National Institute for Health and Care Excellence

Draft for Consultation

Brain tumours (primary) and brain metastases in adults

Clinical evidence tables and health economic global evidence search

NICE guideline <number>

Supplementary Material D

January 2018

Draft for Consultation

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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ISBN:

Contents

Clinical evidence tables

Evidence tables for review 1a - Diagnosing radiologically identified glioma and meningioma

Study	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Caulo, M., Panara, V., Tortora, D., Mattei, P. A., Briganti, C., Pravata, E., Salice, S., Cotroneo, A. R., Tartaro, A., Data-driven grading of brain gliomas: a multiparametric MR imaging study, Radiology, 272, 494-503, 2014 Ref Id 603434 Study dates Patients underwent MR imaging from January 2008 to September 2012 Source of funding Not reported Country/ies where the study was carried out	Sample size 110 patients from a single university hospital database. Characteristics All patients presented with a histologically proven diagnosis of previously untreated brain glioma (diffuse and anaplastic astrocytoma, glioblastoma, gliosarcoma, and oligodendrial and oligoastrocytic tumours). 66 men and 44 women, aged 24-82 years; mean age, 54 years. Diagnosis and classification according to WHO criteria were confirmed with either surgery (97 of 110 patients) or biopsy (13 of 110 patients). Gliomas were divided into low (WHO grade II) and high (WHO grades III and IV) grades. Inclusion criteria	Index test (1) Conventional MR imaging: Pre- and postgandolinium enhanced: 0.1mL/kg gadobutrol administered Three-dimensional turbo field-echo T1-weighted: sagittal acquisition; repetition time (msec)/echo time (msec), 7.6/3.7 section thickness, 1 mm; matrix, 300x256 Fluid-attenuated inversion recovery: 3-mm axial acquisition, 11000/125; inversion time (msec), 2800; matrix, 320 x 256 T1-weighted fast field echo: 3-mm axial acquisition, 1039/16; matrix, 256 x 197 Index test (2) Advanced MR imaging Difussion-weighted imaging: single shot echo-planar imaging, 28 sections (4mm) obtained Diffusion-tensor imaging: single-shot spin-echo echo-	Methods Conventional and advanced MR imaging sequences were performed during a single imaging session. Images were obtained with a 3-T MR imaging system by “using a sensitivity-encoding eight-channel head coil”. Each patient was evaluated with 3 different methods: Semiqualitative: radiologic report written at initial patient presentation was considered; 2	Results Quantitative analyses - Results of the ROC analysis of the glioma-grading index yielded a cutoff value of -0.3096 for distinguishing high- and low-grade gliomas. [advanced MRI imaging techniques: perfusion-weighted imaging; MRS; DWI and DTI) LR- = 15.8% Quantitative analyses - Results of the ROC analysis of the glioma-grading index yielded a cutoff value of -0.3096 without including oligodendroglioma (ODG) [which has a “different pattern of vascularization compared with diffuse astrocytoma”]	Limitations Limitations assessed with the QUADAS-2 Checklist: Domain 1: Patient selection 1. Risk of bias Was a consecutive or random sample of patients enrolled? yes Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? yes Could the selection of patients have introduced bias? no Risk: low 2. Concerns regarding applicability

		Histology	Histology
		HGG	LGG
Advanced MRI	HGG	65	0
Advanced MRI	LGG	12	33
		Sensitivity = 83.7%	Specificity = 100%

	Histology	Histology
Advanced MRI	64	2

Study	Participants	Tests	Methods	Outcomes and results	Comments
Italy Study type Retrospective cohort study Aim of the study To grade brain gliomas by using conventional MR imaging (pre-and postgandolinium enhanced; three-dimensional turbo fields-echo T1-weighted; turbo spin-echo T2-weighted; fluid-attenuated inversion recovery; T2-weighted fast field echo) and advanced MR imaging (diffusion-weighted imaging [DWI]; diffusion-tensor imaging [DTI]; MR spectroscopy [MRS] and perfusion weighted imaging)	Not reported Exclusion criteria Not reported	planar imaging; 15 diffusion-sensitive sections MR spectroscopy: “metabolic scatter graph, metabolic ratio image, and metabolic anatomy image were obtained by using the built-in software in Phillips-extended MR WorkSpace; identical 10x10x15-mm”. “Axial turbo spin-echo T2- and T1- weighted sequences” were completed immediately before and after MRS, respectively. Perfusion-weighted imaging: “T2-weighted fast field-echo echo-planar imaging was performed; a series of 50 volumes was acquired during a intravenous bolus injection of 0.1 mmol per kilogram of body weight of contrast media at flow rate of 4mL/sec, followed by a 20-mL saline flush”. Reference standard All patients received a histologic diagnosis of glioma <table><tr><td></td><td>No of patients</td></tr><tr><td>Grade II</td><td></td></tr></table>	neuroradiologists used the colour map images from the perfusion-weighted images, MR spectroscopy, and cut off data reported in the literature (thresholds of 1.75 for relative cerebral blood volume, 1.5 for choline and 1.5 for Cho/NAA) Qualitative: done by consensus of 2 different neuroradiologists who were blinded to glioma grade. Evaluation was based on conventional MR imaging sequences only Quantitative: volumes of interest were placed by 2	<table><tr><td>Advanced MRI</td><td>9</td><td>24</td></tr><tr><td></td><td>Sensitivity = 87.7%</td><td>Specificity = 92%</td></tr></table> LR+ = 11.39; LR- = 0.1336 Qualitative analyses (conventional MRI) <table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td></td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Advanced MRI</td><td>HGG</td><td>64</td><td>13</td></tr><tr><td>Advanced MRI</td><td>LGG</td><td>13</td><td>20</td></tr><tr><td></td><td></td><td>Sensitivity = 82.9%</td><td>Specificity =61.8 %</td></tr></table> LR+ = 2.1702 ; LR- = 0.2767 Semiquantitative analysis (perfusion imaging and MRS) <table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td></td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Advanced MRI</td><td>HGG</td><td>63</td><td>17</td></tr><tr><td>Advanced MRI</td><td>LGG</td><td>14</td><td>17</td></tr><tr><td></td><td></td><td>Sensitivity = 81.6%</td><td>Specificity = 50%</td></tr></table> LR+ = 1.6364 ; LR- = 0.3636	Is there concern that the included patients do not match the review question? no Concern: low Domain 2: Index test(s) 1a. Risk of bias-quantitative method Were the index test results interpreted without knowledge of the results of the reference standard? unclear Did the study provide a clear definition of what was considered to be a positive result? yes If a threshold was used, was it pre-specified? no Could the conduct or

Study	Participants	Tests	Methods	Outcomes and results	Comments
		Diffuse astrocytoma: 21 Oligoastrocytoma: 4 ODG: 8 Grade III: Anaplastic astrocytoma: 13 Anaplastic oligoastrocytoma: 1 Anaplastic ODG: 3 Grade IV: Glioblastoma: 59 Gliosarcoma: 1	neuroradiologists in consensus and 2 independent neuroradiologists in 5 different tumour regions: contrast-enhacing regions; regions with highest signal intensity on T2-weighted images; regions with lowest signal intensity on T2-weighted images; regions with most restricted diffusivity and areas in contralateral normal-appearing white matter. The volumes of interest, varying from 30 mm3 to 60 mm3, were positioned to	Concordance of the 3 types of analysis (qualitative, quantitative and semiquantitative) and histologic findings: r qualitative analysis (k=0.523); semiquantitative (k=0.563) and good quantitative analysis (k=0.803)	interpretation of the index test have introduced bias? yes Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Risk: high 2. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no Concern: low Domain 3: Reference standard 1. Risk of bias Is the reference standard likely to correctly classify the target condition? yes

Study	Participants	Tests	Methods	Outcomes and results	Comments
			avoid partial-volume contamination from adjacent nontumour tissue. Blood volume and mean transit time maps were generated from perfusion-weighted imaging data, and rCBV and relative mean transit time were assessed in each area. MR spectroscopy-derived metabolite ratios were estimated in voxels that corresponded to each area. From diffusion-weighted imaging data, ADC maps were generated, and values were assessed		Were the reference standard results interpreted without knowledge of the results of the index test? unclear Could the reference standard, its conduct, or its interpretation have introduced bias? no Risk: low 2. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does not match the review question? no Concern: low Domain 4: Flow and timing

Study	Participants	Tests	Methods	Outcomes and results	Comments
			in each area. Diffussion-tensor imaging fractional anisotropy was calculated in each area from respective maps.		1. Risk of bias Was there an appropriate interval between index test(s) and reference standard? uncl ear Did all patients receive a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes Could the patient flow have introduced bias? unclear Was the study free of commercial funding? unclear Risk: low (MSH: I woulod say unclear as we don't know how long time

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>elapsed between the index test and reference standard and that can be crucial)
Other information</td></tr>
<tr><td>Full citation
Zou, Q. G., Xu, H. B., Liu, F., Guo, W., Kong, X. C., Wu, Y., In the assessment of supratentorial glioma grade: the combined role of multivoxel proton MR spectroscopy and diffusion tensor imaging, Clinical RadiologyClin Radiol, 66, 953-60, 2011
Ref Id
606094
Study dates
Not reported.
Source of funding
Partially funded by Nature Science</td><td>Sample size
30 patients with supratentorial gliomas.
Characteristics
All patients presented with symptoms and a suspicion of a previously untreated brain glioma. All lesions were confirmed histologically as supratentorial gliomas.
Gender of patients not reported. Age 20-77 years; mean age, 46.
Diagnosis and classification according to WHO criteria were confirmed with either surgery or biopsy. Gliomas were divided into low (WHO grade I-II) and high (WHO grades III and IV) grades.
Inclusion criteria</td><td>Index test (1)
Conventional MR imaging:
T-1 weighted contrast was administered. T2-weighted, axial, fast spin-echo sequence (“4000 msec TR, 90 msec TE, 23 cm field of view (FOV), 5 mm section thickness with 2mm intersection gap”) and a fluid-attenuated inversion recovery (FLAIR) sequence in three orthogonal planes (“9000 msec TR, 120 msec TE, 2000 msec inversion time, 23 cm FOV, 5 mm section thickness with 2 mm intersection gap”).
Index test (2)
Advanced MR imaging
MRS imaging: spectra obtained using multivoxel point-resolved spectroscopic sequence (PRESS) with 1350 msec TR/135 msec</td><td>Methods
Conventional MRI, DWI and MRS performed during a single imaging session. Images were acquired using a 1.5 T whole-body MRI system (Siemens Magnetom Avanto system, Siemens Medical Solutions, Erlangen, Germany), using a standard circular polarized head</td><td>Results
Statistically significant differences in grading low- and high-grade gliomas were observed for Cho/Cr, NAA/Cr, NAA/Cho ratio, ADC (P < 0.01) and FA value (P < 0.05) parameters. The NAA/CR and NAA/Cho ratios and calculated ADC value significantly correlated to grading of tumours (P < 0.01).
For the purpose of this systematic review, and for consistency with the PICO criteria, only data relevant to conventional MRI and combined advanced MRI strategies was reported.

Conventional MRI
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Conventional MRI</td><td>HGG</td><td>13</td><td>4</td></tr>
<tr><td>conventional MRI</td><td>LGG</td><td>5</td><td>8</td></tr>
</table></td><td>Limitations
Limitations assessed with the QUADAS-2 Checklist:
Domain 1: Patient selection
1. Risk of bias
Was a consecutive or random sample of patients enrolled? unclear
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? unclear
Could the selection of</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Foundation of China and Hubei Key Laboratory of Molecular Imaging, and National Fundamental Key Projection of Science.
Country/ies where the study was carried out
China
Study type
Prospective cohort study
Aim of the study
To determine whether proton magnetic resonance spectroscopy (1H-MRS) and diffusion tensor imaging (DTI) can improve the diagnostic accuracy of conventional MR imaging in grading supratentorial gliomas.</td>
<td>Patients with
Exclusion criteria
Not reported</td>
<td>TE, collection of four, scan time 7 min 12 sec. Automatic optimisation of gradient shimming, transmitter pulse power, and water suppression used. Volumes of interest (VOIs) 15 mm X 15 mm x 20 mm.
DT imaging: single shot spin-echo echo planar imaging (SE-EPI) sequence, 4800 msec TR, 83 msec TE, 23 cm FOV, 128 X 128 matrix, b = 0 sec/mm2 (reference) and b = 1000 sec/mm2, 12 diffusion sensitive dimensions, acquisition frequency of four, scan time 4 min 22 sec.
Reference standard
All patients received a histologic diagnosis of glioma
<table>
<tr><td></td><td>No of patients</td></tr>
<tr><td>Grade I</td><td></td></tr>
<tr><td>Astrocytoma</td><td>1</td></tr>
<tr><td>Grade II</td><td></td></tr>
<tr><td>Astrocytoma</td><td>7</td></tr>
</table>
</td>
<td>coil. Post-processing performed using a Siemens Avanto workstation.
Two neuroradiologists were blinded to the histopathological results, evaluated conventional MRI images. The NAA/Cr, Cho/Cr, NAA/Cho, ADC value and FA value of each ROI were measured and mean values calculated. Receiver operating characteristic (ROC) analyses were used to determine optimum thresholds for glioma grading.</td>
<td>
<table>
<tr><td></td><td></td><td>Sensitivity = 72%</td><td>Specificity = 67%</td></tr>
</table>
LR+= 2.1; LR=0.4

Combination NAA/Cho (< 0.265) and ADC < 1118.1 X 10-6 mm2/sec:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>15</td><td>0</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>3</td><td>12</td></tr>
<tr><td></td><td></td><td>Sensitivity = 83.3%</td><td>Specificity = 100.0%</td></tr>
</table>
Fraction misclassified = 10%
LR-=0.16
</td>
<td>patients have introduced bias? unclear
Risk: unclear
2. Concerns regarding applicability
Is there concern that the included patients do not match the review question? no
Concern: low
Domain 2: Index test(s)
1a. Risk of bias-
Were the index test results interpreted without knowledge of the results of the reference standard? unclear
Did the study provide a clear definition of what was considered to be a positive result? yes</td>
</tr>
</table>

Study	Participants	Tests	Methods	Outcomes and results	Comments
		Oligodendrogliomas: 4 Grade III: Anaplastic astrocytoma: 1 Anaplastic oligoastrocytoma: 2 Grade IV: Glioblastoma: 15	Parameters were analysed using the independent sample t-test, Spearman's rank correlation, and the Fisher's exact test.		If a threshold was used, was it pre-specified? no Could the conduct or interpretation of the index test have introduced bias? unclear Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Risk: unclear 2. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no Concern: low Domain 3: Reference standard

Study	Participants	Tests	Methods	Outcomes and results	Comments
					1. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? yes Could the reference standard, its conduct, or its interpretation have introduced bias? no Risk: low 2. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does

Study	Participants	Tests	Methods	Outcomes and results	Comments
					not match the review question? no Concern: low Domain 4: Flow and timing 1. Risk of bias Was there an appropriate interval between index test(s) and reference standard? unclear Did all patients receive a reference standard? yes Did patients receive the same reference standard? yes Were all patients included in the analysis? yes Could the patient flow have introduced bias? unclear Was the study free of

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>commercial funding? yes
Risk: unclear
Other information</td></tr>
<tr><td>Full citation
Law, M., Yang, S., Wang, H., Babb, J. S., Johnson, G., Cha, S., Knopp, E. A., Zagzag, D., Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging, AJNR Am J Neuroradiol, 24, 1989-98, 2003
Ref Id
644328
Study dates
November 1999 to July 2002.
Source of funding</td><td>Sample size
160 patients with primary cerebral gliomas.
Characteristics
All patients presented with a histologically confirmed primary cerebral glioma.
108 men and 52 women, aged 4-82 years; mean age, 43 years.
Gliomas were classified as follows: grade 1, low-grade glioma; grade 2, anaplastic glioma; and grade 3, glioblastoma multiforme.
Inclusion criteria
Not reported.
Exclusion criteria
Not reported.</td><td>Index test (1)
Conventional MR imaging:
1.5-T unit (Vision or Symphony; Siemens AG, Erlangen, Germany).
Localising sagittal T1-weighted image obtained followed by nonenhanced axial T1-weighted (600/14 TR/TE), axial fluid-attenuated inversion-recovery (FLAIR, 9000/110/2500 TR/TE/TI), and T2-weighted (3400/119) images.
Index test (2)
Advanced MR imaging
Dynamic contrast-enhanced perfusion MR imaging: Dynamic contrast agent-enhanced T2*-weighted gradient echo echo-planar images acquired during the first pass of a standard dose (0.1 mmol/kg) bolus of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ). Using T2-weighted and</td><td>Methods
Contrast material-enhanced axial T1-weighted imaging for the conventional MR images was performed after the acquisition of the perfusion MR imaging data and reviewed by two blinded board certified neuroradiologists. Data processing for perfusion MR imaging was performed using a Unix workstation with analytic programs developed in-house by</td><td>Results

Conventional MRI
<table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td></td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Conventional MRI</td><td>HGG</td><td>86</td><td>14</td></tr><tr><td>Conventional MRI</td><td>LGG</td><td>34</td><td>26</td></tr><tr><td></td><td></td><td>Sensitivity =72%</td><td>Specificity =65%</td></tr></table>
LR+ =2.05; LR-=0.43

rCBV for tumour/normal tissue with a threshold value of 1.75 and minimal C2 error (the % of observed data points misclassified):
<table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td>Advanced MRI</td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Advanced MRI</td><td>HGG</td><td>114</td><td>17</td></tr></table></td><td>Limitations
Limitations assessed with the QUADAS-2 Checklist:
Domain 1: Patient selection
1. Risk of bias
Was a consecutive or random sample of patients enrolled? unclear
Was a case-control design avoided? yes
Did the study avoid inappropriate exclusions? unclear
Could the selection of patients have introduced bias? unclear
Risk: unclear</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>The Royal Australian and New Zealand College of Radiologists, Grant RO1CA092992 from NCI/National Institute of Health.
Country/ies where the study was carried out
USA
Study type
Retrospective cohort study.
Aim of the study
To evaluate and compare with conventional MR imaging whether relative cerebral blood volume (rCBV) measurements obtained from perfusion MR imaging and metabolite ratios from proton MR spectroscopy are useful in predicting glioma grade.</td>
<td></td>
<td>FLAIR images, seven to 10 sections through the tumour were selected for perfusion MR imaging.
Proton MR spectroscopic imaging: Multivoxel 2D proton chemical shift imaging (CSI) or spectroscopic imaging performed after gadopentetate dimeglumine was administered. Volume of interest (VOI) confirmed by half-Fourier acquisition single-shot turbo spin-echo images (5/6/500 1 TR/TE/TI/NEX). Ten sections with 5-mm section thickness obtained in 1 minute 15 seconds in the axial, coronal, and sagittal planes. Volume selective 2D CSI sequence with 1500/144, with point-resolved spectroscopy (PRESS) double spin-echo sequence. A 16 X 16 phase-encoding matrix was used to obtain a 8 X 8 array of spectra in the VOI (in plane resolution of 1 x 1 cm, voxel size 1 X 1 X 1.5 cm3 or 1 X 1 X2 cm3, depending on the size of the lesion.
Reference standard</td>
<td>using C and IDL programming languages. Measurements for rCBV were obtained by a neuroradiologst (blinded to conventional and MR spectroscopic findings) experienced with perfusion data acquisition. For the MR specotroscopic imaging, metabolite ratios were obtained by a neuroradiologist experienced with spectroscopy (blinded to perfusion and conventional MR imaging data). Maximal Cho/Cr and Cho/NAA ratios and minimum NAA/Cr ratios</td>
<td>
<table>
<tr><td></td><td>LGG</td><td>6</td><td>23</td></tr>
<tr><td></td><td></td><td>Sensitivity = 95.0%</td><td>Specificity = 57.5%</td></tr>
</table>
LR+ = 2.2093; LR- = 0.0870
rCBV for tumour/normal tissue with a threshold value of 2.97 and minimal C1 error (maximised average of the observed sensitivity and specificity):
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>87</td><td>5</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>33</td><td>35</td></tr>
<tr><td></td><td></td><td>Sensitivity = 72.5%</td><td>Specificity = 87.5%</td></tr>
</table>
LR+ = 5.8000; LR- = 0.3143

rCBV for tumour/normal tissue with a threshold value (2.97) adjusted to provide the same sensitivity as cMRI
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>86</td><td>5</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>34</td><td>35</td></tr>
</table>
</td>
<td>2. Concerns regarding applicability
Is there concern that the included patients do not match the review question? no
Concern: low
Domain 2: Index test(s)
1a. Risk of bias-
Were the index test results interpreted without knowledge of the results of the reference standard? yes
Did the study provide a clear definition of what was considered to be a positive result? yes
If a threshold was used, was it pre-specified? no
Could the conduct or</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>All patients received a histological diagnosis of glioma and/or metastases.
<table>
<tr><td></td><td>No of patients</td></tr>
<tr><td>Grade 1</td><td></td></tr>
<tr><td>Low-grade glioma</td><td>40</td></tr>
<tr><td>Oligogodendroglioma</td><td>10</td></tr>
<tr><td>Grade 2</td><td></td></tr>
<tr><td>Anaplastic astrocytomas</td><td>26</td></tr>
<tr><td>Anaplastic oligodendrogliomas</td><td>7</td></tr>
<tr><td>Anaplastic mixed oligoastrocyomas</td><td>40</td></tr>
<tr><td>Grade 3</td><td></td></tr>
<tr><td>Glioblastoma multiforme</td><td>47</td></tr>
</table>
</td>
<td>were obtained from spectral maps. Normal values for Cho/NAA and NAA/Cr were obtained in normal-appearing white matter.
High-grade gliomas were identified by calculating sensitivity, specificity, PPV, and NPV values. Receiver operating characteristic (ROC) curve analyses were used to evaluate the performance of rCBV and metabolite ratios. Mann-Whitney tests were used to analyse parameters</td>
<td>
<table>
<tr><td></td><td></td><td>Sensitivity = 72%</td><td>Specificity = 88%</td></tr>
</table>
LR+= 6.00; LR-= 0.31

rCBV for tumour/normal tissue with a threshold value (2.18) adjusted to provide the same specificity as cMRI
<table>
<tr><td></td><td></td><td>Histology</td><td>Advanced MRI</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>105</td><td>14</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>15</td><td>26</td></tr>
<tr><td></td><td></td><td>Sensitivity = 88%</td><td>Specificity =65%</td></tr>
</table>
LR+= 2.50; LR-= 0.19

Cho/Cr ratio for tumour/normal tissue with a threshold value of 1.08 and minimal C2 error:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>117</td><td>35</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>3</td><td>5</td></tr>
</table>
</td>
<td>interpretation of the index test have introduced bias? no
Are there concerns that the index test, its conduct, or interpretation differ from the review question? no
Risk: low
2. Concerns regarding applicability
Is there concern that the index test, its conduct, or interpretation differ from the review question? no
Concern: low
Domain 3: Reference standard
1. Risk of bias
Is the reference standard likely to correctly classify the target condition? yes</td>
</tr>
</table>

Study	Participants	Tests	Methods	Outcomes and results	Comments
				<table><tr><td></td><td></td><td>Sensitivity = 97.5%</td><td>Specificity = 12.5%</td></tr></table> LR+ = 1.1143; LR- = 0.2000 Cho/Cr ratio for tumour/normal tissue with a threshold values of 1.56 and minimal C1 error: <table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td></td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Advanced MRI</td><td>HGG</td><td>91</td><td>21</td></tr><tr><td>Advanced MRI</td><td>LGG</td><td>29</td><td>19</td></tr><tr><td></td><td></td><td>Sensitivity = 75.8%</td><td>Specificity = 47.5%</td></tr></table> LR+ = 1.4438; LR- = 0.5095 Cho/Cr for tumour/normal tissue with a threshold value (1.61) adjusted to provide the same sensitivity as cMRI: <table><tr><td></td><td></td><td>Histology</td><td>Histology</td></tr><tr><td></td><td></td><td>HGG</td><td>LGG</td></tr><tr><td>Advanced MRI</td><td>HGG</td><td>86</td><td>20</td></tr><tr><td>Advanced MRI</td><td>LGG</td><td>34</td><td>20</td></tr><tr><td></td><td></td><td>Sensitivity = 72%</td><td>Specificity =50%</td></tr></table>	Were the reference standard results interpreted without knowledge of the results of the index test? yes Could the reference standard, its conduct, or its interpretation have introduced bias? no Risk: low 2. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does not match the review question? no Concern: low Domain 4: Flow and timing 1. Risk of bias

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>LR+= 1.44; LR-= 0.56

Cho/Cr for tumour/normal tissue with a threshold value (1.88) adjusted to provide the same specificity as cMRI:

<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>66</td><td>7</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>54</td><td>13</td></tr>
<tr><td></td><td></td><td>Sensitivity = 55%</td><td>Specificity =65%</td></tr>
</table>
LR+= 1.57; LR-= 0.69

Cho/NAA ratio for tumour/normal tissue with a threshold value of 0.75 and minimal C2 error:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>116</td><td>36</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>4</td><td>4</td></tr>
<tr><td></td><td></td><td>Sensitivity = 96.7%</td><td>Specificity = 10.0%</td></tr>
</table>
</td><td>Was there an appropriate interval between index test(s) and reference standard? unclear
Did all patients receive a reference standard? yes
Did patients receive the same reference standard? yes
Were all patients included in the analysis? yes
Could the patient flow have introduced bias? unclear
Was the study free of commercial funding? yes
Risk: unclear
Other information</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>LR+ = 1.0744 LR- = 0.0870

Cho/NAA ratio for tumour/normal tissue with a threshold value of 1.60 and minimal C1 error:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>89</td><td>15</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>31</td><td>25</td></tr>
<tr><td></td><td></td><td>Sensitivity = 74.2%</td><td>Specificity = 62.5%</td></tr>
</table>
LR+ = 1.9787; LR- = 0.4128

Cho/NAA ratio for tumour/normal tissue with a threshold value (1.66) adjusted to provide the same sensitivity as cMRI:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>86</td><td>15</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>34</td><td>25</td></tr>
<tr><td></td><td></td><td>Sensitivity = 72%</td><td>Specificity = 63%</td></tr>
</table>
LR+ = 1.94; LR- = 0.44</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Cho/NAA ratio for tumour/normal tissue with a threshold value (1.78) adjusted to provide the same specificity as cMRI:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>82</td><td>14</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>38</td><td>126</td></tr>
<tr><td></td><td></td><td>Sensitivity = 68%</td><td>Specificity = 65%</td></tr>
</table>
LR+ = 1.94; LR- = 0.49

Combined rCBv, Cho/Cr ratio, and Cho/NAA ratio parameters for minimal C2 error:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>112</td><td>16</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>8</td><td>24</td></tr>
<tr><td></td><td></td><td>Sensitivity = 93.3%</td><td>Specificity = 60.0%</td></tr>
</table>
LR+ = 2.3325; LR- = 0.1117</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Combined rCBv, Cho/Cr ratio, and Cho/NAA ratio parameters for minimal C1 error:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>85</td><td>35</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>3</td><td>37</td></tr>
<tr><td></td><td></td><td>Sensitivity = 70.8%</td><td>Specificity = 92.5%</td></tr>
</table>
LR+ = 10.1429; LR- = 0.3157

Combined rCBv, Cho/Cr ratio, and Cho/NAA ratio parametersadjusted to provide the same sensitivity as cMRI:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>87</td><td>5</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>33</td><td>35</td></tr>
<tr><td></td><td></td><td>Sensitivity = 72%</td><td>Specificity = 88%</td></tr>
</table>
LR+ = 5.800; LR- = 0.3143</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Combined rCBv, Cho/Cr ratio, and Cho/NAA ratio parametersadjusted to provide the same specificity as cMRI:
<table>
<tr><td></td><td></td><td>Histology</td><td>Histology</td></tr>
<tr><td></td><td></td><td>HGG</td><td>LGG</td></tr>
<tr><td>Advanced MRI</td><td>HGG</td><td>107</td><td>14</td></tr>
<tr><td>Advanced MRI</td><td>LGG</td><td>13</td><td>26</td></tr>
<tr><td></td><td></td><td>Sensitivity = 89%</td><td>Specificity = 65%</td></tr>
</table>
LR+ = 2.5429; LR- = 0.1692</td><td></td></tr>
<tr><td>Full citation
Qin, J. B., Liu, Z., Zhang, H., Shen, C., Wang, X. C., Tan, Y., Wang, S., Wu, X. F., Tian, J., Grading of gliomas by using radiomic features on multiple magnetic resonance imaging (MRI) sequences, Medical Science Monitor, 23, 2168-2178, 2017</td><td>Sample size
n=66. All presented with sequences of T2-FLAIR and T1WI-CE n=63 presented with DWI sequences were included.

Characteristics
33 males; 22-73 years old ;mean age 51.5 years

Inclusion criteria
MRI performed prior to intervention</td><td>Index test (1)
All patients underwent conventional MRI sequences axial T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Axial contrast-enhanced T1WI was repeated after intravenous administration of 0.1mmol/kg of gandolinium contrast gadopentetate dimeglumine.
T1WI had a repetition time (ms)/echo time (ms) of 195/4.76 and axial T2-weighted imaging (T2WI)</td><td>Methods
The MR image of the T2WI-FLAIR , T1WI-CE, and ADC maps were transmitted from the PACS workstation and then transferred into processable DICOM format images.
Due to the heterogeneity</td><td>Results
The radiomic features found to have statistical differential feature found were as follows: 1) T2-WI - FLAIR GLCM cluster shade; 2) T1 W1-CE GLCM Entropy on the T1-WI sequence; 3) ADC homogeneity on the ADC map
ROC analysis of the diagnostic efficiency of the individual radiomic features and the combined feature for differentiating LGGs from HGGs
1) The AUC value of FLAIR GLCM Cluster Shade
Cut off= 10.217 (p<0.05)
AUC = 0.654
Sensitivity = 75%</td><td>Limitations
Limitations assessed with the QUADAS-2 Checklist:
Domain 1: Patient selection
1. Risk of bias
Was a consecutive or random sample of patients enrolled? no</td></tr>
</table>

Study	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 660717 Study dates February 2012 to October 2015 Source of funding Natural Science Foundation of China Country/ies where the study was carried out China Study type Retrospective cohort study Aim of the study To improve the power of glioma grading by combining different radiomic features	(chemoradiotherapy/surgical resection); histopathological diagnoses of LGG or HGG using the WHO criteria; Exclusion criteria Not reported	with 4000/98 and T2WI-FLuid Attenuated Inversion Recovery (T2WI-FLAIR) with 8000/95 and inversion time (TI) of 2371.8 ms. Index test (2) A total of 62 patients underwent axial DWI. DWI scans used the SE/EPI sequence, and the diffusion coefficient of sensitivity as selected as 0.1000 s/mm2. The original DWI maps were transmitted to ADW4.4 to generate axial ADC maps using GE software processing. Reference standard Histopathology. GTR was performed in 65 gliomas, with 1 glioma partially resected. These were classified according to WHO 2007 criteria.	of gliomas, D regions of interest were delineated manually by 2 way-blinded neuroradiologists until they reached an agreement on areas of enhancement in each axial T post-contrast MR slice, tumour parenchyma T2-FLAIR, and ADC maps layer-by-layer. 2-sample t test was used to compare the values of all strategies to differentiate between LGGs and HGGs on the T2WI-FLAIR, T1WI-CE and ADC map. Radiomic features that showed statistical difference between LGGs	Specificty = 84.6% LR+= 4.8, LR-= 0.2 2) T1W1-CE GLCM Entropy on the T1W1-CE sequence Cut off=1.176 (p<0.005) AUC = 0.920 Sensitivity = 97.5% Specificty = 80.8% LR+= 5.07; LR-=0.03 3) ADC homogeneity on the ADC map Cut off = 1.176 (p<0.005) AUC = 0.684 Sensitivity = 97.5% Specificity = 80.8% LR+= 5.07; LR-=0.03 4)Combined feature AUC = 0.943 Sensitivity = 90% Specificty = 89% LR+=8.1; LR-=0.1	Was a case-control design avoided? yes Did the study avoid inappropriate exclusions? yes Could the selection of patients have introduced bias? no Risk: low 2. Concerns regarding applicability Is there concern that the included patients do not match the review question? no Concern: low Domain 2: Index test(s) 1a. Risk of bias-quantitative method Were the index test results interpreted without knowledge of

Study	Participants	Tests	Methods	Outcomes and results	Comments
			and HGGs were further compared using 1-way ANOVA to test for differences among grade II, III and IV gliomas. Finally, ROC analysis of these statistical significant diagnostic features were compared with the combined feature.		the results of the reference standard? yes (2-way blinded experienced neuroradiologists) Did the study provide a clear definition of what was considered to be a positive result? no If a threshold was used, was it pre-specified? no Could the conduct or interpretation of the index test have introduced bias? yes Are there concerns that the index test, its conduct, or interpretation differ from the review question? no Risk: high

Study	Participants	Tests	Methods	Outcomes and results	Comments
					2. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? no Concern: low Domain 3: Reference standard 1. Risk of bias Is the reference standard likely to correctly classify the target condition? yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear Could the reference standard, its conduct, or its

Study	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation have introduced bias? no Risk: low 2. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does not match the review question? no Concern: low Domain 4: Flow and timing 1. Risk of bias Was there an appropriate interval between index test(s) and reference standard? yes (2 weeks) Did all patients receive a reference standard? yes

Study	Participants	Tests	Methods	Outcomes and results	Comments
					(although 2 patients did not receive DWI sequence) Did patients receive the same reference standard? yes Were all patients included in the analysis? yes Could the patient flow have introduced bias? unclear Was the study free of commercial funding? unclear Risk: low Other information

1

2 # Evidence tables for review 1b - Diagnosing radiologically identified brain metastases

3 Not applicable - no evidence was identified.

1 Evidence tables for review 1c - Timing and extent of initial surgery for low-grade glioma

Study details	Participants	Interventions	Methods/risk of bias	Results
Full citation Alattar, A. A., Brandel, M. G., Hirshman, B. R., Dong, X., Carroll, K. T., Ali, M. A., Carter, B. S., Chen, C. C. Oligodendroglioma resection: a Surveillance, Epidemiology, and End Results (SEER) analysis. Journal of Neurosurgery, 2017 p.1-8 Ref Id 657217 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “we used the Surveillance, Epidemiology,	N = 2378 patients had grade II oligodendroglioma (patient characteristics only given for whole group, not split by extent of resection): Median age (IQR) = 41 (32-51) years (please note N = 146 aged < 18 years); males / females: N = 1325 / 1053; tumour locations frontal lobe / temporal lobe/ parietal lobe / occipital lobe / brain stem / overlapping lesion of brain / cerebrum / brain NOS / ventricle NOS / cerebellum NOS: N = 1257 / 453 / 232 / 36 / 8 / 233 / 60 / 70 / 13 / 16; tumour size cm < 5 / 5-7 / > 7: 859 / 442 / 180; divided into 4 groups, based on extent of resection: - No surgery: N = 438 - Local excision/biopsy (LEB): N = 550 - Subtotal resection (STR): N = 557. - Total resection (GTR): N = 833. Inclusion criteria Patients of all ages with a diagnosis of oligodendroglioma (ICD-O-3 histology code 9450) or anaplastic oligodendroglioma (ICD-O-3 histology codes 9451 and 9460). Please note only grade II is in PICO so no details	- No surgery (tissue diagnosis obtained from autopsy) versus - Local excision/biopsy (LEB) versus - STR versus - GTR (assignment to LEB, STR or GTR based on operative/ radiographic reports of postoperative MR images). Other treatments: Radiotherapy yes / no: N = 816 / 1491 (not split by resection group) Follow up: Not reported	-Bias due to confounding: serious risk of bias (unadjusted for performance status, unclear if anyone received chemotherapy) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: unclear risk of bias (no information reported) -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (uncontrolled confounders) Other information: Please note N = 146 aged < 18 years). Population had confirmed, not suspected LGG.	Overall survival: Multivariate analysis controlling for sex, age, race, marital status, tumour size, tumour site, year of diagnosis, and radiotherapy found the following HRs for extent of resection: - No surgery (75ST* = 38): HR = 1.69, 95% CI 1.15-2.49, p = 0.008 - LEB (75ST* = 93): HR = 1 (reference) - STR (75ST* = 52): HR = 1.21, 95% CI 0.83-1.75, p = 0.32 - GTR (75ST* = 100): HR = 1.06, 95% CI 0.73-1.53, p = 0.75 *75ST = Months at which 25% of the patient population had died.

