial tumors: Clinical article, Journal of NeurosurgeryJ Neurosurg, 116, 1172-1181, 2012	N < 100 LGG (38/100 were grade III)
Senft, C., Franz, K., Ulrich, C. T., Bink, A., Szelenyi, A., Gasser, T., Seifert, V., Low field intraoperative MRI-guided surgery of gliomas: a single center experience, Clinical Neurology & NeurosurgeryClin Neurol Neurosurg, 112, 237-43, 2010	LGG in 22/103 patients
Shaw, E. G., Berkey, B., Coons, S. W., Bullard, D., Brachman, D., Buckner, J. C., Stelzer, K. J., Barger, G. R., Brown, P. D., Gilbert, M. R., Mehta, M., Recurrence following neurosurgeon-determined gross-total resection	Analyses/population not in PICO; N not ≥ 50 in at least 2 treatment groups

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
of adult supratentorial low-grade glioma: results of a prospective clinical trial, Journal of NeurosurgeryJ Neurosurg, 109, 835-41, 2008	
Shaw, E., Arusell, R., Scheithauer, B., O'Fallon, J., O'Neill, B., Dinapoli, R., Nelson, D., Earle, J., Jones, C., Cascino, T., Nichols, D., Ivnik, R., Hellman, R., Curran, W., Abrams, R. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. Journal of Clinical Oncology, 2002 20 p.2267-76	All patients received adjuvant RT (high or low dose within a trial), therefore not possible to adjust for receipt of adjuvant radiotherapy but only for dose of received radiotherapy
Shinohara, C., Muragaki, Y., Maruyama, T., Shimizu, S., Tanaka, M., Kubota, Y., Oikawa, M., Nakamura, R., Iseki, H., Kubo, O., Takakura, K., Hori, T., Long-term prognostic assessment of 185 newly diagnosed gliomas: Grade III glioma showed prognosis comparable to that of Grade II glioma, Japanese Journal of Clinical OncologyJpn J Clin Oncol, 38, 730-3, 2008	N < 100
Skardelly, M., Brendle, E., Noell, S., Behling, F., Wuttke, T. V., Schittenhelm, J., Bisdas, S., Meisner, C., Rona, S., Tatagiba, M. S., Tabatabai, G., Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study, Annals of NeurologyAnn Neurol, 78, 917-28, 2015	N < 100 with LGG
Veeravagu, A., Jiang, B., Ludwig, C., Chang, S. D., Black, K. L., Patil, C. G., Biopsy versus resection for the management of low-grade gliomas, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 4, CD009319, 2013	Cochrane review on biopsy versus resection, but no included studies (only looked for RCTs)
Wang, J., Liu, X., Ba, Y. M., Yang, Y. L., Gao, G. D., Wang, L., Duan, Y. Y., Effect of sonographically guided cerebral glioma surgery on survival time, Journal of Ultrasound in MedicineJ Ultrasound Med, 31, 757-62, 2012	N < 100 with LGG
Wegman-Ostrosky, T., Reynoso-Noveron, N., Mejia-Perez, S. I., Sanchez-Correa, T. E., Alvarez-Gomez, R. M., Vidal-Millan, S., Cacho-Diaz, B., Sanchez-Corona, J., Herrera-Montalvo, L. A., Corona-Vazquez, T., Clinical prognostic factors in adults with astrocytoma: Historic cohort, Clinical Neurology and Neurosurgery, 146, 116-122, 2016	N < 100 with LGG
Xu, D. S., Awad, A. W., Mehalechko, C., Wilson, J. R., Ashby, L. S., Coons, S. W., Sanai, N., An extent of resection threshold for seizure freedom in patients with low-grade gliomas, Journal of Neurosurgery, 1-7, 2017	N not ≥ 50 in at least 2 treatment groups

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
You, G., Sha, Z. Y., Yan, W., Zhang, W., Wang, Y. Z., Li, S. W., Sang, L., Wang, Z., Li, G. L., Li, S. W., Song, Y. J., Kang, C. S., Jiang, T., Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study, Neuro Oncol, 14, 230-41, 2012	Unclear if analyses adjusted for adjuvant RT and CT, which 92% and 11.9% of patients received

Clinical studies from the search for observational studies

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Study	**Reason for Exclusion**
Abrey, L. E., Gross total resection of low-grade glioma in adults, Current Neurology & Neuroscience ReportsCurr Neurol Neurosci Rep, 9, 181-2, 2009	Published as abstract only, not enough information available to ascertain relevance
Agushi, E., Lekka, E., Mohanraj, R., Gkolemis, C., Karabatsou, K., Epilepsy following low-grade glioma surgery: Single centre experience, Neuro-Oncology, 17, v188, 2015	Published as abstract only, not enough information available to ascertain relevance
Agushi, E., Mohanraj, R., Lekka, E., Gkolemis, C., Karabatsou, K., Epilepsy following low-grade glioma surgery: Single-centre experience, British Journal of Neurosurgery, 29 (4), 481-482, 2015	Published as abstract only, not enough information available to ascertain relevance
Ahmadi, R., Dictus, C., Hartmann, C., Zurn, O., Edler, L., Hartmann, M., Combs, S., Herold-Mende, C., Wirtz, C. R., Unterberg, A., Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients., Acta Neurochirurgica, 151, 1359-65, 2009	Not at least 50 patients in at least 2 relevant treatment groups
Aizer, A. A., Ancukiewicz, M., Nguyen, P. L., MacDonald, S. M., Yock, T. I., Tarbell, N. J., Shih, H. A., Loeffler, J. S., Oh, K. S. Natural history and role of radiation in patients with supratentorial and infratentorial WHO grade II ependymomas: Results from a population-based study. Journal of Neuro-Oncology 2013 115 p.411-419	Outcome not in PICO (ependymoma-specific survival); at least 12 /112 patients were aged < 18 years
Bagley, J. H., Babu, R., Friedman, A. H., Adamson, C., Improved survival in the largest national cohort of adults with cerebellar versus supratentorial low-grade astrocytomas, Neurosurgical focus, 34, E7, 2013	Not at least 50 patients in at least 2 relevant treatment groups
Bauman, G., Fisher, B., Watling, C., Cairncross, J. G., Macdonald, D., Adult Supratentorial Low-Grade Glioma: Long-Term Experience at a Single Institution, International Journal of Radiation Oncology Biology Physics, 75, 1401-1407, 2009	Not at least 50 patients in at least 2 relevant treatment groups
Bauman, G., Lote, K., Larson, D., Stalpers, L., Leighton, C., Fisher, B., Wara, W., Macdonald, D., Stitt, L., Cairncross, J. G., Pretreatment factors predict overall survival for patients with low-grade glioma: A recursive partitioning analysis, International Journal of Radiation Oncology Biology Physics, 45, 923-929, 1999	Analyses not in PICO (not adjusted for other/adjuvant treatment)

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Berger, M. S., Surgical resection strategies for optimizing glioma removal, Neuro-Oncology, 11 (6), 879-880, 2009	Published as abstract only, not enough information available to ascertain relevance
Bonney, P. A., Boettcher, L. B., Burks, J. D., Baker, C., Conner, A. K., Fujii, T., Mehta, V. A., Briggs, R. G., Sughrue, M. E., Rates of Seizure Freedom after Surgical Resection of Diffuse Low-Grade Gliomas, World NeurosurgeryWorld Neurosurg, 30, 30, 2017	Systematic review with different inclusion criteria to the present review; included studies checked for relevance
Brandel, M. G., Alattar, A. A., Hirshman, B. R., Dong, X., Carroll, K. T., Ali, M. A., Carter, B. S., Chen, C. C., Survival trends of oligodendroglial tumor patients and associated clinical practice patterns: a SEER-based analysis, J NeurooncolJournal of neuro-oncology, 133, 173-181, 2017	Analyses not in PICO
Brown, T. J., Bota, D. A., Maher, E. A., Aregawi, D. G., Liau, L. M., Brown, P. D., Buckner, J. C., Weller, M., Van Den Bent, M. J., Berger, M. S., Glantz, M. J., Association of aggressive resection with survival and progression-free survival in adult low-grade glioma: A systematic review and meta-analysis with numbers needed to treat, Journal of Clinical Oncology. Conference, 35, 2017	Published as an abstract only, not enough information available to evaluate the study
Chaichana, K. L., McGirt, M. J., Laterra, J., Olivi, A., Quinones-Hinojosa, A., Recurrence and malignant degeneration after resection of adult hemispheric low-grade gliomas, J NeurosurgJournal of neurosurgery, 112, 10-7, 2010	Secondary resection in 25% of patients; results not presented for the target population separately, or adjusted for this covariate
Chaichana, K. L., McGirt, M. J., Niranjan, A., Olivi, A., Burger, P. C., Quinones-Hinojosa, A., Prognostic significance of contrast-enhancing low-grade gliomas in adults and a review of the literature, Neurological ResearchNeurol Res, 31, 931-9, 2009	Analyses not in PICO
Chang, E. F., Clark, A., Smith, J. S., Polley, M. Y., Chang, S. M., Barbaro, N. M., Parsa, A. T., McDermott, M. W., Berger, M. S., Functional mapping-guided resection of low-grade gliomas in eloquent areas of the brain: Improvement of long-term survival - Clinical article, J NeurosurgJournal of neurosurgery, 114, 566-573, 2011	Analyses not in PICO
Chang, E. F., Potts, M. B., Keles, G. E., Lamborn, K. R., Chang, S. M., Barbaro, N. M., Berger, M. S., Seizure characteristics and control following resection in 332 patients with low-grade gliomas, Journal of Neurosurgery, 108, 227-235, 2008	Analyses not in PICO (not adjusted for adjuvant treatment)
Chang, E. F., Smith, J. S., Chang, S. M., Lamborn, K. R., Prados, M. D., Butowski, N., Barbaro, N. M., Parsa, A. T., Berger, M. S., McDermott, M. M., Preoperative prognostic classification system for hemispheric low-grade gliomas in adults: Clinical article, Journal of Neurosurgery, 109, 817-824, 2008	Analyses not in PICO

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Claus, E. B., Horlacher, A., Hsu, L., Schwartz, R. B., Dello-Iacono, D., Talos, F., Jolesz, F. A., Black, P. M., Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance, CancerCancer, 103, 1227-33, 2005	Duplicate
Cordier, D., Goze, C., Schadelin, S., Rigau, V., Mariani, L., Duffau, H., A better surgical resectability of WHO grade II gliomas is independent of favorable molecular markers, J NeurooncolJournal of neuro-oncology, 121, 185-93, 2015	Analyses not in PICO
Deng, S., Li, Y., Guan, Y., Xu, S., Chen, J., Zhao, G., Gliomas in the sellar turcica region: A retrospective study including adult cases and comparison with craniopharyngioma, European NeurologyEur Neurol, 73, 135-143, 2015	Analyses not in PICO
Duffau, H., Capelle, L., Denvil, D., Sichez, N., Gatignol, P., Taillandier, L., Lopes, M., Mitchell, M. C., Roche, S., Muller, J. C., Bitar, A., Sichez, J. P., van Effenterre, R., Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients, Journal of Neurosurgery, 98, 764-78, 2003	Not at least 50 patients in at least 2 relevant treatment groups
Duffau, H., Peggy Gatignol, S. T., Mandonnet, E., Capelle, L., Taillandier, L., Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere, J NeurosurgJournal of neurosurgery, 109, 461-71, 2008	Not at least 50 patients in at least 2 relevant treatment groups
Erridge, S. C., Hart, M. G., Kerr, G. R., Smith, C., McNamara, S., Grant, R., Gregor, A., Whittle, I. R., Trends in classification, referral and treatment and the effect on outcome of patients with glioma: A 20 year cohort, Journal of Neuro-Oncology, 104, 789-800, 2011	Analyses not in PICO
Eseonu, C. I., Eguia, F., ReFaey, K., Garcia, O., Rodriguez, F. J., Chaichana, K., Quinones-Hinojosa, A., Comparative volumetric analysis of the extent of resection of molecularly and histologically distinct low-grade gliomas and its role on survival, Journal of Neuro-OncologyJ Neurooncol, 1-10, 2017	Analyses not in PICO (not adjusted for post-operative RT and chemotherapy)
Franklin, C. I., The treatment of low-grade cerebral astrocytomas by radiotherapy in Queensland, Australasian RadiologyAustralas Radiol, 35, 68-71, 1991	Not at least 50 patients in at least 2 relevant treatment groups
Gousias, K., Schramm, J., Simon, M., Extent of resection and survival in supratentorial infiltrative low-grade gliomas: analysis of and adjustment for treatment bias, Acta Neurochirurgica, 1-11, 2013	Duplicate
Grossman, R., Nossek, E., Sitt, R., Hayat, D., Shahar, T., Barzilai, O., Gonen, T., Korn, A., Sela, G., Ram, Z., Outcome of elderly patients undergoing awake-craniotomy for tumor resection, Annals of Surgical OncologyAnn Surg Oncol, 20, 1722-8, 2013	N < 100 LGG

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Hardie, J. G., Kizilbash, S., Buckner, J., Parney, I., Giannini, C., Uhm, J., Laack, N., Factors contributing to survival in patients with anaplastic astrocytoma: A retrospective study of patients treated at a single institution, International Journal of Radiation Oncology Biology Physics, 1), S104, 2013	Published as abstract only, not enough information available to ascertain relevance
Hartmann, C., Hentschel, B., Tatagiba, M., Schramm, J., Schnell, O., Seidel, C., Stein, R., Reifenberger, G., Pietsch, T., Von Deimling, A., Loeffler, M., Weller, M., Molecular markers in low-grade gliomas: Predictive or prognostic?, Clinical Cancer ResearchClin Cancer Res, 17, 4588-4599, 2011	Analyses not in PICO (all done separately on data from two cohorts, each with N < 100; no combined relevant analyses of the cohorts)
Hervey-Jumper, S. L., Berger, M. S., Maximizing safe resection of low- and high-grade glioma, Journal of Neuro-OncologyJ Neurooncol, 130, 269-282, 2016	Narrative review
Innocenzi, G., Salvati, M., Cervoni, L., Delfini, R., Cantore, G., Prognostic factors in intramedullary astrocytomas, Clinical Neurology and Neurosurgery, 99, 1-5, 1997	N < 100
Ius, T., Isola, M., Budai, R., Pauletto, G., Tomasino, B., Fadiga, L., Skrap, M., Low-grade glioma surgery in eloquent areas: Volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients - Clinical article, Journal of Neurosurgery, 117, 1039-1052, 2012	Analyses not adjusted for adjuvant treatments
Jakola, A. S., Myrmel, K. S., Kloster, R., Torp, S. H., Lindal, S., Unsgard, G., Solheim, O., Comparison of a strategy favoring early surgical resection versus a strategy favoring watchful waiting in low-grade gliomas, JAMAJama, 308, 1881-8, 2012	Duplicate
Jakola, A. S., Skjulsvik, A. J., Myrmel, K. S., Sjavik, K., Unsgard, G., Torp, S. H., Aaberg, K., Berg, T., Dai, H. Y., Johnsen, K., Kloster, R., Solheim, O., Surgical resection versus watchful waiting in low-grade gliomas, Annals of Oncology, 2017	Analyses not in PICO (not adjusted for adjuvant/other treatments)
Jakola, A. S., Unsgard, G., Myrmel, K. S., Kloster, R., Torp, S. H., Losvik, O. K., Lindal, S., Solheim, O., Surgical strategy in grade II astrocytoma: A population-based analysis of survival and morbidity with a strategy of early resection as compared to watchful waiting, Acta Neurochirurgica, 155, 2227-2235, 2013	Analyses not in PICO
Keles, G. E., Lamborn, K. R., Berger, M. S., Low-grade hemispheric gliomas in adults: A critical review of extent of resection as a factor influencing outcome, Journal of Neurosurgery, 95, 735-745, 2001	Duplicate
Johnson, D. R., Brown, P. D., Galanis, E., Hammack, J. E. Pilocytic astrocytoma survival in adults: Analysis of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Journal of Neuro-Oncology, 2012 108 p.187-193	Outcome not in PICO (cancer-specific survival)/analyses not in PICO (for overall survival they are not adjusted for adjuvant treatment).

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Korshunov, A., Golanov, A., Sycheva, R., Timirgaz, V., The Histologic Grade Is a Main Prognostic Factor for Patients with Intracranial Ependymomas Treated in the Microneurosurgical Era: An Analysis of 258 Patients, Cancer, 100, 1230-1237, 2004	N < 100 (in PICO population)
Kumabe, T., Sato, K., Iwasaki, M., Shibahara, I., Kawaguchi, T., Saito, R., Kanamori, M., Yamashita, Y., Sonoda, Y., Iizuka, O., Suzuki, K., Nagamatsu, K. I., Seki, S., Nakasato, N., Tominaga, T., Summary of 15 years experience of awake surgeries for neuroepithelial tumors in Tohoku University, Neurologia Medico-Chirurgica, 53, 455-466, 2013	Analyses not in PICO
Lassen, B., Helseth, E., Ronning, P., Scheie, D., Johannesen, T. B., Maehlen, J., Langmoen, I. A., Meling, T. R., Surgical mortality at 30 days and complications leading to recraniotomy in 2630 consecutive craniotomies for intracranial tumors, NeurosurgeryNeurosurgery, 68, 1259-68; discussion 1268-9, 2011	Analyses not in PICO
Laws, E. R., Jr., Taylor, W. F., Clifton, M. B., Okazaki, H., Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres, Journal of Neurosurgery, 61, 665-73, 1984	Reporting on patients treated between 1915 and 1975
Liu, J., Zhang, B., Gan, W., Zhou, D., Wang, Z., Zhou, Y., Han, J., Huang, Y., Clinical manifestations and outcomes of typical versus atypical pleomorphic xanthoastrocytoma: A single-institution experience, International Journal of Clinical and Experimental Medicine, 9, 20145-20150, 2016	N < 100
Luyken, C., Blumcke, I., Fimmers, R., Urbach, H., Elger, C. E., Wiestler, O. D., Schramm, J., The spectrum of long-term epilepsy-associated tumors: Long-term seizure and tumor outcome and neurosurgical aspects, Epilepsia, 44, 822-830, 2003	Not at least 50 patients in 2 treatment groups
McGirt, M. J., Chaichana, K. L., Attenello, F. J., Weingart, J. D., Than, K., Burger, P. C., Olivi, A., Brem, H., Quinones-Hinojosa, A., Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas, NeurosurgeryNeurosurgery, 63, 700-707, 2008	Not at least 50 patients in at least 2 treatment groups (primary resection)
Nitta, M., Muragaki, Y., Maruyama, T., Ikuta, S., Komori, T., Maebayashi, K., Iseki, H., Tamura, M., Saito, T., Okamoto, S., Chernov, M., Hayashi, M., Okada, Y., Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection, Neurosurgical FocusNeurosurg, 38, E7, 2015	Not at least 50 patients in at least 2 treatment groups
Nitta, M., Muragaki, Y., Maruyama, T., Iseki, H., Ikuta, S., Konishi, Y., Saito, T., Tamura, M., Chernov, M., Watanabe, A., Okamoto, S., Maebayashi, K., Mitsuhashi, N., Okada, Y., Updated therapeutic strategy for adult low-grade glioma stratified by resection and tumor subtype, Neurologia Medico-ChirurgicaNeurol Med Chir (Tokyo), 53, 447-54, 2013	Analyses not in PICO (not adjusted for radiotherapy and chemotherapy also received by some patients)

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Oertel, J., von Buttlar, E., Schroeder, H. W., Gaab, M. R., Prognosis of gliomas in the 1970s and today, Neurosurgical FocusNeurosurg, 18, e12, 2005	N < 100 with LGG
Orina, J. N., Meyer, F., Parney, I., Extent of resection as a predictor of survival in a modern series of low-grade gliomas: A volumetric analysis, J NeurosurgJournal of neurosurgery, 122 (6), A1579, 2015	Published as abstract only, not enough information available to ascertain relevance
Rezvan, A., Christine, D., Christian, H., Olga, Z., Lutz, E., Marius, H., Stephanie, C., Christel, H. M., Rainer, W. C., Andreas, U., Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients, Acta NeurochirurgicaActa Neurochir (Wien), 151, 1359-1365, 2009	Not at least 50 patients in at least 2 treatment groups
Ribom, D., Smits, A., Hartman, M., Persson, L., Blomquist, E., On the issue of early and aggressive treatment in grade 2 gliomas, Journal of Cancer Research & Clinical OncologyJ Cancer Res Clin Oncol, 129, 154-60, 2003	Not at least 50 patients in at least 2 treatment groups
Rieken, S., Mohr, A., Schlusche, M., Rieber, J., Forster, R., Rief, H., Welzel, T., Lindel, K., Combs, S. E., Debus, J., Long term outcome, prognostic factors, and toxicitiy in patients with low-grade gliomas following radiotherapy, Strahlentherapie und Onkologie, 191, S148, 2015	Published as abstract only; not enough information to ascertain relevance
Roessler, K., Hofmann, A., Sommer, B., Grummich, P., Coras, R., Kasper, B. S., Hamer, H. M., Blumcke, I., Stefan, H., Nimsky, C., Buchfelder, M., Resective surgery for medically refractory epilepsy using intraoperative MRI and functional neuronavigation: the Erlangen experience of 415 patients, Neurosurgical focus, 40, E15, 2016	N < 100 with LGG
Sankar, T., Moore, N. Z., Johnson, J., Ashby, L. S., Scheck, A. C., Shapiro, W. R., Smith, K. A., Spetzler, R. F., Preul, M. C., Magnetic resonance imaging volumetric assessment of the extent of contrast enhancement and resection in oligodendroglial tumors, J NeurosurgJournal of neurosurgery, 116, 1172-81, 2012	N < 100 with LGG
Scerrati, M., Roselli, R., Iacoangeli, M., Pompucci, A., Rossi, G. F., Prognostic factors in low-grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery, Journal of Neurology, Neurosurgery & PsychiatryJ Neurol Neurosurg Psychiatry, 61, 291-6, 1996	Not at least 50 patients in at least 2 treatment groups
Schomas, D. A., Laack, N. N., Rao, R. D., Meyer, F. B., Shaw, E. G., O'Neill, B. P., Giannini, C., Brown, P. D., Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic, Neuro-Oncology, 11, 437-45, 2009	Included patients treated 1960-1992; analyses not adjusted or subgrouped for this and no further details reported, so unclear how many patients out of PICO/treated before 1980