Study details	Participants	Interventions	Methods/risk of bias	Results
and End Results (SEER; https://seer.cancer.gov) population-based database to examine whether extended resection is associated with improved survival for O2s and O3s." (p. 1-2) Study dates 1999-2010 Source of funding Not reported.	pertaining to grade III will be reported. Exclusion criteria Other cancer diagnosis			
Full citation Coburger et al. Low-grade glioma surgery in intraoperative magnetic resonance imaging: Results of a multicenter retrospective assessment of the German study group for intraoperative magnetic resonance imaging. Clinical Neurosurgery. 78 (6) (pp 775-785), 2016. Ref Id 617052	288 patients (patient characteristics only given for whole group: mean (range) age 39 (18-75) years, gender not reported; histological subtype diffuse astrocytoma / oligoastrocytoma / oligodendroglioma: N = 173 / 63 / 52 tumour locations frontal / temporal / parietal / occipital / basal ganglia / corpus callosum: N = 162 / 74 / 34 / 7 / 9 / 2; tumour size not reported; divided into 4 groups, based on extent of resection: - GTR: N = 138 - Intended STR: N = 105 - Failed GTR: N = 44	GTR ("complete removal of fluid-attenuated inversion recovery (FLAIR) hyperintensity on postoperative imaging at 3 months"; p. 777) versus STR ("Any residual changes in FLAIR imaging at 3-month follow-up were regarded as residual tumor"; p. 777) Adjuvant treatment:	-Bias due to confounding: low risk of bias (patient characteristics not reported split by resection group, but results adjusted, although not for performance status, which may be less important given the comparisons are surgery v surgery, and not no surgery v surgery) -Bias in selection of participants into the study: low risk of bias (all consecutive patients) -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias	Progression-free survival: Multivariate analysis controlling for low- vs high-field intraoperative MRI, eloquent location, age, recurrent surgery, new neurological deficits, presence of an oligodendroglial component, and adjuvant treatment : - GTR (mean, 95% CI = 86, 71-101 months) v STR (mean, 95% CI = 51, 40-63 months): HR = 0.444, 95% CI 0.274-0.72, p < 0.001, favouring GTR. - Adjuvant therapy: -- Chemo v no adj treatment: HR = 1.726, 95% CI 0.891-3.344, p < 0.11 -- Radiation v no adj treatment: HR = 1.716, 95% CI 0.927-3.175, p < 0.09

Study details	Participants	Interventions	Methods/risk of bias	Results
Country/ies where the study was carried out Germany Study type Retrospective cohort study Aim of the study "to investigate patients' neurological outcome and PFS after iMRI-guided surgery for LGGs and to evaluate the influence of EoR and adjuvant treatment on PFS." (p. 776) Study dates 2000-2014 Source of funding Not reported	- GTR when intended: N = 138/182. It seem that N = 49 had recurrent surgery Inclusion criteria Patients who had received surgical treatment using intraoperative MRI for a histologically verified WHO grade II glioma Exclusion criteria Patients aged < 18 or > 75 years.	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 failed GTR; 29/57 had STR; 16/57 had recurrent surgery Follow up: Mean = 52 months.	-Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: Low Other information: Patients had histologically verified, not suspected grade II glioma	-- Combined v no adj treatment: HR = 2.841, 95% CI 1.291-6.25, p < 0.01, favouring no treatment. (No other covariates were significant) Neurological function (new deficits): Measure by the National Institute of Health Stroke Scale; neurological deficits were graded as none, mild, or severe, and graded as mild if the patient's score decreased ≤ 1 point. Deficits defined as new if still present at 3 months follow-up. - GTR: 9.4% - STR: 20% (of whom 2 experienced a severe new deficit)
Full citation Gousias, K., Schramm, J., Simon, M. Extent of resection and survival in supratentorial infiltrative low-grade	N = 148 patients (patient characteristics only given for whole group, not split by extent of resection): Median age (range) = 38 (18-74.1) years; males / females: N = 83 / 65; KPS ≥90% / < 90%: 117/31; histopathology astrocytoma / oligoastrocytoma /	GTR (defined as cases without residual FLAIR signal abnormalities on postoperative MRI) versus STR (2-4 patients in this group had also	-Bias due to confounding: low risk of bias (authors analyse which factors influences extent of resection and control for these in the analyses) -Bias in selection of participants into the study: low risk of bias	Descriptive statistics not reported for the outcomes below split by treatment group. Progression-free survival: Univariate: - Biopsy: HR = 1 (reference)

Study details	Participants	Interventions	Methods/risk of bias	Results
gliomas: Analysis of and adjustment for treatment bias. Acta Neurochirurgica 2014 156 p.327-337 Ref Id 657257 Country/ies where the study was carried out Germany Study type Retrospective cohort study Aim of the study "to critically reevaluate oncological outcomes and in particular the impact of surgical resections on patient survival." (p. 328) Study dates 1996-2011 Source of funding	oligodendroglioma: 76 / 54 / 18; tumour locations eloquent / semi-eloquent / non-eloquent: 31 / 79 /38; tumour size > 3cm / 3-5 cm / > 5 cm: 16 / 86 / 46; divided into 3 groups, based on extent of resection: - Biopsy: N = 11 (as there is 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 them) - Incomplete resection (STR): N = 75. - Complete (GTR): N = 62 Inclusion criteria Patients undergoing primary surgery for WHO grade II supratentorial astrocytoma, oligodendroglioma or oligoastrocytoma, aged > 18 years. Exclusion criteria Patients without data for critical parameters (e.g., tumor size and location, histology, and extent of resection)	radiation and/or chemotherapy) Follow up: Median (range) = 59 (1-196) months	-Bias in classification of interventions: low risk of bias -Bias due to missing data: unclear risk of bias (not reported how many patients were originally excluded due to missing data cf exclusion criteria) -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: Moderate (unclear re missing data) Other information: Biopsy: N = 11 (and not at least 50 patients) However, analyses are only reported relative to biopsy and have been included as such. This should be borne in mind when evaluating them. Patients had confirmed, not suspected, LGG.	- STR: HR = 0.306, 95% CI 0.148-0.633, p = 0.001 - GTR: HR = 0.045, 95% CI 0.018-0.108, p < 0.001 - Adjuvant therapy: HR = 2.449, 95% CI 1.045-5.738, p = 0.039 2 multivariate analyses controlling for KPS, preoperative neurodeficit, epilepsy, duration of symptoms, MRI contrast enhancement, tumour size, adjuvant therapy, and a two- or three-tiered classification of eloquence of location: 2-tiered classification: - Biopsy: HR = 1 (reference) - STR: HR = 0.865, 95% CI 0.308-2.421, p = 0.78 - GTR: HR = 0.221, 95% CI 0.067-0.723, p = 0.013 (Adjuvant therapy and preoperative neurodeficit were also significant) 3-tiered classification: - Biopsy: HR = 1 (reference) - STR: HR = 0.234, 95% CI 0.111-0.493, p < 0.001 - GTR: HR = 0.039, 95% CI 0.016-0.096, p < 0.001 (MRI contrast enhancement and preoperative neurodeficit were also significant) Malignant progression-free survival: Univariate: - Biopsy: HR = 1 (reference)

Study details	Participants	Interventions	Methods/risk of bias	Results
Not reported				- STR: HR = 0.358, 95% CI 0.157-0.819, p = 0.015 - GTR: HR = 0.053, 95% CI 0.019-0.149, p < 0.001 - Adjuvant therapy: HR = 1.723, 95% CI 0.616-4.814, p = 0.3 Multivariate analysis controlling for KPS, preoperative neurodeficit, epilepsy, MRI contrast enhancement, and a two- or three-tiered classification of eloquence of location: - Biopsy: HR = 1 (reference) - STR: HR = 0.354, 95% CI 0.153-0.816, p = 0.015 - GTR: HR = 0.053, 95% CI 0.018-0.151, p < 0.001 (Preoperative neurodeficit was also significant) Overall survival: The authors report that they did not analyse this outcome as no patient with GTR died during follow up (which precluded a proportional hazards analysis of this outcome).
Full citation Pallud, J., Audureau, E., Blonski, M., Sanai, N., Bauchet, L., Fontaine, D., Mandonnet, E., Dezamis, E., Psimaras, D., Guyotat, J., Peruzzi, P., Page, P., Gal, B.,	N = 1509 had grade II glioma (patient characteristics only given for whole group, not split by extent of resection): Age <30 / 30-45 / > 45 years: N = 390 / 726 / 393; males / females: N = 857 / 652; histological subtype astrocytoma / oligodendroglioma / mixed glioma / other: N = 327 / 781 / 280 / 121; KPS score >70 /	- Bx versus - PaR resection (residual tumour 10 cm3 or more) versus - STR (residual tumour < 10 cm3) versus	-Bias due to confounding: low risk of bias (adjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias	Descriptive statistics not reported for the outcomes below split by treatment group. Malignant progression-free survival: Multivariate analyses adjusting for gender, age, performance status, increased intracranial pressure, neurological deficit, history of seizures at histological diagnosis, uncontrolled

Study details	Participants	Interventions	Methods/risk of bias	Results
Parraga, E., Baron, M. H., Vlaicu, M., Guillevin, R., De'aux, B., Duffau, H., Taillandier, L., Capelle, L., Huberfeld, G. Epileptic seizures in diffuse low-grade gliomas in adults. Brain, 2014 137 p.449-462 Ref Id 605089 Country/ies where the study was carried out France Study type Retrospective cohort study Aim of the study "We aimed to explore the natural course of epileptic seizures, their predictors and the prognostic significance of their occurrence in adult patients harbouring a	≤70 / missing: N = 1402 / 30 / 77; tumour locations frontal / temporal / parietal / insular / other: N = 759 / 274 / 142 / 241 / 93; tumour volume cm3 < 100 / ≥ 100 / missing: 808 / 346 / 355; divided into 2 groups, based on extent of resection: - Biopsy (Bx): N = 619 - Partial resection (PaR): N = 427 - Subtotal resection (STR): N = 313. - Total resection (GTR): N = 150. Inclusion criteria Patients in the database of a French glioma cooperative study group (Re´ seau d'Etude des Gliomes) with a histopathologically diagnosed WHO diffuse grade II glioma with a supratentorial hemispheric location, and a neuropathological reassessment for all cases diagnosed before 2007, aged > 18 years at diagnosis who had follow-up data estimate epileptic seizure history. Patients had to be followed until March 2012. Exclusion criteria None reported	- GTR (no residual tumour) All classifications based on 3-month postoperative MRIs on FLAIR sequences. Other treatments: - Radiotherapy: N = 424 - Chemotherapy: N = 251 Follow up: Mean (SD?) = 82 (65)	-Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: low Other information: Population had confirmed low grade glioma rather than suspected.	seizures after oncological treatment, cerebral lobes involved, corpus callosum involvement, anatomical location, functional location, contrast enhancement, cortex involvement, tumour volume, histological subtype radiotherapy and chemotherapy: - Bx: HR = 1 (reference) - PaR: HR = 0.68, 95% CI 0.58-0.81, p < 0.001 favouring PaR - STR: HR = 0.43, 95% CI 0.35-0.53, p < 0.001, favouring STR - GTR: HR = 0.22, 95% CI 0.16-0.32, p < 0.001, favouring GTR (Gender, increased neurocranial pressure, history of seizures at histological diagnosis, contrast enhancement, cortex involvement, tumour volume, histological subtype, radiotherapy and chemotherapy were also significant) Overall survival and progression-free survival analyses not reported as not adjusted for radiotherapy and chemotherapy.

Study details	Participants	Interventions	Methods/risk of bias	Results
diffuse low-grade glioma." (p. 449) Study dates 1992-2011 Source of funding Not reported				
Full citation Schupper, A. J., Hirshman, B. R., Carroll, K. T., Ali, M. A., Carter, B. S., Chen, C. C., Effect of Gross Total Resection in World Health Organization Grade II Astrocytomas: SEER-Based Survival Analysis, World Neurosurgery, 103, 741-747, 2017 Ref Id 657600 Country/ies where the study was carried out USA Study type	N = 4113 patients had grade II astrocytoma (patient characteristics only given for whole group, not split by extent of resection): Median age (IQR) = 44 (29-59) years (please note N = 528 aged < 18 years); males / females: N = 2354 / 1759; tumour locations frontal lobe / temporal lobe/ parietal lobe / occipital lobe / brain stem / overlapping lesion of brain / cerebrum / brain NOS / ventricle NOS / cerebellum NOS: N = 1179 / 821 / 450 / 79 / 197 / 579 / 330 / 262 / 74 / 142; tumour size cm < 5 / 5-7 / > 7: 1568 / 620 / 248; divided into 4 groups, based on extent of resection: - No surgery: N = 1487 - biopsy: N = 806 - Subtotal resection (STR): N = 904 - Total resection (GTR): N = 916 Inclusion criteria	- No surgery (code 00; tissue diagnosis obtained from autopsy) versus - STR (codes 20, 21, and 40) versus - GTR (codes 30 and 55; based on radiographic reports of postoperative MR images). Other treatments: Radiotherapy yes / no: N = 2109 / 1884 (not split by resection group) Follow up: Not reported, but min 120 months (as per inclusion criteria)	-Bias due to confounding: serious risk of bias (unadjusted for performance status, unclear if anyone received chemotherapy) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: unclear risk of bias (no information reported) -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (uncontrolled confounders) Other information: Please note N = 528 aged < 18 years). Population had confirmed, not suspected LGG.	Overall survival: Please note that it seems that biopsy and STR have been combined into one group for the analyses. Multivariate analysis controlling for sex, race/ethnicity, marital status, tumour size, tumour site, year of diagnosis, and radiotherapy found the following HRs for extent of resection: - No surgery (median =23, 95% CI 20-27, months): HR = 1.32, 95% CI 1.14-1.53, p < 0.0001 - STR/biopsy (STR median = 56, 95% CI 47-63, months): HR = 1 (reference) - GTR (median = 120, 95% CI 103->120, months): HR = 0.72, 95% CI 0.6-0.85, p < 0.0001 Overall survival pre- and post temozolomide: Please note that it seems that biopsy and STR have been combined into one group for the analyses. Multivariate analysis controlling for sex, race/ethnicity, marital status, tumour size, tumour site, and

Study details	Participants	Interventions	Methods/risk of bias	Results
Retrospective cohort study Aim of the study To assess the effect of extent of resection on survival in patients with grade II astrocytoma. Study dates 1999-2010 Source of funding Not reported.	Patients of all ages with a diagnosis of grade II astrocytoma (ICD-O-3 histology code 9400, 9410, 9411, 9420 [diffuse astrocytoma]) in the SEER database and a follow up period of 120 months. Exclusion criteria None reported			radiotherapy found the following HRs for extent of resection: Pre-temozolomide (diagnosis 1999-2004) - No surgery: HR = 1.41, 95% CI 1.15-1.71, p = 0.001 - STR/biopsy: HR = 1 (reference) - GTR: HR = 0.77, 95% CI 0.61-0.97, p = 0.027 Post-temozolomide (diagnosis 2005-2010) - No surgery: HR = 1.22, 95% CI 0.98-1.51, p = 0.07 - STR/biopsy: HR = 1 (reference) - GTR: HR = 0.64, 95% CI 0.49-0.84, p = 0.001
Full citation Yang, P., Peng, X., You, G., Zhang, W., Yan, W., Bao, Z., Wang, Y., Qiu, X., Jiang, T. Management and survival rates in patients with glioma in China (2004-2010): A retrospective study from a single-institution. Journal of Neuro-Oncology, 2013 113 p.259-266	N = 831 had grade II glioma (patient characteristics only given for whole group, not split by extent of resection): Age ≤40 / 40-60 / ≥60 years: N = 495 / 310 / 26; males / females: N = 504 / 327; histological diagnoses (WHO 2007) astrocytoma (A) / oligodendroglioma (O) / oligoastrocytoma (OA): N = 464 / 68 / 299; pre-operative KPS score ≥80 / < 80: N = 525 / 206; tumour locations (involved lobe) frontal / temporal / parietal / occipital / insular: N = 569 / 284 / 134 / 33 / 138; divided into 2 groups, based on extent of resection:	Subtotal resection (defined as “nodular or thin residual T2 or FLAIR signal abnormality as seen from axial, coronal or sagittal images” p. 260) versus Gross total resection (defined as “complete resection of the preoperative T2 or FLAIR signal abnormality as seen from axial, coronal or	-Bias due to confounding: serious risk of bias (patient characteristics not reported split by surgery group, but results adjusted for some covariates) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: high risk of bias (Follow up data available for 408 of the 831) -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias	Descriptive statistics not reported for the outcomes below split by treatment group. Overall survival and progression-free survival: Multivariate analysis with the following covariates included (chosen based on the clinical experience of the authors): - Age > 40 (N = 241) v ≤ 40 (N = 167), - male (N = 244) v female (N = 164), - pre-operative KPS ≥ 80 (N = 316) v < 80 (N = 92), - O/OA (N = 232) v A (N = 176), - high p53 expression (N = 174) v low (N = 166), - high MGMT expression (N = 51) v low (N = 290),

Study details	Participants	Interventions	Methods/risk of bias	Results
Ref Id 657661 Country/ies where the study was carried out China Study type Retrospective cohort study Aim of the study “To analyze the clinical characteristics and prognostic factors in patients with glioma in an academic institute in China.“ (p. 259) Study dates Oct 2004-Aug 2010 Source of funding National Key Project of Science and Technology Supporting Programs of China (No. 2007BAI05B08), National Basic Research Program of China (973	- Gross total resection (GTR): N = 357. - Subtotal resection (STR): N = 474. Inclusion criteria All patients who within the study dates received surgical resection for pathologically diagnosed glioma at the Glioma Center of Beijing Tiantan Hospital. Exclusion criteria Patients who received only biopsy as not followed up at the authors’ centre.	sagittal images” p. 260) Other treatment (not reported split by extent of resection): Radiotherapy given / not given / unknown: 315 / 70 / 445 Chemotherapy given / not given / unknown: 106 / 275 / 450 Follow up: Not reported	-Overall bias: serious (uncontrolled confounders; missing data) Other information: Patients had pathologically diagnosed, rather than suspected, low grade glioma	- high PTEN expression (N = 312) v low (N = 29), - high Ki-67 expression (N = 19) v low (N = 322), - radiotherapy (N = 208) v no (N = 89), - chemotherapy (N = 49) v no (N = 154), showed that after adjustment for these factors extent of resection did not influence -overall survival: GTR (N = 175) v STR (reference; N = 233): HR = 0.7801* (95% CI 0.526-1.157); p = 0.217, or -progression-free survival: HR = 0.926 (95% CI 0.745-1.152); p = 0.492, * In the paper, this is given as 0.217, which it can’t be if the 95% CI is correct. 0.217 is also the p-value corresponding to the 95% CI so the HR has been calculated based on the 95% CI and p-value.

Study details	Participants	Interventions	Methods/risk of bias	Results
Program) (No. 2010CB529406, 2011CB707804).				
Full citation 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-oncology, 2013 15 p.1102-10 Ref Id 606015 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study	N = 852 patients divided into two groups: Group 1 patients received a diagnosis 1960-1989 (N = 281); Group 2 patients received a diagnosis 1990-2011 (N = 571). Only data from Group 2 will be reported (cf. review protocol): N = 571 had grade II glioma (patient characteristics only given for whole group, not split by extent of resection): Age mean (range) = 39.4 (18.2-76); males / females: N = 335 / 236; histological diagnoses astrocytoma / oligodendroglioma / mixed oligoastrocytoma: N = 126 / 193 / 252; KPS score not reported; tumour location cortical / cerebellum / deep structures / brain stem / multiple: N = 546 / 5 / 175 / 11 / 14; tumour size ≥ 5 cm / < 5 cm / unknown: N = 122 / 164 / 285; divided into 4 groups, based on extent of resection: - Gross total resection (GTR): N = 176. - Radical subtotal resection (rSTR): N = 55. - Subtotal resection (STR): N = 118. Biopsy only (Bx): N = 222	GTR (“no evidence of remaining tumor after excision”, p. 1103) versus rSTR (“>90% of the tumor removed with some residual tumor present postoperatively”, p. 1103) versus STR (“<90% of the tumor removed after debulking”, p. 1103) Versus Biopsy (“tissue was solely obtained for diagnosis without debulking”, p. 1103) Adjuvant treatment (not reported split by extent of resection): Radiotherapy alone / chemotherapy alone / chemotherapy + radiotherapy / observation: 244 / 13 / 88 / 226	-Bias due to confounding: serious risk of bias (performance status not reported or adjusted for) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (uncontrolled confounder) Other information: Patients with pathologically confirmed, not suspected, low grade glioma	Descriptive statistics not reported for the outcomes below split by treatment group. For the analyses GTR and rSTR were grouped together versus STR and Bx grouped together Progression-free survival (339 events): Multivariate analysis with the following covariates included age, headaches, seizures alone, seizures with other neurological symptoms, speech dysfunction, sensory/motor dysfunction, astrocytoma, deep location, contrast enhancement, size ≥ 5 cm, adjuvant radiotherapy and adjuvant chemotherapy: GTR/rSTR v STR/Bx: Risk ratio = 0.45 (95% CI 0.35-0.59); p < 0.0001. (Astrocytoma, size ≥ 5 cm, adjuvant radiotherapy and adjuvant chemotherapy were also significant). Overall survival (244 events): Multivariate analysis with the following covariates included age, headaches, seizures alone, seizures with other neurological symptoms, speech dysfunction, sensory/motor dysfunction, astrocytoma, deep location, contrast enhancement, size ≥

Study details	Participants	Interventions	Methods/risk of bias	Results
"to evaluate changes in prognostic factors, treatment indications, and outcomes in adult patients with LGG over the past 50 years." (p. 1103) Study dates 1960-2011 Source of funding Not reported	Inclusion criteria Patients aged ≥ 18 years diagnosed with WHO grade II glioma by a Mayo Clinic neuropathologist. Exclusion criteria Patients with neurofibromatosis type 1, or grade I glioma.	Follow up: Median (?) = 8.7 (0.02-21.6) years		5 cm, adjuvant radiotherapy and adjuvant chemotherapy: GTR/rSTR v STR/Bx: Risk ratio = 0.61 (95% CI 0.43-0.86); p = 0.004. (Age, astrocytoma, and adjuvant radiotherapy were also significant).

1 Evidence tables for review 1d - Molecular markers to inform prognosis / guide treatment

2 Not applicable - no evidence was identified.

3 Evidence tables for review 2a - Further management of low-grade glioma

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Baumert, B. G., Hegi, M. E., van den Bent, M. J., von Deimling, A., Gorlia, T., Hoang-Xuan, K., Brandes, A. A., Kantor, G., Taphoorn, M. J. B., Hassel, M. B.,	Sample size 707 patients assessed for eligibility, of which 237 were included in the TMZ arm and 240 included in the RT arm (477 in total) Characteristics RT / TMZ Gender, women: 102 (43%) / 100 (42%)	Interventions People in the RT group received standard RT, which consisted of 3-D conformal	Details This trial was undertaken in 78 clinical centres in 19 countries. Random treatment allocation was done by a minimisation	Results Results of PFS of TMZ vs RT (95% CI, p-value) Total (n=318) Median PFS=46 months (95% CI 40-56) with RT and 39 months (35-44) with TMZ HR 1.16 (95% CI 0-9-1.5), p= 0.22 IDHmt/codel (n=104)	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
Hartmann, C., Ryan, G., Capper, D., Kros, J. M., Kurscheid, S., Wick, W., Enting, R., Reni, M., Thiessen, B., Dhermain, F., Bromberg, J. E., Feuvret, L., Reijneveld, J. C., Chinot, O., Gijtenbeek, J. M. M., Rossiter, J. P., Dif, N., Balana, C., Bravo-Marques, J., Clement, P. M., Marosi, C., Tzuk-Shina, T., Nordal, R. A., Rees, J., Lacombe, D., Mason, W. P., Stupp, R., Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3	WHO performance status 0 | 151 (63%) | 143 (60%) WHO performance status I | 79 (33%) | 86 (33%) WHO performance status II | 10 (4%) | 8 (3%) Age < 40 | 92 (38%) | 85 (36%) Age≥40 | 148 (62%) | 152 (64%) Inclusion criteria Adult people (≥ 18 years old) with a histologically confirmed, WHO performance status of 2 or lower, diffusively infiltrating LGG who did not have any medical condition (such as HIV or chronic hepatitis B or C) that could interfere with the oral medication intake. In order to be included, people also had to require other intervention rather than surgery (i.e. these were not candidates for surgical treatment only), defined by at least one characteristic of the following: age 40 years or older, having radiological tumour progression, new or worsening tumour			RT up to 50.4 Gy (28 x 1.8 Gy once daily, 5 days pw, over 5-6 weeks, and up to a maximum treatment period of 6.5 weeks). The treatment volumes were defined based on T2 or fluid-attenuated inversion recovery (FLAIR) MRI. In case of tumour resection, postoperative imaging was used. People in the TMZ group received oral TZ in a dose-dense	technique with prospective stratification by WHO performance status (0-1 vs 2) age (<40 vs ≥40), presence vs absence of contrast enhancement on MRI, 1p status (deleted vs non-deleted vs indeterminate), and by the medical institution in which they received treatment. Patients had to begin the treatment within 6 weeks after randomisation. The trial was open-label and patients, treating doctors and researchers were all aware of the assigned intervention.	HR 1.04 (95% CI 0.56-1.93), p=0.91 IDHmt/non-codel (n=165) HR 1.86 (95% CI 1.21 – 2.87),p= 0.91 IDHwt (n=49) HR 0.67 (95% CI 0.34 -1.32)	generation: Low risk (Random treatment allocation was done by a minimisation technique with prospective stratification) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: High risk (open-label) Blinding of outcome assessment: High risk (open-label) Blinding (performance bias and detection bias): High risk (open-label)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
intergroup study, The Lancet Oncology, 17, 1521-1532, 2016 Ref Id 575703 Country/ies where the study was carried out Multicentre study Study type Phase III RCT Aim of the study To compare standard radiotherapy and primary temolozomide and asses PFS outcomes and correlative analyses between these and molecular markers Study dates 23rd September 2005 and 26th of March 2010 Source of funding Unrestricted educational grant and free supply	neurological symptoms, or refractory seizures. Exclusion criteria People whose tumour had transformed into a higher grade before randomisation and people who had received previous RT or chemotherapy.	schedule of 75mg/m2 per day for 21 das, repeated every 28 days (one cycle) for up to or until disease progression or unacceptable toxicity (defined as grade 4 haematological toxicity or grade 3-3 non haematological toxicity - except for alopecia, nausea and vomiting-).	Analyses were done on an ITT bass, defined as all patients assigned to a treatment.		Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported) Other information See Reijnevel 2016 for further details about HRQoL

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>of TMZ by Merck Sharp& Dohme-Merck. The trial was also supported by different sponsors.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

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., Curran, W. J., Abrams, R., Shaw, E. G., Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the Folstein mini-mental state examination, Journal of Clinical OncologyJ Clin Oncol, 21, 2519-2524, 2003</td><td>Sample size

See Shaw 2002
Characteristics
See Shaw 2002
Inclusion criteria
See Shaw 2002
Exclusion criteria
See Shaw 2002</td><td>Interventions

See Shaw 2002</td><td>Details

People were evaluated with the MMSE at study entry (baseline) and after the completion of protocol therapy (every 4 months for 3 years, every 6 months for 3 years, and yearly until year 15). The MMSE begins with an assessment of orientation of place and time, a memory test, in which the person needs to recall the name of 3 objects</td><td>Results

The study only reported results for those patients without tumour progression. Progression was declared if the neurologic examination results worsened or there was an increase in tumour size of at least 25%, based on measurement of perpendicular diameters or a clear increase in the size of the tumours on imaging compared with baseline.
Results for change in MMSE score by treatment arm at key evaluations for patients without tumour progression
Year 1:
<table>
<tr><td></td><td>50.4 Gy</td><td>64.8 Gy</td></tr>
<tr><td>Stable score</td><td>46</td><td>33</td></tr>
<tr><td>Significant decrease*</td><td>4</td><td>6</td></tr>
<tr><td>Significant increase*</td><td>4</td><td>4</td></tr>
<tr><td>Total</td><td>54</td><td>43</td></tr>
</table>
Year 2:
231</td><td>Limitations

See Shaw 2002
Other information
This study reported the results of the MMSE until year 5, and is discussed whether this length of time is sufficient for neurocognitive deficits to develop. In the discussion section, the authors claim this 5 years is enough since "most late radiation neurotoxicity occurs within 3 years"</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Ref Id
554627
Country/ies where the study was carried out
USA
Study type
RCT
Aim of the study
To assess the effects of radiotherapy on cognitive function in patients with low-grade glioma as measured with the MMSE
Study dates
May 1986 to December 1994
Source of funding
Not reported</td>
<td></td>
<td></td>
<td>previously said. The final section evaluates aphasia and apraxia. The maximum score that can be obtained for the entire test is 30 points.
For the purpose of this study, a decrease of more than 3 points in the MMSE was considered to represent clinically significant deterioration.
Data were recorded at baseline for 187 of the 203 patients.</td>
<td>
<table>
<tr><td></td><td>50.4 Gy</td><td>64.8 Gy</td></tr>
<tr><td>Stable score</td><td>35</td><td></td></tr>
<tr><td>Significant decrease*</td><td>3</td><td></td></tr>
<tr><td>Significant increase*</td><td>2</td><td>1</td></tr>
<tr><td>Total</td><td>40</td><td>25</td></tr>
</table>
Year 3:
<table>
<tr><td></td><td>50.4 Gy</td><td>64.8 Gy</td></tr>
<tr><td>Stable score</td><td>15</td><td>19</td></tr>
<tr><td>Significant decrease*</td><td>2</td><td>-</td></tr>
<tr><td>Significant increase*</td><td>-</td><td>2</td></tr>
<tr><td>Total</td><td>17</td><td>21</td></tr>
</table>
*Change of more than 3 points from baseline MMSE score was clinically significant
</td>
<td></td>
</tr>
<tr>
<td>Full citation
Buckner, J. C., Shaw, E. G., Pugh, S. L., Chakravarti, A., Gilbert, M. R.,</td>
<td>Sample size
254 patients underwent randomisation, of which 251 were included in the study. Radiation therapy alone (n=126) and radiation therapy plus PCV (n=125)</td>
<td>Interventions
Radiotherapy: the radiation dose was</td>
<td>Details
People were stratified according to age, histologic findings, KPS</td>
<td>Results
Results for OS (HR, 95% CI) and PFS (HR, 95% CI)
Overall survival (total)
HR 0.59 (0.42-0.83)</td>
<td>Limitations
Methodological limitations assessed using the Cochrane collaboration's</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Barger, G. R., Coons, S., Ricci, P., Bullard, D., Brown, P. D., Stelzer, K., Brachman, D., Suh, J. H., Schultz, C. J., Bahary, J. P., Fisher, B. J., Kim, H., Murtha, A. D., Bell, E. H., Won, M., Mehta, M. P., Curran, W. J., Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma, New England Journal of Medicine, 374, 1344-1355, 2016 Ref Id 657236 Country/ies where the study was carried out USA Study type RCT Aim of the study To assess whether RT and PCV prolong the	Characteristics RT only / RT + PCV Median age: 40 / 41 Sex, women n (%): 49 (39%) / 60 (48%) KPS 60-80: 33 (26%) / 31(25%) KPS 90-100: 93 (74%) / 94 (75%) Astrocytoma: 9 (23%) / 36 (29%) Oligodendroglioma: 57 (45%) / 50 (40%) Oligoastrocytoma - astrocytoma features dominant: 19 (15%) / 19 (15%) Oligoastrocytoma - astrocytoma features equivalent to oligodendroglioma features: 5 (4%) / 1 (1%)	54 Gy, administered in 30 fractions of 1.8 Gy each over a period of 6 weeks. Radiation volume was defined according to the abnormality of the T2 weighed MR signal, including any surgical defect. People who had been randomly assigned to have chemotherapy, receive it after RT. Chemotherapy consisted of 6 cycles of procarbaine (60mg per square meter of	and presence or absence of contrast enhancement on preoperative images. OS was measured from the day of randomisation to the date of death or the last follow-up date on which the patient was reported to be alive. PFS was calculated from the day of randomisation to the date of disease progression or death of the last follow-up date on which the patient was reported to be alive. Median follow-up was 11.9 years	Overall survival (grade 2 oligodedroglioma) HR 0.43 (0.23-0.82) Overall survival (grade 2 oligoastrocytoma) HR 0.56 (0.32-1.00) Overall survival (grade 2 oligodedroglioma) HR 0.73 (0.40-1.34) Overall survival among those with IDH1 R132H Mutation HR 0.42 (0.20-0.86) Progression free survival (total) HR 0.50 (0.36-0.68) Progression free survival (grade 2 oligodedroglioma) HR 0.36 (0.21-0.62) Progression free survival (grade 2 oligoastrocytoma) HR 0.52 (0.30-0.89) Progression free survival (grade 2 oligodedroglioma) HR 0.58 (0.33-1.03) Progression free survival among those with IDH1 R132H Mutation HR 0.32 (0.17-0.62)	tool for assessing risk of bias Random sequence generation: unclear risk (randomisation method was not reported) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: Unclear risk Blinding of outcome assessment: Unclear risk Blinding (performance bias and detection bias): Unclear risk Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for)