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Shastin, D., Wright, E., Boyer, G., O'Hara, D., Maguire, M., Loughrey, C., Goodden, J., Chumas, P., Low-grade glioma: A survey of UK national practice, Neuro-Oncology, 18, iv63, 2016	Abstract only, not enough relevant information to ascertain relevance
Shaw, E. G., Wisoff, J. H., Prospective clinical trials of intracranial low-grade glioma in adults and children, Neuro-OncologyNeuro-oncol, 5, 153-160, 2003	Narrative review
Shinohara, C., Muragaki, Y., Maruyama, T., Shimizu, S., Tanaka, M., Kubota, Y., Oikawa, M., Nakamura, R., Iseki, H., Kubo, O., Takakura, K., Hori, T., Long-term prognostic assessment of 185 newly diagnosed gliomas - Grade III glioma showed prognosis comparable to that of grade II glioma, Japanese Journal of Clinical Oncology, 38, 730-733, 2008	N < 100
Skardelly, M., Brendle, E., Noell, S., Behling, F., Wuttke, T. V., Schittenhelm, J., Bisdas, S., Meisner, C., Rona, S., Tatagiba, M. S., Tabatabai, G., Predictors of preoperative and early postoperative seizures in patients with intra-axial primary and metastatic brain tumors: A retrospective observational single center study, Annals of NeurologyAnn Neurol, 78, 917-28, 2015	N < 100 with LGG
Smith, J. S., Chang, E. F., Lamborn, K. R., Chang, S. M., Prados, M. D., Cha, S., Tihan, T., Vandenberg, S., McDermott, M. W., Berger, M. S., Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 26, 1338-1345, 2008	Analyses not in PICO (not adjusted for chemotherapy and radiotherapy also received by some patients)
Snyder, L. A., Wolf, A. B., Oppenlander, M. E., Bina, R., Wilson, J. R., Ashby, L., Brachman, D., Coons, S. W., Spetzler, R. F., Sanai, N., The impact of extent of resection on malignant transformation of pure oligodendrogliomas: Clinical article, Journal of Neurosurgery, 120, 309-314, 2014	N < 100
Stander, M., Peraud, A., Leroch, B., Kreth, F. W., Prognostic impact of TP53 mutation status for adult patients with supratentorial World Health Organization Grade II astrocytoma or oligoastrocytoma: A long-term analysis, Cancer, 101, 1028-1035, 2004	Not at least 50 patients in at least 2 relevant treatment groups
Varshneya, K., Sarmiento, J. M., Nuno, M., Lagman, C., Mukherjee, D., Nuno, K., Babu, H., Patil, C. G., A national perspective of adult gangliogliomas, Journal of Clinical Neuroscience, 30, 65-70, 2016	Not at least 50 patients in at least 2 relevant treatment groups
Wegman-Ostrosky, T., Reynoso-Noveron, N., Mejia-Perez, S. I., Sanchez-Correa, T. E., Alvarez-Gomez, R. M., Vidal-Millan, S., Cacho-Diaz, B., Sanchez-Corona, J., Herrera-Montalvo, L. A., Corona-Vazquez, T., Clinical prognostic factors in adults with astrocytoma: Historic cohort, Clinical Neurology and Neurosurgery, 146, 116-122, 2016	N < 100

Excluded studies - What is the optimal timing and extent of initial surgery for suspected low-grade glioma?	
Wu, Z. M., Wu, T., Yuan, X. H., Chen, W. G., Jaing, P. C., Analysis of variables affecting survival of patients with astracytomas, Chinese Journal of Cancer Research, 16, 208-211, 2004	N < 100 with LGG
Yilmaz, E. R., Gurer, B., Kertmen, H., Dolgun, H., Sanli, A. M., Sekerci, Z., The outcome of surgically resected anaplastic astrocytoma and glioblastoma: Results of single center retrospective study, Journal of Neurological Sciences, 28, 347-354, 2011	N < 100 with LGG
You, G., Huang, L., Yang, P., Zhang, W., Yan, W., Wang, Y., Bao, Z., Li, S., Li, S., Li, G., Jiang, T., Clinical and molecular genetic factors affecting postoperative seizure control of 183 Chinese adult patients with low-grade gliomas, European Journal of Neurology, 19, 298-306, 2012	Analyses not in PICO (not adjusted for chemotherapy and radiotherapy received by some of the patients)
You, G., Sha, Z. Y., Yan, W., Zhang, W., Wang, Y. Z., Sang, L., Wang, Z., Li, G. L., Li, S. W., Song, Y. J., Kang, C. S., Jiang, T., Seizure characteristics and outcomes in 508 Chinese adult patients undergoing primary resection of low-grade gliomas: A clinicopathological study, Neuro-Oncology, 14, 230-241, 2012	Duplicate
Youland, R. S., Brown, P. D., Giannini, C., Parney, I. F., Uhm, J. H., Laack, N. N., Adult low-grade glioma: 19-year experience at a single institution, American Journal of Clinical OncologyAm J Clin Oncol, 36, 612-9, 2013	Analyses not in PICO (not adjusted for chemotherapy also received by some patients)
Youland, R. S., Schomas, D. A., Brown, P. D., Nwachukwu, C., Buckner, J. C., Giannini, C., Parney, I. F., Laack, N. N., Changes in presentation, treatment, and outcomes of adult low-grade gliomas over the past fifty years, Neuro OncolNeuro-oncology, 15, 1102-10, 2013	Duplicate
Youland, R. S., Kreofsky, C. R., Schomas, D. A., Brown, P. D., Buckner, J. C., Laack, N. N. The impact of adjuvant therapy for patients with high-risk diffuse WHO grade II glioma. Journal of Neuro-Oncology 2017 p.1-9	Subsection of the same patients that are already included in Youland 2013

Economic studies

Not applicable – no economic evidence was identified.

Excluded studies for review 2a – further management of low-grade glioma

Clinical studies

Excluded studies - What is the optimal management (observation, surgery, radiotherapy, chemotherapy or combinations of these) for histologically proven low-grade glioma?	
Study	**Reason for Exclusion**
Aghi, M. K., Nahed, B. V., Sloan, A. E., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of surgery in the management of patients with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-OncologyJ Neurooncol, 125, 503-30, 2015	This systematic review included both observational and randomised studies; the randomised studies have been included (Shaw 2002 and Karim 2002) in the current review
Baumert, B. G., Stupp, R., European Organization for, Research, Treatment of Cancer Radiation Oncology, Group, European Organization for, Research, Treatment of Cancer Brain Tumor, Group, Low-grade glioma: a challenge in therapeutic options: the role of radiotherapy, Annals of Oncology, 19 Suppl 7, vii217-22, 2008	Review of the different therapeutic options in low-grade glioma, but including no randomised studies
Bell, Eh, Zhang, P, Fisher, Bj, Macdonald, Dr, McElroy, Jp, Lesser, Gj, Fleming, J, Chakraborty, A, Liu, Z, Becker, Ap, Fabian, D, Aldape, Kd, Ashby, Ls, Werner-Wasik, M, Walker, Em, Bahary, J-P, Kwok, Y, Yu, M, Laack, Nn, Schultz, Cj, Gray, Hj, Robins, Hi, Mehta, Mp, Chakravarti, A, MGMT status predicts survival outcomes in NRG oncology/RTOG 0424: a phase ii trial of temozolomide-based chemoradiotherapy for high risk low-grade gliomas, Neuro-oncology. Conference: 21st annual scientific meeting and education day of the society for neuro-oncology. United states. Conference start: 20161117. Conference end: 20161120, 18, vi115, 2016	Abstract
Brada, M., Viviers, L., Abson, C., Hines, F., Britton, J., Ashley, S., Sardell, S., Traish, D., Gonsalves, A., Wilkins, P., Westbury, C., Phase II study of primary temozolomide chemotherapy in patients with WHO grade II gliomas, Annals of oncology : official journal of the European Society for Medical Oncology, 14, 1715-21, 2003	Not a randomised study
Brown, P. D., Anderson, S. K., Carrero, X. W., O'Neill, B. P., Giannini, C., Galanis, E., Shah, S. A., Abrams, R. A., Curran, W. J., Jr., Buckner, J. C., Shaw, E. G., Adult patients with supratentorial pilocytic astrocytoma: long-term follow-up of prospective multicenter clinical trial NCCTG-867251 (Alliance), Neuro-Oncology PracticeNeurooncol Pract, 2, 199-204, 2015	Not a randomised study
Brown, P. D., Buckner, J. C., O'Fallon, J. R., Iturria, N. L., Brown, C. A., O'Neill, B. P., Scheithauer, B. W., Dinapoli, R. P., Arusell, R. M., Abrams, R. A., Curran, W. J., Shaw, E. G., North Central Cancer Treatment, Group, Mayo, Clinic, Adult patients with supratentorial pilocytic astrocytomas: a prospective multicenter	Not a randomised study

Excluded studies - What is the optimal management (observation, surgery, radiotherapy, chemotherapy or combinations of these) for histologically proven low-grade glioma?	
clinical trial, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 58, 1153-60, 2004	
Brown, P. D., Buckner, J. C., O'Fallon, J. R., Iturria, N. L., O'Neill, B. P., Brown, C. A., Scheithauer, B. W., Dinapoli, R. P., Arusell, R. M., Curran, W. J., Abrams, R., Shaw, E. G., Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma, International Journal of Radiation Oncology Biology Physics, 59, 117-125, 2004	Not a randomised study
Brown, P. D., Buckner, J. C., Uhm, J. H., Shaw, E. G., The neurocognitive effects of radiation in adult low-grade glioma patients, Neuro-Oncology, 5, 161-7, 2003	Narrative review
Brown, Pd, Buckner, Jc, Brown, Ca, O'Fallon, Jr, Iturria, Nl, O'Neill, Bp, Dinapoli, Rp, Cascino, Tl, Arusell, Rm, Shaw, Eg, The effects of radiation on cognitive function in patients with low-grade glioma, International Journal of Radiation Oncology Biology Physics, 51, 135, 2001	Abstract
Buckner, J. C., Gesme Jr, D., O'Fallon, J. R., Hammack, J. E., Stafford, S., Brown, P. D., Hawkins, R., Scheithauer, B. W., Erickson, B. J., Levitt, R., Shaw, E. G., Jenkins, R., Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: Efficacy and associations with chromosomal abnormalities, Journal of Clinical OncologyJ Clin Oncol, 21, 251-255, 2003	Not a randomised study
Buckner, J., Giannini, C., Eckel-Passow, J., Lachance, D., Parney, I., Laack, N., Jenkins, R., Management of diffuse low-grade gliomas in adults - use of molecular diagnostics, Nature Reviews Neurology, 13, 340-351, 2017	Narrative review
Fisher, B. J., Hu, C., Macdonald, D. R., Lesser, G. J., Coons, S. W., Brachman, D. G., Ryu, S., Werner-Wasik, M., Bahary, J. P., Liu, J., Chakravarti, A., Mehta, M., Phase 2 study of temozolomide-based chemoradiation therapy for high-risk low-grade gliomas: Preliminary results of radiation therapy oncology group 0424, International Journal of Radiation Oncology Biology Physics, 91, 497-504, 2015	Single-arm study
Fitzek, M. M., Thornton, A. F., Harsh, G. th, Rabinov, J. D., Munzenrider, J. E., Lev, M., Ancukiewicz, M., Bussiere, M., Hedley-Whyte, E. T., Hochberg, F. H., Pardo, F. S., Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: results of an institutional phase I/II trial, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 51, 131-7, 2001	Not a randomised study
Hiesiger, Em, Green, Sb, Shapiro, Wr, Burger, Pc, Selker, Rg, Mahaley, Ms, Ransohoff, J, VanGilder, Jc, Mealey, J, Robertson, Jt, Results of a randomized trial comparing intra-arterial cisplatin and intravenous PCNU for the treatment of primary brain tumors in adults: brain Tumor Cooperative Group trial 8420A, Journal of Neuro-Oncology, 25, 143-154, 1995	Study included patients with WHO grade III and IV tumours

Excluded studies - What is the optimal management (observation, surgery, radiotherapy, chemotherapy or combinations of these) for histologically proven low-grade glioma?	
Kesari, S., Schiff, D., Drappatz, J., LaFrankie, D., Doherty, L., Macklin, E. A., Muzikansky, A., Santagata, S., Ligon, K. L., Norden, A. D., Ciampa, A., Bradshaw, J., Levy, B., Radakovic, G., Ramakrishna, N., Black, P. M., Wen, P. Y., Phase II study of protracted daily temozolomide for low-grade gliomas in adults, Clinical Cancer Research, 15, 330-7, 2009	Not a randomised study
Koekkoek, J. A. F., Kerkhof, M., Dirven, L., Heimans, J. J., Reijneveld, J. C., Taphoorn, M. J. B., Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: A systematic review, Neuro-Oncology, 17, 924-934, 2015	Only observational studies have been included
Lashkari, H. P., Saso, S., Moreno, L., Athanasiou, T., Zacharoulis, S., Using different schedules of Temozolomide to treat low-grade gliomas: Systematic review of their efficacy and toxicity, Journal of Neuro-OncologyJ Neurooncol, 105, 135-147, 2011	This systematic review included both observational and randomised studies; the RCT is part of the included studies (van den bent 2005)
Levin, N., Lavon, I., Zelikovitsh, B., Fuchs, D., Bokstein, F., Fellig, Y., Siegal, T., Progressive low-grade oligodendrogliomas: response to temozolomide and correlation between genetic profile and O6-methylguanine DNA methyltransferase protein expression, Cancer, 106, 1759-65, 2006	Not a randomised study
Mazzocco, P., Honnorat, J., Ducray, F., Ribba, B., Increasing the Time Interval between PCV Chemotherapy Cycles as a Strategy to Improve Duration of Response in Low-Grade Gliomas: Results from a Model-Based Clinical Trial Simulation, Computational & Mathematical Methods in MedicineComput, 2015, 297903, 2015	Simulation study
Quinn, J. A., Reardon, D. A., Friedman, A. H., Rich, J. N., Sampson, J. H., Provenzale, J. M., McLendon, R. E., Gururangan, S., Bigner, D. D., Herndon, J. E., 2nd, Avgeropoulos, N., Finlay, J., Tourt-Uhlig, S., Affronti, M. L., Evans, B., Stafford-Fox, V., Zaknoen, S., Friedman, H. S., Phase II trial of temozolomide in patients with progressive low-grade glioma, Journal of Clinical OncologyJ Clin Oncol, 21, 646-51, 2003	Some of the people included in the study presented with recurrent LGG and, as part of the eligibility criteria, biopsy was not required for all the participants
Ragel, B. T., Ryken, T. C., Kalkanis, S. N., Ziu, M., Cahill, D., Olson, J. J., The role of biopsy in the management of patients with presumed diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-OncologyJ Neurooncol, 125, 481-501, 2015	This systematic review included observational studies only
Regine, W. F., Patchell, R. A., Strottmann, J. M., Meigooni, A., Sanders, M., Young, B., Combined stereotactic split-course fractionated gamma knife radiosurgery and conventional radiation therapy for unfavorable gliomas: a phase I study, Journal of Neurosurgery, 93 Suppl 3, 37-41, 2000	12/18 patients presented with high-grade or recurrent gliomas
Ruda, R, Pellerino, A, Franchino, F, Pace, A, Carapella, Cm, Dealis, C, Caroli, M, Faedi, M, Bomprezzi, C, Soffietti, R, A phase II trial of temozolomide (TMZ) 1 week on/1 week off as initial treatment for high risk low-grade oligodendroglial tumors: an AINO (Italian Association for Neuro- Oncology) study, Journal of clinical	Abstract

Excluded studies - What is the optimal management (observation, surgery, radiotherapy, chemotherapy or combinations of these) for histologically proven low-grade glioma?	
oncology. Conference: 2017 annual meeting of the american society of clinical oncology, ASCO. United states, 35, 2017	
Starke, R. M., Connolly, E. S., Komotar, R. J., A Randomized Clinical Trial of Radiation with or Without Chemotherapy for Low-grade Gliomas, Neurosurgery, 79, N17-N18, 2016	Abstract only
Wahl, M., Phillips, J. J., Molinaro, A. M., Lin, Y., Perry, A., Haas-Kogan, D. A., Costello, J. F., Dayal, M., Butowski, N., Clarke, J. L., Prados, M., Nelson, S., Berger, M. S., Chang, S. M., Chemotherapy for adult low-grade gliomas: clinical outcomes by molecular subtype in a phase II study of adjuvant temozolomide, Neuro-Oncology, 19, 242-251, 2017	Non-randomised study
Fadel, N., Eldahab, H. A., Wageh, O., Wafik, H., Awake craniotomy versus conventional general anaesthesia in surgical removal of low-grade glioma primary experience of Kasr El-Aini Hospital, Egyptian Journal of Anaesthesia, 24, 275-284, 2008	Paper unavailable
Oberheim Bush NA, Chang S. Treatment strategies for low-grade glioma in adults. Journal of oncology practice. 2016 Dec; 12(12):1235-41.	Paper unavailable
Ziu, M., Kalkanis, S. N., Gilbert, M., Ryken, T. C., Olson, J. J., The role of initial chemotherapy for the treatment of adults with diffuse low-grade glioma : A systematic review and evidence-based clinical practice guideline, J NeurooncolJournal of neuro-oncology, 125, 585-607, 2015	This systematic review included both observational studies and 1 randomised study; the RCT (Shaw 2012) has been included in this review

Economic studies

Not applicable – no economic evidence was identified.

Excluded studies for review 2c – initial management of high-grade glioma

Clinical studies

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Study	Reason for Exclusion

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma--final evaluation. E.O.R.T.C. Brain Tumor Group, European Journal of CancerEur J Cancer, 14, 851-6, 1978	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Evaluation of CCNU, VM-26 plus CCNU, and procarbazine in supratentorial brain gliomas. Final evaluation of a randomized study. European Organization for Research on Treatment of Cancer (EORTC) Brain Tumor Group, Journal of NeurosurgeryJ Neurosurg, 55, 27-31, 1981	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 19, 509-18, 2001	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Treatment of elderly patients with glioblastoma a systematic evidence-based analysis, JAMA Neurology. 72 (5) (pp 589-596), 2015. Date of Publication: May 2015., 2015	This review included the same studies as Hart 2013 with the only exception of Reifenberger 2012, which is an observational study
Cisplatin does not enhance the effect of radiation therapy in malignant gliomas. EORTC Brain Tumor Group, European journal of cancer (Oxford, England : 1990), 27, 568-71, 1991	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Gliadel wafer implantation combined with standard radiotherapy and concurrent followed by adjuvant temozolomide for treatment of newly diagnosed high-grade glioma: A systematic literature review, World Journal of Surgical Oncology. 14 (1) (no pagination), 2016. Article Number: 225. Date of Publication: 24 Aug 2016., 2016	The publications included in this systematic literature review were either phase I/II studies or cohort (prospective and retrospective) studies; which are not eligible for inclusion in this review question
Abrey, L. E., Concomitant chemoradiotherapy followed by adjuvant temozolomide improves survival in glioblastoma multiforme, Current Neurology & Neuroscience ReportsCurr Neurol Neurosci Rep, 5, 167-8, 2005	This study is evaluating the efficacy of radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention.
Akasaki, Y., Kikuchi, T., Homma, S., Koido, S., Ohkusa, T., Tasaki, T., Hayashi, K., Komita, H., Watanabe, N., Suzuki, Y., Yamamoto, Y., Mori, R., Arai, T., Tanaka, T., Joki, T., Yanagisawa, T., Murayama, Y., Phase I/II trial of combination of temozolomide chemotherapy and immunotherapy with fusions of dendritic and glioma	Phase I/II trial

Excluded studies - 2. Management of HGG - Randomized controlled trials	
cells in patients with glioblastoma, Cancer Immunology, ImmunotherapyCancer Immunol Immunother, 65, 1499-1509, 2016	
Ananda, S., Nowak, A. K., Cher, L., Dowling, A., Brown, C., Simes, J., Rosenthal, M. A., Cooperative Trials Group for, Neuro-Oncology, Phase 2 trial of temozolomide and pegylated liposomal doxorubicin in the treatment of patients with glioblastoma multiforme following concurrent radiotherapy and chemotherapy, Journal of Clinical NeuroscienceJ Clin Neurosci, 18, 1444-8, 2011	Phase II trial
Anonymous, Cisplatin does not enhance the effect of radiation therapy in malignant gliomas. EORTC Brain Tumor Group, European Journal of CancerEur J Cancer, 27, 568-71, 1991	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Anonymous, Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma--final evaluation. E.O.R.T.C. Brain Tumor Group, European Journal of Cancer (Oxford)Eur J Cancer, 14, 851-6, 1978	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Anonymous, Chemotherapy for high-grade glioma, Cochrane database of systematic reviews (Online), CD003913, 2002	Control group did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Aoki, T., Nishikawa, R., Sugiyama, K., Nonoguchi, N., Kawabata, N., Mishima, K., Adachi, J. I., Kurisu, K., Yamasaki, F., Tominaga, T., Kumabe, T., Ueki, K., Higuchi, F., Yamamoto, T., Ishikawa, E., Takeshima, H., Yamashita, S., Arita, K., Hirano, H., Yamada, S., Matsutani, M., A Multicenter Phase I/II Study of the BCNU Implant (Gliadel() Wafer) for Japanese Patients with Malignant Gliomas, Neurologia Medico ChirurgicaNeurol Med Chir (Tokyo), 29, 29, 2013	Phase I/II trial
Arcicasa, M., Roncadin, M., Bortolus, R., Bassignano, G., Boz, G., Franchin, G., De Paoli, A., Trovo, M. G., Results of three consecutive combined treatments for malignant gliomas. Ten-year experience at a single institution, American Journal of Clinical OncologyAm J Clin Oncol, 17, 437-43, 1994	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Ardon, H, Gool, Sw, Verschuere, T, Maes, W, Fieuws, S, Sciot, R, Wilms, G, Demaerel, P, Goffin, J, Calenbergh, F, Menten, J, Clement, P, Debiec-Rychter, M, Vleeschouwer, S, Integration of autologous dendritic cell-based immunotherapy in the standard of care treatment for patients with newly diagnosed glioblastoma: Results of the HGG-2006 phase I/II trial, Cancer Immunology, ImmunotherapyCancer Immunol Immunother, 61, 2033-44, 2012	Phase I/II trial

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Armstrong, T. S., Wefel, J. S., Wang, M., Gilbert, M. R., Won, M., Bottomley, A., Mendoza, T. R., Coens, C., Werner-Wasik, M., Brachman, D. G., Choucair, A. K., Mehta, M., Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma, Journal of Clinical OncologyJ Clin Oncol, 31, 4076-84, 2013	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Athanassiou, H., Synodinou, M., Maragoudakis, E., Paraskevaidis, M., Verigos, C., Misailidou, D., Antonadou, D., Saris, G., Beroukas, K., Karageorgis, P., Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme, Journal of Clinical OncologyJ Clin Oncol, 23, 2372-2377, 2005	Phase II study; control group did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Azoulay, M., Ho, C. K., Fujimoto, D. K., Modlin, L. A., Gibbs, I. C., Hancock, S. L., Li, G., Chang, S. D., Adler, J. R., Jr., Harsh, G. R., Nagpal, S., Thomas, R., Recht, L., Choi, C. Y., Soltys, S. G., A Phase I/II Trial of 5 Fraction Stereotactic Radiosurgery With 5-mm Margins With Concurrent and Adjuvant Temozolomide in Newly Diagnosed Supratentorial Glioblastoma Multiforme, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 96, E131-E132, 2016	Abstract
Balana, C, Las, Penas R, Sepulveda, J, Gil, Gil M, Luque, R, Gallego, O, Reynes, G, Herrero, A, Perez-Segura, P, Berrocal, A, RANO criteria applied to a phase II randomized, multicenter trial comparing temozolomide (TMZ) versus TMZ-plus-bevacizumab (BEV) before standard treatment in unresectable glioblastoma (GBM) patients (P). Genom 009 study by the geino group, Neuro-OncologyNeuro-oncol, 16, ii107, 2014	Abstract
Balana, C., De Las Penas, R., Sepulveda, J. M., Gil-Gil, M. J., Luque, R., Gallego, O., Carrato, C., Sanz, C., Reynes, G., Herrero, A., Ramirez, J. L., Perez-Segura, P., Berrocal, A., Vieitez, J. M., Garcia, A., Vazquez-Estevez, S., Peralta, S., Fernandez, I., Henriquez, I., Martinez-Garcia, M., De la Cruz, J. J., Capellades, J., Giner, P., Villa, S., Bevacizumab and temozolomide versus temozolomide alone as neoadjuvant treatment in unresected glioblastoma: the GENOM 009 randomized phase II trial, Journal of Neuro-OncologyJ Neurooncol, 127, 569-79, 2016	Phase II trial
Barnett, G. H., Voigt, J. D., Alhuwalia, M. S., A Systematic Review and Meta-Analysis of Studies Examining the Use of Brain Laser Interstitial Thermal Therapy versus Craniotomy for the Treatment of High-Grade Tumors in or near Areas of Eloquence: An Examination of the Extent of Resection and Major Complication Rates Associated with Each Type of Surgery, Stereotactic & Functional NeurosurgeryStereotact Funct Neurosurg, 94, 164-73, 2016	Not relevant intervention (surgery)

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Batchelor, T., Temozolomide for malignant brain tumours, LancetLancet, 355, 1115-6, 2000	Control group did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Bell, E. H., Pugh, S. L., McElroy, J. P., Gilbert, M. R., Mehta, M., Klimowicz, A. C., Magliocco, A., Bredel, M., Robe, P., Grosu, A. L., Stupp, R., Curran, W., Jr., Becker, A. P., Salavaggione, A. L., Barnholtz-Sloan, J. S., Aldape, K., Blumenthal, D. T., Brown, P. D., Glass, J., Souhami, L., Lee, R. J., Brachman, D., Flickinger, J., Won, M., Chakravarti, A., Molecular-Based Recursive Partitioning Analysis Model for Glioblastoma in the Temozolomide Era: A Correlative Analysis Based on NRG Oncology RTOG 0525, JAMA OncologyJAMA Oncol, 3, 784-792, 2017	Control group did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Bent, Mj, Brandes, Aa, Taphoorn, Mj, Kros, Jm, Kouwenhoven, Mc, Delattre, Jy, Bernsen, Hj, Frenay, M, Tijssen, Cc, Grisold, W, Sipos, L, Enting, Rh, French, Pj, Dinjens, Wn, Vecht, Cj, Allgeier, A, Lacombe, D, Gorlia, T, Hoang-Xuan, K, Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 31, 344-50, 2013	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Bent, Mj, Brandes, Aa, Taphoorn, Mj, Kros, Jm, Kouwenhoven, Mc, Delattre, J-Y, Bernsen, Hj, Frenay, M, Tijssen, Cc, Grisold, W, Sipos, L, Enting, Rh, French, Pj, Dinjens, Wn, Vecht, Cj, Allgeier, A, Lacombe, D, Gorlia, T, Xuan, Kh, Long-term follow-up of EORTC 26951, a randomized trial on adjuvant PCV chemotherapy in anaplastic oligodendroglial tumors. A report of the EORTC BTG, Neuro-OncologyNeuro-oncol, 14, vi56, 2012	Control and experimental groups did not receive standard of care as a baseline intervention
Bent, Mj, Carpentier, Af, Brandes, Aa, Sanson, M, Taphoorn, Mj, Bernsen, Hj, Frenay, M, Tijssen, Cc, Grisold, W, Sipos, L, Haaxma-Reiche, H, Kros, Jm, Kouwenhoven, Mc, Vecht, Cj, Allgeier, A, Lacombe, D, Gorlia, T, Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 24, 2715-22, 2006	Control and experimental groups did not receive standard of care as a baseline intervention
Beresford, M. J., Power, D., Alexander, E., Brock, C., Thompson, J., Roncaroli, F., Waldman, A. D., Van Dellen, J., Glaser, M., Treatment of newly diagnosed glioblastoma with concomitant and adjuvant temozolomide and radiotherapy: UK experience, American Journal of Cancer, 5, 427-432, 2006	Not randomised
Blumenthal, D. T., Gorlia, T., Gilbert, M. R., Kim, M. M., Burt Nabors, L., Mason, W. P., Hegi, M. E., Zhang, P., Golfinopoulos, V., Perry, J. R., Hyun Nam, D., Erridge, S. C., Corn, B. W., Mirimanoff, R. O., Brown, P. D.,	This pooled analysis included phase II RCTs

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Baumert, B. G., Mehta, M. P., van den Bent, M. J., Reardon, D. A., Weller, M., Stupp, R., Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG, Neuro-Oncology, 19, 1119-1126, 2017	
Blumenthal, D. T., Rankin, C., Stelzer, K. J., Spence, A. M., Sloan, A. E., Moore, D. F., Jr., Padula, G. D., Schulman, S. B., Wade, M. L., Rushing, E. J., A Phase III study of radiation therapy (RT) and O6-benzylguanine + BCNU versus RT and BCNU alone and methylation status in newly diagnosed glioblastoma and gliosarcoma: Southwest Oncology Group (SWOG) study S0001, International Journal of Clinical OncologyInt J Clin Oncol, 20, 650-8, 2015	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Boiardi, A., Silvani, A., Milanesi, I., Botturi, M., Broggi, G., Carboplatin combined with carmustine and etoposide in the treatment of glioblastoma, Italian Journal of Neurological SciencesItal J Neurol Sci, 13, 717-22, 1992	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Brandes, A. A., Franceschi, E., Tosoni, A., Benevento, F., Scopece, L., Mazzocchi, V., Bacci, A., Agati, R., Calbucci, F., Ermani, M., Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status, CancerCancer, 115, 3512-8, 2009	Not randomised
Buatti, J., Ryken, T. C., Smith, M. C., Sneed, P., Suh, J. H., Mehta, M., Olson, J. J., Radiation therapy of pathologically confirmed newly diagnosed glioblastoma in adults, Journal of Neuro-OncologyJ Neurooncol, 89, 313-37, 2008	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Buckner, J. C., Ballman, K. V., Michalak, J. C., Burton, G. V., Cascino, T. L., Schomberg, P. J., Hawkins, R. B., Scheithauer, B. W., Sandler, H. M., Marks, R. S., O'Fallon, J. R., North Central Cancer Treatment, Group, Southwest Oncology Group, Trials, Phase III trial of carmustine and cisplatin compared with carmustine alone and standard radiation therapy or accelerated radiation therapy in patients with glioblastoma multiforme: North Central Cancer Treatment Group 93-72-52 and Southwest Oncology Group 9503 Trials, Journal of Clinical OncologyJ Clin Oncol, 24, 3871-9, 2006	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Buckner, J. C., Schomberg, P. J., McGinnis, W. L., Cascino, T. L., Scheithauer, B. W., O'Fallon, J. R., Morton, R. F., Kuross, S. A., Mailliard, J. A., Hatfield, A. K., Cole, J. T., Steen, P. D., Bernath, A. M., A Phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma, CancerCancer, 92, 420-433, 2001	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Buckner, Jc, Ballman, Kv, Michalak, Jc, Burton, Gv, Cascino, Tl, Schomberg, Pj, Hawkins, Rb, Scheithauer, Bw, Sandler, Hm, Marks, Rs, O'Fallon, Jr, Phase III trial of carmustine and cisplatin compared with carmustine alone and standard radiation therapy or accelerated radiation therapy in patients with glioblastoma multiforme:	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
North Central Cancer Treatment Group 93-72-52 and Southwest Oncology Group 9503 Trials, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 24, 3871-9, 2006	
Chen, W., Wu, Q., Mo, L., Nassi, M., Intra-arterial chemotherapy is not superior to intravenous chemotherapy for malignant gliomas: a systematic review and meta-analysis, European NeurologyEur Neurol, 70, 124-32, 2013	Not relevant outcome (efficacy of method of administration)
Chin, H. W., Young, A. B., Maruyama, Y., Survival response of malignant gliomas to radiotherapy with or without BCNU or methyl-CCNU chemotherapy at the University of Kentucky Medical Center, Cancer Treatment ReportsCancer Treat Rep, 65, 45-51, 1981	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Cianfriglia, F., Pompili, A., Riccio, A., Grassi, A., CCNU-chemotherapy of hemispheric supratentorial glioblastoma multiforme, CancerCancer, 45, 1289-99, 1980	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Clarke, J. L., Iwamoto, F. M., Sul, J., Panageas, K., Lassman, A. B., DeAngelis, L. M., Hormigo, A., Nolan, C. P., Gavrilovic, I., Karimi, S., Abrey, L. E., Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma, Journal of Clinical OncologyJ Clin Oncol, 27, 3861-7, 2009	Phase II trial
Cohen, M. H., Johnson, J. R., Pazdur, R., Food and drug administration drug approval summary: Temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme, Clinical Cancer ResearchClin Cancer Res, 11, 6767-6771, 2005	This study is evaluating the efficacy of radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention
Combs, S. E., Nagy, M., Edler, L., Rausch, R., Bischof, M., Welzel, T., Debus, J., Schulz-Ertner, D., Comparative evaluation of radiochemotherapy with temozolomide versus standard-of-care postoperative radiation alone in patients with WHO grade III astrocytic tumors, Radiotherapy and Oncology, 88, 177-182, 2008	Not randomised
Combs, S. E., Wagner, J., Bischof, M., Welzel, T., Edler, L., Rausch, R., Wagner, F., Zabel-du Bois, A., Debus, J., Schulz-Ertner, D., Radiochemotherapy in patients with primary glioblastoma comparing two temozolomide dose regimens.[Erratum appears in Int J Radiat Oncol Biol Phys. 2008 Sep 1;72(1):307], International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 71, 999-1005, 2008	Not randomised

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Duncan, W., McLelland, J., Jack, W. J., Arnott, S. J., Davey, P., Gordon, A., Kerr, G. R., Williams, J. R., The results of a randomised trial of mixed-schedule (neutron/photon) irradiation in the treatment of supratentorial Grade III and Grade IV astrocytoma, British Journal of RadiologyBr J Radiol, 59, 379-83, 1986	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Eyre, Hj, Quagliana, Jm, Eltringham, Jr, Frank, J, O'Bryan, Rm, McDonald, B, Rivkin, Se, Randomized comparisons of radiotherapy and CCNU versus radiotherapy, CCNU plus procarbazine for the treatment of malignant gliomas following surgery. A Southwest Oncology Group Report, Journal of Neuro-OncologyJ Neurooncol, 1, 171-7, 1983	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Fulton, D. S., Urtasun, R. C., Shin, K. H., Geggie, P. H., Thomas, H., Muller, P. J., Moody, J., Tanasichuk, H., Mielke, B., Johnson, E., et al., Misonidazole combined with hyperfractionation in the management of malignant glioma, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 10, 1709-12, 1984	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Gaber, M., Selim, H., El-Nahas, T., Prospective study evaluating the radiosensitizing effect of reduced doses of temozolomide in the treatment of Egyptian patients with glioblastoma multiforme, Cancer management and researchCancer Manag Res, 5, 349-56, 2013	Observational study
Galanis, E., Wu, W., Cloughesy, T., Lamborn, K., Mann, B., Wen, P. Y., Reardon, D. A., Wick, W., Macdonald, D., Armstrong, T. S., Weller, M., Vogelbaum, M., Colman, H., Sargent, D. J., van den Bent, M. J., Gilbert, M., Chang, S., Phase 2 trial design in neuro-oncology revisited: A report from the RANO group, The Lancet Oncology, 13, e196-e204, 2012	Phase II trial
Glaser, S. M., Dohopolski, M. J., Balasubramani, G. K., Flickinger, J. C., Beriwal, S., Glioblastoma multiforme (GBM) in the elderly: initial treatment strategy and overall survival, Journal of neuro-oncology, 134, 107-118, 2017	Abstract
Glioma Meta-Analysis Trialists, Group, Chemotherapy for high-grade glioma, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD003913, 2002	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Grossman, S. A., O'Neill, A., Grunnet, M., Mehta, M., Pearlman, J. L., Wagner, H., Gilbert, M., Newton, H. B., Hellman, R., Eastern Cooperative Oncology, Group, Phase III study comparing three cycles of infusional carmustine and cisplatin followed by radiation therapy with radiation therapy and concurrent carmustine in patients with newly diagnosed supratentorial glioblastoma multiforme: Eastern Cooperative Oncology Group Trial 2394, Journal of Clinical OncologyJ Clin Oncol, 21, 1485-91, 2003	Control and experimental group did not receive standard of care as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Hamilton, D. A., Adding concomitant and adjuvant temozolomide to radiotherapy does not reduce health-related quality of life in people with glioblastoma, Cancer Treatment ReviewsCancer Treat Rev, 32, 483-6, 2006	This study is asessing the quality of life of adults who received radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention.
Hart, M. G., Grant, R., Garside, R., Rogers, G., Somerville, M., Stein, K., Chemotherapeutic wafers for High-grade Glioma, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD007294, 2008	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Herrlinger, U, Schafer, N, Steinbach, Jp, Weyerbrock, A, Hau, P, Goldbrunner, R, Friedrich, F, Rohde, V, Ringel, F, Schlegel, U, Sabel, M, Ronellenfitsch, Mw, Uhl, M, Maciaczyk, J, Grau, S, Schnell, O, Hanel, M, Krex, D, Vajkoczy, P, Gerlach, R, Kortmann, R-D, Mehdorn, M, Tuttenberg, J, Mayer-Steinacker, R, Fietkau, R, Brehmer, S, Mack, F, Stuplich, M, Kebir, S, Kohnen, R, Dunkl, E, Leutgeb, B, Proescholdt, M, Pietsch, T, Urbach, H, Belka, C, Stummer, W, Glas, M, Bevacizumab Plus irinotecan versus temozolomide in newly diagnosed O⁶-methylguanine-DNA methyltransferase nonmethylated glioblastoma: The randomized GLARIUS trial, Journal of Clinical OncologyJ Clin Oncol, 34, 1611-9, 2016	Phase II trial
Huncharek, M., Muscat, J., Geschwind, J. F., Multi-drug versus single agent chemotherapy for high-grade astrocytoma; results of a meta-analysis, Anticancer ResearchAnticancer Res, 18, 4693-7, 1998	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Intergroup Radiation Therapy Oncology Group, Trial, Cairncross, G., Berkey, B., Shaw, E., Jenkins, R., Scheithauer, B., Brachman, D., Buckner, J., Fink, K., Souhami, L., Laperierre, N., Mehta, M., Curran, W., Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402, Journal of Clinical OncologyJ Clin Oncol, 24, 2707-14, 2006	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Jie, X., Hua, L., Jiang, W., Feng, F., Feng, G., Hua, Z., Clinical application of a dendritic cell vaccine raised against heat-shocked glioblastoma, Cell Biochemistry & BiophysicsCell Biochem Biophys, 62, 91-9, 2012	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Julka, P. K., Awasthy, B. S., Rath, G. K., Agarwal, S., Varna, T., Mahapatra, A. K., Singh, R., A study of concurrent radiochemotherapy with paclitaxel in glioblastoma multiforme, Australasian RadiologyAustralas Radiol, 44, 84-87, 2000	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Karacetin, D., Okten, B., Yalcin, B., Incekara, O., Concomitant temozolomide and radiotherapy versus radiotherapy alone for treatment of newly diagnosed glioblastoma multiforme, Journal of B.U.ON., 16, 133-137, 2011	This study is evaluating the efficacy of radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention.
Knerich, R., Adinolfi, D., Giunta, F., Buoncristiani, P., Gaetani, P., Assietti, R., D'Ettorre, F., Butti, G., Schiffer, D., Single versus multiple drug therapy in the combined treatment of malignant gliomas. A multicenter study, Journal of Neurosurgical SciencesJ Neurosurg Sci, 34, 251-5, 1990	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Lou, X., Chen, T., Huang, X., Zheng, J., Zheng, X., Zhang, H., Wu, H., Guo, J., Radiotherapy plus chemotherapy in the treatment of malignant glioma: A systematic review and meta-analysis, International Journal of Clinical and Experimental Medicine, 9, 20519-20530, 2016	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Ludgate, C. M., Douglas, B. G., Dixon, P. F., Steinbok, P., Jackson, S. M., Goodman, G. B., Superfractionated radiotherapy in grade III, IV intracranial gliomas, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 15, 1091-5, 1988	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Mahaley Jr, M. S., Whaley, R. A., Krigman, M. R., Randomized phase III trial of single versus multiple chemotherapeutic treatment following surgery and during radiotherapy for patients with anaplastic gliomas, Surgical NeurologySurg Neurol, 27, 430-432, 1987	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Mastronardi, L., Puzzilli, F., Couldwell, W. T., Farah, J. O., Lunardi, P., Tamoxifen and carboplatin combinational treatment of high-grade gliomas. Results of a clinical trial on newly diagnosed patients, Journal of Neuro-OncologyJ Neurooncol, 38, 59-68, 1998	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
McCarthy, D. J., Komotar, R. J., Starke, R. M., Connolly, E. S., Randomized Trial for Short-Term Radiation Therapy With Temozolomide in Elderly Patients With Glioblastoma, Neurosurgery, 81, N21-N23, 2017	Narrative review
Medical Research Council Brain Tumor Working, Party, Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial, Journal of Clinical OncologyJ Clin Oncol, 19, 509-18, 2001	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Mehta, Mp, Wang, M, Aldape, K, Stupp, R, A, Jaeckle K, Blumenthal, D, Brown, P, Erridge, S, Curran, W, Gilbert, M, RTOG 0525: Exploratory subset analysis from a randomized phase III Trial comparing standard (STD) adjuvant temozolomide (TMZ) with a dose-dense (DD) schedule for glioblastoma (GBM), International Journal of Radiation Oncology Biology Physics, 81, S128-s129, 2011	Abstract
Minniti, G., Filippi, A. R., Osti, M. F., Ricardi, U., Radiation therapy for older patients with brain tumors, Radiation Oncology, 12, 101, 2017	Narrative review
Mizoe, J. E., Tsujii, H., Hasegawa, A., Yanagi, T., Takagi, R., Kamada, T., Tsuji, H., Takakura, K., Organizing committee of the Central Nervous System Tumor Working, Group, Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 69, 390-6, 2007	Phase I/II
Muggeri, A., Vago, M., Perez, S., Rubio, M., Gonzalez, C., Magarinos, C., Rosenberg, M., Costa, F., Perez-Lloret, S., A Randomized, Open-Label, Two-Way Crossover, Single-Dose Bioequivalence Study of Temozolomide 200 mg/m² (Dralitem vs. Temodal Capsules) in Patients with Primary Tumors of the Central Nervous System Under Fasting Conditions, Drugs in R and D, 1-8, 2017	Control group did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention; results were not stratified by histology
Muller, H., Brock, M., Ernst, H., Long-term survival and recurrence-free interval in combined surgical, radio- and chemotherapy of malignant brain gliomas, Clinical Neurology and Neurosurgery, 87, 167-171, 1985	This study is evaluating the efficacy of radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention.
Muni, R., Minniti, G., Lanzetta, G., Caporello, P., Frati, A., Enrici, M. M., Marchetti, P., Enrici, R. M., Short-term radiotherapy followed by adjuvant chemotherapy in poor-prognosis patients with glioblastoma, TumoriTumori, 96, 60-4, 2010	Non-randomised studies
Nowosielski, M., Chinot, O. L., Radbruch, A., Stockhammer, G., Garcia, J., Revil, C., Nishikawa, R., Mason, W. P., Henriksson, R., Saran, F., Bendszus, M., Abrey, L. E., Cloughesy, T. F., Wick, W., Radiologic progression types are treatment specific: An exploratory analysis of a phase 3 study of bevacizumab plus	Conference abstract