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
overall survival of people with LGG in comparison with RT alone Study dates 31st of October 1998 to 27th of June 2002 Source of funding Study supported by a Radiation Therapy Oncology Group grant and a Community Clinical Oncology Program grant from the National Cancer Institute, a grant from the North Central Cancer Treatment Group, grants from the Cancer Therapy Evaluation Program of the National Cancer Institute	<table><tr><td>Oligodendroglioma features dominant</td><td>16 (13%)</td><td>9 (15%)</td></tr><tr><td>IDH1 R132H mutation -present</td><td>35/57 (61%)</td><td>36/56 (64%)</td></tr><tr><td>MMSE score <27</td><td>11 (9%)</td><td>17 (14%)</td></tr><tr><td>MMSE score 27-30</td><td>111 (8%)</td><td>99 (79%)</td></tr></table> Inclusion criteria People with grade 2 WHO astrocytoma, oligodendroglioma, or oligoastrocytoma histologicall confirmed on pathological review by a central laboratory before randomisation. Patients between 18 and 39 years of age were eligible if they had undergone a subtotal resection or biopsy, those who were above 40 years old, were eligible if they had undergone biopsy or resection of any of the tumour. In order to be included, patients should present with a KPS of 60 or more, and a neurologic-function score of 3 or less. Exclusion criteria			body-surface orally), CCNU (110 mg per square meter of body surface on day 1 of each cycle) and vincristine (1.4 mg per square meter administered intravenously on days 8 and 29 of each cycle). The cycle length was 8 weeks			Selective reporting: low risk (all prespecified outcomes were reported) Other information

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td>People whose tumour had spread to non-contiguous leptomeninges, if they had gliomatosis cerebri , if they had had synchronous cancer within the previous years, if they had received prior radiation therapy to the brain or head or neck reagion, if they had received chemotherapy for any reason, if they had presented with chronic lung disease, if pregnant, breastfeeding or unwilling to use effective contraception during treatment.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Eyre, H. J., Crowley, J. J., Townsend, J. J., Eltringham, J. R., Morantz, R. A., Schulman, S. F., Quagliana, J. M., Al-Sarraf, M., A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: A Southwest Oncology Group study, Journal of NeurosurgeryJ</td><td>Sample size
Characteristics<table><tr><td></td><td>RT</td><td>RT +CCNU</td></tr><tr><td>Median age</td><td>36 (range 22 to 73)</td><td>39 (17 to 72)</td></tr><tr><td>male</td><td>13 (68%)</td><td>15 (43%)</td></tr><tr><td>biopsy</td><td>7 (37%)</td><td>13 (37%)</td></tr><tr><td>Partial resection</td><td>12 (63%)</td><td>22 (63%)</td></tr></table>People presented with Grade II tumours, including pilocytic astrocytomas, gemistocytic astrocytomas, midly anaplastic astrocytomas, mixed gliomas, oligodendrogliomas, and gangliogliomas</td><td>Interventions
Radiotherapy was given using megavolt apparatus with a minimum peak energy of 1 MeV and a target distance (source to skin or axis distance) of 80 cm. The target volume was defined as primary</td><td>Details
Not reported</td><td>Results
Median survival time for patients who received RT alone = 4.5 years
Median survival time for patients who received RT and CCNU= 7.4 years</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: unclear risk of bias (randomisation method was not reported)
Allocation concealment: unclear risk of bias (not reported)
Blinding of participants and</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neurosurg, 78, 909-914, 1993 Ref Id 555031 Country/ies where the study was carried out USA Study type RCT Aim of the study To assess the effects in long term survival of radiotherapy (55 Gy) or radiotherapy in combination with CCNU Study dates February 1980 to March 1985 Source of funding Not reported	Inclusion criteria A histological diagnosis of a grade I or II primary brain tumour, classified according to Kernohan and Sayre, with incomplete surgical resection Exclusion criteria Patients with cerebellar astrocytoma	tumour as identified on CT sans, with a 2cm margin. A total of 55 Gy was delivered to the target volume in 32 fractions, given 5 days pw over a total of 6 and a half weeks. CCNU was begun 2 days prior to the onset of RT. Patients received CCNU as a dose of 100mg/sq every 6 weeks. Doses of CCNU were modified according to Standard Southwest Oncology Group guidelines			personnel: unclear risk of bias (not reported) Blinding of outcome assessment: unclear risk of bias (not reported) Incomplete outcome data: unclear risk of bias (not enough information was provided to assess whether all the proposed outcomes were reported) Selective reporting: low risk Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		based on the nadir white blood cell and platelet counts. Patients were also treated with dexamethasome in divided doses, beginning at 10mg/sq m and tapered and /or discontinued as appropriate. If the patient had a partial or complete response, CCNU was continued for a total period not to exceed 2 years.			
Full citation Karim, A. B. M. F., Afra, D., Cornu, P.,	Sample size Total sample size was 290, 150 in the irradiated arm and 140 in the control arm	Interventions Postoperative	Details People were randomised using a	Results TTP - HR (95% CI)*: 0.71 (0.52 - 0.97) OS - HR (95% CI)*: 1.04 (0.61-1.78)	Limitations Methodological limitations assessed using

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Bleehan, N., Schraub, S., De Witte, O., Darcel, F., Stenning, S., Pierart, M., Van Glabbeke Jr, M., Randomized trial on the efficacy of radiotherapy for cerebral low-grade glioma in the adult: European Organization for Research and Treatment of Cancer Study 22845 with the Medical Research Council study BRO4: An interim analysis, International Journal of Radiation Oncology Biology Physics, 52, 316-324, 2002
Ref Id
660563
Country/ies where the study was carried out</td>
<td>Characteristics
Patients characteristics n (%)
<table>
<tr><th></th><th>Postoperative RT</th><th>Deferred RT</th></tr>
<tr><td>Gender - male</td><td>90 (60%)</td><td>90 (64%)</td></tr>
<tr><td>Performance status (WHO 0)</td><td>67 (45%)</td><td>60 (43%)</td></tr>
<tr><td>Performance status (WHO 1)</td><td>66 (44%)</td><td>61 (44%)</td></tr>
<tr><td>Performance status (WHO 2)</td><td>15 (10%)</td><td>16 (11%)</td></tr>
<tr><td>Performance status (WHO 3)</td><td>0</td><td>2 (1%)</td></tr>
<tr><td>Astrocytoma, grade I</td><td>1 (1%)</td><td>6 (4%)</td></tr>
<tr><td>Astrocytoma, grade II</td><td>90 (60%)</td><td>83 (59%)</td></tr>
<tr><td>Oligodendroglioma</td><td>38 (25%)</td><td>34 (24%)</td></tr>
<tr><td>Mixed oligo-astrocytoma</td><td>17 (11%)</td><td>12 (9%)</td></tr>
</table>
</td>
<td>RT: people were treated with a linear accelerator or, when this was not available, a Co apparatus, with a dose of 54 Gy/ 6 weeks was used. A maximal interval of 8 weeks was allowed between the day of surgery and the first day of RT. Usually this interval was < 6 weeks after surgery.
Deferred RT: people randomised to this arm did not receive any treatment after</td>
<td>minimization technique and then stratified by institution, tumour histology, and amount of tumour removed surgically (biopsy vs partial, subtotal or total resection).

Analysis was performed according to ITT, using the EORTC standard operating procedures.</td>
<td>*Calculated with the calculator developed by Tieney et al. 2007</td>
<td>the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: Low risk (people were centrally randomised at the data centre of the Cancer Trials Office using a minimisation technique)
Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used)
Blinding of participants and personnel: High risk (open-label)
Blinding of outcome assessment: High risk (open-label)
Blinding (performance bias and detection</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multicentre study Study type RCT Aim of the study To report the primary results of a randomised controlled trial comparing the efficacy of early RT versus delayed RT Study dates March 1986 to September 1997 Source of funding Foundation Cancer (Belgium) and by the National Cancer Institute, Bethesda, MD	<table><tr><td>Unknown</td><td>4 (3%)</td><td>5 (4%)</td></tr></table> Inclusion criteria Age between 16 and 65 years old with a definite histopathologic diagnosis of LGG, KPS ≥ 60 and WHO score ≤ 2. Exclusion criteria People with major functional impairment after surgery with difficulties in conscious response were not eligible. Pregnant women, or people with gross hepatic, renal or cardiovascular disease were not eligible.	surgery after the tumour show progression (this was defined as clinical-neurological deterioration confirmed by definitive evidence of tumour activity clinically and on CT scan)			bias): High risk (open-label) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported) Other information
Full citation Karim, A. B. M. F., Maat, B., Hatlevoll, R., Menten, J., Rutten, E. H. J. M., Thomas, D. G. T., Mascarenhas, F., Horiot, J. C., Parvinen, L. M.,	Sample size Of the initial 379 patients accrued for the trial, n=171 were randomised to the low dose (45Gy) arm and n=172 to the the high dose (59.4 Gy) arm Characteristics <table><tr><td></td><td>Low dose (45 Gy)</td><td>High dose (59.4 Gy)</td></tr></table>	Interventions In both arms 1.8 Gy as daily fraction dose was undertaken. For one arm, a low dose of 45	Details People were randomised and stratified by histologic grade (this was done for astrocytomas only, oligodendroglio mas, or mixed	Results Overall survival: 58% in the low-dose arm and 59% for the high-dose arm Progression free survival: 47% in the low-dose arm and 50% for the high-dose arm	Limitations Other information Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Van Reijn, M., Jager, J. J., Fabrini, M. G., Van Alphen, A. M., Hamers, H. P., Gaspar, L., Noordman, E., Pierard, 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, Cancer/Radiotherapie, 1, 260-261, 1997 Ref Id 660564 Country/ies where the study was carried out Multicentre study Study type RCT Aim of the study To study the efficacy of RT	<table><tr><td>Age (median)</td><td>38</td><td>39</td></tr><tr><td>Gender (M:F)</td><td>105:66</td><td>91:81</td></tr><tr><td>Astrocytoma - grade 1</td><td>15</td><td>17</td></tr><tr><td>Astrocytoma - grade 2</td><td>105</td><td>101</td></tr><tr><td>Oligodendoglioma</td><td>35</td><td>38</td></tr><tr><td>Mixed oligoastrocytoma</td><td>16</td><td>16</td></tr></table> Inclusion criteria Not reported Exclusion criteria Pregnant women, or patients with gross hepatic, renal or cardiovascular diseases or malignancy other than curable skin cancers, although patients who had previously had cancer but were thought to be cured at least 5 years before inclusion in the protocol were eligible.	Gy in 25 fractions in 5 weeks was chosen and for the other arm a dose of 59.4 in 33 fractions in 6.6 weeks. Follow up with CT scans was advised to detect progression of the disease.	tumours were grade 2 for pracmatic reasons). Cerebral pilocytic astrocytoma was not included in the trial when totally excised. Up to to 8 weeks was the interval allowed between the day of surgery and the initiation of radiation therapy. This interval was usually <4 weeks. Participating centres were advised to use 4-10-MV photons with build-up when necessary. Co y apparatus was allowed when a linear accelerator was		generation: Unclear risk (Authors do not report the method used for randomisation) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: Unclear risk (no details reported) Blinding of outcome assessment: Unclear risk (no details reported) Blinding (performance bias and detection bias): Unclear risk (no details reported) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and the presence of a dose-response relationship for these tumours Study dates April 1985 to September 1991 Source of funding Not reported			not avaiable (2 institutions used this and the centre was visited by once of the researchers, who found the quality of treatment to be satisfactory)		Selective reporting: low risk (all prespecified outcomes were reported)
Full citation Kiebert, G. M., Curran, D., Aaronson, N. K., Bolla, M., Menten, J., Rutten, E. H. J. M., Nordman, E., Silvestre, M. E., Pierart, M., Karim, A. B. M. F., Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: Results of a randomised phase III trial on dose response (EORTC trial 22844), European	Sample size Of the initial 379 patients accrued for the trial, n=180 completed at least one QoL questionnaire (47% of the total patient sample) Characteristics See Karim 1996 Inclusion criteria See Karim 1996 Exclusion criteria See Karim 1996	Interventions See Karim 1996	Details A quality of life questionnaire consisting of 47 items was constructed to meet the requirements of the study protocol as no well-validated, standardised QoL questionnaire was available. This assessed a range of physical, psychological, social and symptom domains was included in the	Results Results have been reported narratively as the study did not report the relevant information to calculate a change from baseline (for further information, see 'other information' section below. "The adults who had received higher radiation dose (59.4 Gy) tended to report lower levels of functioning and more symptom burden than those who had received the lower dose. These group differences were statistically significant for fatigue/malaise and insomnia only). At the 7-15 months postrandomisation follow-up a similar pattern of results favouring the lower dose radiotherapy arm was observed. Statistically significant group differences favouring the low-dose radiotherapy arm were found for leisure activity and emotional functioning. No statistically significant changes from baseline (pre-treatment) to post-treatment score on any of the QoL composed functioning scales were observed.	Limitations See Karim 1996 Other information Study did not report baseline results for adults treated on the high radiation dose (59.4 Gy), therefore it has not been possible to calculate the change from baseline in both groups. Medians and confident intervals were only presented graphically, making it difficult to interpret the results systematically. Of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Cancer, 34, 1902-1909, 1998 Ref Id 628942 Country/ies where the study was carried out Multicentre study Study type RCT Aim of the study To evaluate the effects of radiation therapy on quality of life of adults with low-grade glioma Study dates April 1985 - September 1991 Source of funding Not reported			trial to measure the impact of treatment over time.		the 27 institutions which initially participated in the EORTC study 22844, 14 completed the QoL questionnaires. Reasons for drop out are not clear, according to the investigators; which raises concern about selection bias.
Full citation Laack, N. N., Brown, P. D., Ivnik, R. J., Furth, A. F., Ballman, K. V., Hammack, J. E., Arusell, R. M., Shaw, E. G.,	Sample size Of the initial 203 adults randomised in the study conducted by Shaw 2002, 20 participated in this study (the first 20 Mayo Clinic patients [10 in the 50.4 Gy group, 10 in the 64.8 Gy group]). Characteristics	Interventions See Shaw 2002	Details Adults were evaluated with psychometric tests at baseline (before RT) and at approximately	Results Change from baseline of the psychometric tests - values are mean (SD) Mean (SD) 18 months from baseline Mean (SD) 36 months from baseline	Limitations Other information These patients are a subset from Brown 2003

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Buckner, J. C., Cognitive function after radiotherapy for supratentorial low-grade glioma: A North Central Cancer Treatment Group prospective study, International Journal of Radiation Oncology Biology Physics, 63, 1175-1183, 2005
Ref Id
657284
Country/ies where the study was carried out
USA
Study type
RCT
Aim of the study
To assess the effects of cranial RT on cognitive function in patients with suprarentorial LGG</td>
<td>
<table>
<tr><td></td><td>n (%)</td></tr>
<tr><td>Age 18-40 y/o</td><td>9 (45)</td></tr>
<tr><td>>40</td><td>11 (55)</td></tr>
<tr><td>Women</td><td>6 (30)</td></tr>
<tr><td>Astrocytoma</td><td>2 (10)</td></tr>
<tr><td>Oligoastrocytoma</td><td>9 (45)</td></tr>
<tr><td>Oligodendroglioma</td><td>9 (45)</td></tr>
</table>
Inclusion criteria
See Shaw 2002
Exclusion criteria
See Shaw 2002
</td>
<td></td>
<td>18 months intervals for as long as 5 years after completing RT.
Neuropsychologic tests
MMSE - Folstein Mini Mental State Examination
WAIS - R: Wechsler Adult Intelligence Scale- Revised
AVLT: Auditory - Verbal Learning Test
TMT: Trail-Making test
COWAT: Controlled Oral Words Association Test</td>
<td>
<table>
<tr><td>Attention/cognitive speed and flexibility</td><td></td><td></td></tr>
<tr><td>TMT part A</td><td>0.2 (9.1)</td><td>-2 (8.1)</td></tr>
<tr><td>TMT part B</td><td>3.6 (48)</td><td>5.7 (39.6)</td></tr>
<tr><td>Stroop: words</td><td>2 (21.3)</td><td>-1.9 (23.3)</td></tr>
<tr><td>Stroop: colours</td><td>1.6 (14.4)</td><td>-1.4 (21.6)</td></tr>
<tr><td>Stroop: colours and words</td><td>1.3 (11.2)</td><td>0.3 (17.3)</td></tr>
<tr><td>MMSE score</td><td>0.6 (1.6)</td><td>0.7 (1.1)</td></tr>
<tr><td>Intelligence (WAIS - R)</td><td></td><td></td></tr>
<tr><td>Verbal comprehension</td><td>3.7 (6.2)</td><td>4.3 (7.6)</td></tr>
<tr><td>Freedom from distractibility</td><td>2.9 (9.7)</td><td>-2.8(11.3)</td></tr>
<tr><td>Perceptual organisation</td><td>5.2 (7.8)</td><td>6.5 (8.6)</td></tr>
<tr><td>Memory/learning</td><td></td><td></td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
Study dates May 1986 - December 1994 Source of funding Not reported				AVLT total learning	1.9 (10.5)	0 (11)	
				AVLT 1-h delayed free call	0.2 (2.9)	0.3 (3)	
				AVLT percent forgetting at 1 h	4.6 (29.2)	-5 (26.7)	
				BVRT expectednumber correct	0.1 (0.3)	-0.1 (0.7)	
				BVRT obtained number correct	0.2 (1.3)	0.5 (2)	
				BVRT obtained-expected number correct	0.0 (1.4)	0.6 (2.2)	
				BVRT expected number of errors	-0.2 (0.7)	-0.1 (0.6)	
				BVRT obtained number of errors	-1.3 (2.1)	-0.6 (3.3)	
				BVRT obtained-expected number of errors	-0.9 (2.5)	-0.5 (3.4)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation
Prabhu, R. S., Won, M., Shaw, E. G., Hu, C., Brachman, D. G., Buckner, J. C., Stelzer, K. J., Barger, G. R., Brown, P. D., Gilbert, M. R., Mehta, M. P., Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: Secondary analysis of RTOG 98-02, Journal of Clinical OncologyJ Clin Oncol, 32, 535-541, 2014</td>
<td>Sample size
n= 187; n= 74 RT alone and n=51 in the RT + PCV
Characteristics
<table>
<tr><td></td><td></td></tr>
<tr><td>Age < 40 y/o</td><td>124 (66%)</td></tr>
<tr><td>Age ≥ 40 y/o</td><td>63 (34%)</td></tr>
<tr><td>Male</td><td>102 (55%)</td></tr>
<tr><td>KPS 60-80</td><td>39 (21%)</td></tr>
<tr><td>KPS 90-100</td><td>148 (79%)</td></tr>
<tr><td>Astrocytoma</td><td>36 (19%)</td></tr>
<tr><td>Oligodendroglioma</td><td>94 (50%)</td></tr>
<tr><td>Oligoastrocytoma (astrodominant)</td><td>19 (10%)</td></tr>
<tr><td>Oligoastrocytoma (astro=oligo)</td><td>8 (4%)</td></tr>
<tr><td>Oligoastrocytoma (oligodominant)</td><td>30 (16%)</td></tr>
</table>
</td>
<td>Interventions
See Buckner 2016</td>
<td>Details
MMSE data was collected as part of the patient clinical evaluation at each study follow-up data and discontinued at the time of tumour progression. Key evaluations were done at baseline and years 1, 2 ,3 and 5 from the start of RT.
Significant MMSE score decline was defined as a decrease of > 3 points; significant gain</td>
<td>Results
Categorical change in MMSE sore by baseline MMSE score (MMSE decline, > 3 point decline, MMSE gain, > 3 point gain; MMSE no change ≤ 3 point change)
<table>
<tr><td></td><td>MMSE score < 27</td></tr>
<tr><td>Y1 (n=17) decline</td><td>0</td></tr>
<tr><td>Y1 no change</td><td>7(41%)</td></tr>
<tr><td>Y1 gain</td><td>10 (59%)</td></tr>
<tr><td>Y2 (n=10) decline</td><td>0</td></tr>
<tr><td>Y2 no change</td><td>2 (20%)</td></tr>
</table>
</td>
<td>Limitations
Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results		Comments
Ref Id 556341 Country/ies where the study was carried out USA Study type RCT Aim of the study To assess the effect of therapy intensification through the addition of PCV to RT on cognitive function on adults with LGG Study dates 31st October 1998 to 27th June 2002 Source of funding See Buckner 2016	Inclusion criteria See Buckner 2016 Exclusion criteria See Buckner 2016		was defined as an increase of > 3 points; no change was defined as any MMSE score change ≤ 3 points.	Y2 gain	8 (80%)	
				Y3 (n=11) decline	0	
				Y3 no change	4 (36%)	
				Y3 gain	7 (64%)	
				Y5 (n=7) decline	1 (14%)	
				Y5 no change	2 (27%)	
				Y5 gain	4 (57%)	
					MMSE score 27 to 30	
				Y1 (n=170) decline	7 (4%)	
				Y1 no change	163(96%)	
				Y1 gain	-	
				Y2 (n=149) decline	1 (1%)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Y2 no change</td><td>148 (99%)</td></tr>
<tr><td>Y2 gain</td><td>-</td></tr>
<tr><td>Y3 (n=127) decline</td><td>1 (1%)</td></tr>
<tr><td>Y3 no change</td><td>123 (99%)</td></tr>
<tr><td>Y3 gain</td><td>-</td></tr>
<tr><td>Y5 (n=67) decline</td><td>1 (2%)</td></tr>
<tr><td>Y5 no change</td><td>66 (99%)</td></tr>
<tr><td>Y5 gain</td><td>-</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation
Reijneveld, J. C., Taphoorn, M. J. B., Coens, C., Bromberg, J. E. C., Mason, W. P., Hoang-Xuan, K., Ryan, G., Hassel, M. B., Enting, R. H., Brandes, A. A., Wick, A., Chinot, O., Reni, M., Kantor, G., Thiessen, B.,</td><td>Sample size
See Baumert 2016
Characteristics
See Baumert 2016
Inclusion criteria
See Baumert 2016
Exclusion criteria
See Baumert 2016</td><td>Interventions
See Baumert 2016</td><td>Details
HRQoL was assessed the EORTC QLQ-C30 and the EORTC Brain Cancer Module (QLQ-BN 20). The MMSE was used for the assessment of neurocognitive function. Data collection was</td><td>Results
Global health-related quality of life - change from baseline - Mean (SD)*
<table>
<tr><td></td><td>TMZ</td><td>RT</td></tr>
<tr><td>3 months</td><td>-0.5 (1)</td><td>-6.5 (1)</td></tr>
</table>
</td><td>Limitations
See Baumert 2016
Other information</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Klein, M., Verger, E., Borchers, C., Hau, P., Back, M., Smits, A., Golfinopoulos, V., Gorlia, T., Bottomley, A., Stupp, R., Baumert, B. G., Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study, The Lancet Oncology, 17, 1533-1542, 2016
Ref Id
576660
Country/ies where the study was carried out
Multicentre study
Study type
Phase III RCT
Aim of the study
To assess whether people with a diagnosis</td><td></td><td></td><td>stopped in the case of progression, death, loss to follow-up, or if the patient refused further participation. Time points for the assessment were 6 weeks before and 4 weeks after the scheduled follow-up assessment.</td><td>
<table>
<tr><td>6 months</td><td>-0.4 (1)</td><td>2.1 (1)</td></tr>
<tr><td>24 months</td><td>3.3 (1)</td><td>4.9 (1)</td></tr>
<tr><td>36 months</td><td>2.5 (1)</td><td>2.7 (1)</td></tr>
</table>
*Change from baseline has been calculated by the NGA using the following calculator: ChangeFromBaseline_0.75correlation_Calc
MMSE scores - change from baseline Mean (SD)**
<table>
<tr><td></td><td>TMZ</td><td>RT</td></tr>
<tr><td>3 months</td><td>0.2 (0.1)</td><td>3 (0.09)</td></tr>
</table>
</td><td></td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of LGG treated with TM or chemotherapy present with different effects of HRQoL. Study dates 6th December 2005 to 1st December 2012 Source of funding See Baumert 2016				<table><tr><td>6 months</td><td>0.1 (0.1)</td><td>3.1 (0.09)</td></tr><tr><td>24 months</td><td>0.5 (0.1)</td><td>3.4 (0.09)</td></tr><tr><td>36 months</td><td>0.5 (0.1)</td><td>3.4 (0.09)</td></tr></table>**Change from baseline has been calculated by the NGA using the following calculator: ChangeFromBaseline_0.75correlation_Calc using the information provided in the appendix of this study (Table 5)	
Full citation 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	Sample size Of 211 accrued people, 101 were assigned to low-dose radiation (50.4 Gy) and n=102 to high-dose radiation (N=203) Characteristics<table><tr><td></td><td>Low-dose (50.4 Gy)</td><td>High-dose (64.8 Gy)</td></tr></table>	Interventions Arm A consisted of 50.4 Gy in 28 fractions over 5.5 weeks and arm B consisted of 64.8Gy in 36 fractions over 7 weeks	Details Central pathology review was performed at the Mayo Clinic in Rochester and patients were randomised (by an adaptive stratified randomisation method) to	Results Survival At 2 years, 94/101 adults in the low-dose arm were alive and at 5 years follow- up, 60/101 adults were alive. In the high-dose arm, 83/102 adults were alive at the 2 year follow-up and 54/102 adults were alive at the 5 year follow-up Progression At 2 years,82/101 of adults in the low-dose arm had not shown progression and 44/101 had not shown progression at the 5 year follow-up. At 2 years, 70/102 adults in the	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: Low risk of bias (the authors report having used an

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
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 : official journal of the American Society of Clinical Oncology, 20, 2267-76, 2002 Ref Id 629365 Country/ies where the study was carried out USA Study type RCT Aim of the study	Age < 40 y/o: 49(49%); 51 (50%) Age> 40 y/o: 52 (51%); 51 (50%) Male: 57(56%); 60(59%) Female: 44 (44%); 42 (41%) MMSE (28-30): 74 (73%); 66 (65%) MMSE (0-27): 20 (20%); 25 (25%) Inclusion criteria > 18 years old; have a histologic proof of a suprarentorial Kernohan grade 1 or 2 astrocytoma, oligodendroglioma, or mixed oligoastrocytoma within 3 months of study entry Exclusion criteria Pilocytic astrocytomas and other low-grade glioma variants				either arm A or arm B. Radiation therapy treatment fields were localized and included the preoperative tumour volume (defined y a CT scan in the early years of the study and an MRI scan in the later years of the study).	high-dose arm had not shown progression ad 40/102 had not shown progression at the 5 year follow-up. Toxicity At year 2, 93/101 adults had not reported any grade 3, 4 or 5 toxicity in the low- dose arm and at 5 years, 59/101 had not reported any grade 3, 4 or 5 toxicity in the low-dose arm. At year 2, 79/102 adults has not reported any grade 3, 4 or 5 toxicity in the high-dose arm and, at year 5, 48/102 had not reported any grade 3, 4 or 5 toxicity in the high-dose arm	adaptive stratified randomisation method) Allocation concealment: unclear risk of bias (not reported) Blinding of participants and personnel: unclear risk of bias (not reported) Blinding of outcome assessment: unclear (not reported) Incomplete outcome data: low risk of bias (all drop outs have been accounted for) Selective reporting: low risk Other information

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>To determine whether a higher dose of radiation therapy (64.8 Gy) in comparison with a lower dose (50.4 Gy) would improve survival in people with low-grade astrocytomas, oligodendrogliomas, or oligoastrocytomas
Study dates
May 1986 to December 1994
Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Van Den Bent, M. J., Afra, D., De Witte, O., Ben Hassel, M., Schraub, S., Hoang-Xuan, K., Malmstrom, P. O., Collette, L., Pierart, M., Mirimanoff, R., Karim, A. B. M. F., Long-term</td><td>Sample size
n= 311; n=157 in the deferred RT group and n= 154 in the early radiotherapy group
Characteristics<table><tr><td></td><td>Deferred RT</td><td>Early RT</td></tr><tr><td>Male</td><td>100 (64%)</td><td>91 (59%)</td></tr></table></td><td>Interventions
See Karim 2002</td><td>Details
Patients were followed - up for a median of 7.8 years (until March 2004). Analysis was ITT</td><td>Results
PFS
5.3 years in the early RT group and 3.4 years in the deferred radiotherapy group (HR 0.59 95% ci 0.45 TO 0.77)
OS
7.4 years in the early RT group and 7.2 years in the deferred RT group (HR 0.71 95% CI 0.71 to 1.34)</td><td>Limitations
See Karim 2002
Other information</td></tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: The EORTC 22845 randomised trial, LancetLancet, 366, 985-990, 2005 Ref Id 557076 Country/ies where the study was carried out Multicentre study Study type RCT Aim of the study To present the long-term efficacy results of the efficacy of postoperative radiotherapy in comparison with deferred radiotherapy Study dates March 2004 Source of funding	<table><tr><td>Age- median (range)</td><td>41 (17 to 68)</td><td>36.5 (15 to 69)</td></tr><tr><td>WHO performance status = O</td><td>63 (40%)</td><td>67 (44%)</td></tr><tr><td>WHO performance status = 1</td><td>68 (43%)</td><td>68 (44%)</td></tr><tr><td>WHO performance status = 2</td><td>18 (12%)</td><td>16 (10%)</td></tr></table> Inclusion criteria See Karim 2002 Exclusion criteria See Karim 2002						

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported					

Evidence tables for review 2b - Resection of glioma

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gupta, D. K., Chandra, P. S., Ojha, B. K., Sharma, B. S., Mahapatra, A. K., Mehta, V. S., Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex--a prospective randomised study, Clinical Neurology & NeurosurgeryClin Neurol Neurosurg, 109, 335-43, 2007 Ref Id 617203 Country/ies where the study was carried out	Sample size Awake group, n=26 General anesthesia group, n=27 Characteristics [table] Inclusion criteria not reported Exclusion criteria Age < 12 years old at the time of presentation, those with developmental delay or mental retardation, patients unwilling or apprehensive about procedure, patients with significant communication problems or with severe preoperative neurological deficits (hemiplegia, aphasia)	Interventions Motor areas (bilateral precentral gyrus) and speech areas (left frontal operculum and anular gyrus, superior temporal gyrus) were defined as eloquent cortex in the present study. A preoperative functional MRI was done to evaluate the relationship of tumour with the eloquent cortex. A contrast enhanced CT scan/Gad MRI brain was obtained postoperatively	Details Patients were randomised by computer generated random number allocation by an independent person not involved in operating the patients.	Results Deteriorated speech area lesions Immediate postoperatively Awake group= 4/26 GA group= 2/27 At 3 month follow-up Awake group= 3/26 GA group= 2/27 Deteriorate motor cortex lesions Immediate postoperatively Awake group= 7/26 GA group= 2/27 At 3 month follow-up Awake group= 10/26 GA group= 9/27 Residual tumour Awake group= 11/21 GA group= 7/19 Karnofsky performance score Awake group. Mean 80.81, median 90, range 50 to 90 GA group. Mean 82.30, median 90, range 70 to 100	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool Random sequence generation (selection bias): low risk (Patients were randomised by computer generated random number allocation by an independent person not involved in operating the patients.) Blinding of outcome assessment (Detection bias): high risk Incomplete outcome data (attrition bias): high risk (drop outs not accounted for). Selective reporting (reporting bias): high risk (no data regarding survival or adverse events has been reported).

	Awake group (n=26)	GA group (n=27)
Male sex (total n)	20	20
Age (mean ±SD)	42.7± 15.8	41.3 ± 17.3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
India Study type Prospective RCT Aim of the study To compare the efficacy of surgery under awake conditions with surgery under general anesthesia (GA) for intrinsic lesions of eloquent cortex (motor and speech areas) in preventing development of new neurological deficits and in achieving greater radical resection. Study dates January 2001 to May 2003 Source of funding Not reported		after 6 to 8 weeks to evaluate the extent of resection. Awake craniotomy: All surgeries were done in supine position. Infiltration with local anesthetic was given circumferentially to block the nerves. Along with this, the proposed incision line was also infiltrated. Incision was made aprox 20 mins after infiltration, and flap was tailored to be as small as possible. After the skin incision a rapid craniotomy was performed using a high-speed pneumatic drill. The lesion was			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		approached via transsucal or transcortical route over the most superficial part of the lesion. Once the lesion was entered, resection was performed with continuous monitoring performed by observing the patient for any interference with counting and naming. Al patients were evaluated for motor/speech deficits immediately after surgery, at the time of discharge and at 3 months during follow up visit and improvement/worsening of neurological status. For patients being operated under general			

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>GA, standard surgical techniques were applied as felt comfortable by the operating surgeon.</td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Senft, C., Bink, A., Franz, K., Vatter, H., Gasser, T., Seifert, V., Intraoperative MRI guidance and extent of resection in glioma surgery: A randomised, controlled trial, The Lancet Oncology, 12, 997-1003, 2011
Ref Id
576758
Country/ies where the study was carried out
Germany
Study type
RCT
Aim of the study
To assess whether use of</td><td>Sample size
N=49; n= 24 in the iMRI group (intraoperative MRI) and n=25 in the conventional treatment group
Characteristics<table><tr><td></td><td>iMRI group</td><td>Conv surgery</td></tr><tr><td>WHO grade I</td><td>1</td><td>0</td></tr><tr><td>WHO grade II</td><td>0</td><td>0</td></tr><tr><td>WHO grade III</td><td>1</td><td>1</td></tr><tr><td>WHO grade IV</td><td>22</td><td>24</td></tr><tr><td>Male sex</td><td>16- 67%</td><td>14- 56%</td></tr><tr><td>Mean age (range, SD)</td><td>55.3 - 38 to 76 SD 12.5</td><td>55 - 30 to 84. SD 13.6</td></tr><tr><td>Median KPS score (range, IQR)</td><td>90, 60 to 100, 80 to 100</td><td>90, 70 to 100, 85 to 95</td></tr></table></td><td>Interventions
Intervention consisted ofmobile intra-operative ultralow field (015 Tesla)MRI system (PoleStarN-20, OdinMedical Technologies, Yokneam, Israel andMedtronic, Louisville, CO, USA)13,14 for procedures guided by intra-operative MRI. The control arm used ’conventional micro neurosurgical resection’ including CUSA and neuronavigatio</td><td>Details

The sample size calculation was done to detect a difference of 25% between groups for the primary endpoint with a power of 80%. Randomis ation was done in participant s in blocks of four on a one-to-one ratio using BiAS for Windows</td><td>Results
Complete tumour resections
Achieved in 23 (96%) of 24 patients in the iMRI group and in 17 of 25 in the control group.
Adverse events

Participants with new or aggravated neurological deficits were present in 2/25 (8%) of participants in the conventional group and 3/24 (13%) participants in the intraoperative MRI group; intra-operative imaging had not tumour resection in any of the participants. Two participants had symptomatic haematomas, which were not attributable to the use of intra-operative MRI. In one patient, hemianopia was deliberately accepted due to tumour extension around the temporal horn of the lateral ventricle involving the optic radiation. No wound infections were reported. Due to the low number of events, RRs and CIs were not deemed appropriate
Progression</td><td>Limitations
Limitations assessed with the Cochrane Risk of bias Assessment tool:
Random sequence generation (selection bias): Low risk (Patients randomly allocated in a one-to-one ratio, in blocks of four using BiAS for Windows 9.01 by an assistant with no clinical involvement in the trial)

Blinding of outcome assessment (Detection bias): high risk (not blinded)

Incomplete outcome data (attrition bias): low risk (all drop outs have been accounted for)
Selective reporting (reporting bias): low risk (all pre-specified outcomes have been reported).

Other bias: high risk (Diagnostic MRI machine changed during the study from</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
intraoperative MRI guidance leads to a higher rate of radiologically complete tumour resections than does conventionally microsurgical resection. Study dates 1st Oct 2007 to 1st July 2010 Source of funding None	Inclusion criteria Adults ≥ 18 years old with known or suspected gliomas showing distinct contrast enhancement on t1 weighted MRI amenable to radiologically complete resection were eligible, patients suitable to undergo general anesthesia (were assessed prior the study) - patients not eligible, were offered stereotactic biopsy instead of tumour resection Exclusion criteria Tumours that crossed the midline or were located in the basal ganglia, cerebellum, brain stem, or otherwise close proximity to eloquent brain structures prohibiting or questioning complete resectability, contraindication to MRI examination (i.e. pacemaker), and inability to give consent because of neuropsychological deficits or a language barrier	n. The use of intra-operative ultrasound or fluorescence guided surgery with 5-aminolaevulinic acid was not allowed in either group.	9.01 by an assistant who had no clinical involvement in the trial. Investigators who assessed eligibility of participants and scheduled surgeries were masked to treatment group assignment by use of a sealed envelope design. Surgeons and participants were not masked to the treatment group assignment, but the neuroradiologist who analysed	8 out of 24 patients presented with progression in the intervention arm and 16 out of 25 patients presented with progression in the control arm	1.5 T to 3.0 T device, with a better display of contrast enhancement. Intraoperative MRI group used a mobile ultra-low-field MRI device (which rendered an inferior image resolution. The lead author received an honoraria as a speaker from Medronic Navigation and is a member on the scientific advisor board of Medtronic. Medtronic manufacture StealthStation neuronavigation systems used in the study. A p value of less than 0.04 was used as significant for endpoint data due to an adjusted sample size of 58, rather than 80).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			MRI data was masked		
Full citation Stummer, W., Pichlmeier, U., Meinel, T., Wiestler, O. D., Zanella, F., Reulen, H. J., Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial, Lancet OncologyLancet Oncol, 7, 392-401, 2006 Ref Id 617405 Country/ies where the study was carried out Germany Study type	Sample size N=270; n= 139 in the G-ALA group and n= 1331 in the white light group Characteristics 5-ALA / White light ≤55 y/o, median (%): 45 (32%) / 43 (33%) >55 y/o, median (%): 94 (68%) / 88 (67%) KPS 70-80: 28 (20%) / 31 (24%) KPS>80: 111 (80%) / 100 (76%) Inclusion criteria Participants aged 18-72 y with suspected (as assessed by study surgeon) newly diagnosed intreated malignant glioma. Tumours were to have a distinct ring-like pattern of contrast enhancement with thick irregular walls on MRI and a core area of reduced signal suggestive of tumour necrosis. Exclusion criteria	Interventions Participants were randomly assigned to 5-aminolevulinic acid (20 mg/kg bodyweight; medac, Wedel, Germany) for fluorescence guided resection or to conventional microsurgery with white light. Those randomly allocated to 5-aminolevulinic acid were scheduled to receive freshly prepared solutions of 5-aminolevulinic acid orally 3h (range 2 - 4) pre-operatively. Solutions were prepared by dissolving the contents of a	Details Randomisation was done by use of a dynamic allocation algorithm at a separate research unit, in which participants were allocated to keep the imbalance between treatment groups to a minimum. No permuted block randomisation was applied. Treatment allocation was communic	Results Complete resection RR 1.80 (1.39-2.34) PFS HR= 0.73 (0.57-0.93) OS Older patients HR= 0.73 (0.53-1.01) Younger patients HR= 1.04 (0.64-1.70) KPS At 6 weeks, the 5ALA group had a KPS of 90 (range 20-100); at 6 months, 28% (95% CI 19-36) had deterioration of KPS to 60 or less White light: 90 (10-100); at 6 months 31% (95% CI 20-40) had deterioration of KPA to 60 or less Convulsions: 5-ALA group: presented with 3 out 139 WL microsurgery: 1 out of 131 Grade 3 and 4 neurological adverse events: 5-ALA group: presented with 10 out of 139 adverse events WL microsurgery: presented with 7 out of 131 adverse events	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool: Random sequence generation (selection bias): low risk (performed independently with a dynamic allocation algorithm and treatment allocation was communicated by telephone and fax) Blinding of participants and personnel: high risk (not blinded) Blinding of outcome assessment (Detection bias): low risk (Central neuropathological, neuroradiological reviewers and pathology reviewer were blinded to treatment allocation. MRI scans labelled with patient initials, randomisation number) Incomplete outcome data (attrition bias): high risk (reasons for dropouts have not been provided) Selective reporting (reporting bias): high risk (Full outcome data not present for PFS and AEs. Timing and severity of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled multicentre phase III trial Aim of the study To assess the use of porphyrin fluorescence in malignant glioma after administration of 5-ALA for improving resection as defined by postoperative MRI. Study dates 11th October 1999- 19 July 2004 Source of funding medac GmbH, Wedel, Germany. W Stummer is a paid consultant to medac and Zeiss; U.Pichmeier is a medac employee; T Meinel is under contract by medac; and H-J	Tumours in the midline, basal ganglia, cerebellum or brain stem; more than one contrast enhancing lesion; substantial, non-contrast enhancing tumour with areas suggesting low grade glioma with malignant transformation; medical reasons precluding MRI; inability to give consent; a tumour location that did not enable complete resection; KPS of 60 or less; renal or liver insufficiency; and a history of previous systemic malignancy.	vial (1·5g) in 50 mL of drinking water. There was no placebo. Surg ery was done by use of a modified neurosurgical microscope (OPMI Neuro/NC4 systemwith fluorescence kit, Carl Zeiss Surgical GmbH, Oberkochen,G ermany), which enabled switching from conventional white xenon illumination to violet-blue excitation light. For participants assigned white light, the tumour was resected by use of conventional illumination.	ated to local investigato rs first by telephone and additionally by fax. Initial power calculation s estimated 350 participant s were required for an 80% power but to allow premature study termination an interim analysis was scheduled after 270 participant s whereby a 20\5 difference in PFS could be identified with a		AEs were not fully documented - no data on wound infections). Other bias: Unclear risk (Study sponsors responsible for study design, quality control and assurance. An organisation contracted by the study sponsors was responsible for data monitoring and collection; Differences noted in frequency of interventions depending on the age of the patient, which affect long-term outcomes, e.g. as overall survival). Other information Residual tumour was defined as contrast enhancement with a volume more than 0·175 cm^3. Progression was defined as the occurrence of a new tumour lesion with a volume greater than 0·175 cm^3, or an increase in residual tumour volume of more than 25%. Progression-free survival at 6 months was defined as the proportion of patients without radiological progression at this time. Patients who died from any cause before documented pregression were counted as an event for this endpoint. Overall survival was defined as the number of patients who had not died from any cause.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Reulen has received secretarial help from medac and travel reimbursement. All other authors declare no conflicts of interest.			power of 80%		Adverse events were classified according to the US National Cancer Institute common toxicity criteria (version 1.0). The US National Institutes of Health stroke score (NIH-SS) was used to measure postoperative deficits at 2 and 7 days after surgery, radiological progression at 6 weeks, then at 3, 6, 9, 12, 15 and 18 months post-surgery Inter-centre consistency was not presented. The manufacturer of 5-ALA (medac GmbH) was involved with the trial and authors had received assistance from the sponsor.
Full citation Stummer, W., Tonn, J. C., Mehdorn, H. M., Nestler, U., Franz, K., Goetz, C., Bink, A., Pichlmeier, U., Counterbalancing risks and gains from extended resections in malignant glioma surgery: A supplemental	Sample size See Stummer 2006 Characteristics See Stummer 2006 Inclusion criteria See Stummer 2006 Exclusion criteria See Stummer 2006	Interventions See Stummer 2006	Details Data obtained in all patients from Stummer 2006 in the final intent-to-treat analysis formed the basis of the present analysis. See Stummer 2006 for	Results Grade 3/4 neurological AEs 5ALA group: 10/139 WL microsurgery: 7/131	Limitations See Stummer 2006

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
analysis from the randomized 5-aminolevulinic acid glioma resection study: Clinical article, Journal of NeurosurgeryJ Neurosurg, 114, 613-623, 2011 Ref Id 617407 Country/ies where the study was carried out Germany Study type Supplemental analysis from the 5ALA vs white light RCT (Stummer 2006) Aim of the study To focus on risks associated with fluorescence-guided resection in the final, larger, intent-to-treat group from this study that is now available, presenting more			further details. For assessment of acute changes in neurological functions, the NIH-SS score was adapted as an outcomes parameter. The NIH-SS score assesses 15 neurological functions, grading the severity of impairment for each function individually, ranging from 0 (best) to 36 (worst) points. The score was measured 2 and 7		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
rigorous data on safety. Study dates See Stummer 2006 Source of funding See Stummer 2006			days after surgery and until radiological progression at 6 weeks and at 3, 6,9, 12,15 and 18 months after surgery. Adverse events were recorded and coded according to the NIH list of Common Toxicology Criteria. Serious AEs were coded according to the WHO Adverse Reaction Terminology criteria.		
Full citation	Sample size	Interventions	Details	Results Gross total removal	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Willems, P. W., Taphoorn, M. J., Burger, H., Berkelbach van der Sprenkel, J. W., Tulleken, C. A., Effectiveness of neuronavigation in resecting solitary intracerebral contrast-enhancing tumors: a randomized controlled trial, Journal of NeurosurgeryJ Neurosurg, 104, 360-8, 2006 Ref Id 557279 Country/ies where the study was carried out The Netherlands Study type RCT Aim of the study To assess the impact of neuronavigation on the cytoreductive	N=45, n= 22 in the SS group and n=23 in the SN group Characteristics <table><tr><td></td><td>SS group</td><td>SN group</td></tr><tr><td>male sex (%)</td><td>36</td><td>26</td></tr><tr><td>age in years (mean ± SD)</td><td>60.8 ± 12.1</td><td>60.6 ± 12.1</td></tr><tr><td>total tumour volume in cm3 (mean ± SD)</td><td>68.4± 48.9</td><td>54.2 ± 31.4</td></tr><tr><td>KPS score (mean ± SD9</td><td>78.6 ± 15.5</td><td>77.4 ± 19.4</td></tr></table> Inclusion criteria Patients harbouring a solitary intracerebral space-occupying lesion with (partial) contrast enhancement that was eligible for surgical debulking with the intention of GTR. Exclusion criteria Patients who received previous surgical treatment or if they harboured a known primary tumour elsewhere in the body.	Neuronavigation was performed with bone fiducial markers. Pre-operative MR images were obtained using a 0.5 tesla system with contrast enhanced T1 weighted images. Volumetric measurements were performed to assess total lesion volume. Functional grading was recorded according to the MD Anderson scheme. Planning involved localisation using fiducial markers, trajectory planning and segmentation of the tumour boundary.	Based on the results of a power analysis (details not specified in the paper) the authors planned to include 182 participants in the study, but the trial was stopped at 45 participants after an early pilot analysis. The participants were stratified by age (< 45 or ≥ 45) and KPS (≤ 70 or > 70), and they were evenly randomized to SS (without neuronavig	Achieved in 5 out of 22 patients in the SS group and 3 out of 23 patients in the SN group Neurological deficits 45.5% (n= 10) in the SS group and 18.2% (n=4) in the SN group, p=0.10 had exhibited new or worsened neurological deficits Survival The median survival was 9 months in the control arm and 5.6 months in the intervention arm (HR=1.6). No CIs were available PFS has not been reported QoL Quality of life questionnaire at 3 months postoperatively were completed by 19 patients (8 in the neuronavigation arm and 11 in the standard surgery arm) comprising 64.5% of all eligible patients. The questionnaire included 1 part of 30 general questions and another part of 20 brain-specific questions. Out of 26 outcome measures that were presented, the direction of change differed in 7 (all in the BN-20 group): 4 were in favour of the neuronavigation group and 3 were in favour of standard surgery. No statistical analyses were presented.	Limitations assessed with the Cochrane risk of bias tool Random sequence generation: low risk (randomised using a computer generated list with allocation codes in random order, balanced for each stratum using blocks of four. Blinding of outcome assessment (detection bias): high risk for gross total removal, neurological deficits and QoL and low risk for OS. Incomplete outcome data (attrition bias): 1 patient was excluded due to an alternative diagnosis (meningioma). Post-operative imaging was only assessed in 34/45 participants for tumour volume and 40/45 for contrast enhancing volume. Data for QoL at 3 months was only reported on 64.5% of the total eligible population. Selective reporting: high risk [All outcomes measures were reported to a degree. However full data with suitable presentation and analysis were not available for survival (no Kaplan-Meier plots), PFS was not reported, QoL (no statistical analysis) and adverse events (no presentation of numbers of events)]

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment of solitary contrast-enhancing intracerebral tumours and outcomes of this treatment in cases in which neuronavigation was preoperatively judged to be redundant Study dates November 1999 to December 2002 Source of funding Not reported		Tools included an infrared pointer or mechanically tracked operating microscope.	ation) or SN (with neuronavigation) by using a computer-generated list with allocation codes in random order, balanced for each stratum using blocks of four. There was no blinding.		Other bias: high risk (trial was significantly underpowered and terminated prematurely. Out of 280 potentially eligible patients, only 46 were included) Other information There were 3 early deaths in the navigation arm from systemic causes, which with the low numbers in each arm skewed the results. The trial was stopped early.
Full citation Wu, Js, Zhou, Lf, Tang, Wj, Mao, Y, Hu, J, Song, Yy, Hong, Xn, Du, Gh, Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation : a prospective,	Sample size n=238; n=118 in the DTI-based functional neuronavigation and n=120 in the routine neuronavigation group Characteristics Median age or gender have not been reported. The sample consisted of n=129 (n=61 in the research group and n=68 in the control group) patients with low grade glioma and n=85 (n=43 in the research group and n=42 in the	Interventions The control arm included those participants who underwent craniotomies using neuronavigational guidance with the routine 3-D navigational	Details Power calculation and randomisation technique were not stated. The peri-operative evaluation regarding age, sex,	Results Extent of resection for HGG: DTI based functional neuronavigation: 32/42 Routine neuronavigation: 14/43 Extent of resection for LGG: DTI based neuronavigation: 40/61 Routine neuronavigation:42/68 Overall survival Overall, HR = 0.570 (0.33-1) WHO IV vs WHO III, HR= 2.18 (1.14, 4.17)	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool: Random sequence generation (selection bias): high risk (stated via e-mail correspondence) Blinding of outcome assessment (Detection bias): high risk (Early postoperative imaging assessment performed by independent neuroradiologists blinded to the treatment strategies. However

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
controlled study in patients with gliomas involving pyramidal tracts, Neurosurgery, 61, 935-48; discussion 948-9, 2007 Ref Id 557310 Country where the study was carried out China Study type Prospective randomised controlled study Aim of the study To evaluate diffusion tensor imaging (DTI)-based functional neuronavigation in surgery of cerebral gliomas with pyramidal tract (PT) involvement with respect to both perioperative assessment and	control group_ patients with high grade glioma. Inclusion criteria Patients aged 6 to 75 years with an initial imaging diagnosis of single, unilateral, suprarentorial primary glioma. The lesions were involved in patients comprising cortical regions in the motor or somatosensory areas, cortical regions adjacent to the central gyrus, subcortical regions with an infiltrative progression along the patients, and temporal or insular regions in relation to the internal capsule. No contraindications for MRI were present Exclusion criteria Patients with secondary or recurrent gliomas, patients with contraindications for MRI, and patients for whom initial muscle strength grade of the affected extremities was 0/5 (no contraction at all).	MRI data set only. The research arm included participants to be examined by DTI for PT mapping and who later underwent operations using neuronavigation with the co-registered data sets of both 3-D navigational MRI and functional anisotropy (FA) maps of DTI. Images were acquired with either a 1.5 or 3.0 tesla MR scanner using either contrast-enhanced T1 weighted or FLAIR (if no enhancement) images. The DTI was performed with single-shot spin-echo echo planar	lesion location, tumour volume, initial motor function, final histological diagnosis, navigational predicted accuracy value as well as post-operative motor function and surgical complications was conducted by both the resident neurosurgeon and the operating neurosurgeon. They werememb ers of the treatment team and	Postoperative motor function Research group: 18 (15.3%) experienced postoperative motor deterioration, 22 (18.6%) demonstrated improvement of preoperative motor deficits and 78 (66.1%) remained functionally unaffected Control group: 39 (32.8%) experienced postoperative motor deterioration (Additional or aggravated motor deficit), 7 (5.9%) demonstrated improvement of preoperative motor deficits, and 73 (61.3%) displayed no motor function impairment or remained unchanged compared with preoperative function. KPS score Research group (mean)= 86 ± 20; LGG = 93 ± 10; HGG = 77 ± 27 . 1 patient died before discharge from the hospital and 1 6 months after surgery Control group (mean)= 74 ± 28; LGG = 86 ± 17; HGG= 53 ± 32. 4 patients died within 6 months after surgery	perioperative evaluations and postoperative motor function and surgical complications conducted by the resident neurosurgeon and operating neurosurgeon who were not blinded. Patient follow up data based on self-completed questionnaire forms) Incomplete outcome data (attrition bias): high risk (Details on attrition and dropouts not provided) Selective reporting (reporting bias): low risk (all expected outcomes have been reported). Other information 24 of 238 excluded Median follow-up of 21.3 months (maximum 50.5 months) Follow-up of LGG at 3 months then 6 monthly intervals

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>follow-up outcome.
Study dates
Between 2001 and 2005
Source of funding
National Natural Science Foundation of China</td>
<td></td>
<td>sequence and image processing completed to calculate FAmaps and fiber tracking (23 participants) of the PTs. StealthStation Treon neuronavigator (Medtronic) was used image integration with StealthMerge software, Stealth station with stealth merge, iPlan cranial software</td>
<td>were not blinded to the treatment strategies. The early post-operative imaging assessment was performed by independent neuroradiologists who were blinded to the treatment strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full citation
Wu, J. S., Gong, X., Song, Y. Y., Zhuang, D. X., Yao, C. J., Qiu, T. M., Lu, J. F., Zhang, J., Zhu, W., Mao, Y., Zhou, L. F., 3.0-T Intraoperative</td>
<td>Sample size
Total N= 87; n= 44 iMRI group and n= 43 in the control group
Characteristics
<table>
<tr><td></td><td>iMRI</td><td>Control</td></tr>
<tr><td>Female, n(%)</td><td>15 (34%)</td><td>19 (44.19%)</td></tr>
<tr><td>KPS (100), n(%)</td><td>40 (90%)</td><td>38, 88%</td></tr>
</table>
</td>
<td>Interventions
Patients in the intervention group received iMRI acquisition for image-updated neuronavigation with a 3.0-T high-field iMRI system</td>
<td>Details
Randomisation was done using a software specially designed for this trial according to a dynamic</td>
<td>Results
Rate of gross total resection
<table>
<tr><td></td><td>iMRI</td><td>Control</td><td>p-value</td></tr>
<tr><td>HGG (N=37) GTR (100%), N(%)</td><td>22</td><td>15</td><td>0.20</td></tr>
</table>
</td>
<td>Limitations
Limitations assessed with the Cochrane Risk of bias Assessment tool:
Random sequence generation (selection bias): low risk of bias
Blinding of outcome assessment (Detection bias): low risk of bias</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Magnetic Resonance Imaging-Guided Resection in Cerebral Glioma Surgery: Interim Analysis of a Prospective, Randomized, Triple-Blind, Parallel-Controlled Trial, Clinical NeurosurgeryClin Neurosurg, 61, 145-154, 2014 Ref Id 617456 Country where the study was carried out China Study type Single-center, prospective, randomised, triple-blind, parallel-controlled trial Aim of the study To assess the effect of 3.0 T iMRI-guided glioma resection on surgical	<table><tr><td>Noneloquent tumour location, n(%)</td><td>17 (38%)</td><td>18 (41%)</td></tr><tr><td>Eloquent tumour location, n(%)</td><td>27 (61%)</td><td>25 (58%)</td></tr><tr><td>Grade II, n(%)</td><td>25 (50%)</td><td>25 (65%)</td></tr><tr><td>Grade III, n(%)</td><td>12 (27%)</td><td>7 (16%)</td></tr><tr><td>Grade IV, n(%)</td><td>10 (22%)</td><td>8 (18%</td></tr></table> Inclusion criteria Individuals 18 to 70 years of age with newly diagnosed (diagnosed presurgically by board-certified radiologists and neurosurgeons), untreated malignant cerebral glioma (WHO grade II-IV); with supraretorial lesion involving the frontal, temporal, parietal, occipital and/or insular globe; with or without the lesion in an eloquent area; with preoperative assessment of attainable radiologically gross total tumour resection (by board-certified anesthesiologists and neurosurgeons); and with presurgical KPS score ≥70 Exclusion criteria Individuals with recurrent glioma after initial surgical intervention (except needle biopsy); primary	(MAGNETOM Verio 3.0 T, Siemens AG, Erlangen, Germany) with its integrated post processing workstation (Syngo Multimodality Workplace, Siemens AG). All intraoperative imaging data (foe example, T1-weighted contrast-enhanced 3-dimensional magnetization-prepared rapid-gradient echoc ardiograms for HGG, T1-weighted fluid-attenuated inversion recovery for LGG, diffusion tensor imaging and blood oxygen level-dependent functional MRI if necessary)	allocation algorithm. This software ensure that no one could predict the randomisation results. Participants, surgeons, assessment personnel and statisticians were blinded. Maximal safe resection was based on surgeon's assessment in accordance with conventional neuronavigation and intraoperative neurophysi	<table><tr><td></td><td>First iMRI: 12 (54.55 %) Final: 20 (90.91 %)</td><td>11 (73.3%)</td><td></td></tr><tr><td>LGG (N=50) GTR (100%), N(%)</td><td>22</td><td>28</td><td>0.01</td></tr><tr><td></td><td>First iMRI: 9 (40%) Final: 18 (81%)</td><td>12 (42%)</td><td></td></tr></table> Extent of resection iMRI group: 100% resection (range, 70.87%-100%; IQR, 100%-100%) Control group: 100% resection (range, 51.81%-100%; IQR, 87.77%-100%) p=0.001 PFS HR= 1.00 (0.96-1.04)	Incomplete outcome data (attrition bias): low risk (no missing data) Selective reporting (reporting bias): low risk (all expected outcomes have been reported). Selective reporting: Unclear (Insufficient information provided to determine if all outcomes are reported) Other bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
efficiency, morbidity, OS and PSF on cerebral glioma (WHO grade II-IV).The main hypothesis was that iMRI will enable more complete tumour resection than conventional neuronavigation, reducing morbidity and leading to improved OS, PFS and quality of life in patients. Study dates February 2012-August 2013 Source of funding National Key Technology R&D Program of China and the Shanghai Municipal Health Bureau. Authors have not disclosed personal,	glioma with prior radiotherapy or chemotherapy; leasions of the midline, basal ganglia, cerebellum, or brainstem; renal insufficiency; history of malignancy at the body sity; other critical tumour location or physical status that did not enable complete resection of the tumour or restricted life expectancy; and contraindications precluding iMRI acquisition.	were conducted and valuated by consultant neurosurgeons to decide whether to do additional resection. All additional resections were performed under the image-updated neuronavigation. Intraoperative imaging was performed until the neurosurgeons confirmed that the tumour was unable to be dealt with any more by final iMRI confirmation. Patients allocated to the control group underwent conventional neuronavigation surgery without any	cological monitoring. Primary endpoint was extent of resection (EOR). Secondary endpoints were PFS, OS and surgery-related morbidity. GTR was defined as the complete disappearance of all enhancing lesions (T1-weighted) for HGG and the complete disappearance of all non-enhancing lesions (T1-weighted fluid-attenuated	New or aggravated language deficits iMRI group: occurred in 6 (13.64%) Control group: 13 (30.23%) Alt 6-month follow-up, there was only 1 participant with delayed language deficits in each group.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
financial or institutional interest in any of the drugs, materials, or devices described in this article.		iMRI evaluation. The MRI confirmation was instantly conducted for volumetric analysis after wound closure. The i7 neuronavigation system was used in both groups. Either intraoperative neurophysiological monitoring or conventional microneurosurgical monitoring or conventional microneurosurgical facilities were allowed in both groups, but neither intraoperative ultrasound for 5ALA was allowed in either group. For all participants, surgery was to be followed by radiotherapy and/or	inversion recovery) lesions for LGG. The EORs were assessed quantitatively in volumetric analyses. Progression was define by any of the following: ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumour measurement obtained at either baseline (if no		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		chemotherapy according to standard protocols and clinical guidelines. No restrictions were imposed on treatment after disease progression.	decrease) or best response on stable or increasing doses or corticosteroids; significant increase in T2-weighted fluid-attenuated inversion recovery nonenhancing lesion on stable or increasing doses of cortecosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events;		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			any new lesion; clear clinical deterioration not attributable to other causes besides the tumour or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable diasease.		

1 Evidence tables for review 2c - Initial management of high-grade glioma

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation	Sample size RT+TMZ n= 97	Interventions	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chang, Susan., Zhang, Peixin., Cairncross, J. Gregory., Gilbert, Mark R., Bahary, Jean-Paul., Dolinskas, Carol A., Chakravarti, Arnab., Aldape, Kenneth D., Bell, Erica H., Schiff, David., Jaeckle, Kurt., Brown, Paul	RT+ NU n= 99 Characteristics Demographics and tumour characteristics: RT + TMZ vs RT + NU Age (median): 42 vs 43 KPS (60-80): 27 (27.8%) vs 29 (29.3%) KPS (90-100): 70 (72.2%) vs 70 (70.7%) AA: 94 (96.9%) vs 97 (98%) Oligodendroglioma: 3 (3.1%) vs 2 (2%) IDH1-R132H Mutation: RT + TMZ vs RT + NU Negative: 31 (51.7%) vs 23 (45.1%) Positive: 24 (40%) vs 25 (49%) Not scored: 5 (8.3%) vs 3 (5.9) Inclusion criteria Patients ≥18 years of age with unifocal, newly diagnosed, centrally reviewed anaplastic astrocytoma or oligoastrocytoma for which the oligodendroglial component was ≤25% were eligible. Other criteria included KPS status of at least 60 and an adequate haematological and laboratory values, and no prior malignancy within 5 years. Exclusion criteria Patients who received prior cranial radiation or chemotherapy or have a pre-existing lung disease that would prevent administration or completion of therapy with BCNU (carmustine) or CCNU (lomustine).	RT was given in 1.8 Gy fractions, 1 fraction per day, 5 days per week to a dose of 59.4 Gy in 33 fractions. The initial 50.4 Gy in 28 fractions included the initial target volume (T2 abnormality plus 2cm margin) or contrast-enhancing lesion + 2.5cm when no T2 abnormality was present. The final 9 Gy in 5 fractions included the boost volume (T1-enhances	Patients were randomised under permuted block randomisation, and stratified by age (<50 y vs >50y),KPS (60-80 vs 90-100), and extent of surgery (biopsy vs resection) and then randomly assigned to RT plus TMZ or RT + NU.NU therapy was either BCNU or CCNU. OS was measured from the date of randomisation to the date of death, or otherwise the last follow-up date on which the patient was reported alive. PFS was measured from the date of randomisation to the date of death, or otherwise the last follow-up date on which the patient was	OS (median years [95% CI] , p-value and HR [95% CI], p-value) RT + TMZ: median 3.9 years (3.0-7.0) RT + NU: median 3.8 years (2.2 -7.0) HR 0.94 (0.67 - 1.32) p=0.36 PFS (HR [95% CI], p-value) Univariate analysis: HR 0.85 (0.61-1.17) p = 0.31 Multivariate analysis (adjusted for the stratification factors and other pretreatment characteristics): HR 0.70 (0.50-0.98), p=0.039 OS and PFS by IDH1-R132H mutation status Univariate analysis: OS: HR 0.50 (0.31-0.81), p= 0.004 PFS: HR 0.59 (0.37 - 0.92), P = 0.02 Multivariate analysis (adjusted for the stratification factors and other pretreatment characteristics): OS: HR 0.42 (0.25-0.72) p= 0.001 PFS: HR 0.53 (0.32-0.86) P= 0.010 Toxicity (Grade ≥ 3, overall by treatment) RT + TMZ: 46 (47.9%) RT + NU: 75 (75.8%) p <0.001	Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk of bias (random permuted blocks) Allocation concealment: unclear (the study does not describe the technique used to implement the sequence) Blinding of participants and personnel:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
D., Barger, Geoffrey R., Werner-Wasik, Maria., Shih, Helen., Brachman, David., Penas-Prado, Marta., Robins, H. Ian., Belanger, Karl., Schultz, Christopher., Hunter, Grant., Mehta, Minesh., Phase III randomized study of		MR plus 1-cm margin). The target volumes received 95% to 105% of the prescribed dose. TMZ (200 mg/m2) was administered orally on days 1 through 5 of the first week of RT and then repeated every 28 days for a total of 12 cycles. BCNU (80 mg/m2) was administered intravenously on days 1, 2, and 3 of the first week of RT AND ON DAYS 56,	reported alive without disease progression. The prognostic value of IDH1-R132H mutation status by IHC was investigated using the Cox proportional hazard model, with OS and PFS as the outcome.		low risk of bias (it is not possible to blind participants and personnel in this type of interventions) Blinding of outcome assessment: low risk of bias (not described, but even if assessors were unblinded, will not have an impact on the outcomes reported) Incomplete outcome data: low risk of bias (all drop-outs/discontinuations clearly

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
radiation and temozolomide versus radiation and nitrosourea therapy for anaplastic astrocytoma: results of NRG Oncology RTOG 9813., Neuro-Oncology, 236, 2016 Ref Id 574351 Country/ies where the study was		57 , and 58, and then every 8 weeks or 4 more cycles for a total of 6 cycles (maximum BCNu dose: 1440mg/m2) CCNU dose was 130 mg/m2 orally every 8 weeks for a total of 6 cycles. Concurrent therapy with corticosteroids and Pneumocystis carinii prophylaxis was allowed.			accounted for) Selective reporting: low risk (all pre-specified outcomes reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
carried out USA Study type Phase III, randomised, multicentre, prospective trial Aim of the study To compare the overall survival of patients with anaplastic astrocytoma treated with radiotherapy and either					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
temozolomide (TMZ) or nitrosourea (NU). Secondary endpoints were time to tumour progression, toxicity and the effect of IDH1 mutation status on clinical outcome. Study dates October 15, 2002, was temporarily					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
closed to accrual between October 7, 2005 and April 6, 2006 due to supply shortage of BCNU. The study was then amended to allow either use CCNU or BCNU for the standard arm. The study was closed on					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
March 30, 2007 because the accrual rate did not meet the target. Source of funding NRG Oncology Operations, NRG Oncology SDMC, National Cancer Institute (NI) and Merck & Co. Grant funding for correlat					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>ive studies : Ohio State University Comprehensive Cancer Centre</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Chinot, O. L., Wick, W., Mason, W., Henriksson, R., Saran, F., Nishikawa, R., Carpentier, A. F., Hoang-Xuan, K., Kavan,</td><td>Sample size

n= 921 underwent randomisation and all analysed as ITT population

Characteristics

<table><tr><td></td><td>Bevacizumab + RT + TMZ</td><td>RT + TMZ</td></tr><tr><td>Age YR</td><td></td><td></td></tr><tr><td>Median</td><td>57</td><td>56</td></tr><tr><td>Range</td><td>20-84</td><td>18-79</td></tr><tr><td>Age - no %</td><td></td><td></td></tr><tr><td><50 yr</td><td>116 (25.3)</td><td>113 (24.4)</td></tr><tr><td>50-59 yr</td><td>158 (34.5)</td><td>165 (35.6)</td></tr><tr><td>60-69 yr</td><td>145 (31.7)</td><td>151 (32.6)</td></tr></table></td><td>Interventions

Intervention

Surgical resection/biopsy + RT @ 60Gy (administered as 2-Gy fractions 5 days per week) and oral TMZ (75mg/m2 for a maximum of 49 days), in combination with I.V.</td><td>Details

Randomisation
Patients were randomly assigned, in a 1:1 ratio, to bevacizumab or placebo. Randomization was performed centrally with the use of an interactive voice-response system, with stratification according to study region (Western Europe, Eastern Europe, Asia, United States, or other) and</td><td>Results

Overall Survival and PFS (extracted from Chinot 2014)

<table><tr><td></td><td>Bev+RT+TMZ</td><td>RT + TMZ</td><td>HR (95% CI)</td><td>P value</td></tr><tr><td>Median Progression free Survival months</td><td>10.6</td><td>6.2</td><td>0.64 (0.55-0.74)</td><td><0.001</td></tr><tr><td>Methylated MGMT</td><td></td><td></td><td>0.76 (0.56-1.04)</td><td></td></tr><tr><td>Non-Methylated MGMT</td><td></td><td></td><td>0.56 (0.46-0.68)</td><td></td></tr></table></td><td>Limitations

Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation:

low risk of bias
Allocation concealme</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>P., Cernea, D., Brandes, A. A., Hilton, M., Abrey, L., Cloughesy, T., Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma, New England Journal of MedicineN Engl J Med, 370, 709-</td>
<td>
<table>
<tr><td>>70 yr</td><td>39 (8.5)</td><td>34 (7.3)</td></tr>
<tr><td>Sex - no %</td><td></td><td></td></tr>
<tr><td>Male</td><td>282 (61.6)</td><td>298 (64.4)</td></tr>
<tr><td>Female</td><td>176 (38.4)</td><td>165 (35.6)</td></tr>
<tr><td>RPA class no/ total no (%)</td><td></td><td></td></tr>
<tr><td>III</td><td>76/458 (16.6)</td><td>75/462 (16.2)</td></tr>
<tr><td>IV</td><td>261/458 (57)</td><td>279/462 (60.4)</td></tr>
<tr><td>V</td><td>121/458 (26.4)</td><td>108/462 (23.4)</td></tr>
<tr><td>KPS - no/ total no (%)</td><td></td><td></td></tr>
<tr><td>50-80</td><td>149/457 (32.6)</td><td>140/462 (30.3)</td></tr>
<tr><td>90-100</td><td>308/457 (67.4)</td><td>322/462 (69.7)</td></tr>
<tr><td>MMSE score - no/ total no (%)</td><td></td><td></td></tr>
<tr><td><27</td><td>106/451 (23.5)</td><td>108/459 (23.5)</td></tr>
<tr><td>>27</td><td>345/451 (76.5)</td><td>351/459 (76.5)</td></tr>
<tr><td>WHO performance status - no/ total no (%)</td><td></td><td></td></tr>
<tr><td>0</td><td>227/458 (49.6)</td><td>238/462 (51.5)</td></tr>
<tr><td>1 or 2</td><td>231/458 (50.4)</td><td>224/462 (48.5)</td></tr>
</table>
</td>
<td>Bevacizumab (10mg/kg) every 2 weeks. Followed by oral TMZ (150mg/m2 per day on days 1-5 during the first cycle and 200mg/m2 during subsequent cycles if unacceptable toxic effects did not develop) plus I.V Bevacizumab (10mg/kg) every 2 weeks, for 6 cycles. In the monotherapy phase, I.V Bevacizumab (15mg/kg)</td>
<td>recursive partitioning analysis class (III, IV, or V).23 (There are six recursive partitioning analysis classes, of which classes III, IV, V, and VI are used to categorize glioblastoma, with higher numbers representing a worse prognosis. Class VI patients were considered too frail to participate in this study.)The study sponsor, study investigators, and patients were unaware of the study-group assignments. Unblinding of the assignments was allowed at any time for safety reasons or at the time of disease progression if deemed</td>
<td>
<table>
<tr><td>Median Overall Survival months</td><td>16.8</td><td>16.7</td><td>0.88 (0.76-1.02)</td><td>0.1</td></tr>
<tr><td>Methylated MGMT</td><td></td><td></td><td>0.93 (0.65-1.32)</td><td></td></tr>
<tr><td>Non-Methylated MGMT</td><td></td><td></td><td>0.91 (0.74-1.11)</td><td></td></tr>
</table>

Time to deterioration (TTD) and Disease free survival (DFS) ≥10 points deterioration in scores in quality of life score according to intervention arm. HR [95% CI], P (extracted from Taphoorn 2016)
<table>
<tr><td></td><td>DFS</td><td>TTD</td></tr>
<tr><td>Cognitive functioning</td><td>0.62 [0.54 to 0.72], P < 0.0001</td><td>0.74 [0.6 to 0.89], P = 0.0018</td></tr>
<tr><td>Role functioning</td><td>0.67 [0.58–0.78], P < 0.0001</td><td>0.82 [0.68 to 0.99], P = 0.0435</td></tr>
<tr><td>Emotional functioning</td><td>0.65 [0.56 to 0.75], P < 0.0001</td><td>0.78 [0.63 to 0.97], P = 0.0246</td></tr>
<tr><td>Difficulty with bladder control</td><td>0.59 [0.51 to 0.68], P < 0.0001</td><td>0.71 [0.55 to 0.92], P = 0.0082</td></tr>
</table>
</td>
<td>nt: low risk of bias

Blinding of participants and personnel: low risk of bias (study sponsor, investigators and patients were unaware of the study-group assignments. Unblinding was allowed at any time for safety reasons or at the time of disease progression if deemed necessary by the investigator)</td>
</tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results			Comments
22, 2014 Ref Id 554773 Country/ies where the study was carried out International (23 countries) Study type RCT Aim of the study Evaluate the effect of the addition of Bevacizumab to radiotherapy-temozo	MGMT status - %			was continued every 3 weeks until the disease progressed or unacceptable toxic side effects. Control Surgical resection/biopsy + RT @ 60Gy (administered as 2-Gy fractions 5 days per week) and oral TMZ (75mg/m2 for a maximum of 49 days), in combination with placebo every 2 weeks. Followed by oral TMZ (150mg/m2 per day on	necessary by the investigator. Assessments The determination of progression was based on imaging assessment (MRI), clinical assessment, and glucocorticoid use25 (Table S1 in the Supplementary Appendix). Radiographic criteria were adapted to address specific concerns related to the effect of antiangiogenic therapy on imaging. Specifically, assessment of nonenhancing tumor components was included, and a specific algorithm was used to assess pseudoprogressio	Weakness in both legs	0.65 [0.56 to 0.75], P < 0.0001	0.81 [0.66 to 0.99], P = 0.0396	Blinding of outcome assessment: low risk of bias Blinding (performance bias and detection bias): low risk of bias Incomplete outcome data: low risk of bias Selective reporting: low risk of bias Other information Saran et al. Bevacizumab, temozolomide, and radiotherapy for newly diagnosed glioblastoma: comprehen
	Methylated	117 (25.5)	120 (25.9)			Visual disorder	0.65 [0.56 to 0.75], P < 0.0001	0.80 [0.65 to 0.99], P = 0.0433	
	Non Methylated	225 (49.1)	236 (51)			Appetite loss	0.78 [0.67 to 0.89], P = 0.0004	1.13 [0.94 to 1.35], P = 0.1958	
	Data Missing	116 (25.3)	107 (23.1)			Headaches	0.78 [0.67 to 0.90], P = 0.0006	1.05 [0.84 to 1.31], P = 0.6519	
	Surgical Status - no/ total no (%)					Nausea and vomiting	0.77 [0.66 to 0.88], P = 0.0002	1.10 [0.90 to 1.35], P = 0.3301	
	Biopsy only	60 (13.1)	44 (9.5)			Constipation	0.69 [0.60 to 0.80], P < 0.0001	0.95 [0.77 to 1.18], P = 0.6524	
	Partial resection	210 (45.9)	223 (48.2)			Fatigue	0.64 [0.55 to 0.74], P < 0.0001	0.74 [0.62 to 0.89], P = 0.0013	
	Complete resection	188 (41)	196 (42.3)			Pain	0.76 [0.66 to 0.87], P = 0.0001	1.05 [0.86 to 1.27], P = 0.6351	
	Inclusion criteria Patients 18 years of age or older with newly diagnosed, histologically confirmed, surpatentorial glioblastoma. Additional inclusion criteria were a WHO performance status of 2 or lower, the use of stable or decreasing glutocorticoid doses within the 5 days before randomisation, adequate healing of craniotomy or cranial-biopsy site, adequate haematologic, hepatic, and renal function, and acceptable blood coagulation levels. Treatment had to be initiated between 29-48 days after the most recent surgery. Exclusion criteria					Dyspnea	0.65 [0.56 to 0.76], P < 0.0001	0.85 [0.69 to 1.05], P = 0.1390	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>lomide for the treatment of newly diagnosed glioblastoma
Study dates
June 2009-March 29,2011
Source of funding
F. Hoffmann-La Roche
N=</td>
<td>Patients were excluded if they had evidence of recent symptomatic intracranial haemorhhage on MRI, prior chemo or immunotherapy for glioblastoma or low grade astrocytoma, prior RT to the brain, a history of intracranial abscess within 6 months before randomisation, or a serious non healing wound.RT</td>
<td>days 1-5 during the first cycle and 200mg/m2 during subsequent cycles if unacceptable toxic effects did not develop) plus placebo every 2 weeks, for 6 cycles. In the monotherapy phase, placebo was continued every 3 weeks until the disease progressed or unacceptable toxic side effects.</td>
<td>n.25 These adaptations are consistent with current international consensus guidelines.26 Assessments were carried out at baseline; 28 days after completion of the concurrent-therapy phase; during cycles 2, 4, and 6 of the maintenance phase; every 9 weeks throughout the monotherapy phase; and at the time of disease progression. Pseudoprogression was assessed at the end of the treatment break with the use of a strict algorithm, 26 and confirmatory imaging was performed after two cycles of maintenance therapy In addition to</td>
<td>
<table>
<tr><td>Insomnia</td><td>0.73 [0.63 to 0.85], P < 0.0001</td><td>1.09 [0.87 to 1.36], P = 0.4665</td></tr>
<tr><td>Diarrhea</td><td>0.73 [0.63 to 0.84], P < 0.0001</td><td>1.10 [0.87 to 1.40], P = 0.4129</td></tr>
<tr><td>Financial difficulties</td><td>0.61 [0.52 to 0.70], P < 0.0001</td><td>0.80 [0.63 to 1.00], P = 0.0487</td></tr>
<tr><td>Future uncertainty</td><td>0.66 [0.57 to 0.77], P < 0.0001</td><td>0.83 [0.66 to 1.04], P = 0.1051</td></tr>
<tr><td>Seizures</td><td>0.62 [0.53 to 0.72], P < 0.0001</td><td>0.86 [0.65 to 1.15], P = 0.3084</td></tr>
<tr><td>Drowsiness</td><td>0.72 [0.62 to 0.83], P < 0.0001</td><td>0.95 [0.78 to 1.15], P = 0.5781</td></tr>
<tr><td>Hair loss</td><td>0.67 [0.58 to 0.77], P < 0.0001</td><td>0.81 [0.66 to 0.98], P = 0.0337</td></tr>
<tr><td>Itchy skin</td><td>0.69 [0.59 to 0.79], P < 0.0001</td><td>0.91 [0.75 to 1.10], P = 0.3331</td></tr>
</table>
Overall incidences of adverse events of special interest for Bevacizumab (all grades and grade >3) (Extracted from Saran 2016)
</td>
<td>sive safety results during and after first-line therapy, Neuro-OncologyNeuro-oncol, 18, 991-1001, 2016 and Taphoorn et al. Health-Related Quality of Life in a Randomized Phase III Study of Bevacizumab, Temozolomide, and Radiotherapy in Newly Diagnosed Glioblastoma, Journal of clinical oncology : official journal of the American</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			investigator-assessed progression, radiologists at an independent review facility analyzed all MRI scans. The independent reviewers were unaware of the study-group assignments, with read-only access to previous reviews until the final imaging data set was reviewed; at completion of the study, a review of the entire scan series verified the time of progression on MRI. In a final independent review, the determination of progression was calculated with the use of a prespecified algorithm that combined the assessment of the scans by the	<table><tr><td></td><td>Bevacizumab + RT + TMZ n= 461</td><td></td><td>RT + TMZ n=450</td><td></td></tr><tr><td></td><td>All grades (%)</td><td>Grade >3 (%)</td><td>All grades (%)</td><td>Grade >3 (%)</td></tr><tr><td>Bleeding (cerebral Haemorrhage)</td><td>15 (3.3)</td><td>9 (2)</td><td>9 (2)</td><td>4 (0.9)</td></tr><tr><td>Other bleeding (including mucocutaneous bleeding)</td><td>171 (37.1)</td><td>6 (1.3)</td><td>88 (19.6)</td><td>4 (0.9)</td></tr><tr><td>Wound-healing complications</td><td>32 (6.9)</td><td>15 (3.3)</td><td>21 (4.7)</td><td>7 (1.6)</td></tr><tr><td>Arterial Thromboembolic Event</td><td>27 (5.9)</td><td>23 (5.0)</td><td>7 (1.6)</td><td>6 (1.3)</td></tr><tr><td>Venous Thromboembolic event</td><td>38 (8.2)</td><td>35 (7.6)</td><td>43 (9.6)</td><td>36 (8.0)</td></tr><tr><td>Hypertension</td><td>181 (39.3)</td><td>52 (11.3)</td><td>57 (12.7)</td><td>10 (2.2)</td></tr><tr><td>Proteinuria</td><td>72 (15.6)</td><td>25 (5.4)</td><td>19 (4.2)</td><td>0</td></tr></table>	Society of Clinical Oncology, 33, 2166-75, 2015 are both sub-group analysis of AVAglio (NCT00943826) which is published in Chinot et al 2014. Results of both trials are entered under the Chinot trial for comprehension.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>independent reviewer with the investigator’s neurologic evaluation and assessment of glucocorticoid use. Quality of life was measured with the use of the validated core quality-of-life questionnaire (QLQ-C30) and a quality-of-life questionnaire specifically for patients with brain tumors (BN20) of the European Organization for Research and Treatment of Cancer.27-29 Patients completed the questionnaires without assistance. Five scales were prespecified for the primary analysis of deterioration-free survival: global health status,</td><td>
<table>
<tr><td>GI perforation (including GI fistula/abscess)</td><td>8 (1.7)</td><td>5 (1.1)</td><td>2 (0.4)</td><td>1 (0.2)</td></tr>
<tr><td>Abscess and fistulae (non GI)</td><td>2 (0.4)</td><td>2 (0.4)</td><td>3 (0.7)</td><td>3 (0.7)</td></tr>
<tr><td>Congestive heart failure</td><td>2 (0.4)</td><td>2 (0.4)</td><td>1 (0.2)</td><td>0</td></tr>
</table>

Adverse events of interest in protocol at incidence of > 10% (Extracted from Saran 2016)
<table>
<tr><td></td><td>Bevacizumab + RT + TMZ n=450</td><td>RT + TMZ n=450</td></tr>
<tr><td>Fatigue</td><td>191 (41.4)</td><td>178 (39.6)</td></tr>
</table>
</td><td></td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			physical functioning, social functioning, motor dysfunction, and communication deficit. An additional 21 nonprespecified scales were assessed in exploratory analyses. The score on the Mini–Mental State Examination (MMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function) was used to assess neurocognitive function (see Section 4 in the Supplementary Appendix). These assessments were performed at each disease-assessment time point (before the clinical evaluation). The Karnofsky		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			performance status was graded by the treating physician. Adverse events were assessed throughout the study, according to National Cancer Institute Common Terminology Criteria, version 3.0.30 Statistical Analysis The coprimary end points were investigatorassessed progression-free survival and overall survival. The overall 0.05 level of significance was split asymmetrically between the two coprimary end points, with 0.01 allocated to progressionfree survival and 0.04 to overall survival.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			For the analysis of progression-free survival, assuming median durations of 9.1 months in the group receiving bevacizumab plus radiotherapy–temozolomide (bevacizumab group) and 7.0 months in the group receiving placebo plus radiotherapy–temozolomide (placebo group) (hazard ratio for progression or death with bevacizumab, 0.77), we estimated that 677 events would be required for the study to have 80% power, with the use of the log-rank test at a two-sided alpha level of 1%. For the analysis of overall survival, assuming a median survival of		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			18.3 months in the bevacizumab group and 14.6 months in the placebo group (hazard ratio for death, 0.80), we estimated that 683 events would be required for the study to have 80% power, with the use of the log-rank test at a two-sided overall alpha level of 4%. Two interim analyses were planned for overall survival, and the O'Brien−Fleming group sequential boundary function, in conjunction with the alpha-spending function of Lan and DeMets, was used to adjust for sequential testing of overall survival.31 Progression-free survival and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			overall survival were measured from the date of randomization, and survival estimates were determined with the use of Kaplan–Meier methods. The between-group difference in survival was assessed with the use of a two-sided stratified logrank test. The hazard ratio was estimated with the use of a stratified Cox regression model. Subgroup analyses of progression-free survival and overall survival were prespecified in the statistical analysis plan. Hazard ratios in the subgroups were estimated with the use of an unstratified Cox regression model that included only		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			treatment as a covariate. The planned sample size (920 patients) was based on an assumed enrollment period of 42 months and a follow-up time of at least 17 months for the last patient enrolled, allowing for a 10% dropout rate for the analysis of progression-free survival at 3 years and a 5% dropout rate for the analysis of overall survival at 4 years. Secondary end points included progression-free survival as assessed by independent review, 1-year and 2-year survival rates, safety, and quality of life (as assessed with the use of the QLQ-C30 and BN20).		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>We analyzed quality of life using Kaplan–Meier methods, applying a specific definition of deterioration-free survival (see Section 2 in the Supplementary Appendix). Exploratory end points included betweengroup comparisons of glucocorticoid use and Karnofsky performance status. Further details are provided in the Supplementary Appendix.</td><td></td><td></td></tr>
<tr><td>Full citation
Gilbert, M. R., Dignam, J. J., Armstrong, T. S., Wefel, J. S.,</td><td>Sample size
n= 978 enrolled
[n= 637 randomised (341 excluded and reasons explained in flow chart), n = 621 analysed (16 excluded and reasons explained in flow chart)]

Characteristics
Baseline characteristics balanced (Supplementary table S5)</td><td>Interventions

Intervention
Surgery + RT + TMZ + Bevacizumab

Control</td><td>Details

Study Treatment
Fractionated, conformal radiotherapy or intensity-modulated radiotherapy (IMRT) was given at a daily dose of 2 Gy. Treatment</td><td>Results
<table><tr><th></th><th>Bevacizumab (n=312)</th><th>Placebo (n=309)</th><th>Hazard Ratio</th><th>P value</th></tr><tr><td>All patients</td><td></td><td></td><td></td><td></td></tr><tr><td>Median overall survival</td><td>15.7</td><td>16.1</td><td>1.13 (0.93-1.30)</td><td>0.21</td></tr></table></td><td>Limitations

Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Blumenthal, D. T., Vogelbaum, M. A., Colman, H., Chakravarti, A., Pugh, S., Won, M., Jeraj, R., Brown, P. D., Jaeckle, K. A., Schiff, D., Stieber, V. W., Brachman, D. G., Werner-Wasik, M., Tremont-Lukats, I. W.,	<table><tr><td></td><td>Bevacizumab (n = 260)</td><td>Placebo (n = 248)</td></tr><tr><td>Age (years)</td><td>59</td><td>57</td></tr><tr><td>Min-Max</td><td>21-82</td><td>19-82</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Gender</td><td></td><td></td></tr><tr><td>Male</td><td>148 (56.9%)</td><td>156 (62.9)</td></tr><tr><td>Female</td><td>112 (43.1%)</td><td>92 (37.1)</td></tr><tr><td></td><td></td><td></td></tr><tr><td>KPS</td><td></td><td></td></tr><tr><td>70-80</td><td>99</td><td>92</td></tr><tr><td>90-100</td><td>161</td><td>156</td></tr><tr><td></td><td></td><td></td></tr><tr><td>Surgery</td><td></td><td></td></tr><tr><td>Total</td><td>89</td><td>94</td></tr><tr><td>Partial</td><td>166</td><td>146</td></tr></table> Inclusion criteria >18 Years old and newly diagnosed glioblastoma, as confirmed on central review. Additional eligibility criteria included a Karnofsky performance status of at least 70 and adequate haemotological, renal, and hepatic function. Exclusion criteria	Surgery + RT + TMZ	was delivered 5 days a week for 6 weeks, for a total dose of 60 Gy. Conformal therapy was delivered to an initial volume consisting of the area of enhancement, the postoperative cavity plus surrounding edema (or other abnormality as seen on fluid-attenuated inversion recovery [FLAIR] images on MRI), and a 2-cm margin, for a total dose of 46 Gy in 23 fractions, followed by a boost of 14 Gy in 7 fractions to the area of enhancement plus the cavity and a 2.5-cm margin. IMRT was permitted within protocol-defined guidelines at institutions that	<table><tr><td>Median progression-free survival</td><td>10.7</td><td>7.3</td><td>0.79 (0.66-0.94)</td><td>0.007</td></tr><tr><td>Methylated MGMT</td><td></td><td></td><td></td><td></td></tr><tr><td>Favorable molecular profile</td><td></td><td></td><td></td><td></td></tr><tr><td>Median Overall Survival</td><td>16.7</td><td>25</td><td>2.27 (0.91-5.68)</td><td>0.07</td></tr><tr><td>Median Progression Free Survival</td><td>13</td><td>13.5</td><td>1.39 (0.67-2.89)</td><td>0.38</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Unfavorable molecular profile</td><td></td><td></td><td></td><td></td></tr><tr><td>Median overall survival</td><td>21.1</td><td>25.3</td><td>1.24 (0.73-2.12)</td><td>0.43</td></tr><tr><td>Median Progression Free Survival</td><td>16.9</td><td>8.4</td><td>0.63 (0.40-0.98)</td><td>0.04</td></tr><tr><td></td><td></td><td></td><td></td><td></td></tr></table>	Random sequence generation: low risk of bias (permuted block design) Allocation concealment: unclear risk of bias (not clearly stated in the article) Blinding of participants and personnel: Unclear risk of bias (insufficient details as to how blinding was done, other than blinding) Blinding of outcome assessment: Unclear risk of bias (insufficient

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Sulman, E. P., Aldape, K. D., Curran, W. J., Jr., Mehta, M. P., A randomized trial of bevacizumab for newly diagnosed glioblastoma, New England Journal of MedicineN Engl J Med, 370, 699-708, 2014
Ref Id</td>
<td>Patients with active cardiac disease or recent cerebrovascular events were excluded. In addition, patients were required to undergo an imaging study to rule out recent intracranial haemorhage. Patients who were receiving glutocorticoids had to have received a stable or decreasing dose for the 5 days before the study registration. Fractio</td>
<td></td>
<td>fulfilled IMRT-specific quality requirements, and all patients underwent radiotherapy quality assurance with the use of predefined guidelines. Treatment with temozolomide, at a dose of 75 mg per square meter of body-surface area, was started at the initiation of radiotherapy and was continued daily until the completion of radiotherapy, with a maximum of 49 doses.
Patients were randomly assigned to receive either bevacizumab or placebo in a permuted-block design.12 Stratification factors were status with respect to O-6-</td>
<td>
<table>
<tr><td>non-methylated MGMT</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Favorable molecular profile</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Median overall survival</td><td>13.9</td><td>14.6</td><td>1.02 (0.66-1.57)</td><td>0.94</td></tr>
<tr><td>Median progression free survival</td><td>10.1</td><td>7.3</td><td>0.72 (0.48-1.07)</td><td>0.1</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unfavorable molecular profile</td><td></td><td></td><td></td><td></td></tr>
<tr><td>median overall survival</td><td>14</td><td>14.6</td><td>1.13 (0.86-1.49)</td><td>0.36</td></tr>
<tr><td>median progression free survival</td><td>9.8</td><td>5.4</td><td>0.86 (0.67-1.11)</td><td>0.25</td></tr>
</table>
Serious Adverse Events
<table>
<tr><td></td><td>During Chemoradiotherapy</td><td></td><td></td><td>During Adjuvant</td><td></td></tr>
</table>
</td>
<td>details as to whether this was done and how it was done)
Blinding (performance bias and detection bias): Unclear risk
Incomplete outcome data: low risk of bias
Selective reporting: low risk of bias

Other information
Only resected (partial or complete) patients were included in the study, no biopsy patients</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
555229 Country/ies where the study was carried out USA Study type RCT Aim of the study To test the hypothesis that antiangiogenic therapy (bevacizumab) improves the efficacy of standard chemoradiotherapy			methylguanine–DNA methyltransferase (MGMT) and a tumor-based molecular profile based on expression of nine genes.13 MGMT status was determined with the use of a quantitative methylation-specific polymerase-chain-reaction (PCR) assay performed centrally by OncoMethylome Sciences.14 The nine-gene assay was performed with the use of a PCR technique optimized for paraffin-embedded tumor samples, and results were dichotomized as either favorable or unfavorable.13 Bevacizumab (or placebo) was	<table><tr><td></td><td></td><td></td><td></td><td>treatment</td><td></td><td></td><td></td><td></td></tr><tr><td></td><td>Bevacizumab (n=303)</td><td>Placebo (n=300)</td><td></td><td>Bevacizumab (n=260)</td><td>Placebo (n=233)</td><td></td><td></td><td></td></tr><tr><td></td><td>Grade 3</td><td>Grade 4</td><td>Grade 3</td><td>Grade 4</td><td>Grade 3</td><td>Grade 4</td><td>Grade 3</td><td>Grade 4</td></tr><tr><td>Fatigue</td><td>7 (2.3)</td><td>0</td><td>8 (2.7)</td><td>0</td><td>32 (12.3)</td><td>2 (0.8)</td><td>21 (9.0)</td><td>0</td></tr><tr><td>Wound Dehiscence</td><td>3 (1.0)</td><td>0</td><td>1 (0.3)</td><td>0</td><td>3 (1.2)</td><td>1 (0.4)</td><td>2 (0.9)</td><td>0</td></tr></table>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for glioblastoma Study dates April 2009-May 2011 Source of funding Supported by grants from the National Cancer Institute and by an unrestricted educational grant from Genentech.			administered intravenously at a dose of 10 mg per kilogram of body weight every 2 weeks, starting at week 4 of radiotherapy, until disease progression, severe treatment-related toxicity, or completion of adjuvant therapy (maximum number of doses, 24 over 12 cycles). Maintenance treatment with temozolomide began 4 weeks after the completion of radiotherapy at a starting dose of 150 mg per square meter for 5 consecutive days of a 28-day cycle, with an increase to 200 mg per square meter for subsequent cycles if no treatment-related		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			adverse events of grade 2 or higher were noted. Treatment was planned for 6 cycles with the option of extension to a total of 12 cycles if there were no or only low-grade adverse events and there was evidence of continued benefit. Antiemetic therapy with the use of a 5-hydroxytryptamine receptor antagonist was strongly recommended. Pneumocystis prophylaxis was recommended for patients with CD4 counts of less than 200 per cubic millimeter. At the time of tumor progression, patients could be informed about their study-group		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			assignment and either begin or continue a bevacizumab-containing regimen provided as part of the study. Patient Evaluation and Follow-up At baseline, all the patients underwent a physical examination that included a neurologic assessment, complete blood counts, blood chemical analyses (including tests of renal and hepatic function), and tumor imaging with either MRI (preferred) or CT, as well as a serum pregnancy test in women of child-bearing age. Patients were invited to participate in a longitudinal evaluation of the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			net clinical benefits of the treatment (NCB substudy) with the use of the M.D. Anderson Symptom Inventory–Brain Tumor Module (MDASI-BT), a neurocognitive-function test battery (Hopkins Verbal Learning Test-Revised [HVLT-R], Trail Making Test [TMT], and Controlled Oral Word Association [COWA]), and the European Organization for Research and Treatment of Cancer quality-of-life questionnaire with a brain-cancer module (EORTC QLQ-C30/BN20).15-18 Patients were administered the NCB substudy measures at the time of imaging		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			studies. During radiotherapy, patients were assessed for adverse events weekly and underwent weekly complete blood counts and monthly blood chemical analyses. During the maintenance phase of treatment, patients underwent blood counts and blood chemical analyses on days 21 and 28 of each cycle. A repeat tumor-imaging study was performed approximately 4 weeks after completion of radiotherapy and then before the initiation of cycle 4 of maintenance treatment (as well as before the initiation of cycles 7 and 10, if administered).		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Patients who completed adjuvant treatment underwent tumor imaging every 3 months until tumor progression. Response was assessed with the use of serial measures of the product of the two largest cross-sectional diameters, and progression was defined as an increase in tumor size by at least 25% or the development of a new lesion.19 Since early reactions to radiotherapy may emulate tumor progression, investigators were encouraged not to declare tumor progression within the first 12 weeks after completion of radiotherapy		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			unless there was a new lesion or neurologic worsening.20 Toxic effects were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Primary End Points The coprimary end points were the duration of overall survival from randomization, which was defined as the time until death from any cause, and the duration of progression-free survival, which was defined as the time until either disease progression or death.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Study Oversight The trial, which was sponsored by the National Cancer Institute (which also provided the study drug), was developed by the first and last authors in collaboration with the RTOG Brain Committee, the RTOG Statistical Group, the Cancer Therapy Evaluation Program at the National Cancer Institute, the NCCTG, and the ECOG. An unrestricted educational grant for support of the study was provided by Genentech, which had no role in the collection of data, analysis of findings, or preparation of this report. All		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			treatment data were collected by the RTOG data center and reviewed by the first author. The analyses were performed by RTOG statisticians. Central review was performed on all pathological specimens. The first draft of the manuscript was written by the first author with support from all coauthors; all authors reviewed and approved the manuscript. No one who is not an author contributed to the preparation of the manuscript. All the authors vouch for the completeness and accuracy of the data and confirm that the study was conducted according to the protocol, which is		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			available at NEJM.org. Statistical Analysis The trial was designed to concurrently provide a power of 80% for the detection of a 25% relative reduction in the risk of death (hazard ratio, 0.75) and a 30% relative reduction in the risk of either disease progression or death (hazard ratio, 0.70) in the bevacizumab group as compared with the placebo group. To control for type I errors in testing for the coprimary end points by means of the log-rank test,21 the threshold for statistical significance was set at a two-sided P value of 0.046		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			for overall survival and 0.004 for progression-free survival. The enrollment goal was 612 eligible patients, and a definitive analysis would be performed after 390 deaths had occurred. Interim monitoring with early stopping criteria for efficacy and futility was performed, as described in the study protocol, and was overseen by the RTOG data and safety monitoring committee. We used the Kaplan–Meier method to estimate survival distributions and a Cox proportional-hazards model to calculate hazard ratios.22, 23 To determine whether a molecularly		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			defined subgroup had a selective survival benefit from the addition of bevacizumab to standard treatment, we performed protocol-specified subset analyses for each tumor molecular factor and for combinations of molecular profile and MGMT status. We used the Cox model to perform additional analyses that examined the effects of these factors and recursive partitioning analysis (RPA) class,13 a compilation of clinical factors that define a patient's prognosis, with classes ranging from I to VI and higher classes indicating a worse		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			prognosis. This study enrolled patients in RPA classes III, IV, and V. For all these analyses, we used a likelihood-ratio test to evaluate differential treatment effects (interactions). We evaluated the proportionality of hazards using a test based on model residuals and smoothed hazard plots.24,25 In the NCB substudy,18 we assessed net clinical benefits to determine whether there were differences in changes between the two study groups from baseline to week 46 in patient-reported outcomes (on the basis of the MDASI-BT and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			EORTC QLQ-C30/BN20) or neurocognitive function (HVLT-R, TMT, and COWA). As specified in the trial protocol, these analyses were restricted to patients who were deemed to be progression-free at the time of the assessment. General linear models were used for longitudinal assessments, with fixed effects for study group and time factors and inclusion of MGMT status and RPA class to adjust for prognostic status. A treatment-by-time interaction effect was added to the model to determine whether there were between-group differences in patterns of		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>response over time, with a P value of 0.05 considered to indicate statistical significance.</td><td></td><td></td></tr>
<tr><td>Full citation
Gilbert, M. R., Wang, M., Aldape, K. D., Stupp, R., Hegi, M. E., Jaeckle, K. A., Armstrong, T. S., Wefel, J. S., Won, M., Blumenthal, D. T., Mahajan, A., Schultz, C. J.,</td><td>Sample size
Arm 1 (standard dose): n= 411
Arm 2 (dose dense): n=422
Characteristics
<table><tr><td>Characteristics</td><td>Standard dose</td><td>Dose-dense</td></tr><tr><td>Age, years (%)</td><td><50 = 112 (27)≥50 = 299 (73)</td><td><50 = 111 (26)≥50 = 311 (74)</td></tr><tr><td>Gender (%)</td><td>Male = 239 (58)Female = 172 (42)</td><td>Male= 237 (56)Female= 185 (44)</td></tr><tr><td>KPS (%)</td><td>60-80= 138 (34)90-100= 273 (66)</td><td>60-80=146 (35)90-100= 276 (65)</td></tr><tr><td>Radiation (%)</td><td>RTOG/NCCTG = 337 (82)EORTC= 74 (18)</td><td>RTOG/NCCTG = 349 (83)EORTC= 73 (17)</td></tr></table>Inclusion criteria
Patients older than 18 y/0o, newly diagnosed histologically confirmed GBM (WHO grade 4 astrocytoma), KPS > 60 and adequate hematologic, renal and hepatic function.</td><td>Interventions
Radiotherapy consisted of fractionated, conformal radiation given at a daily dose of 2 Gy. Treatment was delivered 5 days a week for a total of 6 weeks to a total dose of 60 Gy. Two radiotherapy protocols were allowed. In North America (RTOG, NCCTG),</td><td>Details
Statistical analyses were based on the modified intent-to-treat principle (including all the eligible and randomly assigned patients, regardless of treatment receipt)</td><td>Results
Overall survival for randomly assigned patients
<table><tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr><tr><td>Standard TMZ</td><td>320</td><td>411</td><td></td><td></td></tr><tr><td>DD TMZ</td><td>332</td><td>420</td><td></td><td></td></tr><tr><td></td><td></td><td></td><td>1.03(0.88-1.20)</td><td>0.63</td></tr></table>PFS for randomly assigned patients
<table><tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr><tr><td>Standard TMZ</td><td>374</td><td>411</td><td></td><td></td></tr><tr><td>DD TMZ</td><td>379</td><td>420</td><td></td><td></td></tr><tr><td></td><td></td><td></td><td>0.87(0.75-1.00)</td><td>0.06</td></tr></table>OS for patients with methylguanine - DNA methyltransferase unmethlylated tumours</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: unclear risk of bias (the authors report the method used, but they do not provide sufficient detail to allow an assessment of whether it should produce</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Erridge, S., Baumert, B., Hopkins, K. I., Tzuk-Shina, T., Brown, P. D., Chakravarti, A., Curran, W. J., Jr., Mehta, M. P., Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial,</td>
<td>Patients taking corticosteroids had to be taking a stable or decreasing dose for the 5 days before study registration. Submission of a tumuor tissue block with a minimum of 1 cm2 of tumour by day 14 of radiotherapy was a requirement.
Exclusion criteria
Not reported</td>
<td>an initial volume consisting of enhancement, postoperative cavity, plus surrounding edema (or fluid-attenuated inversionrecovery [FLAIR] abnormality defined by magnetic resonance imaging [MRI]) and a 2-cm margin received 46 Gy in 23 fractions followed by a boost of 14 Gy in seven fractions to the area of enhancement plus the cavity and a</td>
<td></td>
<td>
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>216</td><td>254</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>217</td><td>262</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>0.99(0.88-1.19)</td><td>0.44</td></tr>
</table>
PFS for patients with methylguanine - DNA methyltransferase unmethlylated tumours
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>242</td><td>254</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>244</td><td>262</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>0.88(0.73-1.05)</td><td>0.15</td></tr>
</table>
OS for patients with MGMT methylated tumours
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>76</td><td>122</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>86</td><td>122</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>1.19(0.87-1.62)</td><td>0.86</td></tr>
</table>
PFS for patients with MGMT methylated tumours
</td>
<td>comparable groups)
Allocation concealment: unclear risk of bias (the authors report the method used, but they do not provide sufficient detail to determine whether intervention allocations should have been foreseen in advance of, or during, enrolment)
Blinding of participants and personnel: unclear
Blinding of outcome assessment: unclear
Incomplete outcome</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Journal of Clinical OncologyJ Clin Oncol, 31, 4085-91, 2013
Ref Id
555238
Country/ies where the study was carried out
USA
Study type
RCT
Aim of the study
To test the hypothesis that prolonged</td>
<td></td>
<td>2.5-cm margin. In European (EORTC) centers, a single planning volume was used to deliver 60 Gy in 30 fractions to the area of enhancement and the cavity with a 2 to 3 cm margin. Temolozomide at a dose of 75 mg/m2 was started along with the radiotherapy and was continued on a daily basis until completion of radiation treatment, with amaximum of 49</td>
<td></td>
<td>
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>101</td><td>122</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>101</td><td>122</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>0.87 (0.66-1.15)</td><td>0.33</td></tr>
</table>
OS based on tumor O-methylguanine - DNA methyltransferase (MGMT) methylation status
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>162</td><td>244</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>433</td><td>516</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>0.58 (0.48-0.69)</td><td><0.001</td></tr>
</table>
PFS based on tumor O-methylguanine - DNA methyltransferase (MGMT) methylation status
<table>
<tr><td></td><td>Deaths</td><td>TOTAL</td><td>HR (95% CI)</td><td>P</td></tr>
<tr><td>Standard TMZ</td><td>202</td><td>244</td><td></td><td></td></tr>
<tr><td>DD TMZ</td><td>486</td><td>516</td><td></td><td></td></tr>
</table>
</td>
<td>data: low risk of bias
Selective reporting: low risk</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
exposure to temolozomide improves survival in patients with newly diagnosed GBM Study dates Not reported Source of funding Not reported		doses. During the concomitant radiotherapy and temozolomide treatment, prophylaxis against Pneumocystis jiroveci pneumonia was required. Antiemetic prophylaxis was recommended at initiation of the concomitant radiotherapy and chemotherapy regimen. Patients were randomly assigned after completion of the		<table><tr><td></td><td></td><td></td><td>0.61 (0.52-0.73)</td><td><0.001</td></tr></table>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		concomitant radiotherapy and chemotherapy treatment to either standard or DD temozolomide in a permuted block design by used the method described by Zelen. Patients on the standard treatment arm received temozolomide as a starting dose of 150mg/m2 for 5 consecutive days of a 28-day cycle, and TMZ was			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		increased for subsequent cycles to 200mg/m2 if no treatment-related adverse events greater than grade 2 were noted. Treatment was planned for six cycles with the potential to extend treatment to a total of 12 cycles if treatment was well tolerated and there was evidence of continued benefit defined as either continued tumor			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		response based on serial MRI, progressive improvement in the patient's performance status or neurologic function, or a decreasing requirement for corticosteroids. Patients randomly assigned to the DD treatment arms received as initial dose of 75 mg/m2 for 21 consecutive days of a 28-day cycle, which was increased for subsequent			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		cycles to 100 mg/m2 if no treatment-related events greater than grade 2 were noted. As with the standard dose arm, six cycles were planned with the potential to extend to a total of 12 cycles if the previously described criteria for benefit were met. Antiemetic therapy using a 5-hydroxytryptamine antagonist was strongly recommended for all			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		patients. Pneumocystis jiroveci prophylaxis was recommended for patients with CD4 counts less than 200/mL.			
Full citation Guedes de Castro, D., Matiello, J., Roa, W., Ghosh, S., Kepka, L., Kumar, N., Sinaika, V., Lomidze, D.,	Sample size n= 61 Characteristics <table><tr><td></td><td>Short course RT</td><td>Commonly used RT</td></tr><tr><td>% male</td><td>34</td><td>45</td></tr><tr><td>KPS<70</td><td>46</td><td>40</td></tr><tr><td>KPS ≥70</td><td>54</td><td>60</td></tr></table> Inclusion criteria Patients ≥ 65 y/o; histopathological diagnosis of GBM; initial surgery (including biopsy)	Interventions Short-course RT: 15-Gy in 5 fractions Commonly used RT: 45 Gy in 15 fractions	Details OS calculated from the day of randomisation to the death; PFS was calculated from the day of randomisation to the date of progression or death.	Results Median OS and median PFS Median OS: short course = 6.8 months; 95% CI, 4.5-9.1 months) compared with patients in commonly used RT = 6.2 months; 95% CI, 4.7-7.7 months; PZ.936). Median PFS difference also was not statistically significant in short course group versus commonly used RT group (4.3 months [95% CI, 2.6- 5.9 months] vs 3.2 months [95% CI, 0.1-6.3 months]; PZ.706). Change from baseline (global health status - QOL) in mean (SD) <table><tr><td></td><td>Short course RT</td><td>Commonly used RT</td></tr></table>	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: unclear risk (No details on actual randomisation process,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hentati, D., Rosenblatt, E., Fidarova, E., Survival Outcomes With Short-Course Radiation Therapy in Elderly Patients With Glioblastoma: Data From a Randomized Phase 3 Trial, International journal of radiation oncolo	performed ≤ 6 weeks prior to randomisation; KPS ≥ 50%; no previous chemotherapy or RT expousure; willigness to complete quality of life questionnaires; accessibility for treatment and follow-up and documentation of treatment Exclusion criteria History of other malignancy (except adequately treated nonmelanoma); patients with a serious active underlying condition or infection that would impair the ability to receive protocol treatment			4 wk after treatment: 4.6 (±15.9); -1.9 (±12.1) 8 wk after treatment: 1.5 (±15.9); -1.6 (±12.1) SD baseline in control group = ±17.2	even though it was performed centrally and stratified) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: Unclear risk (no blinding or dummy, but radiotherapy used, so unethical to do so) Blinding of outcome assessment: unclear risk (no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
gy, biology, physics, 98, 931-938, 2017 Ref Id 676568 Country/ies where the study was carried out Multicentre study Study type RCT Aim of the study To conduct a sub analysis of a study looking at					blinding or dummy, but radiotherapy used, so unethical to do so) Blinding (performance bias and detection bias): unclear risk (no blinding or dummy, but radiotherapy used, so unethical to do so) Incomplete outcome data: low risk (ITT analysis) Selective reporting: low risk (all prespecified outcomes were reported) Other information Follow up: 2.5 years