Excluded studies - 2. Management of HGG - Randomized controlled trials	
radiotherapy plus temozolomide for patients with newly diagnosed glioblastoma (AVAglio), Journal of Clinical Oncology. Conference, 34, 2016	
Nwokedi, E. C., DiBiase, S. J., Jabbour, S., Herman, J., Amin, P., Chin, L. S., Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme, NeurosurgeryNeurosurgery, 50, 41-46, 2002	Non-randomised
Oehler, C, Toepfer, M, Collon, J, Ries, G, Hyperfractionation combined with BCNU versus conventional fractionation in the radiotherapy of glioblastoma multiforme, Strahlentherapie und OnkologieStrahlenther Onkol, 175, 205, 1999	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Payne, D. G., Simpson, W. J., Keen, C., Platts, M. E., Malignant astrocytoma. Hyperfractionated and standard radiotherapy with chemotherapy in a randomized prospective clinical trial, CancerCancer, 50, 2301-2306, 1982	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Perry, J., Chambers, A., Spithoff, K., Laperriere, N., Gliadel wafers in the treatment of malignant glioma: a systematic review, Current OncologyCurr, 14, 189-94, 2007	This review included the same studies as Ashby 2016
Qi, W. X., Fu, S., Zhang, Q., Guo, X. M., Bevacizumab increases the risk of infections in cancer patients: A systematic review and pooled analysis of 41 randomized controlled trials, Critical Reviews in Oncology/Hematology, 94, 323-336, 2015	Mixed treatment populations and cancer types
Qian, Zz, Wang, Hq, Liu, Xm, Yang, Sy, Fu, Z, Chang, Y, A multicenter randomized controlled study of temozolomide in 97 patients with malignant brain glioma, Chinese Medical JournalChin Med J, 89, 2059-62, 2009	Study in Chinese
Rhee, D. J., Kong, D. S., Kim, W. S., Park, K. B., Lee, J. I., Suh, Y. L., Song, S. Y., Kim, S. T., Lim, D. H., Park, K., Kim, J. H., Nam, D. H., Efficacy of temozolomide as adjuvant chemotherapy after postsurgical radiotherapy alone for glioblastomas, Clinical Neurology and Neurosurgery, 111, 748-751, 2009	Not randomised
Roosen, N., Kiwit, J. C., Lins, E., Schirmer, M., Bock, W. J., Adjuvant intraarterial chemotherapy with nimustine in the management of World Health Organization Grade IV gliomas of the brain. Experience at the Department of Neurosurgery of Dusseldorf University, CancerCancer, 64, 1984-94, 1989	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Sandberg-Wollheim, M., Malmstrom, P., Stromblad, L. G., Anderson, H., Borgstrom, S., Brun, A., Cronqvist, S., Hougaard, K., Salford, L. G., A randomized study of chemotherapy with procarbazine, vincristine, and lomustine with and without radiation therapy for astrocytoma grades 3 and/or 4, CancerCancer, 68, 22-9, 1991	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Sarkaria, J. N., Mehta, M. P., Loeffler, J. S., Buatti, J. M., Chappell, R. J., Levin, A. B., Alexander, E., 3rd, Friedman, W. A., Kinsella, T. J., Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. Radiation Therapy Oncology Group, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 32, 931-41, 1995	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Seiler, R. W., Zimmermann, A., Markwalder, H., Adjuvant chemotherapy with VM 26 and CCNU after operation and radiotherapy of high-grade supratentorial astrocytomas, Surgical NeurologySurg Neurol, 13, 65-8, 1980	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Selker, R. G., Shapiro, W. R., Burger, P., Blackwood, M. S., Arena, V. C., Gilder, J. C., Malkin, M. G., Mealey, J. J., Jr., Neal, J. H., Olson, J., Robertson, J. T., Barnett, G. H., Bloomfield, S., Albright, R., Hochberg, F. H., Hiesiger, E., Green, S., Brain Tumor Cooperative, Group, The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine, NeurosurgeryNeurosurgery, 51, 343-55; discussion 355-7, 2002	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Skardelly, M., Dangel, E., Gohde, J., Noell, S., Behling, F., Lepski, G., Borchers, C., Koch, M., Schittenhelm, J., Bisdas, S., Naumann, A., Paulsen, F., Zips, D., von Hehn, U., Ritz, R., Tatagiba, M. S., Tabatabai, G., Prolonged Temozolomide Maintenance Therapy in Newly Diagnosed Glioblastoma, OncologistOncologist, 22, 570-575, 2017	Observational study
Solero, C. L., Monfardini, S., Brambilla, C., Vaghi, A., Valagussa, P., Morello, G., Bonadonna, G., Controlled study with BCNU vs. CCNU as adjuvant chemotherapy following surgery plus radiotherapy for glioblastoma multiforme, Cancer Clinical TrialsCancer Clin Trials, 2, 43-8, 1979	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Solomo, M. T., Selva, J. C., Figueredo, J., Vaquer, J., Toledo, C., Quintanal, N., Salva, S., Domingez, R., Alert, J., Marinello, J. J., Catala, M., Griego, M. G., Martell, J. A., Luaces, P. L., Ballesteros, J., de-Castro, N., Bach, F., Crombet, T., Radiotherapy plus nimotuzumab or placebo in the treatment of high-grade glioma patients: Results from a randomized, double blind trial, BMC CancerBMC Cancer, 299, 2013	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Souhami, L., Seiferheld, W., Brachman, D., Podgorsak, E. B., Werner-Wasik, M., Lustig, R., Schultz, C. J., Sause, W., Okunieff, P., Buckner, J., Zamorano, L., Mehta, M. P., Curran, W. J., Jr., Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 60, 853-60, 2004	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Stragliotto, G., Rahbar, A., Solberg, N. W., Lilja, A., Taher, C., Orrego, A., Bjurman, B., Tammik, C., Skarman, P., Peredo, I., Soderberg-Naucler, C., Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: a randomized, double-blind, hypothesis-generating study, International Journal of CancerInt J Cancer, 133, 1204-13, 2013	Phase I/II hypothesis-generating study
Stupp, R, Â , Hegi Me, Â , Mason Wp, Â , van den Bent Mj, Â , Taphoorn Mj, Â , Janzer Rc, Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial, Lancet OncologyLancet Oncol, 10, 459-66, 2009	This study is evaluating the efficacy of radiotherapy alone versus temozolomide and radiotherapy (standard of care). It is not eligible because, to meet the criteria of this review question, comparators of interest should have standard of care and an additional intervention.
Taylor, B. V., Buckner, J. C., Cascino, T. L., O'Fallon, J. R., Schaefer, P. L., Dinapoli, R. P., Schomberg, P., Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma, Journal of Clinical OncologyJ Clin Oncol, 16, 2195-201, 1998	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Trojanowski, T., Peszynski, J., Turowski, K., Markiewicz, P., Goscinski, I., Bielawski, A., Bendarzewska, B., Szymona, J., Dabrowska, A., Lopatkiewicz, J., et al., Quality of survival of patients with brain gliomas treated with postoperative CCNU and radiation therapy, Journal of NeurosurgeryJ Neurosurg, 70, 18-23, 1989	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Valtonen, S., Timonen, U., Toivanen, P., Kalimo, H., Kivipelto, L., Heiskanen, O., Unsgaard, G., Kuurne, T., Interstitial chemotherapy with carmustine-loaded polymers for high- grade gliomas: A randomized double-blind study, NeurosurgeryNeurosurgery, 41, 44-49, 1997	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Walker, M. D., Strike, T. A., Sheline, G. E., An analysis of dose-effect relationship in the radiotherapy of malignant gliomas, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 5, 1725-31, 1979	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Wang, W., Shi, G., Ma, B., Hao, X., Dong, X., Zhang, B., Chemotherapy for Adults with Malignant Glioma: A Systematic Review and Network Meta-Analysis, Turkish NeurosurgeryTurk, 27, 174-181, 2017	Studies included in this systematic review and meta-analysis have been included in this review question or do not meet the inclusion criteria
Weller, M., Muller, B., Koch, R., Bamberg, M., Krauseneck, P., Neuro-Oncology Working Group of the German Cancer, Society, Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma, Journal of Clinical OncologyJ Clin Oncol, 21, 3276-84, 2003	
Wenger, K. J., Wagner, M., You, S. J., Franz, K., Harter, P. N., Burger, M. C., Voss, M., Ronellenfitsch, M. W., Fokas, E., Steinbach, J. P., Bahr, O., Bevacizumab as a last-line treatment for glioblastoma following failure of radiotherapy, temozolomide and lomustine, Oncology LettersOncol, 14, 1141-1146, 2017	Not a randomised trial
Westphal, M., Ram, Z., Riddle, V., Hilt, D., Bortey, E., Executive committee of the Gliadel Study, Group, Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial, Acta NeurochirurgicaActa Neurochir (Wien), 148, 269-75; discussion 275, 2006	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention
Wick, Wolfgang, Alba Ariela Brandes, Thierry Gorlia, Martin Bendszus, Felix Sahm, Walter Taal, Martin J.B. Taphoorn, Julien Domont, Ahmed Idbaih, Mario Campone, Paul M. Clement, Roger Stupp, Michel Fabbro, Emilie Le Rhun, François Dubois, Martin Klein, Michael Platten, Michael Weller, Vassilis Golfinopoulos, Martin J. Van Den Bent, EORTC 26101 phase III trial exploring the combination of bevacizumab and lomustine in patients with first progression of a glioblastoma, Journal of Clinical Oncology, 34, 2001-2001, 2016	Abstract
Wygoda, Z., Kula, D., Bierzynska-Macyszyn, G., Larysz, D., Jarzab, M., Wlaszczuk, P., Bazowski, P., Wojtacha, M., Rudnik, A., Stepien, T., Kaspera, W., Etmanska, A., Skladowski, K., Tarnawski, R., Kokocinska, D., Jarzab, B., Use of monoclonal anti-EGFR antibody in the radioimmunotherapy of malignant gliomas in the context of EGFR expression in grade III and IV tumors, HybridomaHybridoma (Larchmt), 25, 125-132, 2006	Teleradiotherapy as comparator not in protocol
Xu, W., Li, T., Gao, L., Zheng, J., Shao, A., Zhang, J., Efficacy and safety of long-term therapy for high-grade glioma with temozolomide: a meta-analysis, Oncotarget, 24, 24, 2017	Studies included in this meta-analysis do not meet the PICO inclusion criteria
Yang, P., Zhang, C., Cai, J., You, G., Wang, Y., Qiu, X., Li, S., Wu, C., Yao, K., Li, W., Peng, X., Zhang, W., Jiang, T., Radiation combined with temozolomide contraindicated for young adults diagnosed with anaplastic glioma, Oncotarget, 7, 80091-80100, 2016	Observational study
Yin, A. A., Zhang, L. H., Cheng, J. X., Dong, Y., Liu, B. L., Han, N., Zhang, X., The predictive but not prognostic value of MGMT promoter methylation status in elderly glioblastoma patients: a meta-analysis, PLoS ONE [Electronic Resource]PLoS ONE, 9, e85102, 2014	This review included non-randomised studies
Zhang, Y. D., Dai, R. Y., Chen, Z., Zhang, Y. H., He, X. Z., Zhou, J., Efficacy and safety of carmustine wafers in the treatment of glioblastoma multiforme: a systematic review, Turkish NeurosurgeryTurk, 24, 639-45, 2014	Control and experimental groups did not receive temozolomide and radiotherapy (standard of care) as a baseline intervention

Excluded studies - 2. Management of HGG - Randomized controlled trials	
Zheng, M. H., Sun, H. T., Xu, J. G., Zhang, Y. H., Yang, G., Huo, L. M., Tian, J. H., Yang, K. H., A network meta-analysis of treatment for newly diagnosed glioblastoma based on radiotherapy plus temozolomide, Neurology Asia, 22, 49-58, 2017	This NMA included phase II studies
Zhu, P., Zhu, J. J., Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives, Chinese Clinical OncologyChin, 6, 41, 2017	Studies included in this systematic review have already been included in this review question

Economic studies

See Supplementary Material D.

Excluded studies for review 2d – management of recurrent high-grade glioma

Clinical studies

Study	Reason for exclusion
Abdel-Rahman, O., Fouad, M., Irinotecan-based regimens for recurrent glioblastoma multiforme: [corrected] a systematic review.[Erratum appears in Expert Rev Neurother. 2016;16(1):103; PMID: 26666507], Expert Review of NeurotherapeuticsExpert rev, 15, 1255-70, 2015	Most of the included studies in this systematic review were non-randomised phase II trials and observational studies; one phase II randomised trial was included (Friedman 2009), which is part of the included studies of this review
Bleehen, N. M., Freedman, L. S., Stenning, S. P., A randomized study of CCNU with and without benznidazole in the treatment of recurrent grades 3 and 4 astrocytoma. Report to the Medical Research Council by the Brain Tumor Working Party, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 16, 1077-81, 1989	Benznidazole is not part of the interventions of interest
Boiardi, A., Silvani, A., Milanesi, I., Broggi, G., Fariselli, L., Efficacy of '8-drugs-in-one-day' combination in treatment of recurrent GBM patients, Journal of Neuro-OncologyJ Neurooncol, 12, 153-8, 1992	Not an RCT

Study	Reason for exclusion
Bower, M., Newlands, E. S., Bleehen, N. M., Brada, M., Begent, R. J., Calvert, H., Colquhoun, I., Lewis, P., Brampton, M. H., Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma, Cancer Chemotherapy & PharmacologyCancer Chemother Pharmacol, 40, 484-8, 1997	Non-randomised phase II study from 1997
Brada, M, Â Stenning, S, Â Gabe, R, Thompson, Lc, Â Levy, D, Â , Rampling R, Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma, Journal of Clinical OncologyJ Clin Oncol, 28, 4601-10, 2010	Interventions with temozolomide were excluded as NICE Technology Appraisal 23 has already covered this intervention
Brada, M., Hoang-Xuan, K., Rampling, R., Dietrich, P. Y., Dirix, L. Y., Macdonald, D., Heimans, J. J., Zonnenberg, B. A., Bravo-Marques, J. M., Henriksson, R., Stupp, R., Yue, N., Bruner, J., Dugan, M., Rao, S., Zaknoen, S., Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse, Annals of OncologyAnn Oncol, 12, 259-66, 2001	Single-arm study
Brandes, A. A., Tosoni, A., Amista, P., Nicolardi, L., Grosso, D., Berti, F., Ermani, M., How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial, NeurologyNeurology, 63, 1281-4, 2004	Single-arm trial
Brandes, A. A., Tosoni, A., Cavallo, G., Bertorelle, R., Gioia, V., Franceschi, E., Biscuola, M., Blatt, V., Crino, L., Ermani, M., Gicno, Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: phase II study from gruppo italiano cooperativo di neuro-oncologia (GICNO), British Journal of CancerBr J Cancer, 95, 1155-60, 2006	Single arm trial
Brandes, A. A., Tosoni, A., Cavallo, G., Reni, M., Franceschi, E., Bonaldi, L., Bertorelle, R., Gardiman, M., Ghimenton, C., Iuzzolino, P., Pession, A., Blatt, V., Ermani, M., Gicno, Correlations between O6-methylguanine DNA methyltransferase promoter methylation status, 1p and 19q deletions, and response to temozolomide in anaplastic and recurrent oligodendroglioma: a prospective GICNO study, Journal of Clinical OncologyJ Clin Oncol, 24, 4746-53, 2006	Retrospective case series
Butowski, N. A., Sneed, P. K., Chang, S. M., Diagnosis and treatment of recurrent high-grade astrocytoma, Journal of Clinical OncologyJ Clin Oncol, 24, 1273-1280, 2006	The studies included in this systematicreview consisted of non-randomised phase II studies or observational studies
Cabrera, A. R., Cuneo, K. C., Desjardins, A., Sampson, J. H., McSherry, F., Herndon, J. E., 2nd, Peters, K. B., Allen, K., Hoang, J. K., Chang, Z., Craciunescu, O., Vredenburgh, J. J., Friedman, H. S., Kirkpatrick, J. P., Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: a prospective trial, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 86, 873-9, 2013	Retrospective case series
Chen, C., Xu, T., Lu, Y., Chen, J., Wu, S., The efficacy of temozolomide for recurrent glioblastoma multiforme, European Journal of NeurologyEur J Neurol, 20, 223-30, 2013	Most of the included studies in this systematic review are single- arm phase II

Study	Reason for exclusion
	studies. Yung 2000 was included in the systematic review, however is not eligible for inclusion in this review question since interventions with temozolomide were excluded as have already been covered in the NICE Technology Appraisal 23
Clark, G. M., McDonald, A. M., Nabors, L. B., Fathalla-Shaykh, H., Han, X., Willey, C. D., Markert, J. M., Guthrie, B. L., Bredel, M., Fiveash, J. B., Hypofractionated stereotactic radiosurgery with concurrent bevacizumab for recurrent malignant gliomas: the University of Alabama at Birmingham experience, Neurooncol PractNeurooncol Pract, 1, 172-177, 2014	Observational study for glioblastoma
Dinnes, J., Cave, C., Huang, S., Milne, R., A rapid and systematic review of the effectiveness of temozolomide for the treatment of recurrent malignant glioma, British Journal of CancerBr J Cancer, 86, 501-505, 2002	None of the five included studies in this systematic review are eligible for inclusion. For 2 studies (Brada 2000 and Yung 2000), this is because interventions with temozolomide were excluded as NICE Technology Appraisal 23 has already covered this intervention. For 2 studies (Bower 1997 and Yung 1999), this is because they are phase II studies conducted before the year 2000. One of them (Newldand 1996) was not randomised.
Du Four, S., Maenhout, S. K., Benteyn, D., De Keersmaecker, B., Duerinck, J., Thielemans, K., Neyns, B., Aerts, J. L., Disease progression in recurrent glioblastoma patients treated with the VEGFR inhibitor axitinib is associated with increased regulatory T cell numbers and T cell exhaustion, Cancer Immunology, ImmunotherapyCancer Immunol Immunother, 65, 727-40, 2016	Phase II study
Elaimy, A. L., Mackay, A. R., Lamoreaux, W. T., Demakas, J. J., Fairbanks, R. K., Cooke, B. S., Lamm, A. F., Lee, C. M., Clinical outcomes of gamma knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma, World NeurosurgeryWorld Neurosurg, 80, 872-8, 2013	In this systematic review, only observational studies have been included
Figueiredo, E. G., Faria, J. W., Teixeira, M. J., Treatment of recurrent glioblastoma with intra-arterial BCNU [1, 3-bis (2-chloroethyl)-1-nitrosourea], Arquivos de Neuro-PsiquiatriaArq Neuropsiquiatr, 68, 778-82, 2010	Not an RCT