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
short-course RT versus commonly used RT in elderly patients with GBM. The original trial included elderly and frail patients, whereas this new analyses included elderly patients only. Study dates February					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2009-November 2014 Source of funding International Atomic Energy Agency					
Full citation Henriksson, R., Malmstrom, A., Bergstrom, P., Bergh, G., Trojanowski, T., Andreasson, L., Blomquist, E., Jonsborg, S.,	Sample size N=122; n= 63 in the RT arm and n= 59 in the E+RT arm Characteristics Demographic characteristics: Estramustine + RT vs. RT (Grade III) Age, mean (range) years: 52.7 (22-86) vs. 48.7 (25-78) Males/Female: 13/10 vs. 14/9 Inclusion criteria Patients were required to have a WHO performance status of 0-2 and adequate hematological, renal and hepatic functions. No other chemotherapy or hormonal treatment was allowed. Exclusion criteria Previous hypophysectomy or adrenalectomy, prior malignancies with the exception of curatively treated in situ carcinoma of the skin,	Interventions Patients received estramustine phosphate (Estrcyt®), 280 x 2 daily from the day of diagnosis, during radiotherapy and up to a total treatment time of 3 motnhs. Most male patients given	Details Survival data were analysed using the Kaplan-Meier plot and the long rank test. In order to correct for group differences in pre-treatment score in the QLQ-30 (validated instrument to asses quality of life) assessment, the proportion between post-treatment and pre-treatment scores was calculated for the 2 groups and then	Results Overall survival for astrocytoma (III) patients - ITT analysis (RT+EMP vs RT), HR (95%CI) HR 0.99 (0.92-1.08)* Overall survival for astrocytoma (IV) patients - ITT analysis (RT+EMP vs RT), HR (95%CI) non calculable Median survival in months (range) and percentage of surviving patients at 1, 2, and 3 years after diagnosis for grade III astrocytoma: Estramustine + RT (n=23) vs RT (n=23) Median survival (range): 17.3 (0.4-96.9) vs. 10.6 (1.3-92.7) 1 year: 52% vs 47% 2 year: 48% vs 34% 3 year: 39 vs 30%	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: unclear risk of bias (no method has been reported) Allocation concealment: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Edekling, T., Salander, P., Brannstrom, T., Bergenheim, A. T., High-grade astrocytoma treated concomitantly with estramustine and radiotherapy, Journal of Neuro-Oncology Neurooncol, 78, 321-326, 2006 Ref Id 555400	patients with poor medical risk because of non-malignant systemic disease, previous thromboembolism or cardiac infarction indicating a high risk of drop out after estrogen therapy, and patients with positive pregnancy test.	estramistine were treated with prophylactic breast irradiation (single dose of 15 Gy) to avoid adverse effects of the estradiol component with growth simulation in the breast tissues. Irradiation started 3-5 weeks following the surgical procedure. Radiotherapy was delivered once daily five times a week at 2 Gy per fraction, up to a total dose of 56	subjected to statistical testing.	Adverse events (grade III +IV) - RT vs RT + Estramustine Seizures: 6 vs 4 DVT/PE/TF: 8 vs 5 Nausea/vomiting: 3 vs 2 Pneuimonia: 6 vs 3 Quality of life analysed by comparing the proportional values after initiation of treatment in relation to before treatment Global quality of life: RT (mean rank): 33.1 RT+estramustine (mean rank): 35.2 p-value:0.67 *Calculated by the NGA techical team using http://arohatgi.info/WebPlotDigitizer/app/ and the Kaplain Meier plots in the study	risk of bias (no method has been reported) Blinding of participants and personnel: low risk of bias for OS (no blinding, but OS is not likely to be influences by lack of blinding) and high ROB for QOL (no blinding, and QOL reports are likely to be influenced by it) Blinding of outcome assessment: low risk of bias - no blinding but the outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Sweden, Finland and Poland Study type RCT Aim of the study To investigate the effects of estramustine (Estracyt ®) combined with radiotherapy in the treatm		Gy, and was prescribed according to the guidelines of the International Comission of Radiological Units. Radiotherapy was given with 6-8 MV photons from linear accelerators.			assessment is unlikely to be influenced by lack of blinding. Incomplete outcome data: low risk of bias- reasons for missing data are unlikely to be related to true outcome. Selective reporting: low risk of bias

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>ent of patients with high grade astrocytoma
Study dates
Not reported
Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Keime-Guibert, F., Chinot, O., Taillandier, L., Cartalat-Carel, S., Frenay, M., Kantor, G., Guilla</td><td>Sample size
n=85
(n= 81 analysed, only 84/85 were submitted for pathological review, furthermore 2 pts with anaplastic astrocytoma were excluded as such a small population, 1 patient was found to have a stroke and excluded)
Characteristics<table><tr><td>Baseline characteristics</td><td>Supportive Care (n=42)</td><td>Supportive Care + RT (n=39)</td></tr><tr><td>Female</td><td>14</td><td>16</td></tr></table></td><td>Interventions
Intervention
Supportive care + Radiotherapy
Control
Supportive care</td><td>Details
Treatment
After undergoing surgery, patients were randomly assigned to receive supportive care alone (the supportive care group) or supportive care in combination with radiotherapy (the radiotherapy group). Randomization was performed at</td><td>Results
Outcomes in the RT group<table><tr><td></td><td>Patients (n=39)</td></tr><tr><td>Variable</td><td></td></tr><tr><td>Never started radiotherapy, n (%)</td><td>1 (3)</td></tr><tr><td>Received <90% of planned dose, n (%)</td><td>6 (15)</td></tr><tr><td>Dose -Gy</td><td></td></tr></table></td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: Unclear risk</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>mo, J. S., Jadaud, E., Colin, P., Bondiau, P. Y., Menei, P., Loiseau, H., Bernier, V., Honnorat, J., Barrie, M., Mokhtari, K., Mazeron, J. J., Bissery, A., Delattre, J. Y., Association of French-Speaking, Neuro-Oncolo</td>
<td>
<table>
<tr><td>Male</td><td>28</td><td>23</td></tr>
<tr><td>Age, years</td><td></td><td></td></tr>
<tr><td>Mean</td><td>73</td><td>75</td></tr>
<tr><td>Range</td><td>70-85</td><td>70-84</td></tr>
<tr><td>KPS, n</td><td></td><td></td></tr>
<tr><td>70</td><td>23</td><td>20</td></tr>
<tr><td>80</td><td>14</td><td>15</td></tr>
<tr><td>90</td><td>3</td><td>4</td></tr>
<tr><td>100</td><td>2</td><td>0</td></tr>
<tr><td>Extent of Surgery</td><td></td><td></td></tr>
<tr><td>Biopsy</td><td>22</td><td>20</td></tr>
<tr><td>Subtotal Resection</td><td>7</td><td>7</td></tr>
<tr><td>Total Resection</td><td>13</td><td>12</td></tr>
<tr><td>Corticosteroid therapy, n (%)</td><td></td><td></td></tr>
<tr><td>Yes</td><td>36 (86)</td><td>32 (82)</td></tr>
</table>
</td>
<td></td>
<td>the data center of the Delegation for Clinical Research of the Assistance Publique–Hôpitaux de Paris, and patients were stratified according to the treatment center. Randomization and initiation of assigned treatments were required within 4 weeks after surgery. Supportive care consisted of treatment with corticosteroids and anticonvulsant agents, physical and psychological support, and management by a palliative care team. Radiotherapy, delivered by means of linear accelerators with a nominal energy of 6 mV or more, consisted of</td>
<td>
<table>
<tr><td>Median</td><td>50</td></tr>
<tr><td>Range</td><td>10-52</td></tr>
<tr><td>Fraction size - Gy</td><td></td></tr>
<tr><td>Median</td><td>1.8</td></tr>
<tr><td>Range</td><td>1.6-2.0</td></tr>
<tr><td>No. of fractions</td><td></td></tr>
<tr><td>Median</td><td>28</td></tr>
<tr><td>Range</td><td>5-31</td></tr>
<tr><td>Duration of radiotherapy</td><td></td></tr>
<tr><td>Median</td><td>5.9</td></tr>
<tr><td>Range</td><td>1.0-8.4</td></tr>
<tr><td>Time from diagnosis to radiotherapy - wk</td><td></td></tr>
<tr><td>Median</td><td>5.3</td></tr>
<tr><td>Range</td><td>2.6-10.0</td></tr>
<tr><td>Interruption or delay in radiotherapy, n (%)</td><td>11 (28)</td></tr>
</table>

Overall Survival
<table>
<tr><td></td><td>Standard care</td><td>Standard care + RT</td></tr>
<tr><td>Median</td><td>16.9</td><td>29.1</td></tr>
<tr><td>Range (CI, 95%)</td><td>13.4-21.4</td><td>25.4-34.9</td></tr>
</table>
</td>
<td>(Randomization was performed at the data center of the Delegation for Clinical Research of the Assistance Publique–Hôpitaux de Paris, and patients were stratified according to the treatment center. No details on actual randomisation process, even though it was performed centrally and stratified)
Allocation concealment: Unclear risk (no</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>gists, Radiotherapy for glioblastoma in the elderly, New England Journal of MedicineN Engl J Med, 356, 1527-35, 2007
Ref Id
555593
Country/ies where the study was carried out
France
Study type
RCT</td>
<td>
<table>
<tr><td>No</td><td>6 (14)</td><td>7 (18)</td></tr>
</table>
Inclusion criteria
Patients 70 years of age or older were eligible to participate in the study if they had histologically proven, newly diagnosed GBM or anaplastic astrocytoma on the basis of the WHO classificationand a Karnofsky performance score of 70 or more.
Exclusion criteria
Not specified
</td>
<td></td>
<td>fractionated focal irradiation, at a dose of 1.8 Gy per fraction, given once daily 5 days per week, for a total dose of 50 Gy. The dose was defined according to the guidelines of the International Commission on Radiation Units and Measurements. The clinical target volume included the area of contrast enhancement on magnetic resonance imaging (MRI) and a tumor margin of 2 cm
Surveillance and Follow-Up
The baseline examination included computed tomographic (CT) or MRI studies; complete blood counts and</td>
<td>
<table>
<tr><td>HR (CI, 95%)</td><td>0.47 (0.29-0.76)</td><td></td></tr>
<tr><td>P value</td><td>0.002</td><td></td></tr>
</table>
Progression-Free Survival
<table>
<tr><td></td><td>Standard care</td><td>Standard care + RT</td></tr>
<tr><td>Median</td><td>5.4</td><td>14.9</td></tr>
<tr><td>Range (CI, 95%)</td><td>4.4-7.6</td><td>10.9-22.1</td></tr>
<tr><td>HR (CI, 95%)</td><td>0.28 (0.17-0.47)</td><td></td></tr>
<tr><td>P value</td><td><0.001</td><td></td></tr>
</table>
Scores for Health-Related Quality of Life over Time
<table>
<tr><td></td><td>Baseline</td><td>Day 30</td><td>Day 60</td><td>Treatment effect</td><td>Time effect</td><td>Interaction effect</td></tr>
</table>
</td>
<td>details reported if any form of allocation concealment was used)
Blinding of participants and personnel: Unclear risk (no blinding or dummy, but radiotherapy used, so unethical to do so)
Blinding of outcome assessment: high risk (no blinding or dummy radiotherapy used, outcome assessors aware of tx)
Blinding (performance bias and detection bias): high</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Aim of the study
Optimal management of malignant glioma in patients who are in their eighth or ninth decade of life has not been determined, we evaluated the efficacy of radiotherapy in this population.</td>
<td></td>
<td></td>
<td>blood chemical tests; neurologic examination; assessment of the Karnofsky performance status; evaluation of the health-related quality of life with the use of a questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30, version 2.0), which has a specific module for brain cancer (QLQ-BN20); and a neuropsychological evaluation that included the Mini–Mental State Examination (MMSE), the Mattis Dementia Rating Scale (MDRS), and the Neuropsychiatric Inventory. Patients were assessed every</td>
<td>
<table>
<tr><td>QLQ-C30</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Global</td><td></td><td></td><td></td><td>0.79</td><td>0.17</td><td>0.12</td></tr>
<tr><td>Supportive care</td><td>62.7 + 4.1</td><td>61.8 + 4.7</td><td>60.3 + 5.0</td><td></td><td></td><td></td></tr>
<tr><td>Supportive care plus radiotherapy</td><td>62.9 + 3.4</td><td>57.6 + 3.5</td><td>55.6 + 3.9</td><td></td><td></td><td></td></tr>
<tr><td>Functioning</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Physical</td><td></td><td></td><td></td><td>0.57</td><td><0.001</td><td>0.97</td></tr>
<tr><td>Supportive care</td><td>75.4 + 4.6</td><td>64.9 + 6.3</td><td>53.8 + 7.6</td><td></td><td></td><td></td></tr>
<tr><td>Supportive care plus radiotherapy</td><td>70.3 + 6.3</td><td>58.8 + 5.5</td><td>51.9 + 7.3</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>risk (no blinding or dummy radiotherapy used)
Incomplete outcome data: low risk (ITT analysis, 15% drop out rate, all drops outs clearly accounted for)
Selective reporting: low risk (all prespecified outcomes were reported)</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th colspan="8">Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Study dates
February 2001 to January 2005
Source of funding
Programme Hospitalier de Recherche Clinique.</td><td></td><td></td><td>month during the first 3 months and then every 6 weeks by means of CT or MRI, neurologic examination, MMSE, and the health-related EORTC questionnaire (QLQ-C30). The MDRS and Neuropsychiatric Inventory were administered at days 60 and 135 and then every 3 months. Tumor progression was defined as an increase in tumor size by 25% or more or the appearance of new lesions on CT or MRI. Patients with tumor progression received supportive care. Toxic effects were graded according to the National Cancer Institute</td><td colspan="8"><table>
<tr><td>Role (work and household activities)</td><td></td><td></td><td></td><td>0.29</td><td>0.07</td><td>0.9</td></tr>
<tr><td>supportive care</td><td>66.3 + 5.7</td><td>59.1 + 6.8</td><td>61.8 + 8.5</td><td></td><td></td><td></td></tr>
<tr><td>Supportive care plus radiotherapy</td><td>63.1 + 6.4</td><td>56.1 + 6.4</td><td>50.0 + 7.4</td><td></td><td></td><td></td></tr>
<tr><td>Supportive care</td><td>68.7 + 5.0</td><td>60.0 + 6.1</td><td>63.0 + 5.6</td><td></td><td></td><td></td></tr>
<tr><td>Supportive care plus radiotherapy</td><td>66.8 + 4.7</td><td>59.6 + 4.9</td><td>57.4 + 6.7</td><td></td><td></td><td></td></tr>
</table></td><td></td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Common Toxicity Criteria, version 2. Assessment of Health-Related Quality of Life The QLQ-C30 questionnaire7 comprises five scales that measure functioning (physical, role [work and household activities], emotional, cognitive, and social), three symptom scales (fatigue, vomiting, and pain), and six single-item scales (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties). The QLQ-BN20 questionnaire8 includes 20 items covering functional deficits, symptoms, toxic effects of		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			treatment, and uncertainty about the future. The two questionnaires were scored according to the EORTC scoring manual.9 For both questionnaires, scores can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and singleitem measures indicating better performance. Neuropsychological Evaluation The MMSE was used as a measure of general cognitive status. Higher scores on this 30-point scale indicate better cognitive function. The Neuropsychiatric		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Inventory is a 12-item rating instrument that covers a range of psychological and behavioral symptoms (delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, euphoria or elation, apathy or indifference, dysinhibition, irritability or lability, aberrant motor behavior, and problems with sleeping or appetite).10 The scores range from 0 to 144 for the patient's rating (obtained from the caregivers), with 0 indicating the optimal rating. The MDRS examines attention, memory, initiation and maintenance of verbal and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			motor responses, and conceptualization and construction (design copying).11 Scores range from 0 to 144, with higher scores indicating better cognitive function. Statistical Analysis The primary end point was survival; the secondary end points were progression-free survival, tolerance of treatment, health-related quality of life, and cognitive functioning. Comparisons between the two groups were made on an intention-to-treat basis. The trial was initially designed to have 80% statistical power to detect a 100% increase in the median overall		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			survival from 16 to 32 weeks (hazard ratio for death, 0.5) in the radiotherapy group as compared with the supportive care group, with a two-sided significance level of 0.05. Seventy-four patients with a minimum follow-up of 1 year were required for this analysis. However, after the inclusion of the 72nd patient, an amendment to the protocol was made to permit an interim analysis. This was done because the investigators, who had no access to any part of the outcome data at that point, were concerned about the possibility of a premature, inconclusive termination of the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			study. A procedure of sequential planning, associated with the continuation of recruitment, was instituted with a triangular sequential design for twosided alternatives. This sequential design permitted discontinuation of the trial according to preset boundaries (Fig. 1) if radiotherapy was found to be significantly superior to supportive care (the upper boundary) or if there was no significant difference between the two groups (the lower boundary). After termination of the trial, we performed a final analysis, using the sequential		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			method, of the data from all the patients who had undergone randomization by the time the efficacy boundary was crossed. Secondary analyses were performed with the use of the Cox proportional-hazards regression model, with adjustments for relevant covariates. Survival curves were based on Kaplan–Meier estimates. The absolute health-related quality of life scores and all the cognitive scores were analyzed by means of a mixed-effects model for repeated measures; the method of empirical variances		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			was used to estimate the standard error, with a firstorder autoregressive covariance structure. A generalized estimating equation fitting the proportional-odds model for correlated ordinal data was used to analyze changes in the Karnofsky performance status over time. Monitoring of the trial and data collection were performed by the Delegation for Clinical Research of the Assistance Publique–Hôpitaux de Paris. Site visits were performed at all centers. All histologic specimens were subject to a central review.		
Full citation	Sample size	Interventions	Details	Results	Limitations

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Kim, I. H., Park, C. K., Heo, D. S., Kim, C. Y., Rhee, C. H., Nam, D. H., Lee, S. H., Han, J. H., Lee, S. H., Kim, T. M., Kim, D. W., Kim, J. E., Paek, S. H., Kim, D. G., Kim, I. A., Kim, Y. J., Kim, J. H., Park, B. J., Jung,</td>
<td>n = 82
(n = 76 included in the analysis, 6 patients did not meet the inclusion criteria and were therefore excluded from the analysis)
Characteristics
<table>
<tr><th>Characteristics</th><th>Radiotherapy plus adjuvant temozolamide (n=42)</th><th>ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus adjuvant temozolamide group (n=40)</th><th>P value*</th></tr>
<tr><td>Mean age years</td><td>51.1 + 11.8</td><td>51.4 + 12.4</td><td></td></tr>
<tr><td>Age (years), n (%)</td><td></td><td></td><td>0.9</td></tr>
<tr><td><50</td><td>19 (45.2)</td><td>16 (40.0)</td><td></td></tr>
<tr><td>>50</td><td>23 (54.8)</td><td>24 (60.0)</td><td></td></tr>
<tr><td>Gender, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>15 (35.7)</td><td>11 (27.5)</td><td></td></tr>
</table>
</td>
<td>Treatment group
ACNU-CDDP (2 cycles) neoadjuvant chemotherapy, followed by radiotherapy and 6 cycles of adjuvant Temozolamide.

Control Group
Standard conventional radiotherapy followed by 6 cycles of adjuvant Temozolamide.</td>
<td>Study design and treatment
The study population was randomly assigned to either the treatment group or control group. The estimated sample size was 168 (84 for each group) hypothesising a 6-month survival gain for the treatment group compared with the median survival of 12 months for the control group using a level of significance of 10% and power of 80%. Randomization was performed at the medical research collaborating centre (MRCC) at the Seoul National University Hospital stratified by age (cut off value 50 years),</td>
<td>Median Overall Survival (OS)
Intention-To-Treat Analysis
<table>
<tr><th></th><th>Control</th><th>Treatment</th></tr>
<tr><td>Median (Months)</td><td>18.9</td><td>28.4</td></tr>
<tr><td>90% CI for median (months)</td><td>17.1-27.4</td><td>21.1-NA*</td></tr>
<tr><td>P value**</td><td>0.2</td><td></td></tr>
<tr><td>Censored n (%)</td><td>21 (55.3)</td><td>24 (63.2)</td></tr>
</table>
Median Progression Free Survival (PFS)
Intention-To-Treat Analysis
<table>
<tr><th></th><th>Control</th><th>Treatment</th></tr>
<tr><td>Median (Months)</td><td>5.1</td><td>6.6</td></tr>
<tr><td>90% CI for median (months)</td><td>3.8-8.8</td><td>3.5-9.5</td></tr>
<tr><td>P value</td><td>0.8</td><td></td></tr>
<tr><td>Censored n (%)</td><td>16 (42.1)</td><td>14 (36.8)</td></tr>
</table>
*Not available
**Log rank test using level of significance of 0.1

Treatment-related toxicities of NCI CTCAE grade 3 or 4</td>
<td>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: Unclear risk (Randomization was performed at the medical research collaborating centre (MRCC) at the Seoul National University Hospital stratified by age (cut off value 50 years), extent of resection (complete or not,</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>H. W., Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial, Journal of</td>
<td>
<table>
<tr><td>Female</td><td>27 (64.3)</td><td>29 (72.5)</td><td></td></tr>
<tr><td>Resection, n (%)</td><td></td><td></td><td>0.5</td></tr>
<tr><td>Complete</td><td>17 (40.5)</td><td>13 (32.5)</td><td></td></tr>
<tr><td>Incomplete</td><td>12 (28.6)</td><td>22 (55.0)</td><td></td></tr>
<tr><td>Biopsy</td><td>13 (31.0)</td><td>5 (12.5)</td><td></td></tr>
<tr><td>Site, n (%)</td><td></td><td></td><td>0.5</td></tr>
<tr><td>A</td><td>0 (0.0)</td><td>2 (5.0)</td><td></td></tr>
<tr><td>B</td><td>4 (9.5)</td><td>2 (5.0)</td><td></td></tr>
<tr><td>C</td><td>3 (7.1)</td><td>1 (2.5)</td><td></td></tr>
<tr><td>D</td><td>5 (11.9)</td><td>7 (17.5)</td><td></td></tr>
<tr><td>E</td><td>30 (71.4)</td><td>28 (70.0)</td><td></td></tr>
<tr><td>Disposition of patients, n (%)</td><td></td><td></td><td>0.4</td></tr>
<tr><td>Enrollment error</td><td>4 (9.5%)</td><td>2 (5.0)</td><td></td></tr>
<tr><td>Cutoff for analysis</td><td>6 (14.3)</td><td>10 (25.0)</td><td></td></tr>
<tr><td>Completion of study</td><td>32 (76.2)</td><td>28 (70.0)</td><td></td></tr>
</table>
</td>
<td></td>
<td>extent of resection (complete or not, determined by residual enhancing lesions in Magnetic Resonance (MR) images performed within 48 h after surgery), and institute. The assigned treatment had to begin within 2 weeks after randomisation.
The control group received standard conventional radiotherapy followed by 6 cycles of adjuvant temozolamide. Radiotherapy consisted of fractionated focal irradiation at dose of 1.8-2.0 Gy per fraction given once daily over a period of 6 weeks, which falls under a total dose of 60.0-61.2 Gy to the gross tumor volume.</td>
<td>
<table>
<tr><td></td><td>RT</td><td>TMZ</td><td>ACNU-CDDP</td><td>RT</td><td>TMZ</td><td>Total</td></tr>
<tr><td>Any</td><td></td><td></td><td>12 (31.6)</td><td></td><td>1 (2.6)</td><td>13 (34.2)</td></tr>
</table>
</td>
<td>determined by residual enhancing lesions in Magnetic Resonance (MR) images performed within 48 h after surgery), and institute. No details on actual randomisation process, even though it was performed centrally and stratified)
Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neuro-Oncology J Neurooncol, 103, 595-602, 2011 Ref Id 555622 Country/ies where the study was carried out Korea Study type Prospective multicenter RCT - Phase 3 Aim of the study To evaluate the	<table><tr><td>Per-Protocol, n (%)**</td><td></td><td></td><td>0.8</td></tr><tr><td>No</td><td>25 (59.5)</td><td>22 (55.0)</td><td></td></tr><tr><td>Yes</td><td>17 (40.5)</td><td>18 (45.0)</td><td></td></tr><tr><td></td><td></td><td></td><td></td></tr><tr><td>** Only when undergoing > 3 cycles of adjuv</td><td></td><td></td><td></td></tr><tr><td>TMZ and no major violation had occurred</td><td></td><td></td><td></td></tr></table> Inclusion criteria Inclusion criteria included good performance status (Karnofsky performance score of 70 or higher) as well as adequate haematologic, renal, and hepatic function (absolute neutrophil count, >1,500/mm3, platelet count > 100,000/mm3, serum creatinine level, < 1.7 mg/dl, total serum bilirubin level, < 2.0 mg/dl, and liver function values <2.5 times the upper limit of normal in the laboratory where it was measured) Exclusion criteria Not specified		Radiotherapy was planned with dedicated computed tomography and 3D planning systems. Conformal radiotherapy was delivered with linear accelerators with nominal energy of 4 MV or more. 4 weeks after the end of the radiotherapy treatment, patients received up to 6 cycles of adjuvant oral temozolamide (150-200 mg/m2) for 5 days every 28 days. The treatment group received 2 cycles of ACNU-CDDP neoadjuvant chemotherapy, followed by radiotherapy and 6 cycles of adjuvant temozolamide. The neoadjuvant		Blinding of participants and personnel: high risk (no blinding or dummy temozolomide used) Blinding of outcome assessment: high risk (no blinding to outcome assessors) Blinding (performance bias and detection bias): high risk (no blinding or dummy temozolomide used, nor blinding to outcome assessors) Incomplete outcome data: low risk (ITT analysis, all drops outs