Study	Reason for exclusion
Gaya, A., Rees, J., Greenstein, A., Stebbing, J., The use of temozolomide in recurrent malignant gliomas, Cancer Treatment ReviewsCancer Treat Rev, 28, 115-120, 2002	In this systematic review, no relevant phase II studies have been included; one phase III study was included (Brada 2001), which is included in the guideline review
Gilbert, M. R., Kuhn, J., Lamborn, K. R., Lieberman, F., Wen, P. Y., Mehta, M., Cloughesy, T., Lassman, A. B., Deangelis, L. M., Chang, S., Prados, M., Cilengitide in patients with recurrent glioblastoma: the results of NABTC 03-02, a phase II trial with measures of treatment delivery, Journal of Neuro-OncologyJ Neurooncol, 106, 147-53, 2012	Non-comparative study
Glass, J., Silverman, C. L., Axelrod, R., Corn, B. W., Andrews, D. W., Fractionated stereotactic radiotherapy with cis-platinum radiosensitization in the treatment of recurrent, progressive, or persistent malignant astrocytoma, American Journal of Clinical OncologyAm J Clin Oncol, 20, 226-9, 1997	Non-comparative study
Gruber, M. L., Buster, W. P., Temozolomide in combination with irinotecan for treatment of recurrent malignant glioma, American Journal of Clinical OncologyAm J Clin Oncol, 27, 33-8, 2004	In this systematic review, only phase II studies have been included
Han, S. J., Rolston, J. D., Molinaro, A. M., Clarke, J. L., Prados, M. D., Chang, S. M., Berger, M. S., DeSilva, A., Butowski, N. A., Phase II trial of 7 days on/7 days off temozolmide for recurrent high-grade glioma, Neuro-OncologyNeuro-oncol, 16, 1255-62, 2014	Prospective single-arm study
Huncharek, M., Kupelnick, B., Bishop, D., Platinum analogues in the treatment of recurrent high-grade astrocytoma, Cancer Treatment ReviewsCancer Treat Rev, 24, 307-316, 1998	Not an RCT
Huncharek, M., Muscat, J., Treatment of recurrent high-grade astrocytoma; results of a systematic review of 1,415 patients, Anticancer ResearchAnticancer Res, 18, 1303-11, 1998	The studies included in this systematic review were either phase II non-randomised trials or observational studies
Kaprealian, T. B., Tran, A., Yu, V. Y., Rwigema, J. C., Nguyen, D., Woods, K., Cao, M., Low, D., Steinberg, M. L., Kupelian, P. A., Sheng, K., First Prospective Trial in Linear Accelerator-Based 4pi Radiation Therapy: Initial Results in Patients With Recurrent Glioblastoma, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 96, E89-E90, 2016	Abstract
Kong, D. S., Lee, J. I., Kim, J. H., Kim, S. T., Kim, W. S., Suh, Y. L., Dong, S. M., Nam, D. H., Phase II trial of low-dose continuous (metronomic) treatment of temozolomide for recurrent glioblastoma, Neuro-OncologyNeuro-oncol, 12, 289-96, 2010	Low N

Study	Reason for exclusion
Kreisl, T. N., Kim, L., Moore, K., Duic, P., Royce, C., Stroud, I., Garren, N., Mackey, M., Butman, J. A., Camphausen, K., Park, J., Albert, P. S., Fine, H. A., Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma, Journal of Clinical OncologyJ Clin Oncol, 27, 740-5, 2009	Single-arm study
Kreisl, T. N., Zhang, W., Odia, Y., Shih, J. H., Butman, J. A., Hammoud, D., Iwamoto, F. M., Sul, J., Fine, H. A., A phase II trial of single-agent bevacizumab in patients with recurrent anaplastic glioma, Neuro-OncologyNeuro-oncol, 13, 1143-50, 2011	Not an RCT
Kunwar, S., Chang, S., Westphal, M., Vogelbaum, M., Sampson, J., Barnett, G., Shaffrey, M., Ram, Z., Piepmeier, J., Prados, M., Croteau, D., Pedain, C., Leland, P., Husain, S. R., Joshi, B. H., Puri, R. K., Precise Study Group, Phase III randomized trial of CED of IL13-PE38QQR versus Gliadel wafers for recurrent glioblastoma, Neuro-OncologyNeuro-oncol, 12, 871-81, 2010	Convection-enhanced delivery (CED) of cintredekin besudotox (CB)is not an intervention of interest
Nieder, C., Andratschke, N. H., Grosu, A. L., Re-irradiation for Recurrent Primary Brain Tumors, Anticancer ResearchAnticancer Res, 36, 4985-4995, 2016	Not an RCT
Olivi, A, Grossman, Sa, Tatter, S, Barker, F, Judy, K, Olsen, J, Bruce, J, Hilt, D, Fisher, J, Piantadosi, S, Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: a New Approaches to Brain Tumor Therapy CNS Consortium trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 21, 1845-9, 2003	Retrospective case series
Omuro, A., Chan, T. A., Abrey, L. E., Khasraw, M., Reiner, A. S., Kaley, T. J., Deangelis, L. M., Lassman, A. B., Nolan, C. P., Gavrilovic, I. T., Hormigo, A., Salvant, C., Heguy, A., Kaufman, A., Huse, J. T., Panageas, K. S., Hottinger, A. F., Mellinghoff, I., Phase II trial of continuous low-dose temozolomide for patients with recurrent malignant glioma, Neuro-OncologyNeuro-oncol, 15, 242-50, 2013	Non-comparative study
Osman, M. A., Phase II trial of temozolomide and reirradiation using conformal 3D-radiotherapy in recurrent brain gliomas, Annals of Translational MedicineAnn, 2, 44, 2014	Non-randomised, low N
Osoba, D., Brada, M., Yung, W. K. A., Prados, M., Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme, Journal of Clinical OncologyJ Clin Oncol, 18, 1481-1491, 2000	Interventions with temozolomide were excluded as NICE Technology Appraisal 23 has already covered this intervention
Paccapelo, A., Lolli, I., Scoccianti, S., Detti, B., Silvano, G., Fabrini, M. G., Perrone, F., Savio, G., Cascinu, S., Efficacy of nitrosourea-based chemotherapy in recurrent malignant glioma according to time to adjuvant temozolomide failure: A pooled analysis, Journal of Clinical Oncology. Conference: ASCO Annual Meeting, 29, 2011	Conference abstract

Study	Reason for exclusion
Perry, J. R., Belanger, K., Mason, W. P., Fulton, D., Kavan, P., Easaw, J., Shields, C., Kirby, S., Macdonald, D. R., Eisenstat, D. D., Thiessen, B., Forsyth, P., Pouliot, J. F., Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study.[Erratum appears in J Clin Oncol. 2010 Jul 20;28(21):3543], Journal of Clinical OncologyJ Clin Oncol, 28, 2051-7, 2010	Non-randomised study
Prados, M. D., Lamborn, K., Yung, W. K., Jaeckle, K., Robins, H. I., Mehta, M., Fine, H. A., Wen, P. Y., Cloughesy, T., Chang, S., Nicholas, M. K., Schiff, D., Greenberg, H., Junck, L., Fink, K., Hess, K., Kuhn, J., North American Brain Tumor, Consortium, A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study, Neuro-OncologyNeuro-oncol, 8, 189-93, 2006	Non-randomised study
Raizer, J. J., Grimm, S., Chamberlain, M. C., Nicholas, M. K., Chandler, J. P., Muro, K., Dubner, S., Rademaker, A. W., Renfrow, J., Bredel, M., A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas, CancerCancer, 116, 5297-305, 2010	Non-randomised study
Reardon, D. A., Desjardins, A., Peters, K., Gururangan, S., Sampson, J., Rich, J. N., McLendon, R., Herndon, J. E., 2nd, Marcello, J., Threatt, S., Friedman, A. H., Vredenburgh, J. J., Friedman, H. S., Phase II study of metronomic chemotherapy with bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy, Journal of Neuro-OncologyJ Neurooncol, 103, 371-9, 2011	Non-randomised
Reardon, D. A., Herndon, J. E., 2nd, Peters, K., Desjardins, A., Coan, A., Lou, E., Sumrall, A., Turner, S., Sathornsumetee, S., Rich, J. N., Boulton, S., Lipp, E. S., Friedman, H. S., Vredenburgh, J. J., Outcome after bevacizumab clinical trial therapy among recurrent grade III malignant glioma patients, Journal of Neuro-OncologyJ Neurooncol, 107, 213-21, 2012	In this systematic review, only phase II single arm trials have been included
Reardon, Da, Herndon, Ii Je, Peters, K, Desjardins, A, Coan, A, Lou, E, Sumrall, A, Turner, S, Sathornsumetee, S, Rich, Jn, Boulton, S, Lipp, Es, Friedman, Hs, Vredenburgh, Jj, Outcome after bevacizumab clinical trial therapy among recurrent grade III malignant glioma patients, Journal of Neuro-OncologyJ Neurooncol, 107, 213-21, 2012	No relevant treatments, phase II studies have been included
Reynes, G., Martinez-Sales, V., Vila, V., Balana, C., Perez-Segura, P., Vaz, M. A., Benavides, M., Gallego, O., Palomero, I., Gil-Gil, M., Fleitas, T., Reche, E., Phase II trial of irinotecan and metronomic temozolomide in patients with recurrent glioblastoma, Anti-Cancer DrugsAnticancer Drugs, 27, 133-7, 2016	Non-randomised
Santisteban, M., Buckner, J. C., Reid, J. M., Wu, W., Scheithauer, B. W., Ames, M. M., Felten, S. J., Nikcevich, D. A., Wiesenfeld, M., Jaeckle, K. A., Galanis, E., North Central Cancer Treatment, Group, Phase II trial of two	Non-randomised

Study	Reason for exclusion
different irinotecan schedules with pharmacokinetic analysis in patients with recurrent glioma: North Central Cancer Treatment Group results, Journal of Neuro-OncologyJ Neurooncol, 92, 165-75, 2009	
Stockelmaier, L, Renovanz, M, Konig, J, Nickel, K, Hickmann, A-K, Mayer-Steinacker, R, Nadji-Ohl, M, Ganslandt, O, Bullinger, L, Wirtz, Cr, Coburger, J, Therapy for Recurrent High-Grade Gliomas: results of a Prospective Multicenter Study on Health-Related Quality of Life, World neurosurgery, 102, 383-399, 2017	Not a randomised study
Stragliotto, G., Rahbar, A., Soderberg-Naucler, C., Update of valganciclovir add-on therapy in glioblastoma. Effect in new ly diagnosed and in recurrent patients, Neuro-Oncology, 18, iv59, 2016	Abstract study
Trippoli, S., Pelagotti, F., Messori, A., Vacca, F., Vaiani, M., Maltoni, S., Survival of patients with recurrent malignant glioma treated with temozolomide: a retrospective observational study, Drugs in R & DDrugs R D, 4, 285-91, 2003	Retrospective cohort study
van den Bent, M. J., Chinot, O., Boogerd, W., Bravo Marques, J., Taphoorn, M. J., Kros, J. M., van der Rijt, C. C., Vecht, C. J., De Beule, N., Baron, B., Second-line chemotherapy with temozolomide in recurrent oligodendroglioma after PCV (procarbazine, lomustine and vincristine) chemotherapy: EORTC Brain Tumor Group phase II study 26972, Annals of OncologyAnn Oncol, 14, 599-602, 2003	Non-randomised study, small number of participants
van den Bent, M. J., Taphoorn, M. J., Brandes, A. A., Menten, J., Stupp, R., Frenay, M., Chinot, O., Kros, J. M., van der Rijt, C. C., Vecht Ch, J., Allgeier, A., Gorlia, T., European Organization for, Research, Treatment of Cancer Brain Tumor, Group, Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971, Journal of Clinical OncologyJ Clin Oncol, 21, 2525-8, 2003	Non-randomised study
Vredenburgh, J. J., Desjardins, A., Herndon, J. E., 2nd, Dowell, J. M., Reardon, D. A., Quinn, J. A., Rich, J. N., Sathornsumetee, S., Gururangan, S., Wagner, M., Bigner, D. D., Friedman, A. H., Friedman, H. S., Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma, Clinical Cancer ResearchClin Cancer Res, 13, 1253-9, 2007	Non-randomised
Van Den Bent, M. J., Klein, M., Smits, M., Reijneveld, J. C., Idbaih, A., Clement, P., De Vos, F. Y. F. L., Wick, W., Mulholland, Paul James, Taphoorn, Martin J.B., Lewis, Joanne, de Heer, I., Kros, J., Verschuere, Tina, Golfinopoulos, V., Gorlia, T., French, Pim, EORTC Brain Tumor Group, Final results of the EORTC Brain Tumor Group randomized phase II TAVAREC trial on temozolomide with or without bevacizumab in 1st recurrence grade II/III glioma without 1p/19q co-deletion, Journal of Clinical Oncology, 35, 2009-2009, 2017	Abstract
Wick, W., Puduvalli, V. K., Chamberlain, M. C., Van Den Bent, M. J., Carpentier, A. F., Cher, L. M., Mason, W., Weller, M., Hong, S., Musib, L., Liepa, A. M., Thornton, D. E., Fine, H. A., Phase III study of enzastaurin	Enzastaurin is not an intervention of interest

Study	Reason for exclusion
compared with lomustine in the treatment of recurrent intracranial glioblastoma, Journal of Clinical OncologyJ Clin Oncol, 28, 1168-1174, 2010	
Wong, E. T., Gautam, S., Malchow, C., Lun, M., Pan, E., Brem, S., Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis, Journal of the National Comprehensive Cancer NetworkJ, 9, 403-7, 2011	In this systematic review, only observational studies were included
Xu, T., Chen, J., Lu, Y., Wolff, J. E., Effects of bevacizumab plus irinotecan on response and survival in patients with recurrent malignant glioma: a systematic review and survival-gain analysis, BMC CancerBMC Cancer, 10, 252, 2010	Systematic review and survival gain analysis of retrospective studies
Yung, W. K. A., Albright, R. E., Olson, J., Fredericks, R., Fink, K., Prados, M. D., Brada, M., Spence, A., Hohl, R. J., Shapiro, W., Glantz, M., Greenberg, H., Selker, R. G., Vick, N. A., Rampling, R., Friedman, H., Phillips, P., Bruner, J., Yue, N., Osoba, D., Zaknoen, S., Levin, V. A., A phase II study of temozolemide vs. procarbazine in patients with glioblastoma multiforme at first relapse, British Journal of CancerBr J Cancer, 83, 588-593, 2000	Interventions with temozolomide were excluded as NICE Technology Appraisal 23 has already covered this intervention
Yung, W. K., Prados, M. D., Yaya-Tur, R., Rosenfeld, S. S., Brada, M., Friedman, H. S., Albright, R., Olson, J., Chang, S. M., O'Neill, A. M., Friedman, A. H., Bruner, J., Yue, N., Dugan, M., Zaknoen, S., Levin, V. A., Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group.[Erratum appears in J Clin Oncol 1999 Nov;17(11):3693], Journal of Clinical OncologyJ Clin Oncol, 17, 2762-71, 1999	Phase II trial published in 1999

Economic studies

Not applicable – no economic evidence was identified.

Excluded studies for review 2b – resection of glioma

Clinical studies

Glioma surgery - systematic reviews and RCts	
Study	**Reason for Exclusion**
Aghi, M. K., Nahed, B. V., Sloan, A. E., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of surgery in the management of patients with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-OncologyJ Neurooncol, 125, 503-30, 2015	In this systematic review, the studies looking at methods available to increase the extent of resection were retrospective
Bal, J., Camp, S. J., Nandi, D., The use of ultrasound in intracranial tumor surgery, Acta NeurochirurgicaActa Neurochir (Wien), 158, 1179-85, 2016	In this literature review, the studies looking at methods available to increase the extent of resection were retrospective
Banerjee, C., Snelling, B., Berger, M. H., Shah, A., Ivan, M. E., Komotar, R. J., The role of magnetic resonance-guided laser ablation in neurooncology, British Journal of NeurosurgeryBr J Neurosurg, 29, 192-196, 2015	In this systematic review, only non-randomised studies have been included
Barbosa, B. J. A. P., Mariano, E. D., Batista, C. M., Marie, S. K. N., Teixeira, M. J., Pereira, C. U., Tatagiba, M. S., Lepski, G. A., Intraoperative assistive technologies and extent of resection in glioma surgery: a systematic review of prospective controlled studies, Neurosurgical Review, 38, 217-227, 2015	This systematic review included non-randomised studies; the RCTs included have been considered for inclusion in the guideline review
Barone, Damiano Giuseppe, Lawrie, Theresa A, Hart, Michael G, Image guided surgery for the resection of brain tumours, Cochrane Database of Systematic Reviews, 2014	Included some of the trials identified for this systematic review (Stummer 2006, Wu 2007, Willems 2006), but did not account for all the relevant outcomes in the guideline review protocol
Bergsneider, M., Sehati, N., Villablanca, P., McArthur, D. L., Becker, D. P., Liau, L. M., Mahaley Clinical Research Award: extent of glioma resection using low-field (0.2 T) versus high-field (1.5 T) intraoperative MRI and image-guided frameless neuronavigation, Clinical NeurosurgeryClin Neurosurg, 52, 389-399, 2005	Participants were not randomised; observational study
Brown, T., Shah, A. H., Bregy, A., Shah, N. H., Thambuswamy, M., Barbarite, E., Fuhrman, T., Komotar, R. J., Awake craniotomy for brain tumor resection: The rule rather than the exception?, Journal of Neurosurgical Anesthesiology, 25, 240-247, 2013	Only one of the studies included in this systematic review (Gupta 2007) is a RCT, and it has been considered for inclusion in this review
Colditz, M. J., Jeffree, R. L., Aminolevulinic acid (ALA)-protoporphyrin IX fluorescence guided tumour resection. Part 1: Clinical, radiological and pathological studies, Journal of Clinical NeuroscienceJ Clin Neurosci, 19, 1471-4, 2012	Literature review of the studies published to date related to 5ALA

Glioma surgery - systematic reviews and RCts	
De Witt Hamer, P. C., Robles, S. G., Zwinderman, A. H., Duffau, H., Berger, M. S., Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis, Neuro-Oncology, 13, iii154, 2011	Low N (< 20 participants per arm)
Eljamel, M. S., Goodman, C., Moseley, H., ALA and Photofrin Fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: A single centre Phase III randomised controlled trial, Lasers in Medical ScienceLasers Med Sci, 23, 361-367, 2008	Low number of participants; N=13 in the research arm and N=14 in the control group
Eljamel, M. S., Mahboob, S. O., The effectiveness and cost-effectiveness of intraoperative imaging in high-grade glioma resection; a comparative review of intraoperative ALA, fluorescein, ultrasound and MRI, Photodiagnosis & Photodynamic TherapyPhotodiagnosis Photodyn Ther, 1, 1, 2016	In this systematic review and meta-analysis, non-randomised studies have been included; te RCTs included have been considered for inclusion in this review
Eljamel, Ms, Goodman, C, Moseley, H, ALA and Photofrin fluorescence-guided resection and repetitive PDT in glioblastoma multiforme: a single centre Phase III randomised controlled trial, Lasers in Medical ScienceLasers Med Sci, 23, 361-7, 2008	Small number of participants (13 in the research group and 14 in the control group)
Eljamel, S., 5-ALA Fluorescence Image Guided Resection of Glioblastoma Multiforme: A Meta-Analysis of the Literature, International Journal of Molecular SciencesInt, 16, 10443-56, 2015	This meta-analyses included non-randomised studies and studies with small numbers of participants
Eljamel, S., Petersen, M., Valentine, R., Buist, R., Goodman, C., Moseley, H., Eljamel, S., Comparison of intraoperative fluorescence and MRI image guided neuronavigation in malignant brain tumours, a prospective controlled study, Photodiagnosis & Photodynamic TherapyPhotodiagnosis Photodyn Ther, 10, 356-61, 2013	Non-randomised study
Ferraro, N., Barbarite, E., Albert, T. R., Berchmans, E., Shah, A. H., Bregy, A., Ivan, M. E., Brown, T., Komotar, R. J., The role of 5-aminolevulinic acid in brain tumor surgery: a systematic review, Neurosurgical ReviewNeurosurg Rev, 39, 545-55, 2016	This systematic review included retrospective, phase II trials or studies looking at tumours excluded from this review, such as metastatic tumours or recurrent tumours
Guyotat, J., Pallud, J., Armoiry, X., Pavlov, V., Metellus, P., 5-Aminolevulinic Acid-Protoporphyrin IX Fluorescence-Guided Surgery of High-Grade Gliomas: A Systematic Review, Advances & Technical Standards in NeurosurgeryAdv Tech Stand Neurosurg, 61-90, 2016	This systematic review included RCTs as well as observational studies; the RCTs have already been included in this review
Hirschberg, H., Samset, E., Hol, P. K., Tillung, T., Lote, K., Impact of intraoperative MRI on the surgical results for high-grade gliomas, Minimally Invasive NeurosurgeryMinim Invasive Neurosurg, 48, 77-84, 2005	Non-randomised study
Keil, Vc, Pintea, B, Gielen, Gh, Greschus, S, Fimmers, R, Gieseke, J, Simon, M, Schild, Hh, Hadizadeh, Dr, Biopsy targeting with dynamic contrast-enhanced versus standard neuronavigation MRI in glioma: a prospective double-blinded evaluation of selection benefits, Journal of neuro-oncology, 1-9, 2017	Not a randomised trial
Kubben, P. L., Scholtes, F., Schijns, O. E., Ter Laak-Poort, M. P., Teernstra, O. P., Kessels, A. G., van Overbeeke, J. J., Martin, D. H., van Santbrink, H., Intraoperative magnetic resonance imaging versus	Low N (< 20 participants per arm)

Glioma surgery - systematic reviews and RCts	
standard neuronavigation for the neurosurgical treatment of glioblastoma: A randomized controlled trial, Surgical neurology internationalSurg Neurol Int, 5, 70, 2014	
Li, P., Qian, R., Niu, C., Fu, X., Impact of intraoperative MRI-guided resection on resection and survival in patient with gliomas: a meta-analysis, Current Medical Research & OpinionCurr Med Res Opin, 1-10, 2017	This meta-analysis included non-randomised studies
Ng, W. P., Liew, B. S., Idris, Z., Rosman, A. K., Fluorescence-guided versus conventional surgical resection of high-grade glioma: A single-centre, 7-year, comparative effectiveness study, Malaysian Journal of Medical Sciences, 24, 78-86, 2017	Not a randomised trial
Roder, C., Bisdas, S., Ebner, F. H., Honegger, J., Naegele, T., Ernemann, U., Tatagiba, M., Maximizing the extent of resection and survival benefit of patients in glioblastoma surgery: high-field iMRI versus conventional and 5-ALA-assisted surgery, European Journal of Surgical OncologyEur J Surg Oncol, 40, 297-304, 2014	Non-randomised study
Senft, C., Bink, A., Heckelmann, M., Gasser, T., Seifert, V., Glioma extent of resection and ultra-low-field iMRI: interim analysis of a prospective randomized trial, Acta Neurochirurgica - SupplementActa Neurochir Suppl, 109, 49-53, 2011	Low N (< 20 participants per arm)
Stummer, W., Stepp, H., Wiestler, O. D., Pichlmeier, U., Randomized, Prospective Double-Blinded Study Comparing 3 Different Doses of 5-Aminolevulinic Acid for Fluorescence-Guided Resections of Malignant Gliomas, NeurosurgeryNeurosurgery, 01, 01, 2017	No outcomes of interest: the patients received different doses of 5ALA and the main outcomes were macroscopic fluorescence and subjective fluorescence impression.
Su, X., Huang, Q. F., Chen, H. L., Chen, J., Fluorescence-guided resection of high-grade gliomas: a systematic review and meta-analysis, Photodiagnosis & Photodynamic TherapyPhotodiagnosis Photodyn Ther, 11, 451-8, 2014	This systematic review included non-randomised studies; the included RCTs have been considered for inclusion in this review

Economic studies

See Supplementary Material D.

Excluded studies for review 5a – follow-up for glioma

Clinical studies

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Study	**Reason for Exclusion**
Albert, F. K., Forsting, M., Sartor, K., Adams, H. P., Kunze, S., Salcman, M., Wilson, C. B., Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumor and its influence on regrowth and prognosis, Neurosurgery, 34, 45-61, 1994	Not follow up protocol
Aukema, T. S., Valdes Olmos, R. A., Korse, C. M., Kroon, B. B. R., Wouters, M. W. J. M., Vogel, W. V., Bonfrer, J. M. G., Nieweg, O. E., Utility of fDG PET/CT and brain MRI in melanoma patients with increased serum S-100B level during follow-up, Annals of Surgical Oncology, 17, 1657-1661, 2010	Population not in PICO (melanoma patients without symptoms and signs of recurrent disease were referred for total body PET/CT and MRI of the brain because of an increased S-100B); not follow up protocol
Aukema, T. S., Valdes Olmos, R. A., Korse, T. M., Kroon, B. B., Wouters, M. W., Vogel, W. V., Bonfrer, J. M., Nieweg, O. E., Increased serum S-100B level in melanoma patients during followup and utility of FDG PET/CT and brain MRI, Annals of Surgical Oncology, 17, S114-S115, 2010	Abstract only; same study as excluded Aukema (2010)
Baker, J. J., Meyers, M. O., Frank, J., Amos, K. D., Stitzenberg, K. B., Ollila, D. W., Routine restaging PET/CT and detection of initial recurrence in sentinel lymph node positive stage III melanoma, American Journal of SurgeryAm J Surg, 207, 549-554, 2014	Population not in PICO
Baker, J. J., Meyers, M. O., Yeh, J. J., Frank, J., Amos, K. D., Stitzenberg, K. B., Long, P., Ollila, D. W., Routine restaging PET/CT and detection of recurrence in sentinel lymph node positive stage III melanoma, Annals of Surgical Oncology, 18, S114, 2011	Population not in PICO
Becker, G., Hofmann, E., Woydt, M., Hulsmann, U., Maurer, M., Lindner, A., Becker, T., Krone, A., Postoperative neuroimaging of high-grade gliomas: Comparison of transcranial sonography, magnetic resonance imaging, and computed tomography, Neurosurgery, 44, 469-478, 1999	Outcomes not in PICO and non-comparative study

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Becker, G., Krone, A., Schmitt, K., Woydt, M., Hofmann, E., Lindner, A., Bogdahn, U., Gahnl, G., Roosen, K., Preoperative and postoperative follow-up in high-grade gliomas: Comparison of transcranial color-coded real-time sonography and computed tomography findings, Ultrasound in Medicine and Biology, 21, 1123-1135, 1995	Outcomes not in PICO, unclear follow up protocol ("Contrast CT scans, TCCS and neurological follow-up examinations were performed at the same time within a time interval of 6 weeks to 3 months, coinciding with the protocol of adjuvant tumor therapy".), N = 20
Belohlavek, O., Simonova, G., Kantorova, I., Novotny Jr, J., Liscak, R., Brain metastases after stereotactic radiosurgery using the Leksell gamma knife: Can FDG PET help to differentiate radionecrosis from tumour progression?, European Journal of Nuclear Medicine and Molecular Imaging, 30, 96-100, 2003	Outcomes not in PICO
Caresia, A. P., Castell-Conesa, J., Negre, M., Mestre, A., Cuberas, G., Manes, A., Maldonado, X., Thallium-201SPECT assessment in the detection of recurrences of treated gliomas and ependymomas, Clinical and Translational Oncology, 8, 750-754, 2006	Population not in PICO (patients received SPECT if they had equivocal CT or RM images)
Casalino, D. D., Remer, E. M., Bishoff, J. T., Coursey, C. A., Dighe, M., Harvin, H. J., Heilbrun, M. E., Majd, M., Nikolaidis, P., Preminger, G. M., Raman, S. S., Sheth, S., Vikram, R., Weinfeld, R. M., ACR appropriateness criteria post-treatment follow-Up of renal cell carcinoma, Journal of the American College of Radiology, 11, 443-449, 2014	Guideline for asymptomatic patients who have been treated for renal cell carcinoma (RCC) by radical nephrectomy or nephron-sparing surgery.
Chabert, I., Belladjou, I., Poisson, F., Dhermain, F., Martin, V., Ammari, S., Vauclin, S., Pineau, P., Buvat, I., Deutsch, E., Robert, C., Correlation between MRI-based hyper-perfused areas and tumor recurrence in high-grade gliomas, Radiotherapy and Oncology, 119, S885, 2016	Published as abstract only, not enough information available to ascertain relevance although it appears to not be relevant
Chang, J. H., Kim, C. Y., Choi, B. S., Kim, Y. J., Kim, J. S., Kim, I. A., Pseudoprogression and pseudoresponse in the management of high-grade glioma: Optimal decision timing according to the response assessment of the neuro-oncology working group, Journal of Korean Neurosurgical Society, 55, 5-11, 2014	Non-comparative study

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Chang, P. D., Chow, D. S., Yang, P. H., Filippi, C. G., Lignelli, A., Predicting glioblastoma recurrence by early changes in the apparent diffusion coefficient value and signal intensity on FLAIR images, American Journal of Roentgenology, 208, 57-65, 2017	Population not in PICO ("Only patients for whom follow-up MRI examinations performed at Columbia University Medical Center showed definitive contrast-enhancing recurrent tumor were included in the study.")
Chow, D. S., Qi, J., Guo, X., Miloushev, V. Z., Iwamoto, F. M., Bruce, J. N., Lassman, A. B., Schwartz, L. H., Lignelli, A., Zhao, B., Filippi, C. G., Semiautomated volumetric measurement on postcontrast MR imaging for analysis of recurrent and residual disease in glioblastoma multiforme, American Journal of Neuroradiology, 35, 498-503, 2014	Not follow up protocol; outcomes not in PICO
Christensen, M., Kamson, D. O., Snyder, M., Kim, H., Robinette, N. L., Mittal, S., Juhasz, C., Tryptophan PET-defined gross tumor volume offers better coverage of initial progression than standard MRI-based planning in glioblastoma patients, Journal of Radiation Oncology, 3, 131-138, 2014	Non-comparative study, N = 11
Darcourt, J., Dufour, M., Mondot, L., Bourg, V., Bondiau, P., Almairac, F., Saada, E., Fontaine, D., Fauchon, F., Vandenbos, F., Ouvrier, M., Sapin, N., Role of 18F-DOPA in the management of patients suspected of brain tumour recurrence, European Journal of Nuclear Medicine and Molecular Imaging, 41, S312, 2014	Published as abstract only, with not enough information to ascertain relevance
Datta, Niloy Ranjan, Pasricha, Rajesh, Gambhir, Sanjay, Prasad, Shambhu Nath, Phadke, Rajendra Vishnu, Comparative evaluation of 201Tl SPECT and CT in the follow-up of irradiated brain tumors, International Journal of Clinical Oncology, 9, 51-8, 2004	Unclear follow up protocol; outcomes/analyses not in PICO
De Paepe, A., Vandeneede, N., Strens, D., Specenier, P., The economics of the treatment and follow-up of patients with glioblastoma, Value in Health, 18 (7), A448, 2015	Published as abstract only, with not enough information to ascertain relevance
Deng, S. M., Zhang, B., Wu, Y. W., Zhang, W., Chen, Y. Y., Detection of glioma recurrence by 11C-methionine positron emission tomography and dynamic susceptibility contrast-enhanced magnetic resonance imaging: A meta-analysis, Nuclear Medicine Communications, 34, 758-766, 2013	Outcomes (and possibly population) not in PICO

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Dong, Y., Hou, H., Wang, C., Li, J., Yao, Q., Amer, S., Tian, M., The diagnostic value of 18F-FDG PET/CT in association with serum tumor marker assays in breast cancer recurrence and metastasis, BioMed Research International, 2015, no pagination, 2015	Population not in PICO (breast cancer patients who had received modified radical mastectomy and "The patients were diagnosed as suspicion of recurrence and referred to for whole-body 18F-FDG PET/CT scanning at the PET Center fromJuly 2013 to January 2014.")
D'Souza, M. M., Sharma, R., Jaimini, A., Panwar, P., Saw, S., Kaur, P., Mondal, A., Mishra, A., Tripathi, R. P., 11C-MET PET/CT and advanced MRI in the evaluation of tumor recurrence in high-grade gliomas, Clinical Nuclear Medicine, 39, 791-798, 2014	Not follow up protocol; outcomes not in PICO
Ekinci, G., Akpinar, I. N., Baltacioglu, F., Erzen, C., Kilic, T., Elmaci, I., Pamir, N., Early-postoperative magnetic resonance imaging in glial tumors: Prediction of tumor regrowth and recurrence, European Journal of Radiology, 45, 99-107, 2003	Not follow up protocol (only pre-operative scan and early-postoperative magnetic resonance scan)
Ellingson, B. M., Cloughesy, T. F., Lai, A., Nghiemphu, P. L., Pope, W. B., Nonlinear registration of diffusion-weighted images improves clinical sensitivity of functional diffusion maps in recurrent glioblastoma treated with bevacizumab, Magnetic Resonance in Medicine, 67, 237-245, 2012	Not follow up protocol ("Baseline scans were obtained approximately 1.5 weeks before treatment, and follow-up scans were obtained at approximately 6 weeks after the initiation of bevacizumab.")
Fields, R. C., Coit, D. G., Evidence-based follow-up for the patient with melanoma, Surgical Oncology Clinics of North America, 20, 181-200, 2011	Guideline/narrative review
Fink, J. R., Carr, R. B., Matsusue, E., Iyer, R. S., Rockhill, J. K., Haynor, D. R., Maravilla, K. R., Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects, Journal of Magnetic Resonance Imaging, 35, 56-63, 2012	Not follow up protocol; population not in PICO ("All patients who underwent advanced physiologic 3T MRI, including MRS, DSC, and DWI, for evaluation of suspected

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
	malignant glioma recurrence at our institution between October 2006 and December 2008 were identified.")
Forsting, M., Albert, F. K., Kunze, S., Adams, H. P., Zenner, D., Sartor, K., Extirpation of glioblastomas: MR and CT follow-up of residual tumor and regrowth patterns, American Journal of Neuroradiology, 14, 77-87, 1993	Non-comparative study
Fouke, S. J., Benzinger, T., Gibson, D., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of imaging in the management of adults with diffuse low-grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-Oncology, 125, 457-479, 2015	Outcomes not in PICO
Gietema, J. A., Meinardi, M. T., Sleijfer, D. T., Hoekstra, H. J., van der Graaf, W. T. A., Routine chest X-rays have no additional value in the detection of relapse during routine follow-up of patients treated with chemotherapy for disseminated non-seminomatous testicular cancer, Annals of Oncology, 13, 1616-1620, 2002	Non-comparative study; unclear population (not reported how many patients had had brain metastases at study entry)
Goenka, A., Kumar, A., Sharma, R., Seith, A., Kumar, R., Julka, P., Differentiation of glioma progression or recurrence from treatment-induced changes using a combination of diffusion, perfusion and 3D-MR spectroscopy: A prospective study, Journal of Neuroimaging, 20, 99-100, 2010	Published as abstract only, so little information available to use to ascertain relevance; but population appears to not be in PICO
Gomez-Rio, M., Del Valle Torres, D. M., Rodriguez-Fernandez, A., Llamas-Elvira, J. M., Lozano, S. O., Font, C. R., Ramirez, E. L., Katati, M., 201Tl-SPECT in low-grade gliomas: Diagnostic accuracy in differential diagnosis between tumour recurrence and radionecrosis, European Journal of Nuclear Medicine and Molecular Imaging, 31, 1237-1243, 2004	Not follow up protocol/population not in PICO (patients with suspected tumour recurrence)/outcomes not in PICO
Gourcerol, D., Scherpereel, A., Debeugny, S., Porte, H., Cortot, A. B., Lafitte, J. J., Relevance of an extensive follow-up after surgery for nonsmall cell lung cancer, European Respiratory JournalEur Respir J, 42, 1357-1364, 2013	Population not in PICO (only 2 patients had stage 4 lung cancer)

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Grigolato, D., Locantore, L., Cucca, M., Zuffante, M., Ferdeghini, M., 18F-DOPA PET/CT imaging in brain tumors, European Journal of Nuclear Medicine and Molecular Imaging, 43, S264, 2016	Published as abstract only, not enough information available to ascertain relevance, but population appears not to be in PICO
Grosu, A. L., Astner, S. T., Riedel, E., Nieder, C., Wiedenmann, N., Heinemann, F., Schwaiger, M., Molls, M., Wester, H. J., Weber, W. A., An interindividual comparison of O-(2-[18F]fluoroethyl)-L- tyrosine (FET)- and L-[methyl-11C]methionine (MET)-PET in patients with brain gliomas and metastases, International Journal of Radiation Oncology Biology Physics, 81, 1049-1058, 2011	Population not in PICO (All patients had previously been treated for gliomas or brain metastases and now presented with MRI findings suggesting the presence of residual or recurrent tumour tissue)
Hamdan, A., Kane, P., Uncertainty and variability in surveillance imaging after completion of primary treatment in glioblastoma multiforme, Neuro-Oncology, 16, ii80, 2014	Published as abstract only, not enough information available to ascertain relevance
Hamdan, A., Kane, P., Variability in follow up imaging guidelines after the completion of primary therapy in glioblastoma multiforme, Neuro-Oncology, 16, vi1-vi2, 2014	Published as abstract only, not enough information available to ascertain relevance
Hawighorst, H., Essig, M., Debus, J., Knopp, M. V., Engenhart-Cabilic, R., Schonberg, S. O., Brix, G., Zuna, I., van Kaick, G., Serial MR imaging of intracranial metastases after radiosurgery, Magnetic Resonance ImagingMagn Reson Imaging, 15, 1121-32, 1997	Non-comparative study
Hodgson, T. J., Kingsley, D. P. E., Moseley, I. F., The role of imaging in the follow up of meningiomas, Journal of Neurology Neurosurgery and Psychiatry, 59, 545-547, 1995	Not follow up protocol/unclear when/what the patients had (as) follow up
Hojer, C., Hildebrandt, G., Lanfermann, H., Schroder, R., Haupt, W. F., Pilocytic astrocytomas of the posterior fossa - A follow-up study in 33 patients, Acta Neurochirurgica, 129, 131-139, 1994	Not follow up protocol/unclear which patients received what follow up
Hu, X., Ma, L., Li, W., Sun, X., Sun, J., Yu, J., 11C-choline PET/CT detecting tumour recurrence and predicting survival in post-treatment patients with high-grade Glioma, European Journal of Nuclear Medicine and Molecular Imaging, 40, S351, 2013	Published as abstract only, not enough information available to ascertain relevance

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Hu, X., Wong, K. K., Young, G. S., Guo, L., Wong, S. T., Support vector machine multiparametric MRI identification of pseudoprogression from tumor recurrence in patients with resected glioblastoma, Journal of Magnetic Resonance Imaging, 33, 296-305, 2011	Population not in PICO (patients with confirmed radiation necrosis or recurrence)
Huber, P. E., Hawighorst, H., Fuss, M., van Kaick, G., Wannenmacher, M. F., Debus, J., Transient enlargement of contrast uptake on MRI after linear accelerator (linac) stereotactic radiosurgery for brain metastases, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 49, 1339-49, 2001	Not follow up protocol
Ikeda, H., Tsuyuguchi, N., Kunihiro, N., Ishibashi, K., Goto, T., Ohata, K., Analysis of progression and recurrence of meningioma using 11C-methionine PET, Annals of Nuclear Medicine, 27, 772-780, 2013	Not follow up protocol
Ion-Margineanu, A., Van Cauter, S., Sima, D. M., Maes, F., Van Gool, S. W., Sunaert, S., Himmelreich, U., Van Huffel, S., Tumour Relapse Prediction Using Multiparametric MR Data Recorded during Follow-Up of GBM Patients, BioMed Research InternationalBiomed Res Int, 2015 (no pagination), 2015	Not follow up protocol
Jansen, N., Suchorska, B., Graute, V., Lutz, J., Schwarz, S., Bartenstein, P., Kreth, F. W., La Fougere, C., [18F]FET-PET based therapy monitoring after stereotactic 125iodine brachytherapy in patients with recurrent high-grade glioma, NuklearMedizin, 51, A14, 2012	Published as abstract only, with not enough information reported to ascertain relevance
Jora, C., Mattakarottu, J. J., Aniruddha, P. G., Mudalsha, R., Singh, D. K., Pathak, H. C., Sharma, N., Sarin, A., Prince, A., Singh, G., Comparative evaluation of 18F-FDOPA, 13N-AMMONIA, 18F-FDG PET/CT and MRI in primary brain tumors - A pilot study, Indian Journal of Nuclear Medicine, 26, 78-81, 2011	Population not in PICO (15/23 were postoperative cases with suspected recurrence or residual tumor tissue)
Jostel, A., Mukherjee, A., Hulse, P. A., Shalet, S. M., Adult growth hormone replacement therapy and neuroimaging surveillance in brain tumour survivors, Clinical EndocrinologyClin Endocrinol (Oxf), 62, 698-705, 2005	Population not in PICO/mixed population

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Juhasz, C., Mittal, S., Muzik, O., Chugani, D. C., Chakraborty, P. K., Bahl, G., Barger, G. R., Accurate identification of recurrent gliomas by kinetic analysis of alpha-methyl-l-tryptophan unidirectional uptake on PET, Neuro-Oncology, 12, iv113, 2010	Published as abstract only, not enough information reported to ascertain relevance, but it seems that population/outcomes not in PICO
Jung, B. H., Hwang, S., Moon, D. B., Ahn, C. S., Kim, K. H., Ha, T. Y., Song, G. W., Jung, D. H., Lee, S. G., Surveillance protocol for hepatocellular carcinoma recurrence after living donor liver transplantation, HPB, 16, 578-579, 2014	Published as abstract only, not enough information reported to ascertain relevance, but it seems that population not in PICO
Kaplan, M. A., Inal, A., Kucukoner, M., Urakci, Z., Ekici, F., Firat, U., Zincircioglu, S. B., Isikdogan, A., Cranial magnetic resonance imaging in the staging of HER2-positive breast cancer patients, Onkologie, 36, 176-181, 2013	Population not in PICO
Kelly, J, Does the addition of positron emission tomography/computed tomography (PET/CT) to the routine investigation and assessment of patients with melanoma yield clinical and economic benefits? (Structured abstract), Health Technology Assessment Database, 2013	Unavailable/cannot source paper
Klesse, L., Bezner, S., Gargan, L., Leonard, D., Bowers, D., Utility of long term neuro-imaging in patients with cerebellar pilocytic astrocytomas, Pediatric Blood and Cancer, 56, 963, 2011	Population not in PICO (mean age at diagnosis < 10 years)
Klutmann, S., Bohuslavizki, K. H., Brenner, W., Behnke, A., Tietje, N., Kroger, S., Hugo, H. H., Mehdorn, H. M., Clausen, M., Henze, E., Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma, Journal of Nuclear MedicineJ Nucl Med, 39, 1913-7, 1998	Not follow up protocol
Lagman, C, Bhatt, N, Pelargos, P, Lee, S, Mukherjee, D, Yang, I, A meta-analysis of published literature on adjuvant radiosurgery and surveillance following subtotal resection of atypical meningioma, Neuro-oncology. Conference: 21st annual scientific meeting and education day of the society for neuro-oncology. United states. Conference start: 20161117. Conference end: 20161120, 18, vi101, 2017	Duplicate