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
effects of neoadjuvant chemotherapy with nimustine (ACNU)-Cisplatin (CDDP) when used in conjunction with radiotherapy plus adjuvant temozolamide in patients with newly diagnosed glioblastoma. Study dates			chemotherapy with ACNU (40mg/mm2/day) and CDDP (40mg/mm2/day) was administered by continuous infusion for 72 hours and was repeated after 6 weeks. However, the 2nd cycle of ACNU-CDDP chemotherapy was delayed for up to 10 weeks unless laboratory finidngs met the haemotologic criteria (absolute neutrophil count, >1,500/mm3, platelet count >100,000/mm3, serum creatinine < 1.7 mg/dl) or nonhaemotologic criteria (< National Cncer Institute Common Terminology Criteria Adverse Events (NCI CTCAE, version		clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported) Other information Enrollment ceased after interim analysis revealed a frequency of toxicity related to the neoadjuvant chemotherapeutic agents that is not acceptable in modern cancer management.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1st August 2005-31st December 2007 Source of funding Study partially supported by a grant of Korea health, Ministry of Health and by a grant from the Seoul university hospital research fund			3.0) grade 1). Additionally, the dose of ACNU-CDDP was reduced to 75% of the dose administered in the previous cycle if haemotologic toxicities (absolute neutrophil count, < 100/mm3,, absolute neutrophil count, < 500/mm3,, platelet count <100,000/mm3) developed for more than 1 week during the first cycle of ACNU-CDDP chemotherapy, and adjuvant temozolamide was administered in the same manner as in the control group. Surveillance and follow-up		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			The baseline examination included MR imagine, full blood counts, blood chemistry test, and a physcial examination. Beofre the first cycle of neoadjuvant chemotherapy, patients underwent a comprehensive evaluation, which included audiometry. During ACNU-CDDP chemotherapy, patients were seen every 2 weeks, and MR imaging was performed at 6 weeks after the initiation of the first cycle and at 6 weeks after completion of the second cycle. During radiotherapy, patients were seen every week.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Six weeks after the completion of radiotherapy, patients underwent a comprehensive evaluation, including a radiologic assessment of the tumor. During adjuvant temozolomide therapy, patients underwent a monthly clinical evaluation and were subjected to MR Imagine at the end of cycles 3 and 6, and every 3 months thereafter. The assessment of radiological outcome was defined as previously described. Briefly, complete response was defined as absence of enhancement lesion, while partial		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			responsewas defined as >50% decrease in maximum cross-sectional area of enhancement lesion of tumor. Progessive disease was defined as increase in tumor size by 25%, appearance of new lesions, or increased need for corticosteroids. If disease progression was confirmed during the treatment, the next phase of the treatment protocol was performed, for example, if progression occured after the first cycle of ACNU-CCDP neoadjuvant chemotherapy, the patient was treated with radiotherapy skipping the rest of the cycles and followed by		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			adjuvant temozolomide. When disease progression occurred during or after the adjuvant temozolomide, these patients were definedas censored, and a secondary treatment was adinistered such as gamma knife radiosurgery, reoperation, or salvage chemotherapy at the discretion of the treating physician. Statistical Analysis The primary end point was median survival time, and secondary end-points were progression-free survival and safety. Survival analysis was performed via the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Kaplan-Meoer method with one-sided log-rank statistics using 80% power at significance level of 0.10. All analyses were carried out on an intention to treat (ITT) and per-protocol (PP) basis. Patients were included in the PP analysis only when they had completed the protocol past 3 or more cycles of adjuvant temozolomide without any major protocol violation. Fisher's extract test was used to compare the categorical variables, and students t-test was used to compare all the continuous variables between to two groups. All statistical analyses were		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			performed using SAS.		
Full citation Lecavalier-Barsoum, M., Quon, H., Abdulkarim, B., Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas, Cochrane Database of Systematic Review	Sample size Sample size and number of studies included in the Cochrane SR 3 RCTs, n = 931 Characteristics of relevant studies Cairncross 2006 n = 289 AO or AOA (2 out of 5 anaplastic features) Van den Bent 2006 n = 368 AO or AOA (3 out of 5 anaplastic features) Characteristics Cairncross 2006* PCV + RT (n=147) vs RT (n=142) Age, median years: 43 vs 43.5 KPS, patients (%): 60-70: 15 (10%) vs 15 (11%) 80-100: 132 (90%) vs 127 (89%) Surgery, patient (%): Debulking proceedure: 126 (86%) vs 128 (90%) Biopsy: 21 (14%) vs 14 (10%) Tumor grade, patients (%): Moderately anaplastic: 80 (54%) vs 128 (90%) Highly anaplastic: 67 (46%) vs 62 (44%) Chromosome 1p, patients (%):	Interventions Cairncross 2006 Surgery + PCV + RT vs Surgery + RT *Lomustine 130 mg/m2, procarbazine 75 mg/m2, Vincristine 1.4mg/m2 (up to 4 cycles) Van den Bent 2006 Surgery + RT + PCV vs Surgery + RT *Lomustine 110 mg/m2, procarbazine 60 mg/m2, Vincristine 1.4 mg/m2	Methods Cairncross 2006* n= 79 (54%) of PCV/RT group started 4th cycle of chemo n = 70 (48%) of PCV/RT group finished 4th cycle of chemo MMSE to evaluate cognition, may not capture aspects of cognitive decline that are subtle and important. The test was developed as a screening tool for dementia (19-21): it's sensitivity and specificity in other spheres have not been examined thoroughly. Van den Bent 2006* Cycles of chemo: 1 cycle - 18	Results Cairncross 2006 PCV + RT vs RT Survival Outcomes Median Overall survival, years: 4.6 vs 4.7 (HR 0.79, 95% CI 0.60-1.04, p-value = 0.1) Progression-free survival (early follow-up data only), years (95% CI): 2.6 vs 1.7 (HR 0.69; 95% CI 0.52-0.91, p = 0.004) Median Overall Survival for participants with codeletion of chromosomes 1p and 19q, years: 14.7 vs 7.3 (HR 0.59; 95% CI 0.37-0.95, p-value = 0.03) Median Overall Survival for participants without codeletion of chromosomes 1p and 19q, years: 2.6 vs 2.7 (HR 0.85; 95% CI 0.58-1.23, p-value = 0.39)* discrepancy between cochrane and cairncross 2006, data extracted from original study Progression-free Survival for participants with codeletion of chromosomes 1p and 19q, years: 8.4 vs 2.9 (HR 0.47, 95% CI 0.3-0.72, p-value < 0.001) Progression-free Survival for participants without codeletion of chromosomes 1p and 19q, years: 1.2 vs 1 (HR 0.81, 95% CI 0.56-1.16, p-value= 0.24)	Limitations Limitations Quality of the Cochrane SR Systematic review assessed using AMSTAR checklist. Total score 11/11 Cochrane Risk of Bias Assessment: Cairncross 2006 Random Sequence Generation (selection bias): Low risk ("patients were .... randomly assigned",

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
sCochrane Database Syst Rev, 5, CD007104, 2014 Ref Id 553897 Country/ies where the study was carried out N/A Study type Cochrane Systematic Review Aim of the study To compare postop	Known: 101 vs 101 1p deleted: 50 (50%) vs 59 (58%) 1p intact: 51 (50%) vs 42 (42%) Unknown: 46 vs 41 Chromosome 19q, patients (%) Known: 102 vs 103 19q deleted: 62 (61%) vs 64 (62%) 19q intact: 40 (39%) vs 39 (38%) Unknown: 45 vs 39 Chromosomes 1p and 19q, patients (%) Known: 100 vs 101 Both deleted 43 (43%) vs 50 (50%) One or neither deleted: 57 (57%) vs 51 (50%) Unknown: 47 vs 41 Van Den Bent 2006* RT + PCV (n= 185) vs RT (n= 183) Age, median years: 48.6 vs 49.8 WHO performance status 0-1: 155 (84%) vs 153 (84%) 2: 30 (16%) vs 30 (16%) MMSE Score 27-30: 116 (63%) vs 14 (62%) <27: 46 (25%) vs 53 (29%) Extent of resection Biopsy: 27 (15%) vs 25 (14%) Partial resection: 100 (54%) vs 83 (45%) Total Resection: 58 (31%) vs 75 (41%) Pathology Oligodendroglioma: 139 (75%) vs 126 (69%) Oligoastrocytoma: 44 (24%) vs 56 (31%) Missing: 2 (1%) vs 1 (1%)	(up to 6 cycles)	(11%), 2 cycles 35 (22%), 3 cycles 28 (17%), 4 cycles 20 (12%), 5 cycles 11 (7%), 6 cycles 49 (30%) The data presented in this section has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies were retrieved for accuracy and to check of other outcomes of interest were reported. Data extracted by the review team from the original study has been marked with an *.	Overall Survival for participants with IDH-1 or 2 mutations, years: 9.4 vs 5.7 (HR 0.59, 95% CI 0.40-0.86) Overall Survival for participants without codeletion of chromosomes but with IDH-1 or 2 mutations, years: 5.5 vs 3.3, 95% CI 0.32-0.99) Overall Survival for participants without IDH-1 or 2 mutations, years: 1.3 vs 1.8 (HR 1.14: CI 95% 0.63-2.04) Both groups had similar MMSE and HRQoL scores until the last years of life, when scores declined rapidly No difference in MMSE scores between survivors treated with PCV + RT vs RT and remained in the high normal range (28-29). MMSE trended upwards over 5 year of follow-up for the PCV + RT group. B-QOL scores remained constant in the mid upper range over time for survivors and there was no difference between the treatment arms. Adverse Effects Grade 3 or 4 toxicity: 65% during PCV vs 5% RT only Neurologic Grade 3 or 4 toxicity: 13% during PCV vs 2% RT after PCV vs 1% RT only 2 deaths attributed to PCV neutropenia Health Related Quality of Life - B-QOL and MMSE	comment: probably done) Allocation concealment (selection bias): Low risk ("patients were stratified by age less than 50 years vs >50 years, KPS 60 to 70 vs >80 and moderately anaplastic vs high anaplastic"; "random assignment was performed by randomised pemutated block within each stratification cell", comment:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
erative sequential RT and chemotherapy to RT alone in adults with newly diagnosed anaplastic oligodendroglomas (AO) or mixed anaplastic oligoastrocytomas (AOA). To evaluate the predictive and prognostic impact of the	1p/19q determined: 155 vs 156 1p/19q loss: 42 (27%) 36 (23%) 1p loss 24 (15%) vs 24 (15%) 19q loss: 18 (12%) vs 20 (13%) No loss: 71 (46%) vs 76 (49%) Inclusion criteria Cairncross 2006* >18 years old newly diagnosed, supratentorial AO or AOA Anaplasia was based on an evaluation of the following five microscopic features: tumor cellularity, nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis. To be high grade, the tumor had to contain two analplastic features, one of which was frequent mitoses or endothelial proliferation. To be an oligoastrocytoma, a 25% or greater oligodendroglioma component was required. KPS >60 Van den Bent 2006* Diagnosed by local pathologist with an anaplatic oligodendroglioma or anaplastic mixed oligoastrocytoma with at least 25% oligodendroglial elements Had at least 3 of 5 anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, and necrosis) 16-70 years old ECOG PF status of 0-2 Exclusion criteria Cairncross 2006*			Both groups had similar MMSE and HRQoL scores until the last years of life, when scores declined rapidly No difference in MMSE scores between survivors treated with PCV + RT vs RT and remained in the high normal range (28-29). MMSE trended upwards over 5 year of follow-up for the PCV + RT group. B-QOL scores remained constant in the mid upper range over time for survivors and there was no difference between the treatment arms. In both arms, those who dropped out due to death had the lowest score; mean scores among those who completed assessments and those who dropped out for unspecified reasons were similar between treatments and over time. Analysis of quality of life incorporating available data from survivors will be distorted by the early loss of patients with lower scores who died and had incomplete assessments. Van den Bent 2006 Survival Outcomes Median Overall Survival, years: 3.5 vs 2.6 (HR 0.75: 95% CI 0.60-0.95, p-value = 0.018) Median Progression Free Survival, years: 2.0 vs 1.1 (HR 0.66: 95% CI 0.52-0.83, p-value = 0.0003) Median Overall survival for participants with 1p and 19q codeletion, years: Not reached vs 9.3 (HR 0.56: CI 0.31-1.03, p-value = 0.059) Median Overall survival for participants without 1p and 19q codeletion, years: 2.1 vs 1.8 (HR 0.83: 0.62-1.1, p-value = 0.185)	probably done) Blinding (performance bias and detection bias) All outcomes: High Risk (Not blinded) Incomplete outcome data (attrition bias) All outcomes: Unclear risk (No mention of loss to follow-up) Selective reporting (reporting bias): Low risk (outcomes reported adequately) Van den Bent 2006 Random Sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
following biomarkers: codeletion of chromosomes 1q and 19q, O6-methylguanine-DNA methyltransferase (MGMT) promotor methylation and isocitrate dehydrogenase (IDH)-1 and -2 mutations. Study dates	Patients with other serious illnesses or pregnancy were ineligible Van den Bent 2006* Prior chemotherapy or RT to the skull No diseases inferring with follow up			Median Progression Free Survival for participants with 1p and 19q codeletion, years: 13.1 vs 4.2 (HR 0.42: 0.24-0.74: P-VALUE = 0.002) Median Progression Free Survival for participants without 1p and 19q codeletion years: 1.3 vs 0.8 (HR 0.73: 0.56-0.97, p-value = 0.026) Median Overall Survival for participants with methylated MGMT years: 5.9 vs. 3.6 (HR 0.65, 95% CI 0.43-0.98) Median Overall Survival for participants with unmethylated MGMT years: 1.4 vs 1.3 (HR 0.81, 95% CI 0.44-1.49) Median Progression Free Survival for participants with methylated MGMT years: 4.6 vs 1.3 (HR 0.52, 95% CI 0.35-0.76) Median Progression Free Survival for participants with unmethylated MGMT years: 0.8 vs 0.6 (HR 0.63, 95% CI 0.34-1.16) Median Overall Survival for participants with IDH-1 mutation years: not reached vs 5.4 (HR 0.53, 95% CI 0.3-0.95) Median Overall Survival for participants without IDH-1 mutation years: 1.6 vs 1.2 (HR 0.78, 95% CI 0.52-1.8) Median Progression Free Survival for participants with IDH-1 mutation years: 5.9 vs 3.0 (HR 0.49, 95% CI 0.29-0.84) Median Progression Free Survival for participants without IDH-1 mutation years: 0.8 vs 0.6 (HR 0.56, 95% CI 0.37-0.86) Adverse Effects	Generation (selection bias): Low risk ("patients were randomly assigned", comment: probably done) Allocation concealment (selection bias): Low risk ("patients were stratified by age (<40, >40), extent of resection,WHO ECOG PS (0 or 1 vs 2), and possible prior surgery for low grade oligodendroglioma (yes vs no); treatment was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Last search 21st March 2014 Source of funding None reported				Van den Bent did not update toxicity results, and 30% of the participants randomized to the upfront PCV plus RT arm received 6 cycles as intended. Health Related Quality of Life - QLQ-C30 and QLQ-BN20:* Mean (SD) change from baseline to end of RT of fatigue Health-related quality of life scale RT: 1 (16.3) RT+PCV: 1.9 (16.7) Mean (SD) change from baseline to end of RT + 1 year of fatigue Health- related quality of life scale RT: -5.9 (11.3) RT+PCV: -5.4 (12.3) Mean (SD) change from baseline to end of RT + 2.5 years of fatigue Health- related quality of life scale RT: -4.9 (8.9) RT+PCV: -6.9 (10.9) Mean (SD) change from baseline to end of RT of nausea/vomiting health related quality of life scale RT: 1.2 (8.2) RT+PCV: 3.5 (8.24) Mean (SD) change from baseline to end of RT + 1 year of nausea/vomiting health related quality of life scale	assigned using the minimisation technique of Simon and Pocock to ensure balance with respect to the stratification factors: comment: probably done) Blinding (performance bias and detection bias) All outcomes: High Risk (Not blinded) Incomplete outcome data (attrition bias) All outcomes: Unclear risk (No mention of loss to follow-up)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RT: -1.4 (5.7) RT+PCV: 0.4 (6.09) Mean (SD) change from baseline to end of RT + 2.5 years of nausea/vomiting health related quality of life scale RT: -0.8 (4.5) RT+PCV: -1.5 (5.4) Mean (SD) change from baseline to end of RT of physical functioning health-related quality of life scale RT: -2.7 (18.16) RT+PCV: 5.8 (18.7) Mean (SD) change from baseline to end of RT + 1 year of physical functioning health-related quality of life scale RT: 0.5 (12.7) RT+PCV: -2 (13.7) Mean (SD) change from baseline to end of RT + 2.5 years of physical functioning health-related quality of life scale RT: 1.5(10) RT+PCV: 3.7 (12.2) *Calculated by the NGA technical team	Selective reporting (reporting bias): Low risk (outcomes reported adequately)
Full citation	Sample size N= 342 Characteristics	Interventions	Details RCT phase III study involving 28	Results Outcome measures were: QOL EORTX QLQ-30 and BN20.Assessments were at 6 weeks, 3	Limitations Methodological

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Malmström, A, Grønberg, Bh, Marosi, C, Stupp, R, Frappaz, D, Schultz, H, Abacioglu, U, Tavelin, B, Lhermitte, B, Hegi, Me, Rosell, J, Henriksson, R, Temozolomide versus standard 6-week radiotherapy versus</td>
<td>
<table>
<tr><td></td><td>TMZ (n=93)</td><td>Hypofractioned radiotherapy (n=98)</td><td>Standard radiotherapy (n=100)</td></tr>
<tr><td>Gender: n. %</td><td>Male: n =55, 59%</td><td>Male: n =50, 51%</td><td>Male: n =68, 68%</td></tr>
<tr><td>WHO performance score: n, %</td><td>0-1 : 73 ,78%
2-3: 20, 22%</td><td>0-1 : 78 ,80%
2-3: 20, 20%</td><td>0-1 : 72 ,72%
2-3: 28, 28%</td></tr>
<tr><td>Surgery type: n, %</td><td>Biopsy:24 (26%)
Resection (partial or complete): 69 (74%)</td><td>Biopsy:26 (27%)
Resection (partial or complete): 72 (73%)</td><td>Biopsy: 27 (27%)
Resection (partial or complete): 73 (73%)</td></tr>
</table>

Inclusion criteria
WHO performance score 0-2 (or 3 if a neurological deficit); adequate haematological, renal and liver function; and were expected by the doctor to tolerate all treatment options.
Exclusion criteria
Another primary cancer; WHO performance score 3-4; any disorder likely t interfere with study treatment; previous therapy for a brain tumour; and previous radiotherapy to the head that would prevent further irradiation
</td>
<td>Temolozomide was administered orally in 200mg/m2 doses on days 1-5 of every 28 days for up to 6 cycles or until radiological progression, clinical progression, or both, unacceptable adverse events were seen or until a physician or patient chose to discontinue treatment. Hypofractioned radiotherapy was administered in 6 fractions of 5.0 Gy for 3 days a week over</td>
<td>European oncology centres enrolling 342 patients between 2000 and 2009. It focused on patients over 60 years old with a histologically confirmed WHO grade IV astrocytoma. The primary hypothesis was to test if chemotherapy with temolozomide was better than hypofractioned radiotherapy but with an improved quality of life profile.
Power calculation for 480 patients with 160 per treatment group for 10% survival difference (10-20% at 1 year). 90% power at 5% significance vi the log rank.
Sponsors had no role in study</td>
<td>months, 6 months. AE via the WHO grading system except nausea and vomiting by the NCIC version 2.0. Further therapy at discretion. Central pathology with IDH1 and MGMT via DNA isolated paraffin embedded tumour quantitative methylation specific PCR normalisedto beta-actin (ACTB) with a ratio of >2.0 being positive.

Survival Data
<table>
<tr><th></th><th>Number of deaths /patients</th><th>Hazard Ratio (95% CI)</th><th>Log-rank p value</th><th>Median (95% CI) survival (months)</th><th>1-year (95% CI) survival (months)</th></tr>
<tr><td>TMZ or hypofractionated RT vs standard RT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Overall</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard RT</td><td>100/100</td><td>1</td><td></td><td>6.0 (5.1-6.8)</td><td>17% (10-24)</td></tr>
<tr><td>Hypofractionated RT</td><td>94/98</td><td>0.85 (0.64 - 1.12)</td><td>0.24</td><td>7.5 (6.5-8.6)</td><td>23% (14-31)</td></tr>
</table>
</td>
<td>limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk (central electronic randomisation by an independent organisation)
Allocation concealment: low risk of bias (allocations were revealed by fax transmission to a project manager)
Blinding of participants and</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial, The Lancet. Oncology, 13, 916-26, 2012
Ref Id
555895
Country/ies where the study was</td>
<td></td>
<td>2 weeks or 34.0 Gy devolved in 10 fractions of 3.4 Gy delivered in 10 fractions of 3.4 Gy on 5 days a week over 2 weeks. Standard radiotherapy was 60.0 Gy in 30 fractions of 2.0 Gy over 6 weeks</td>
<td>design, data collection, data analysis, data interpretation, or writing the report.
Randomisation was by computer. Patients were randomised depending on the institution to either 1:1:1 in block of 9 to either temolozomide, hypofractioned radiotherapy, or standard radiotherapy; or in blocks of 8 to either temolozomide or hypofractioned radiotherapy. Blinding was not used.</td>
<td>
<table>
<tr><td>TMZ</td><td>90/93</td><td>0.70 (0.52 - 0.93)</td><td>0.01</td><td>8.3 (7.1-9.5)</td><td>27% (18-36)</td></tr>
<tr><td>Age 60-70</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard RT</td><td>59/59</td><td>1</td><td></td><td>7.6 (5.2-10.1)</td><td>24% (13-35)</td></tr>
<tr><td>Hypofractionated RT</td><td>57/58</td><td>1.06 (0.73 - 1.54)</td><td>0.77</td><td>8.8 (6.9-10.8)</td><td>26% (15-38)</td></tr>
<tr><td>TMZ</td><td>49/51</td><td>0.87 (0.59 - 1.28)</td><td>0.48</td><td>7.9 (6.5-9.3)</td><td>24% (12-35)</td></tr>
<tr><td>Age >70</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Standard RT</td><td>41/41</td><td>1</td><td></td><td>5.2 (4.0-6.3)</td><td>7% (0.6-15)</td></tr>
<tr><td>Hypofractionated RT</td><td>37/40</td><td>0.59 (0.37 - 0.93)</td><td>0.02</td><td>7.0 (5.2-8.8)</td><td>18% (6-29)</td></tr>
<tr><td>TMZ</td><td>41/42</td><td>0.35 (0.21 - 0.56)</td><td><0.0001</td><td>9.0 (6.2-11.8)</td><td>32% (18-46)</td></tr>
</table>
</td>
<td>personnel: High risk (not blinding or placebo used)
Blinding of outcome assessment: High risk (not blinded or placebo used)
Blinding (performance bias and detection bias): High risk (not blinded or placebo used)
Incomplete outcome data: high risk of bias (analysis was on an intention-to-treat basis with all withdrawals and protocol violations</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>carried out
Sweden
Study type
RCT
Aim of the study
To asses the optimum palliative treatment in patients aged 60 years and older with gliobastoma

Study dates

Between Feb</td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td>TMZ vs hypofractionated RT</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Overall</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypofractionated RT</td><td>119/123</td><td>1</td><td></td><td>7.4 (6.4-8.4)</td><td>20% (13-28)</td></tr>
<tr><td>TMZ</td><td>116/119</td><td>0.82 (0.63 - 1.06)</td><td>0.12</td><td>8.4 (7.3-9.4)</td><td>25% (17-32)</td></tr>
<tr><td>Age 60-70</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypofractionated RT</td><td>62/63</td><td>1</td><td></td><td>8.3 (6.5-10.0)</td><td>26% (15-37)</td></tr>
<tr><td>TMZ</td><td>60/62</td><td>0.91 (0.63 - 1.30)</td><td>0.59</td><td>7.8 (6.4-9.2)</td><td>23% (12-33)</td></tr>
<tr><td>Age >70</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypofractionated RT</td><td>57/60</td><td>1</td><td></td><td>6.5 (5.1-7.9)</td><td>15% (6-24)</td></tr>
<tr><td>TMZ</td><td>56/57</td><td>0.72 (0.50 - 1.05)</td><td>0.09</td><td>9.0 (7.8-10.2)</td><td>27% (15-38)</td></tr>
</table>
</td>
<td>clearly pre-specified. There was a high rate of drop-outs for quality of life data in keeping with other studies making it a high risk of bias.
Selective reporting: low risk of bias (all pre-specified outcomes were reported)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results						Comments
2, 2000, and June 18, 2009 Source of funding Supported by a grant from Lion's Cancer Research Foundation, University of Umea, Sweden (AM), Cancer Fonden Conflicts of interest:				MGMT Status						
				non-methylated						
				Any RT	67/68	1		7.0 (5.7-8.3)	26% (16-37)	
				TMZ	43/44	1.16 (0.78 - 1.72)	0.46	6.8 (5.9-7.7)	16% (5-27)	
				Methylated						
				Any RT	62/63	1		8.2 (6.6-9.9)	26% (15-37)	
				TMZ	26/28	0.64 (0.39 - 1.04)	0.07	9.7 (8.0-11.4)	32% (15-49)	
				TMZ						
				Non-methylated	43/44	1		6.8 (5.9-7.7)	16% (5-27)	
				Methylated	26/28	0.56 (0.34 - 0.93)	0.02	9.7 (8.0-11.4)	32% (15-49)	
				Any RT						

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>AM has received consultancy fees for advisory board and travel expenses from Schering-Plough. BHG has received travel expenses from Schering-Plough. RS has served on advisory boards for Merck and Merck</td><td></td><td></td><td></td><td>
<table>
<tr><td>Non-methylated</td><td>67/68</td><td>1</td><td></td><td>7.0 (5.7-8.3)</td><td>26% (16-37)</td></tr>
<tr><td>Methylated</td><td>62/63</td><td>0.97 (0.69 - 1.38)</td><td>0.81</td><td>8.2 (6.6-9.9)</td><td>26% (15-37)</td></tr>
</table>
</td><td></td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Sharp and Dohme. MEH has acted as adviser to MDxHealth and has participated on an advisory board for Merck Sharp and Dohme. RH has served on the advisory board for Schering-Plough. The other authors					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>declare that they have no conflicts of interest.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Malmstrom, A., Poulsen, H. S., Gronberg, B. H., Stragliotto, G., Hansen, S., Asklund, T., Holmlund, B., Lysiak, M., Dowset, J., Kristen</td><td>Sample size
Patients with AA, N= 41 (RT n=20; neoadjuvant TMZ n=21)
Patients with GBM, n= 103 (RT n= 52; neoadjuvant TMZ n= 51)
Characteristics
People with a AA diagnosis:<table><tr><td></td><td>RT</td><td>Neoadjuvant TMZ</td></tr><tr><td>Concomitant TMZ (%)</td><td>13 (65)</td><td>16 (76.2)</td></tr><tr><td>Age median (range)</td><td>47.5 (27-60)</td><td>45 (28-57)</td></tr><tr><td>% male</td><td>75</td><td>52</td></tr><tr><td>WHO performance status 0-1 (%)</td><td>95</td><td>100</td></tr><tr><td>WHO performance status 2 (%)</td><td>5</td><td>0</td></tr></table></td><td>Interventions
Neoadjuvant TMZ: 200mg/m2, days 1-5, every 28 days.
RT: 60 Gy in 30 fractions - alternative fractions representing standard treatment of the participating centre were also accepted.
After March 2005, all patients received a</td><td>Details
Patients were randomised and stratified 1:1 by center to standard RT or TMZ followed by RT. Primary end point was OS and secondary end points was saferty. Analyses were ITT.</td><td>Results
Results for patients diagnosed with AA in combination with GMB HR (95% CI)
OS, HR = 0.95 (0.66-1.35)
Results for patients diagnosed with AA only HR (95% CI)
OS, HR= 0.40 (0.19-0.90)
Results for patients diagnosed with GMB only HR (95% CI)
OS, HR = 1.40 (0.93 - 2.09)</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: Low risk (randomisation was performed according to a computer-generated code which was available in</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
sen, B. W., Soderkvist, P., Rosell, J., Henriksson, R., Nordic Clinical Brain Tumor Study, Group, Postoperative neoadjuvant temozolomide before radiotherapy versus standard radiotherapy in patients 60 years or younger with	<table><tr><td>IDH1 mt/wt</td><td>6/9 (40.0/60.0)</td><td>11/5 (68.7/31.3)</td></tr><tr><td>1p/19q codeletion/noncodel</td><td>1/13 (6.7/86.6)</td><td>0/15 (0.0/93.7)</td></tr><tr><td>MGMT methylated/ non-methylated</td><td>10/3 (66.7/20)</td><td>14/2 (87.5/12.5)</td></tr></table> People with a GMB diagnosis: <table><tr><td></td><td>RT</td><td>Neoadjuvant TMZ</td></tr><tr><td>Concomitant TMZ (%)</td><td>36 (69.2)</td><td>27 (52.9)</td></tr><tr><td>Age median (range)</td><td>53 (25-60)</td><td>56 (24-60)</td></tr><tr><td>% male</td><td>33 (63.5)</td><td>30 (58.8)</td></tr><tr><td>WHO performance status 0-1 (%)</td><td>47 (90.4)</td><td>46 (90.2)</td></tr><tr><td>WHO performance status 2 (%)</td><td>5 (9.6)</td><td>5 (9.8)</td></tr><tr><td>IDH1 mt/wt</td><td>3/41 (6.8/93.2)</td><td>0/37 (0/100)</td></tr></table>	daily dose of TMZ 75 mg/m2 concurrent with RT. No adjuvant TMZ was planned, but recommended after first recurrence.			sealed enveloped) Allocation concealment: Low risk (sealed envelopes) Blinding of participants and personnel: unclear (no information reported) Blinding of outcome assessment: unclear (no information reported) Incomplete outcome data: Low risk (dropout rate was very low (10 participants in total), making attrition bias less significant. Follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
anaplastic astrocytoma or glioblastoma: a randomized trial, Acta oncologica, 1-10, 2017 Ref Id 676618 Country/ies where the study was carried out Study type Multicentre study Aim of the study	<table><tr><td>1p/19q codeletion/noncodel</td><td>1/42 (2.3/95.4)</td><td>0/36 (0/97.3)</td></tr><tr><td>MGMT methylated/ non-methylated</td><td>24/19 (54.5/43.2)</td><td>24/11 (64.9/29.7)</td></tr></table> Inclusion criteria 18-60 y/o; WHO performance status 0-2; life expectancy >3 months; normal organ function; men and women of child bearing age had to be using adequate contraception. Exclusion criteria Prior RT/chemotherapy for glioma; pregnancy or breastfeeding; presenting with any condition that would prevent treatment and follow-up. Patients with prior surgery for WHO grade 2 glioma recurring as WHO grade or 4 were eligible.				was similar accross all study groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess whether temozolomide followed by radiotherapy resulted in prolonged OS in patients with anaplastic astrocytoma and glioblastoma Study dates 13th January 2003 - 21st May 2008 Source of funding					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cherin g-Plough , Linkopi ng Hospit al for Neuro- researc h, Lion's Cancer Found ation and Cancer Found ation Norrlan d, Umea, LIUCa ncer and South East Swede n FORS S					
Full citation Perry, J. R.,	Sample size N= 562 in total, n= 281 RT alone and n= 281 RT/TMZ Characteristics	Intervention s RT: total dose of	Details Participating centres went through	Results OS - results for RT+ TMZ vs RT alone HR (95% CI) Overall OS 0.67 (0.56-0.80), P<0.001	Limitations Methodolog ical limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Laperriere, N., O'Callaghan, C. J., Brandes, A. A., Menten, J., Phillips, C., Fay, M., Nishikawa, R., Cairncross, J. G., Roa, W., Osoba, D., Rossiter, J. P., Sahgal, A., Hirte, H., Laigle-Donadey, F., Franceschi, E., Chinot,	61% male; 29.4% between 65 and 70 y/o; 41.1% between 71 and 75 y/o and 29.5% ≥76. 46.6% of patients presented with MGMT methylated and 53.4% with MGMT non-methylated Median MMSE score was 27 (n= 542) Inclusion criteria 65+ y/o; newly diagmosed GBM histologically confirmed after surgery/biopsy less than 28 days before randomisation, ECOG performance status of 0,1, or 2; receiving glucocorticoids at a stable or decreasing dose. Adults had to present with adequate hematological, renal and hepatic funtion. Exclusion criteria Not reported.	40.05-Gy/ 15 daily fractions over 3 weeks Concurrent TMZ: 75mg/ sq2 per day from day 1 until the end of RT. Adjuvant TMZ: 150-200 mg/sq2 for 5 consecutive days of a 28-day cycle for up to 12 cycles or until progression.	radiotherapy quality assurance. Local pathological diagnosis was accepted, centres had to provide with a tissue for central histologic review and assessment of MGMT status. Progressive disease was defined as objective progression. Primary end point was OS, measured from the day of randomisation until death or censoring at the last day the patient was known to be alive. Analyses were ITT, including 3 patients who did not receive the assigned interventions. Median follow-up was 17 months for the small number	OS- patients 65 to 70 y/o, HR (95% CI) 0.93 (0.68-1.27) OS- patients 71 to 75 y/o, HR (95% CI) 0.63 (0.48-0.83) OS- patients ≥ 76 y/o, HR (95% CI) 0.53 (0.38-0.73) OS methylated HR 0.53 (0.38-0.73), p= 0.0001 OS non-methylated HR 0.75 (0.56-1.01), p=0.055 OS - biopsy vs partial/total resection HR (95% CI)= 1.67 (1.38-2.02) OS- higher MMSE scores vs lower MMSE scores HR (95% CI) =0.96 (0.94-0.98) PFS - results for RT+ TMZ vs RT alone HR (95% CI) Overall PFS = 0.50 (0.41-0.60), P<0.001 PFS- patients 65 to 70 y/o, HR (95% CI) = 0.76 (0.55-1.05), p =0.02 PFS- patients 71 to 75 y/o, HR (95% CI) = 0.42 (0.3-0.57), p =0.02 PFS- patients ≥ 76 y/o, HR (95% CI) = 0.49 (0.35-0.68), p =0.02 PFS methylated HR = 0.33 (0.23-0.47) PFS non-methylated HR = 0.79 (0.59-1.06) PFS - biopsy vs partial/total resection HR (95% CI)= 1.45 (1.20-1.75) PFS- higher MMSE scores vs lower MMSE scores HR (95% CI) = 0.97 (0.95-0.98) Time to quality of life deterioration , HR (95% CI) (HR calculated by the NGA team using the calculator developd by Tieney 2007)	assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: Low risk Blinding of participants and personnel: This consisted of an open-label study. Low risk for OS, and high risk for PFS and quality of life. Blinding of outcome assessment : Low risk Incomplete outcome data: Low risk (all pre-specified outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
O., Golfinopoulos, V., Fariselli, L., Wick, A., Feuvret, L., Back, M., Tills, M., Winch, C., Baumert, B. G., Wick, W., Ding, K., Mason, W. P., Trial, Investigators, Short-Course Radiation plus Temozolomide in Elderly			of patients who remained alive.	Physical HR 0.89 (0.73-1.09) Emotional HR 0.86 (0.69-1.07) Role HR 0.94 (0.76-1.16) Social HR 0.947 (0.76-1.16) Cognitive HR 0.84 (0.68-1.04) Constipation HR 1.11 (0.88 - 1.39) Nausea and vomiting HR 1 (0.79 -1.27) Fatigue HR 0.90 (0.73-1.09) Quality of life results (change from baseline scores) Similar results between both treatment groups. The only exception to this was nausea and vomiting, which was worse during the first week in the RT + TMZ group (change of score 5.14) as comapredd to the RT alone group. Constipation was also worse in the RT+ TMZ group (change of scores varying from 14.4 to 8.7) as compared to the RT+ TMZ group (-2.57 to -3.29, p<0.0001)	have been reported). Selective reporting: Low risk (please note that in the protocol it was stated that QoL will be assessed with the MMSE, and it was finally assessed with the EORTC QLQC30) Other bias: Low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Patients with Glioblastoma, New England Journal of Medicine, 376, 1027-1037, 2017 Ref Id 676644 Country/ies where the study was carried out Multicentre study Study type RCT Aim of the study					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the effectiveness of RT alone or RT in with concomitant and adjuvant TMZ in older adults with newly diagnosed GBM Study dates November 2007 - September 2013 Source of funding Canadian Cancer					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Society Research Institute, unrestricted grant from Schering-Plough and by the EORTC Cancer Research Fund from Belgium</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Roa, W., Brasher, P. M., Bauman, G., Anthes, M., Bruera,</td><td>Sample size
n=100
(n=90 analysed, 2 withdrew after randomisation: one chose to receive the short-course treatment and one pursued alternative therapy. Two other patients died before their RT could be started. Among those randomly assigned to receive RT over 3 weeks, one patient withdrew from the study and declined further treatment)
Characteristics</td><td>Interventions
Intervention