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Lagman, C., Bhatt, N., Pelargos, P., Lee, S., Mukherjee, D., Yang, I., A meta-analysis of published literature on adjuvant radiosurgery and surveillance following subtotal resection of atypical meningioma, Neuro-Oncology, 18, vi101, 2016	Published as abstract only, not enough information available to ascertain relevance (checked for topic 3a)
Lagman, Carlito, Bhatt, Nikhilesh S., Lee, Seung J., Bui, Timothy T., Chung, Lawrance K., Voth, Brittany L., Barnette, Natalie E., Pouratian, Nader, Lee, Percy, Selch, Michael, Kaprealian, Tania, Chin, Robert, McArthur, David L., Mukherjee, Debraj, Patil, Chirag G., Yang, Isaac, Adjuvant Radiosurgery Versus Serial Surveillance Following Subtotal Resection of Atypical Meningioma: A Systematic Analysis, World Neurosurgery, 98, 339-346, 2017	Checked for topic 3a; all included studies checked for relevance for topic 3a
Law, A., Loh, N., Francis, R., Bynevelt, M., McCarthy, M., Segard, T., Morandeau, L., Maton, P., Nowak, A., Atkinson, J., 11C-Methionine and 18F-fluorothymidine PET-CT imaging in suspected residual or recurrent glioma, Journal of Medical Imaging and Radiation Oncology, 56, 32, 2012	Published as abstract only and not enough information is reported to ascertain relevance, although it appears not to be a follow up protocol
Le Jeune, F. P., Dubois, F., Blond, S., Steinling, M., Sestamibi technetium-99m brain single-photon emission computed tomography to identify recurrent glioma in adults: 201 studies, Journal of Neuro-Oncology, 77, 177-183, 2006	Outcomes not in PICO
Lee, J. W., Kang, K. W., Park, S. H., Lee, S. M., Paeng, J. C., Chung, J. K., Lee, M. C., Lee, D. S., 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma, European Journal of Nuclear Medicine and Molecular Imaging, 36, 1574-1582, 2009	Not follow up protocol
Leimgruber, Antoine, Ostermann, Sandrine, Yeon, Eun Jo, Buff, Evelyn, Maeder, Philippe P., Stupp, Roger, Meuli, Reto A., Perfusion and diffusion MRI of glioblastoma progression in a four-year prospective temozolomide clinical trial, International journal of radiation oncology, biology, physics, 64, 869-75, 2006	Not follow up protocol

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Lemasson, B., Chenevert, T. L., Mikkelsen, T., Boes, J. L., Johnson, T. D., Galban, S., Rehemtulla, A., Galban, C., Ross, B. D., Novel MRI-based biomarker for early assessment of glioma recurrence, Cancer Research, 72, no pagination, 2012	Published as an abstract only, not enough information reported to ascertain relevance. N = 14
Li, Wanhu, Ma, Li, Wang, Xiaoyue, Sun, Jujie, Wang, Suzhen, Hu, Xudong, (11)C-choline PET/CT tumor recurrence detection and survival prediction in post-treatment patients with high-grade gliomas, Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine, 35, 12353-60, 2014	Population not in PICO (suspicion of recurrence)
Lorberboym, D., Baram, J., Feibel, M., Hercbergs, A., Lieberman, L., A prospective evaluation of thallium-201 single photon emission computerized tomography for brain tumor burden, International Journal of Radiation Oncology Biology Physics, 32, 249-254, 1995	Unclear follow up protocol/outcomes not in PICO
Loreti, F., Trippa, F., Costa, M., Conti, S., Francesconi, E., Giorgi, C., Carletti, S., Maranzano, E., 99mTc-MIBI SPECT/CT in brain metastases treated with stereotactic radiosurgery (SRS): Experience of the Terni Hospital neuro-oncology group, Clinical and Translational Imaging, 1, S40, 2013	Published as an abstract only. Not enough information reported to ascertain relevance.
Madhavi, T., Raunak, V., Rajnish, S., Jaspriya, B., Abhinav, J., Maria, S. M. D., Pandey Santosh, K., Jyotika, J., Puja, P., Mishra Anil, K., Anupam, M., Comparative evaluation of C-11 methionine (METPET) and F-18 flurodeoxyglucose (FDG) PET/CT for detection of recurrent brain tumors, Indian Journal of Nuclear Medicine, 25, 90, 2010	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol
Makita, Masujiro, Sakai, Takehiko, Ogiya, Akiko, Kitagawa, Dai, Morizono, Hidetomo, Miyagi, Yumi, Iijima, Kotaro, Iwase, Takuji, Optimal surveillance for postoperative metastasis in breast cancer patients, Breast cancer (Tokyo, Japan), 23, 286-94, 2016	Population not in PICO
Massager, N., De Smedt, F., Devriendt, D., Long-term tumor control of benign intracranial tumors after Gamma Knife radiosurgery in 280 patients followed more than 5 years, Acta Neurologica Belgica, 113, 463-467, 2013	Not follow up protocol

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Matsuo, M., Miwa, K., Shinoda, J., Tanaka, O., Krishna, M., Impact Of C11-methionine positron emission tomography (PET) for malignant glioma in radiation therapy: Is C11-methionine PET a superior to magnetic resonance imaging?, International Journal of Radiation Oncology Biology Physics, 81, S182, 2011	Published as abstract only, not enough information reported to ascertain relevance
Menoux, I., Armspach, J. P., Noel, G., Antoni, D., Imaging methods used in the differential diagnosis between brain tumour relapse and radiation necrosis after stereotactic radiosurgery of brain metastases: Literature review, Cancer/Radiotherapie, 20, 837-845, 2016	Narrative review
Meyers, S. P., Wildenhain, S., Chess, M. A., Tarr, R. W., Postoperative evaluation for intracranial recurrence of medulloblastoma: MR findings with gadopentetate dimeglumine, AJNR. American journal of neuroradiology, 15, 1425-34, 1994	Not follow up protocol/population not in PICO (mean age 8.3 years, range 1-42 years; no further details)
Mori, H., Kunimatsu, A., Abe, O., Sasaki, H., Takao, H., Nojo, T., Kawai, K., Saito, N., Ohtomo, K., Diagnostic ability of fluid-attenuated inversion recovery MR imaging to detect remnant or recurrent meningiomas after resection, Neuroradiology Journal, 25, 163-171, 2012	Not follow up protocol
Mori, H., Kunimatsu, A., Abe, O., Sasaki, H., Takao, H., Nojo, T., Ohtomo, K., Resected meningiomas: Diagnostic performance of fluid-attenuated inversion recovery MR imaging for detection of remnant or recurrence, Neuroradiology Journal, 23, 419-420, 2010	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol
Nayeri, A., Prablek, M. A., Brinson, P. R., Weaver, K. D., Thompson, R. C., Chambless, L. B., Short-term postoperative surveillance imaging may be unnecessary in elderly patients with resected WHO Grade i meningiomas, Journal of Clinical NeuroscienceJ Clin Neurosci, 26, 101-104, 2016	Not follow up protocol
Nesbitt, D., Hendry, G., Scoones, D., Kane, P., Routine follow-up imaging after treatment for glioblastoma: How useful is it?, Neuro-Oncology, 12, iii34, 2010	Published as abstract only; non-comparative study

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Nihashi, T., Dahabreh, I. J., Terasawa, T., PET in the clinical management of glioma: Evidence map, American Journal of Roentgenology, 200, W654-W660, 2013	Outcomes not in PICO
Niyazi, M., Schnell, O., Suchorska, B., Schwarz, S. B., Ganswindt, U., Geisler, J., Bartenstein, P., Kreth, F. W., Tonn, J. C., Eigenbrod, S., Belka, C., La Fougere, C., FET-PET assessed recurrence pattern after radio-chemotherapy in newly diagnosed patients with glioblastoma is influenced by MGMT methylation status, Radiotherapy and Oncology, 104, 78-82, 2012	Not follow up protocol
Nowosielski, M., Hutterer, M., Tinkhauser, G., Irschick, R., Waitz, D., Putzer, D., Stockhammer, G., Recheis, W., Jaschke, W., Gotwald, T., Bevacizumab/irinotecan in recurrent malignant glioma: A retrospective analysis of MRI, FET-PET, and clinical performance, Journal of Clinical Oncology, 28, no pagination, 2010	Published as abstract only, not enough information reported to ascertain relevance
Nozawa, A, Rivandi, Ah, Kanematsu, M, Hoshi, H, Piccioni, D, Kesari, S, Hoh, Ck, Glucose-corrected standardized uptake value in the differentiation of high-grade glioma versus post-treatment changes, Nuclear Medicine CommunicationsNucl Med Commun, 36, 573-81, 2015	Not follow up protocol
Nozawa, Asae, Rivandi, Ali Hosseini, Kanematsu, Masayuki, Hoshi, Hiroaki, Piccioni, David, Kesari, Santosh, Hoh, Carl K., Glucose-corrected standardized uptake value in the differentiation of high-grade glioma versus post-treatment changes, Nuclear Medicine Communications, 36, 573-81, 2015	Duplicate
Nuutinen, J., Sonninen, P., Lehikoinen, P., Sutinen, E., Valavaara, R., Eronen, E., Norrgard, S., Kulmala, J., Teras, M., Minn, H., Radiotherapy treatment planning and long-term follow-up with [11C]methionine PET in patients with low-grade astrocytoma, International Journal of Radiation Oncology Biology Physics, 48, 43-52, 2000	Outcomes/analyses not in PICO
Park, Ji Eun, Kim, Ho Sung, Park, Kye Jin, Kim, Sang Joon, Kim, Jeong Hoon, Smith, Seth A., Pre- and Posttreatment Glioma: Comparison of Amide Proton Transfer Imaging with MR Spectroscopy for Biomarkers of Tumor Proliferation, Radiology, 278, 514-23, 2016	Not follow up protocol

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Patel, P., Baradaran, H., Delgado, D., Askin, G., Christos, P., Tsiouris, A. J., Gupta, A., MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: A systematic review and meta-analysis, Neuro-Oncology, 19, 118-127, 2017	Population and outcomes not in PICO
Patel, S. H., Robbins, J. R., Gore, E. M., Bradley, J. D., Gaspar, L. E., Germano, I., Ghafoori, P., Henderson, M. A., Lutz, S. T., McDermott, M. W., Patchell, R. A., Robins, H. I., Vassil, A. D., Wippold, F. J., Videtic, G. M., ACR appropriateness criteria follow-up and retreatment of brain metastases, American Journal of Clinical Oncology: Cancer Clinical Trials, 35, 302-306, 2012	Narrative review/guideline
Pavlicek, R., Garcia, J. R., Baquero, M., Soler, M., Fernandez, Y., Fuertes, S., Carrio, I., Lomena, F., Contribution of 11C-methionine PET to MRI in the differentiation of recurrent brain tumor from radiation necrosis, European Journal of Nuclear Medicine and Molecular Imaging, 38, S342, 2011	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol, appears to be non-comparative with N = 14
Potzi, C., Becherer, A., Marosi, C., Karanikas, G., Szabo, M., Dudczak, R., Kletter, K., Asenbaum, S., [11C] methionine and [18F] fluorodeoxyglucose PET in the follow-up of glioblastoma multiforme, Journal of Neuro-Oncology, 84, 305-314, 2007	Outcomes or analyses not in PICO
Prat, R., Galeano, I., Lucas, A., Martinez, J. C., Martin, M., Amador, R., Reynes, G., Relative value of magnetic resonance spectroscopy, magnetic resonance perfusion, and 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography for detection of recurrence or grade increase in gliomas, Journal of Clinical Neuroscience, 17, 50-53, 2010	Population not in PICO; outcomes not in PICO
Prigent-Le Jeune, F., Dubois, F., Perez, S., Blond, S., Steinling, M., Technetium-99m sestamibi brain SPECT in the follow-up of glioma for evaluation of response to chemotherapy: First results, European Journal of Nuclear Medicine and Molecular Imaging, 31, 714-719, 2004	Not follow up protocol

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Pronin, I., Dolgushin, M., Fadeeva, L., Podoprigora, A., Serkov, S., Golanov, A., Nikitin, K., Kornienko, V., CT perfusion in diagnosis of Radiation Necrosis, Neuroradiology Journal, 23, 354, 2010	Published as abstract only, not enough information reported to ascertain relevance, but outcomes do not appear to be in PICO
Pungavkar, S., Gupta, T., Moiyadi, A., Shetty, P., Shridhar, E., Chinnaswamy, G., Godashastri, J., Jalali, R., 3D arterial spin labeling - A novel, non-invasive technique to assess perfusion in brain tumors - Experience of over 200 cases, European Journal of Cancer, 54, S38, 2016	Published as abstract only, not enough information reported to ascertain relevance
Rachinger, W., Goetz, C., Popperl, G., Gildehaus, F. J., Kreth, F. W., Holtmannspotter, M., Herms, J., Koch, W., Tatsch, K., Tonn, J. C., Positron emission tomography with O-(2-[18F]flouroethyl)-L- tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas, Neurosurgery, 57, 505-511, 2005	Outcomes not in PICO
Radbruch, Alexander, Lutz, Kira, Wiestler, Benedikt, Baumer, Philipp, Heiland, Sabine, Wick, Wolfgang, Bendszus, Martin, Relevance of T2 signal changes in the assessment of progression of glioblastoma according to the Response Assessment in Neurooncology criteria, Neuro-Oncology, 14, 222-9, 2012	Not follow up protocol; unclear when patients had scans
Reiche, W., Schaefer, A., Schmidt, S., Moringlane, J. R., Feiden, W., Kirsch, C. M., Piepgras, U., 18FDG-SPECT imaging of brain tumours: Results in 41 patients, Rivista di Neuroradiologia, 11, 149-160, 1998	Not follow up protocol
Reijneveld, J. C., van der Grond, J., Ramos, L. M. P., Bromberg, J. E. C., Taphoorn, M. J. B., Proton MRS imaging in the follow-up of patients with suspected low-grade gliomas, Neuroradiology, 47, 887-91, 2005	Population not in PICO; non-comparative study with N = 14
Roberts, S., Jones, L., Exley, C., CT follow up after surgery for lung cancer-should the availability of radio-surgery prompt a change in screening protocol to detect early intracerebral recurrence?, Thorax, 70, A159, 2015	Population not in PICO
Rodriguez-Bel, L., Gamez-Cenzano, C., Garciagarzon, J., Sabate-Llobera, A., Vercher-Conejero, J., Gracia-Sanchez, L., Linares-Tello, E. L., Majos-Torro, C., Lucas-Calduch, A., Macia-garau, M., Bruna-Escuer, J., Diagnostic accuracy for F18-FDG-PET/CT and C11-METHIONINEPET/ CT Co-registered with MRI for	Published as abstract only, not enough information reported to ascertain relevance,

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
differentiation of recurrent brain tumor from radiation injury, European Journal of Nuclear Medicine and Molecular Imaging, 43, S260, 2016	but population and outcomes appear not to be in PICO
Rottenburger, C., Hentschel, M., Kelly, T., Trippel, M., Brink, I., Reithmeier, T., Tobias Meyer, P., Nikkhah, G., Comparison of C-11 methionine and C-11 choline for PET imaging of brain metastases: A prospective pilot study, Clinical Nuclear Medicine, 36, 639-642, 2011	Not follow up protocol (N = 8)
Rubinstein, R., Karger, H., Pietrzyk, U., Siegal, T., Gomori, J. M., Chisin, R., Use of 201Thallium brain SPECT, image registration, and semi-quantitative analysis in the follow-up of brain tumors, European Journal of Radiology, 21, 188-95, 1996	Outcomes not in PICO
Sadeghi, N., Lebrun, J. C., Absil, J., Metens, T., Goldman, S., Dynamic susceptibility contrast enhanced (DSC) MR based perfusion imaging to differentiate recurrence from stable disease in brain gliomas, Neuroradiology, 56, 233, 2014	Published as abstract only, not enough information reported to ascertain relevance, but outcomes appear not to be in PICO
Samnick, S., Bader, J. B., Hellwig, D., Moringlane, J. R., Alexander, C., Romeike, B. F. M., Feiden, W., Kirsch, C. M., Clinical value of iodine-123-alpha-methyl-L-tyrosine single-photon emission tomography in the differential diagnosis of recurrent brain tumor in patients pretreated for glioma at follow-up, Journal of Clinical Oncology, 20, 396-404, 2002	Population not in PICO, not follow up protocol
Santoni, M., Berardi, R., Bittoni, A., Paccapelo, A., Nanni, C., Fanti, S., Burattini, L., Cascinu, S., Clinical impact of [11C]-methionine positron emission tomography on the treatment of primary and recurrent gliomas, Annals of Oncology, 23, ix148, 2012	Published as abstract only, not enough information reported to ascertain relevance
Santoni, M., Nanni, C., Bittoni, A., Polonara, G., Paccapelo, A., Trignani, R., De Lisa, M., Rychlicki, F., Burattini, L., Berardi, R., Fanti, S., Cascinu, S., [11C]-Methionine positron emission tomography in the postoperative imaging and followup of patients with primary and recurrent gliomas, ISRN Oncology, 2014, no pagination, 2014	Not follow up protocol/outcomes not in PICO

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Seeger, A., Braun, C., Skardelly, M., Paulsen, F., Schittenhelm, J., Ernemann, U., Bisdas, S., Comparison of Three Different MR Perfusion Techniques and MR Spectroscopy for Multiparametric Assessment in Distinguishing Recurrent High-Grade Gliomas from Stable Disease, Academic Radiology, 20, 1557-1565, 2013	Population not in PICO (patients with the presence of new enhancing lesions after chemoradiotherapy)
Shan, Y., Chen, X., Lin, Y., Wang, Y., Zhong, S., Gong, Y., Value of magnetic resonance spectroscopy and perfusion-weighted imaging in distinguishing glioma recurrence from PTRE: A meta-analysis, International Journal of Clinical and Experimental Medicine, 9, 10006-10017, 2016	Unavailable/cannot source paper
Sharma, R., D'Souza, M., Jaimini, A., Hazari, P. P., Saw, S., Pandey, S., Singh, D., Solanki, Y., Kumar, N., Mishra, A. K., Mondal, A., A comparison study of 11 C-methionine and 18 F-fluorodeoxyglucose positron emission tomography-computed tomography scans in evaluation of patients with recurrent brain tumors, Indian Journal of Nuclear Medicine, 31, 93-102, 2016	Not follow up protocol (one scan); outcomes not in PICO
Shin, K. E., Ahn, K. J., Choi, H. S., Jung, S. L., Kim, B. S., Jeon, S. S., Hong, Y. G., DCE and DSC MR perfusion imaging in the differentiation of recurrent tumour from treatment-related changes in patients with glioma, Clinical Radiology, 69, e264-e272, 2014	Population not in PICO (“patients who subsequently developed new enhancing lesions on follow-up contrast-enhanced MRI”)
Simpson, J. R., Mendenhall, W. M., Schupak, K. D., Larson, D., Bloomer, W. D., Buckley, J. A., Gaspar, L. E., Gibbs, F. A., Lewin, A. A., Loeffler, J. S., Malcolm, A. W., Schneider, J. F., Shaw, E. G., Wharam Jr, M. D., Gutin, P. H., Rogers, L., Leibel, S., Follow-up and retreatment of brain metastasis. American College of Radiology. ACR Appropriateness Criteria, Radiology, 215 Suppl, 1129-1135, 2000	Unavailable/cannot source paper
Skvortsova, T., Savintseva, Z., Brodskaya, Z., Medvedev, S. V., Bechtereva, N. P., Direct comparison of [11C]methionine PET with perfusion magnetic resonance imaging for detection of recurrent brain tumors, European Journal of Nuclear Medicine and Molecular Imaging, 39, S381, 2012	Published as abstract only, not enough information reported to ascertain relevance, but population does not appear to be in PICO

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Smets, T., Lawson, T. M., Grandin, C., Jankovski, A., Raftopoulos, C., Immediate post-operative MRI suggestive of the site and timing of glioblastoma recurrence after gross total resection: A retrospective longitudinal preliminary study, European Radiology, 23, 1467-1477, 2013	Population not in PICO (22/24 were selected to have/had recurrence)
Smith, J. S., Cha, S., Mayo, M. C., McDermott, M. W., Parsa, A. T., Chang, S. M., Dillon, W. P., Berger, M. S., Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury, Journal of Neurosurgery, 103, 428-438, 2005	Not follow up protocol; outcomes not in PICO
Steele, J., Sibtain, A., Brada, M., The content and efficacy of conventional methods of follow-up in neuro-oncology: The need for new strategies, Clinical Oncology, 9, 168-171, 1997	Unclear follow up protocol, non-comparative study, outcomes not in PICO
Stenberg, L., Englund, E., Wirestam, R., Siesjo, P., Salford, L. G., Larsson, E. M., Dynamic susceptibility contrast-enhanced perfusion magnetic resonance (MR) imaging combined with contrast-enhanced MR imaging in the follow-up of immunogene-treated glioblastoma multiforme, Acta radiologica (Stockholm, Sweden : 1987), 47, 852-861, 2006	Unclear follow up protocol, non-comparative study, N = 8
Stupp, R., Brada, M., van den Bent, M. J., Tonn, J. C., Pentheroudakis, G., High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Annals of Oncology, 25, 93-101, 2014	Guideline/narrative review
Thapa, P. K., Tripathi, M., Jaimini, A., D'Souza, M., Chouttani, K., Pandey, S., Sehar, R., Rawat, H., Mishra, A. K., Sharma, R., Mondal, A., Comparative study between Tc-99m labelled Methionine and C-11 Methionine in detection of low-grade astrocytoma, Indian Journal of Nuclear Medicine, 26, S29, 2011	Published as abstract only, not enough information reported to ascertain relevance, but population/outcomes do not appear to be in PICO
Tripathi, M., Sharma, R., Varshney, R., Jaimini, A., Jain, J., Souza, M. M. D., Bal, J., Pandey, S., Kumar, N., Mishra, A. K., Mondal, A., Comparison of F-18 FDG and C-11 methionine PET/CT for the evaluation of recurrent primary brain tumors, Clinical Nuclear Medicine, 37, 158-163, 2012	Population no in PICO (patients referred for evaluation of recurrence); not follow up protocol

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Ueki, K., Higuchi, F., Ohtani, R., Udzuka, T., Sakamoto, S., Kim, P., 11C-methionin-pet enables early detection and subsequent intervention of recurrence in 1p/ 19q co-deleted gliomas, Neuro-Oncology, 17, v169, 2015	Published as abstract only, not enough information reported to ascertain relevance, but study appears to be non-comparative
Unterrainer, M., Schweisthal, F., Suchorska, B., Wenter, V., Schmid-Tannwald, C., Fendler, W. P., Schuller, U., Bartenstein, P., Tonn, J. C., Albert, N. L., Serial 18F-FET PET imaging of primarily 18F-FET-negative glioma: Does it make sense?, Journal of Nuclear Medicine, 57, 1177-1182, 2016	Outcomes not in PICO
Van Laere, K., Ceyssens, S., Van Calenbergh, F., De Groot, T., Menten, J., Flamen, P., Bormans, G., Mortelmans, L., Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: Sensitivity, inter-observer variability and prognostic value, European Journal of Nuclear Medicine and Molecular Imaging, 32, 39-51, 2005	Not follow up protocol: Data obtained in a single session in patients with a history of previously treated primary brain tumours were referred to the PET centre to differentiate between radiation necrosis and recurrence/progression
Vassilyadi, M., Shamji, M. F., Tataryn, Z., Keene, D., Ventureyra, E., Postoperative surveillance magnetic resonance imaging for cerebellar astrocytoma, Canadian Journal of Neurological Sciences, 36, 707-712, 2009	Population not in PICO (children)
Verburg, N., Hoefnagels, F., Pouwels, P., Boellaard, R., Barkhof, F., Hoekstra, O., Wesseling, P., Reijneveld, J., Heimans, J., Vandertop, P., Zwinderman, K., De Witt Hamer, H., The diagnostic accuracy of neuro-imaging to detect infiltrative glioma within the brain: A meta-analysis based on 1598 patients in 58 publications, Neuro-Oncology, 15, iii194, 2013	Published as abstract only, not enough information available to ascertain relevance, although it appears not to be follow up protocol and outcomes not in PICO
Vigil, C., Caicedo, C., Hernandez, M., Rodriguez-ruiz, M., Olarte, A., Valtuena, G., Moreno-jimenez, M., Penuelas, I., Aristu, J., Arbizu, J., 11C-Methionine-Positron Emission Tomography as prognostic factor of recurrence in glioblastoma, Reports of Practical Oncology and Radiotherapy, 18, S186, 2013	Published as abstract only, not enough information reported to ascertain relevance, but does not appear to be follow up

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Vos, M J, Tony, B N, Hoekstra, O S, Postma, T J, Heimans, J J, Hooft, L, Systematic review of the diagnostic accuracy of 201-Tl single photon emission computed tomography in the detection of recurrent glioma (Structured abstract), Nuclear Medicine Communications, 28, 431-439, 2007	Population not in PICO (patients who were clinically suspected of recurrent tumour growth); outcomes not in PICO
Vos, M. J., Hoekstra, O. S., Barkhof, F., Berkhof, J., Heimans, J. J., Van Groeningen, C. J., Vandertop, W. P., Slotman, B. J., Postma, T. J., Thallium-201 single-photon emission computed tomography as an early predictor of outcome in recurrent glioma, Journal of Clinical Oncology, 21, 3559-3565, 2003	Not follow up protocol/analyses not in PICO
Vos, Mj, Berkhof, J, Hoekstra, Os, Bosma, I, Sizoo, Em, Heimans, Jj, Reijneveld, Jc, Sanchez, E, Lagerwaard, Fj, Buter, J, Noske, Dp, Postma, Tj, MRI and thallium-201 SPECT in the prediction of survival in glioma, Neuroradiology, 54, 539-46, 2012	Not follow up protocol/analyses not in PICO
Vrabec, M., Van Cauter, S., Himmelreich, U., Van Gool, S. W., Sunaert, S., De Vleeschouwer, S., Suput, D., Demaerel, P., MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: A pilot study, Neuroradiology, 53, 721-731, 2011	N = 8, outcomes not in PICO, not follow up protocol
Wang, X, Hu, X, Xie, P, Li, W, Li, X, Ma, L, Comparison of magnetic resonance spectroscopy and positron emission tomography in detection of tumor recurrence in posttreatment of glioma: a diagnostic meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, epub, 2014	Unavailable/cannot source paper
Weber, M. A., Lichy, M. P., Gunther, M., Delorme, S., Thilmann, C., Bachert, P., Schad, L., Debus, J., Schlemmer, H. P., Monitoring of Irradiated Brain Metastases Using Arterial Spin-Labeling MR-Perfusion Imaging and 1H MR Spectroscopy, Rivista di Neuroradiologia, 16, 1118-1122, 2003	Outcomes not in PICO
Weizman, Lior, Sira, Liat Ben, Joskowicz, Leo, Rubin, Daniel L., Yeom, Kristen W., Constantini, Shlomi, Shofty, Ben, Bashat, Dafna Ben, Semiautomatic segmentation and follow-up of multicomponent low-grade tumors in longitudinal brain MRI studies, Medical physics, 41, 052303, 2014	Population not in PICO (children)

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
Winterstein, Marianne, Munter, Marc W., Burkholder, Iris, Essig, Marco, Kauczor, Hans-Ulrich, Weber, Marc-Andre, Partially resected gliomas: diagnostic performance of fluid-attenuated inversion recovery MR imaging for detection of progression, Radiology, 254, 907-16, 2010	Outcomes not in PICO
Yokoi, K., Miyazawa, N., Arai, T., Brain metastasis in resected lung cancer: value of intensive follow-up with computed tomography, The Annals of thoracic surgery, 61, 546-551, 1996	Population not in PICO (patients treated for lung cancer without brain metastasis)
Yondorf, M. Z., Wernicke, A. G., Parashar, B., Schwartz, T. H., Boockvar, J. A., Stieg, P., Pannullo, S., Nori, D., Chao, K. S. C., Kovanlikaya, I., Impact of Serial DWI and ADC Measurements in Assessment of Brain Metastases Treated With Neurosurgical Resection and Intraoperative Cesium- 131 Brachytherapy: Results of a Prospective Trial, Oncology. Conference: 96th Annual Meeting of the American Radium Society, ARS, 28, 2014	Published as abstract only, not enough information reported to ascertain relevance, but does not appear to be follow up

Economic studies

Not applicable – no economic evidence was identified.

Appendix L – Research recommendations

R1. Does the addition of concurrent and adjuvant temozolomide to radiotherapy improve overall survival in patients with IDH wildtype grade II glioma?

Why is this important?

The WHO 2016 reclassification of brain tumours recognised that the molecular characteristics of glioma are extremely important in helping differentiate between disease entities with very different outcomes. Although evidence exists to guide management recommendations for certain molecular gliomas, such as codeleted and non-codeleted grade III glioma, currently no studies have investigated the best approach for the management of grade II glioma with IDH wildtype. The biological behaviour of these tumours is more like a high-grade glioma with a much shorter prognosis than IDH-mutated grade II glioma.

Because of this, some clinicians have advocated treating such tumours with concurrent chemoradiation recommended for grade IV glioma (GBM). However, there is currently no research evidence to support this approach and this regimen is more intensive and people experience increased acute and late side effects compared to radiotherapy alone.

Research is needed to establish whether or not this approach is beneficial in terms of improved survival, and at what cost in terms of toxicity and, potentially, reduced quality of life.

Research recommendation rationale

Research question	Does the addition of concurrent and adjuvant TMZ to radiotherapy improve overall survival in patients with IDH wildtype grade II glioma?
Importance to 'patients' or the population	The new WHO 2016 classification of glioma recognised a subgroup of IDH wildtype grade II glioma that have an inferior outcome but currently there is no evidence on the best way to treat this tumour subtype, and establishing evidence is of prime importance to people with this type of brain tumour.
Relevance to NICE guidance	High priority: the guideline recommendations are currently consensus based for IDH wildtype despite evidence for treatment in IDH mutant low-grade gliomas.
Relevance to NHS	It is unclear what the best treatment for this subtype of glioma is. This leads to large variation in practice, with some gliomas being treated with radiotherapy alone and others with chemo-radiation despite there being no trial evidence to support this. Chemo-radiation is associated with greater toxicity and consequent costs to the NHS. The excess treatment may in turn have an impact on quality of life in people with glioma.
National priorities	This research is supportive of NHS England's Cancer Strategy Implementation Plan, since it supports the use of effective molecular diagnosis in this patient population.

Research question	Does the addition of concurrent and adjuvant TMZ to radiotherapy improve overall survival in patients with IDH wildtype grade II glioma?
Current evidence base	There is no evidence on the management of this specific subtype of glioma.
Equalities	N/A

IDH isocitrate dehydrogenase; TMZ temozolomide; WHO World Health Organisation

Research recommendation PICO

Criterion	Explanation
Population	Adults ≥18 years. IDH 1 or 2 wild type confirmed by sequencing. Surgical resection or biopsy (provided sufficient pathological material for central review) Karnofsky performance status ≥ 70 Life expectancy >6 months Able to give informed consent Able to undergo MRI Able and willing to perform quality of life and neuro-cognitive testing
Intervention	Concurrent and adjuvant TMZ with radiotherapy
Comparator	Radiotherapy alone
Outcomes	Overall survival (primary outcome) Progression-free survival Quality of life Neuro-cognition Health economics
Study design	Phase III randomised controlled trial
Timeframe	5 - 10 years

IDH isocitrate dehydrogenase; MRI magnetic resonance imaging; TMZ temozolomide

R2. Does a dedicated supportive care clinic in addition to standard care improve outcomes for people with low-grade gliomas?

Why is this important?

People with low-grade gliomas have significant symptoms and complex health care needs across multiple physical, cognitive, emotional and social domains. This is often from the initial diagnosis onwards. There are indications from research literature and patient reports that these needs are currently unmet. Helping people with low-grade gliomas maintain their quality of life and function is important, especially as there is currently no cure, because earlier supportive care interventions and care plans may help reduce unplanned or emergency contact with secondary and tertiary providers.

As no research literature exists which establishes the effectiveness of a specific health care intervention, uncertainty exists about the most appropriate intervention to address unmet needs and improve patient-reported outcome measures (or to establish whether current healthcare provision can meet these needs). Current uncertainty is likely to have led to

variations in service provision across the UK. It is also possible that no specific intervention is available in some areas.

Research is needed to identify whether, in addition to standard care, a specific supportive care intervention can significantly improve patient-reported outcome measures, and if so to establish what this intervention should consist of.

Research recommendation rationale

Research question	Does a dedicated supportive care clinic in addition to standard care improve outcomes for people with low-grade gliomas?
Importance to 'patients' or the population	People with low-grade gliomas have complex needs, often from initial diagnosis, which impact on their quality of life (and for some people their ability to independently carry out activities of daily living). Quality of life and personal independence are important factors for people living with a low-grade glioma. The negative impacts of living with a low-grade glioma are confirmed in surveys undertaken by brain tumour charities. Current research and patient/caregiver feedback would suggest that a high proportion of these needs are unmet by existing healthcare provision.
Relevance to NICE guidance	High Priority: NICE has not been able to make any recommendations on specific interventions to improve supportive care needs despite identifying high health and social care needs.
Relevance to NHS	Incidence of brain tumours is low compared with many other cancers. However, patients are frequently younger, economically active and have dependent children. Their care givers report high levels of distress and carer burden in supporting them.
National priorities	This research is supportive of NHS England's Cancer Strategy Implementation Plan, since it supports the objectives of the 'Living with and beyond cancer' ideals. Additionally, Cancer Research UK has made brain tumours one of its strategic research priorities. Four of the top 10 clinical research priorities set by the James Lind Alliance were related to supporting people to live with the impact of a brain tumour.
Current evidence base	There are a limited number of studies, which are mainly qualitative and confined to people with high-grade glioma, which identify needs rather than interventions to address them. A systematic review of supportive care needs states that there are few trials of interventions, currently no defined follow up and that multidisciplinary teams identified ‘a well-

Research question	Does a dedicated supportive care clinic in addition to standard care improve outcomes for people with low-grade gliomas?
	resourced specialist nurse… integrated service/team clinic including a counsellor' as an intervention that would improve supportive care.
Equality	Brain tumour incidence is relatively consistent across, race, ethnic group, gender, sexuality and economic group. People who do not have English as their first language may not be as readily able to access current information and may find asking for additional supportive care difficult they are therefore likely to require additional support to access supportive care.

Research recommendation PICO

Criterion	Explanation
Population	Histological diagnosis of low-grade glioma (diffuse astrocytoma II IDH mutant, oligodendroglioma II) People aged >18 years People whose first language is not English should not be excluded
Intervention	In addition to standard care, a 6-monthly clinic appointment at: 1. supportive care clinic comprising all or combination of CNS/AHP/counsellor. 2. supportive care clinic comprising all or combination of CNS/AHP/counsellor (as above) and additionally complete a Holistic Needs Assessment (HNA) tool prior to clinic attendance
Comparison	Standard care, which is currently 6-monthly MRI and clinical review appointment with the neurosurgeon or neurologist with or without CNS presence at clinic appointment within the patient's existing neuro oncology service
Outcomes	Primary outcomes: Patient-reported outcome measures (PROMs), validated health-related quality of life measures (for example, EORTC QLQ-C30 or FACT-Br), validated measure of mental health (for example Hospital Anxiety & Depression Scale or Beck depression inventory score), Piper fatigue score, a neuro-cognitive function measure, employment status. Secondary outcome: progression-free survival and overall survival.
Study design	Non-blinded 3-arm randomised controlled trial of a complex intervention.

Criterion	Explanation
Timeframe	Seven years or until malignant transformation of tumour.

AHP allied health professional; CNS cancer nurse specialist; EORTC QLQ European Organisation for Research and Treatment of Cancer quality of life questionnaire; FACT Br Functional Assessment of Cancer Therapy-Brain; IDH isocitrate dehydrogenase; PROMs patient reported outcome measures

R3. Does early referral to palliative care improve outcomes for people with glioblastomas in comparison with standard oncology care?

Why is this important?

People with grade IV brain tumours (glioblastomas) have a poor prognosis which has not improved in over a decade. Median overall survival is 14-18 months even with gold-standard chemoradiation following surgery.

From initial diagnosis people experience multiple complex symptoms resulting from neurological impairment. These can significantly impact on their quality of life, function, and psychological wellbeing. Their caregivers report high levels of distress and carer burden.

The aim of palliative care is to relieve symptoms and improve people's quality of life and function - not just towards the end of life but throughout the duration of illness. There is some evidence that early palliative care referral significantly improves overall survival, quality of life and mood.

Research in this area is important because this group of people have substantial health needs, which use significant health care resources. Supportive care interventions such as early palliative care may improve quality of life and function throughout the duration of illness. It may also help people to manage the distress associated with a reduced life expectancy and participate in advanced care planning.

Research recommendation rationale

Research question	Does early referral to palliative care improve outcomes for people with glioblastomas in comparison with standard oncology care?
Importance to 'patients' or the population	People with glioblastomas have a very poor prognosis, and they and their carers live with complex health and social care needs, which current available literature suggests are largely unmet. There are multiple reasons why people diagnosed with a glioblastoma are not able to openly discuss issues surrounding palliative care so there is little direct information to evaluate how important this is to people. People with glioblastomas often have questions about prognosis, symptom management, and what to expect from caregivers. One qualitative study suggested that people with glioblastomas would like support to discuss reduced life expectancy. There is evidence to suggest barriers on the part of healthcare providers to facilitate discussions

Research question	Does early referral to palliative care improve outcomes for people with glioblastomas in comparison with standard oncology care?
	surrounding prognosis and advanced care planning.
Relevance to NICE guidance	Medium Priority: This guideline has recommended supportive care for people with brain tumours throughout their treatment and care pathway. However, there remains uncertainty about what supportive care should comprise. Research on what supportive care is needed should ultimately reduce variation in interpretation of the guideline recommendations.
Relevance to NHS	Well focused anticipatory support may reduce overall demand for services, improve planned care interventions and patient experience. Supporting people as they approach the end of their life may reduce clinically inappropriate interventions and improve the person's quality of life.
National priorities	This research is supportive of NHS England's Cancer Strategy Implementation Plan, since it evaluates the benefit of earlier palliative care. Additionally, early referral to palliative care is one of the top 10 identified research priorities of the James Lind Alliance
Current evidence base	A recent systematic review found limited evidence for palliative care interventions in people with malignant glioma. Whilst the review did recommend early intervention there is little direct evidence to indicate the most appropriate timing of referral and whether early intervention can improve patient-reported outcome measures (PROMs) such as quality of life or improved symptom control. There is some evidence that early palliative care referral significantly improves quality of life, psychological wellbeing and survival. However, research in brain tumours has focused on identifying needs rather than establishing supportive care interventions which may address these needs.
Equality	Early involvement of palliative care services may help facilitate advanced care planning enabling people to make choices about their care before cognitive impairment results in a loss of decision-making capacity.

Research recommendation PICO

Criterion	Explanation
Population	People with a histological diagnosis of glioblastoma IDH wildtype (WHO grade IV) brain tumour Age >18 years Undergoing chemoradiation
Intervention	In addition to standard oncology care, referral to palliative care within 2 months of diagnosis, initial monthly outpatient meeting/home visit with a palliative care healthcare provider.
Comparison	Standard oncology care as recommended in the guideline, which is currently referral to palliative care agreed by patient and treating oncology team at appropriate timepoint or when anticipate approaching end of life (last 3 months of life).
Outcomes	Primary outcomes: quality of life measure validated within brain tumour population, Hospital Anxiety & Depression Scale (HADS) or similar, symptom burden score (for example, fatigue or seizure frequency), documented advanced care planning. Secondary outcomes: overall survival and carer reported psychological wellbeing.
Study design	Non-blinded randomised controlled trial, as it is not possible to blind participants to whether they have been referred early or not.
Timeframe	Nine months.

IDH isocitrate dehydrogenase; WHO World Health Organisation

R4. Does early detection of recurrence after treatment improve overall survival/outcomes in molecularly stratified glioma?

Why is this important?

Prognosis for brain tumours is inherently uncertain, and recent advances in treatment mean many people with a brain tumour will live for a long time after the initial diagnosis. For these individuals, follow-up is the longest component of their treatment and it is both expensive for the NHS and (sometimes) a burden for the person. There is no high-quality evidence that follow-up after treatment is beneficial, no high-quality evidence on the optimal frequency of imaging and clinical uncertainty about whether such follow-up is likely to alter outcomes of importance to people with tumours (such as overall life expectancy or quality of life).

Research is needed to establish at what point the value of identifying recurrence early is outweighed by the harms of increasing burden to patients.

Research recommendation rationale

Research question	Does early detection of recurrence after treatment improve overall survival/outcomes in molecularly stratified glioma?
Importance to 'patients' or population	Follow-up is burdensome to patients, and - while some patients value the increased contact with the healthcare system - some find it anxiety-inducing. There is clinical uncertainty about whether follow-up is actually beneficial to patients, and therefore it is of high priority to establish if the harms of follow-up are outweighed by an increase in overall survival or improvement in quality of life.
Relevance to NICE guidance	High priority: the committee based their suggested follow-up times on their clinical experience and judgement, but even given this there was large uncertainty about timing and frequency of follow-up.
Relevance to NHS	As many people with brain tumours, especially low-grade glioma, will live a long time after their initial diagnosis, follow-up is the longest component of most people's brain tumour treatment. As such it involves a large number of NHS contacts, which is burdensome for the person with the tumour, expensive for the NHS and of uncertain value. Additionally, the optimal schedule of imaging is unknown, and this trial would help direct future research in this area.
National priorities	This research is supportive of NHS England's Cancer Strategy Implementation Plan, since it supports the use of risk-stratified follow-up pathways. This research is also supportive of a top 10 priority from the James Lind Alliance - ' What is the effect on prognosis of interval scanning to detect tumour recurrence, compared with scanning on symptomatic recurrence, in people with a brain tumour?'
Current evidence base	There is no high-quality evidence on this topic, and the low-quality evidence that exists is inconsistent and incomplete.
Equality	Follow-up is more burdensome for certain protected groups, such as people with physical or mental disabilities. Additionally, there are implications for people living in rural areas or caring for dependents if follow-up is more frequent. Identifying whether the excess burden on these groups is justifiable is an important equalities question.

Research recommendation PICO

Criterion	Explanation
Population	Adults (18 years onwards) with newly treated glioma stratified by molecular subtypes
Prognostic or risk factor	Routine imaging (as per guideline recommendations) with intervention when needed
Comparator (without the risk factor)	Imaging on symptoms only with immediate intervention
Outcomes	Overall survival (primary outcome) Neurological function Cost effectiveness
Study design	A prospective multi-centre study collecting prospective community (GP) service, imaging service and hospital data
Timeframe	Will vary by subgroup, but in some groups the timeframe will be 10 years at a minimum