3-week abbreviated course of RT

Control
6-week standard</td><td>Details
Interventions
Patients were randomly assigned to standard adjuvant RT (60 Gy in 30 fractions over 6 weeks) or short-course regimen (40 Gy in 15 fractions over 3</td><td>Results
Median Overall Survival (measured from randomisation)
<table><tr><td></td><td>6-weeks RT (n=47)</td><td>3-weeks RT (n=48)</td></tr><tr><td>Median (Months)</td><td>5.1</td><td>5.6</td></tr><tr><td>HR (95%, CI range)</td><td>0.89 (0.59-1.36)</td><td></td></tr></table></td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>E., Chan, A., Fisher, B., Fulton, D., Gulavita, S., Hao, C., Husain, S., Murtha, A., Petruk, K., Stewart, D., Tai, P., Urtasun, R., Cairncross, J. G., Forsyth, P., Abbreviated course of radiation therapy in older patient</td>
<td>
<table>
<tr><td>Baseline characteristics</td><td>6-week regimen (n=47)</td><td>3-week regimen (n=48)</td></tr>
<tr><td>Sex, n</td><td></td><td></td></tr>
<tr><td>Female</td><td>22</td><td>18</td></tr>
<tr><td>Male</td><td>25</td><td>30</td></tr>
<tr><td>Age, years</td><td></td><td></td></tr>
<tr><td>Mean</td><td>72.4</td><td>71</td></tr>
<tr><td>Standard Deviation</td><td>5.4</td><td>5.5</td></tr>
<tr><td>KPS</td><td></td><td></td></tr>
<tr><td>Median</td><td>70</td><td>70</td></tr>
<tr><td>IQR</td><td>60-80</td><td>60-80</td></tr>
<tr><td>Fact-Br</td><td></td><td></td></tr>
<tr><td>Mean</td><td>75.1</td><td>77.7</td></tr>
<tr><td>Standard Deviation</td><td>15.5</td><td>15.6</td></tr>
<tr><td>Extent of Surgery</td><td></td><td></td></tr>
</table>
</td>
<td>course of RT</td>
<td>weeks). RT started within 6 weeks of surgery. Patients receiving standard RT were treated in two phases. In the first phase, the prescribed dose was 46 Gy in 23 daily fractions. The planning target volume (PTV) was based on preoperative computed tomography and magnetic resonance imaging studies and included the enhancing tumor plus peritumoral edema with a 2-cm margin or a 2.5-cm margin if there was no peritumoral edema. In the second phase, the prescribed dose was 14 Gy in seven daily fractions, and the PTV was preoperative</td>
<td>
<table>
<tr><td>P value</td><td>0.57</td><td></td></tr>
</table>
In the case of any imbalance in the two arms with respect to the number of patients with total resection, the models were refit excluding those patients. In this case, the median survival was 5.0 months in both groups (HR, 1.0; 95% CI, 0.65-1.53, P=0.99)
Stratified analysis on extent of resection yielded similar results. Moreover, our patients were retrospectively regrouped as class IV (n=10), V (n=43), and VI (n=42) according to the RTOG recursive partitioning analysis. Their median survival times were 8.8, 6.9, and 4.8 months respectively

Health-Related QoL
<table>
<tr><td></td><td>Baseline</td><td>3 weeks</td><td>6 weeks</td><td>First follow-up</td><td>Second follow-up</td></tr>
<tr><td>KPS*</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>6-weeks regimen</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Completion rate, n</td><td>47/47</td><td>42/45</td><td>34/38</td><td>25/34</td><td>13/21</td></tr>
<tr><td>Median</td><td>70</td><td>65</td><td>70</td><td>70</td><td>60</td></tr>
<tr><td>IQR</td><td>60-80</td><td>50-80</td><td>50-80</td><td>50-70</td><td>60-70</td></tr>
<tr><td>3-week regimen</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>Random sequence generation: Low risk (An independent statistician at the coordinating center (Cross Cancer Institute) produced computer-generated randomization lists.)
Allocation concealment: Low risk (See random sequence generation, also strata-specific, sequentially numbered, sealed opaque envelopes containing the treatment assignment</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>s with glioblastoma multiforme: a prospective randomized clinical trial, Journal of Clinical OncologyJ Clin Oncol, 22, 1583-8, 2004
Ref Id
556511
Country/ies where the study was carried out
Canada
Study type</td>
<td>
<table>
<tr><td>Biopsy</td><td></td><td></td></tr>
<tr><td>No</td><td>20</td><td>17</td></tr>
<tr><td>%</td><td>42.5</td><td>35.4</td></tr>
<tr><td>Subtotal Resection</td><td></td><td></td></tr>
<tr><td>No</td><td>25</td><td>24</td></tr>
<tr><td>%</td><td>52.3</td><td>50</td></tr>
<tr><td>Total Resection</td><td></td><td></td></tr>
<tr><td>No</td><td>2</td><td>7</td></tr>
<tr><td>%</td><td>4.2</td><td>14.6</td></tr>
<tr><td>Days to beginning RT</td><td></td><td></td></tr>
<tr><td>Median</td><td>34</td><td>33</td></tr>
<tr><td>IQR</td><td>25-41</td><td>26-41</td></tr>
</table>

Inclusion criteria
The principal eligibility criteria included age > 60 years, histologically confirmed GBM, and KPS > 50.
Exclusion criteria
Previous cranial RT, concomitant or prior invasive cancer (except nonmelanomatous skin cancer and carcinoma in situ), failure to commence RT for GBM within 6 weeks of surgical diagnosis, and inability to comply with
</td>
<td></td>
<td>enhancing tumor with a 2.5-cm margin. Patients who were randomly assigned to shorter-course treatment received a total dose of 40 Gy in 15 daily fractions to a PTV that was identical to that used in the first phase of standard treatment. A photon energy of 4 MV or higher was used. Treatment plans included opposed lateral fields, wedge pair fields, rotation, or multiple field techniques. Computer-aided treatment planning was recommended but not required. The absorbed dose was to be within 10% of the prescribed dose. Attempts were</td>
<td>
<table>
<tr><td>Completion rate, n</td><td>48/48</td><td>43/45</td><td>8/40</td><td>34/38</td><td>21/27</td></tr>
<tr><td>Median</td><td>70</td><td>70</td><td>70</td><td>65</td><td>60</td></tr>
<tr><td>IQR</td><td>60-80</td><td>60-80</td><td>50-80</td><td>50-80</td><td>40-70</td></tr>
<tr><td>FACT-Br**</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>6-weeks regimen</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Completion rate, n</td><td>44/47</td><td>6/45</td><td>8/38</td><td>18/34</td><td>12/21</td></tr>
<tr><td>3-week regimen</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Completion rate, n</td><td>43/48</td><td>7/45</td><td>2/40..</td><td>23/38</td><td>10/27</td></tr>
</table>

*There was no difference in either average KPS over time or change in KPS over time between the two groups (p=0.99 and 0.15, respectively)
**Completion rates for the FACT-Br were too low to compare the two groups
</td>
<td>were supplied by the statistician to the research nurse at the coordinating center. Once patient eligibility had been determined and consent was obtained, participating centers contacted the coordinating nurse by fax to request randomization.)
Blinding of participants and personnel: Unclear risk (no blinding or dummy radiotherap</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A prospective RCT Aim of the study To prospectively compare standard radiation therapy (RT) with an abbreviated course of RT in older patients with glioblastoma mutliforme Study dates 1996-2001	follow up requirements. Patients were also ineligible if pre- and postoperative imaging studies were unavailable for review.		made to limit the dose of RT to the optic chiasm (54 Gy), retina (50 Gy), and brainstem (54 Gy), provided this could be accomplished without shielding gross tumor. If the location of the tumor was such that these critical structures would inadvertently receive higher doses, the patient was advised in advance of the potential for radiation toxicity. Chemotherapy was not prescribed before or during RT but could be given at the time of disease recurrence. Randomization An independent statistician at the coordinating		y used, however this is very difficult and unethical as radiotherapy) Blinding of outcome assessment: High risk (no blinding or dummy radiotherapy used, nor blinding to assessor) Blinding (performance bias and detection bias): High risk (no blinding or dummy radiotherapy used, nor blinding to assessor) Incomplete outcome data: Low risk (ITT

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Alberta Cancer Board			center (Cross Cancer Institute) produced computer-generated randomization lists. Patients were stratified by extent of resection (biopsy v any degree of resection, as defined by the operative report) and KPS (70 v 70). Strata-specific, sequentially numbered, sealed opaque envelopes containing the treatment assignment were supplied by the statistician to the research nurse at the coordinating center. Once patient eligibility had been determined and consent was obtained, participating centers contacted the coordinating		analysis was performed, there was a low drop out rate of 5% in equal distribution in both arms, also all drop outs were clearly explained) Selective reporting: Low risk (All pre-specified outcomes were reported) Other information Study not sufficiently powered to prove statistical equivalence between two treatments of similar outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			nurse by fax to request randomization. The next envelope in the appropriate strata was opened to determine treatment assignment. Outcomes and Patient Assessments The primary end point of the study was overall survival, measured from the date of randomization to death from any cause. The secondary end points were overall survival from the date of diagnosis, the proportion of patients alive at 6 months, health-related quality of life (HRQoL), and the corticosteroid requirement of the		and exclude a small difference in survival.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			two groups. HRQoL was assessed using the KPS and Functional Assessment of Cancer Therapy–Brain (FACT-Br; version 3) at baseline, 3 weeks after starting RT, at the conclusion of RT, and at 3-month intervals thereafter. At each assessment, the oncologist determined the KPS and the patient completed the FACT-Br. Corticosteroid use was recorded in the format of total daily dexamethasone dose. To compare with the Radiation Therapy Oncology Group (RTOG)–established recursive partitioning analysis class survival, study patients were also		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			classified retrospectively as class IV, V, and VI according to the published criteria for possible concordance.2 Statistical Considerations The target sample size was calculated following the method of Makuch and Simon.12 We expected 50% of the patients receiving standard RT would be alive at 6 months, and we considered the clinical efficacy of the shorter course to be equivalent if the proportion surviving at 6 months was at least 35%. For an 80% probability that the one-sided 90% CI for a difference at 6 months did not		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			exceed 15% when in reality the treatments were equivalent, 101 patients would be required in each treatment arm. Allowing for a 10% loss to follow-up rate, we intended to randomly assign 224 patients. In October 2001, the steering committee met after having recruited 100 patients and decided to close the trial. It became apparent that to prove statistical equivalence between two treatments of similar outcomes and exclude a small difference in survival (eg, of 5%), the target sample size would render further study not feasible.13		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Survival curves were generated using the Kaplan-Meier method. Relative risk was calculated using a proportional hazards model. A one-sided 95% CI for the difference in the proportion of patients surviving at 6 months was calculated. Both survival analyses based on patients who began (but may not have finished) their assigned treatment, and intent-to-treat, were performed. Interquartile range was used to describe variability in KPS. Me		
Full citation Roa, W., Kepka,	Sample size n= 98 (n= 96 analysed, 2 lost to follow up due to unavoidable situations) Characteristics	Interventions Intervention RT in a total dose	Details Statistical Analysis Analysis was conducted as per	Results Overall Survival and PFS	Limitations Methodological limitations assessed

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>L., Kumar, N., Sinaika, V., Matiello, J., Lomidze, D., Hentati, D., Guedes de Castro, D., Dyttus-Cebulok, K., Drodge, S., Ghosh, S., Jeremic, B., Rosenblatt, E., Fidarova, E., International Atomic Energy Agency Randomized</td>
<td>
<table>
<tr><td></td><td>Short-Course RT (n=48)</td><td>Conventional RT (n=50)</td><td>P value</td></tr>
<tr><td>KPS</td><td></td><td></td><td>0.853</td></tr>
<tr><td>50%</td><td>12 (25)</td><td>11 (22)</td><td></td></tr>
<tr><td>60%</td><td>17 (35)</td><td>16 (32)</td><td></td></tr>
<tr><td>70%</td><td>11 (23)</td><td>10 (20)</td><td></td></tr>
<tr><td>80%</td><td>6 (13)</td><td>9 (18)</td><td></td></tr>
<tr><td>90%</td><td>2 (4)</td><td>4 (8)</td><td></td></tr>
<tr><td>Sex</td><td></td><td></td><td>0.83</td></tr>
<tr><td>Male</td><td>22 (46)</td><td>24 (48)</td><td></td></tr>
<tr><td>Female</td><td>26 (54)</td><td>26 (52)</td><td></td></tr>
<tr><td>Age</td><td></td><td></td><td>0.106</td></tr>
<tr><td>50-65</td><td>22 (46)</td><td>15 (30)</td><td></td></tr>
<tr><td>>65</td><td>26 (54)</td><td>35 (70)</td><td></td></tr>
<tr><td>Surgical Proceedure</td><td></td><td></td><td>0.549</td></tr>
<tr><td>Stereotactic Biopsy</td><td>4 (8)</td><td>9 (18)</td><td></td></tr>
<tr><td>Partial resection</td><td>34 (71)</td><td>30 (61)</td><td></td></tr>
</table>
</td>
<td>of 25 Gy in five daily fractions (dose/fraction = 5Gy) over 1 week

Control
RT in a total dose of 40.05 Gy in 15 daily fractions (dose/fraction = 2.67 Gy) over 3 weeks</td>
<td>protocol as well as per intent to treat, as recinnebded by a noninferiority trial.Detailed results of ITT analysis were not included in this report, but the analysis did not show any differences in the outcomes.</td>
<td>
<table>
<tr><td></td><td>Short Course RT</td><td>Conventional RT</td><td>P value</td></tr>
<tr><td>Median Overall Survival Months (95% CI)</td><td>7.9 (6.3-9.6)</td><td>6.4 (5.1-7.6)</td><td>0.988</td></tr>
<tr><td>Median Progression Free Survival Months (95% CI)</td><td>4.2 (2.5-5.9)</td><td>4.2 (2.6-5.7)</td><td>0.716</td></tr>
</table>

Global Health Status (QoL)
<table>
<tr><td>Global Health Status/ QoL</td><td>Short-Course RT</td><td>Conventional RT</td><td>P value</td></tr>
<tr><td>Baseline</td><td></td><td></td><td></td></tr>
<tr><td>No of patients</td><td>44</td><td>49</td><td>0.042</td></tr>
<tr><td>Mean (+ SD)</td><td>42.6 (+22.5)</td><td>51.2 (+17.6)</td><td></td></tr>
<tr><td>4 weeks after treatment</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk of bias (The randomisation sequence was generated using Excel with the RAND option function)
Allocation concealment: unclear risk of bias (insufficient details on allocation concealment)
Blinding of participants and personnel:</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme, Journal of Clinical OncologyJ Clin Oncol, 33, 4145-50, 2015 Ref Id 556512 Country/ies	<table><tr><td>Total Macrospcopic resection</td><td>8 (17)</td><td>8 (16)</td><td></td></tr></table> Inclusion criteria Elderly and/or frail patients diagnosed with GBM. Frail patients were defined as >50 years old wit ha KPS of 50% to 70%; elderly and frail patients were defined as >60 years old with a KPS of 50% to 70%, and elderly patients were defined as >65 years old with a KPS of 80-100%. Before trial admission, patients were screened and required to meet all of the following eligibility criteria: histopathologically confirmed newly diagnosed GBM (WHO grade 4): initial surgery/biopsy at diagnosis performed < 6 weeks before random assignment, age >50 years at time of entry, KPS >50%, no previous chemo or RT exposure, ability and willingness to complete QoL, ability and willingness to give informed consent, accessability for treatment and follow-up, and delivery of protocol beginning within 2 weeks of patient random assignment. Exclusion criteria Patients fulfilling either of the following criteria were not eligible for the study, history of other malignancy or history of a serious infection or underlying medical condition.			<table><tr><td>No of patients</td><td>36</td><td>27</td><td>0.99</td></tr><tr><td>Mean (+ SD)</td><td>49.6 (+20)</td><td>49.7 (+23.8)</td><td></td></tr><tr><td>8 weeks after treatment</td><td></td><td></td><td></td></tr><tr><td>No of patients</td><td>20</td><td>17</td><td>0.6</td></tr><tr><td>Mean (+ SD)</td><td>51.3 (+22.5)</td><td></td><td></td></tr></table>	unclear risk of bias (no details on blinding) Blinding of outcome assessment: unclear risk of bias (no details on outcome assessment) Incomplete outcome data: low risk of bias (ITT analysis done and no differences in outcomes between ITT and per-protocol tx, low drop out rate, and all drop outs accounted for)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
where the study was carried out International (belarus, Brazil, Chile, Georgia, Greece, India, Indonesia, Ireland, Poland, Thailand, Tunisia) Study type RCT Aim of the study This trial compared a					Selective reporting: unclear risk (all pre-specified outcomes discussed, however insufficient detail other than no difference between ITT and per protocol analysis reported, individual results of ITT not reported in paper and no referal to supplementary appendix)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
commonly used RT regimen of 40Gy in 15 fractions to a short-course RT regimen for elderly and/or frail patients with GBM Study dates 2010-2013 Source of funding None disclosed					
Full citation Saran, F.,	This study was extracted as part of Chinot 2014				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chinot, O. L., Henriksson, R., Mason, W., Wick, W., Cloughesy, T., Dhar, S., Pozzi, E., Garcia, J., Nishikawa, R., Bevacizumab, temozolomide, and radiotherapy for newly diagnosed glioblastoma: comprehensive safety					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>results during and after first-line therapy, Neuro-OncologyNeuro-oncol, 18, 991-1001, 2016
Ref Id 556600</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Stupp, R., Hegi, M. E., Gorlia, T., Erridge, S. C., Perry, J., Hong, Y. K., Aldape, K. D.,</td><td>Sample size
n = 3471 registered and screened for eligibility
(n= 3060 assessed for methylation status, n= 926 with methylated MGMT promoter eligible, n= 545 eligible patietns randomly assigned, n=521 received intervention, n= 51 completed intervention)
Characteristics<table><tr><td></td><td>Cilengitide (n= 272)</td><td>Control (n 272)</td></tr><tr><td>Age (years)</td><td>58 (50-65)</td><td>58 (50-64)</td></tr><tr><td>Sex</td><td></td><td></td></tr><tr><td>Male</td><td>148 (54%)</td><td>143 (52%)</td></tr></table></td><td>Interventions
Intervention
Standard temozolomide chemoradiotherapy with added cilengitide (standard dose of 2g I.V twice weekly on days 1 and 4,</td><td>Details
Statistical Analysis
Overall survival and PFS using Kaplan -Meier method. Treatment group were compared using a log-rank test stratified for randomisation strata. A cox proportional hazards model with stratification</td><td>Results
Overall Survival<table><tr><td></td><td>Cilengitide (n= 272)</td><td>Control (n= 273)</td><td>Hazard ratio (95% CI)</td><td>P value</td></tr><tr><td>Median Overall Survival (months)</td><td>26.32</td><td>26.32</td><td>1.02 (0.81-1.29)</td><td>0.86</td></tr><tr><td>95% CI</td><td>23.8-28.8</td><td>23.9-34.7</td><td></td><td></td></tr></table></td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: unclear risk of bias (the</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Lhermitte, B., Pietsch, T., Grujicic, D., Steinbach, J. P., Wick, W., Tarnawski, R., Nam, D. H., Hau, P., Weyerbrock, A., Taphoorn, M. J., Shen, C. C., Rao, N., Thurzo, L., Herrlinger, U., Gupta, T., Kortmann, R. D.,</td>
<td>
<table>
<tr><td>Female</td><td>124 (46%)</td><td>130 (48%)</td></tr>
<tr><td>RPA Class</td><td></td><td></td></tr>
<tr><td>III</td><td>44 (16%)</td><td>42 (15%)</td></tr>
<tr><td>IV</td><td>184 (68%)</td><td>171 (63%)</td></tr>
<tr><td>V</td><td>43 (16%)</td><td>55 (20%)</td></tr>
<tr><td>Missing</td><td>1 (<1%)</td><td>5 (2%)</td></tr>
<tr><td>MMSE</td><td></td><td></td></tr>
<tr><td><27</td><td>45 (17%)</td><td>61 (22%)</td></tr>
<tr><td>>27</td><td>225 (83%)</td><td>207 (76%)</td></tr>
<tr><td>Missing</td><td>2 (1%)</td><td>5 (2%)</td></tr>
<tr><td>Extent of resection</td><td></td><td></td></tr>
<tr><td>Total resection</td><td>132 (49%)</td><td>137 (50%)</td></tr>
<tr><td>Partial Resection</td><td>131 (48%)</td><td>127 (47%)</td></tr>
<tr><td>Biopsy</td><td>9 (3%)</td><td>7 (3%)</td></tr>
<tr><td>Missing</td><td>0 (0)</td><td>2 (1%)</td></tr>
</table>
Inclusion criteria
>18 years with newly diagnosed, histologically confirmed supratentorial glioblastoma, methylated MGMT promoter as determined by a central laboratory, and an ECOG PS of 0 or 1. Available tumor tissue from surgery or open biopsy (stereotactic biopsy was not allowed) for analysis of MGMT promoter methylation
</td>
<td>beginning 1 week beforestarting TMZ and RT).
Control
Standard temozolomide chemoradiotherapy

Radiotherapy was given at 2Gy per fractio, 5 days per week, for up to 6-7 weeks and a total of 60Gy. TMZ 75mg/m2 was given orally 7 days per week throughout RT (concomitant phase), thereafter, starting 4 weeks after</td>
<td>according to randomisation strata was used to calculate treatment HRs and 95% CI. No check of proportional hazards assumptions was planned per protocol. We did sensitivity analyses unstratified and for the per-protocol set.
All outcome analyses were done on the ITT population.
The study sample size was based on the assumption of a median overall survival of 23 months for the control group, an HR for the difference in overall survival between the experimental and control groups of 0.71, power of 80%, two-sided</td>
<td>Progression Free Survival
<table>
<tr><td></td><td>Cilengitide (n= 272)</td><td>Control (n= 273)</td><td>Hazard ratio (95% CI)</td><td>P value</td></tr>
<tr><td>Median Progression Free Survival (months)</td><td>13.5</td><td>10.7</td><td>0.93 (0.76-1.13)</td><td>0.46</td></tr>
<tr><td>95% CI</td><td>10.8-15.9</td><td>8.1-13.3</td><td></td><td></td></tr>
</table>
Treatment Emergent Adverse Effects
<table>
<tr><td></td><td>Cilengitide (n=263)</td><td></td><td></td><td>Control (n= 258)</td><td></td><td></td></tr>
<tr><td></td><td>Any grade</td><td>Grade 3</td><td>Grade 4</td><td>Any Grade</td><td>Grade 3</td><td>Grade 4</td></tr>
<tr><td>Fatigue</td><td>102 (39%)</td><td>14 (5%)</td><td></td><td>85 (33%)</td><td>8 (3%)</td><td></td></tr>
<tr><td>Memory Impairment</td><td>27 (10%)</td><td>1 (<1%)</td><td></td><td>18 (7%)</td><td>1 (<1%)</td><td></td></tr>
</table>
</td>
<td>authors do not provide sufficient detail to allow an assessment of whether allocation was randomised using appropriate methods)
Allocation concealment: low risk of bias (central interactive voice response system)
Blinding of participants and personnel: high risk of bias (open label)
Blinding of outcome assessment: low risk of bias (independe</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Adamska, K., McBain, C., Brandes, A. A., Tonn, J. C., Schnell, O., Wiegel, T., Kim, C. Y., Nabors, L. B., Reardon, D. A., van den Bent, M. J., Hicking, C., Markivskyy, A., Picard, M., Weller, M., European Organisation	status and central pathology review, MRI done within 48hrs after surgery or alternatively MRI done before randomisation, stable or decreasing steroid doses for 5 days or more before randomisation, and adequate renal, hepatic, and haemotology. Exclusion criteria Previous chemotherapy within the past 5 years, previous radiotherapy of the head (except low dose for tinea capitis), treatment with other investigational agents 30 days before first dose of cilengitide, previous systemic anti-angiogenic theapy, history of coagulation disorder associated with bleeding or recurrent thromboembolic events, placement of carmustine wafers at surgery, history of malignant disease within the past 5 years (except curatively treated cervical carcinoma in situ or basal cell carcinoma of the skin), and clinically manifest cardiovascular insufficiency (NYHA class III-IV), history of myocardial infarction during the past 6 months, or uncontrolled arterial hypertension.	the end of RT (week 11), TMZ 75mg/m2 150-200 mg/m2 was given for 5 days consecutively every 4 weeks for 6 cycles (adjuvant phase). Cilengitide was continued for up to 18 months or until disease progression or unacceptable toxic effects.	significance level of 5% and accrual of 24 months. Randomisation and Masking Interactive voice response system. Patients were stratified in blocks according to geographic region (Europe, North America, and rest of world) and RTOG recursive partitioning analysis class. Because this study was open label, we did not apply any masking proceedures to study investigators or patients. The independent review committee assessing progression-free survival was masked to treatment allocation, and the databases remained masked		nt review committee assessing progression-free survival were masked to treatment allocation) Blinding (performance bias and detection bias): Unclear risk of bias (open label, however primary outcome measures were blinded to independent review committee for assessment) Incomplete outcome data: high risk of bias (ITT analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for, Research, Treatment of, Cancer, Canadian Brain Tumor, Consortium, Centric study team, Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promot			to primary outcome variables for all parties until final analysis.		with all drop-outs/discontinuations clearly accounted for, however very high drop-out rate of 90%) Selective reporting: low risk (all pre-specified outcomes reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
er (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial, Lancet OncologyLancet Oncol, 15, 1100-8, 2014 Ref Id 556885 Country/ies where the study was carried out					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
International (25 countries worldwide) Study type RCT Aim of the study Assess cilengitide combined with temozolomide chemoradiotherapy in patients with newly diagnosed glioblastoma with methylated MGMT					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>promoter.
Study dates
Oct 31, 2008 - May 12, 2011
Source of funding
Merck KGaA, Germany

(Authors declaration of interests with Merck)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Stupp, R., Taillibert, S., Kanner, A. A., Kesari, S.,</td><td>Sample size
n= 695
(n= 315 analysed in the interim analysis, first 315 patients after at least 18 months of follow-up)
Characteristics
<table>
<tr><th></th><th>All patients</th><th>TTFields plus Temozolomide</th></tr>
</table></td><td>Interventions
Intervention
TTField in combination with standard maintenance</td><td>Details
Study Design
After the completion of treatment with TMZ and radiotherapy (RT), patients were randomised at a ratio of 2:1 to</td><td>Results
Median Overall Survival (OS)
Intention-To-Treat Analysis
<table>
<tr><th></th><th>Control</th><th>Treatment</th></tr>
<tr><td>Median (Months)</td><td>16.6</td><td>19.6</td></tr>
<tr><td>90% CI for median (months)</td><td>13.6-19.2</td><td>16.6-24.4</td></tr>
<tr><td>P value</td><td>0.03</td><td></td></tr>
</table></td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Steinberg, D. M., Toms, S. A., Taylor, L. P., Lieberman, F., Silvani, A., Fink, K. L., Barnett, G. H., Zhu, J. J., Henson, J. W., Engelhard, H. H., Chen, T. C., Tran, D. D., Sroubek, J., Tran, N. D., Hottinger, A. F., Landolf</td>
<td>
<table>
<tr><td></td><td>(n=315)</td><td>omide (n=210)</td><td>alone (n=105)</td></tr>
<tr><td>Age years</td><td></td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>55.8 (11.1)</td><td>55.3 (11.3)</td><td>56.8 (10.5)</td></tr>
<tr><td>Median (range)</td><td>57 (20-83)</td><td>57 (20-83)</td><td>58 (21-80)</td></tr>
<tr><td>Karnofsky Status Score, median (range) %</td><td>90 (60-100)</td><td>90 (60-100)</td><td>90 (70-100)</td></tr>
<tr><td>Gender, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Male</td><td>207 (66)</td><td>140 (67)</td><td>67 (64)</td></tr>
<tr><td>Female</td><td>108 (34)</td><td>70 (33)</td><td>38 (36)</td></tr>
<tr><td>Use at baseline, n (%)</td><td></td><td></td><td></td></tr>
<tr><td>Antiepileptic medication</td><td>126 (40)</td><td>88 (42)</td><td>38 (36)</td></tr>
<tr><td>Corticosteroid therapy</td><td>77 (24)</td><td>51 (24)</td><td>26 (25)</td></tr>
<tr><td>Mini-Mental State Examination Score, n (%)</td><td></td><td></td><td></td></tr>
</table>
</td>
<td>temozolomide
Control
Standard maintenance Temozolomide</td>
<td>receive standard maintenance TMZ (150-200 mg/m2/d for 5 days every 28 days for 6-12 cycles according to the protocol) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4-7 weeks from the last dose of concomitant TMZ and RT. Randomisation was performed through a central web-based randomisation system and was stratified by extent of resection and by MGMT methylation status.
For patients with available paraffin-embedded tumor tissue, evaluation of MGMT gene promoter methylation status was performed as</td>
<td>
<table>
<tr><td>Hazard ratio (CI %, range)</td><td>0.74 (95%, 0.56-0.98)</td><td></td></tr>
</table>

Median Progression Free Survival (PFS)

Intention-To-Treat Analysis
<table>
<tr><td></td><td>Treatment</td><td>Control</td></tr>
<tr><td>Median (Months)</td><td>7.1</td><td>4.0</td></tr>
<tr><td>95% CI for median (months)</td><td>(5.9-8.2)</td><td>3.3-5.2</td></tr>
<tr><td>P value</td><td>0.001</td><td></td></tr>
<tr><td>Hazard ratio (CI %, range)</td><td>0.62 (98.7%, 0.43-0.89)</td><td></td></tr>
</table>

Grade 3 to 4 Treatment Emergent Adverse Events
<table>
<tr><td></td><td>TTFields + TMZ (n=203)</td><td>TMZ (n=101)</td></tr>
<tr><td>Haematologic</td><td>25 (12)</td><td>9 (9)</td></tr>
<tr><td>Neutropenia</td><td>6 (3)</td><td>1(1)</td></tr>
</table>
</td>
<td>assessing risk of bias

Random sequence generation: Low risk (Randomisation was performed through a central web-based randomisation system and was stratified by extent of resection and by MGMT methylation status.)
Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used)</td>
</tr>
</table>

Study details	Participants				Interventions	Methods	Outcomes and Results			Comments
i, J., Desai, R., Caroli, M., Kew, Y., Honnorat, J., Idbaih, A., Kirson, E. D., Weinberg, U., Palti, Y., Hegi, M. E., Ram, Z., Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide	<26	45 (15)	31 (15)	14 (13)		described previously, by a central laboratory blinded to treatment group. If MGMT methylation status could not be determined centrall prior to randomisation, local MGMT methylation status was used for stratification. Patients in the TTFields plus TMZ group received continuous TTFields combined with standard maintenance TMZ. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable deviceset to generate 200-kHz electric fields within the brain. Transducer array	Thrombocytopenia	19 (9)	3 (3)	Blinding of participants and personnel: Unclear risk (open-label, however authors report that a sham arm was not considered practical (patients would be able to sense heat when they received TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). This raises
	27-30	247 (78)	174 (83)	73 (70)			Anaemia	1 (<1)	2 (2)	
	Unknown	23 (7)	5 (2)	18 (17)			Leukopenia or lymphopenia	11 (5)	5 (5)	
	Resection, n (%)						Gastrointestinal Disorders	11 (5)	2 (2)	
	Complete	202 (64)	135 (72)	67 (64)			Abdominal Pain	2 (1)	0	
	Incomplete	79 (25)	52 (25)	27 (26)			Constipation	2 (1)	0	
	Biopsy	34 (11)	23 (11)	11 (10)			Diarrhea	1 (<1)	2 (2)	
	Tissue available and tested, n (%)	227 (72)	152 (72)	75 (71)			Vomiting	3 (1)	1 (1)	
	MGMT methylation	75 (33)	49 (32)	26 (35)			General disorders	17 (8)	5 (5)	
	No methylation	116 (51)	79 (52)	38 (51)			Injury and proceedural complications	14 (7)	5 (5)	
	Invalid test result	36 (16)	24 (16)	11 (15)			fall	6 (3)	2 (2)	
	Region, n (%)						Medial device stite reactions	4 (2)	0	
	United States	191 (61)	127 (60)	64 (61)			Nervous system disorders	45 (22)	25 (25)	
	Rest of World	124 (39)	83 (40)	41 (39)			Seizure	15 (7)	8 (8)	
							Headache	4 (2)	2 (2)	
							Psychiatric Disorders	9 (4)	3 (3)	

Study details	Participants				Interventions	Methods	Outcomes and Results			Comments
Alone for Glioblastoma: A Randomized Clinical Trial, JAMAJama, 314, 2535-43, 2015 Ref Id 556898 Country/ies where the study was carried out United States, Canada, Europe, Israel, and South Korea	Completed Radiation Therapy, n (%)					layouts were determined using a mapping software system for TTFields to optimise field intensity within the treated tumour. After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed. If a patient experienced tumor progression, second-line chemotherapy	Anxiety	2 (1)	0	the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective points, such as cognitive function and QoL, objective end points, such as overall survival and progression free survival, are independent of placebo effects in cancer therapy) Blinding of outcome assessment
	<57 Gy	18 (6)	13 (6)	5 (5)			Bradyphrenia	0	1 (1)	
	60 GY (standard + 5)	291 (92)	191 (91)	100 (95)			Confusional State	2 (1)	1 (1)	
	> 63 Gy	6 (2)	6 (3)	0 (0)			Mental Status changes	4 (2)	1 (1)	
	Concomitant Temozolomide use, n (%)						Psychotic disorder	2 (1)	0	
	Yes	308 (98)	207 (99)	101 (96)			Respiratory disorders	4 (2)	1 (1)	
	Unknown	7 (2)	3 (1)	4 (4)			Skin disorders	0	1 (1)	
	Time from randomisation, median (range), d						Vascular disorders	8 (4)	8 (8)	
	Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)			Deep vein thrombosis	1 (<1)	3 (3)	
	Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)			pulmonary embolism	4 (2)	6 (6)	
	No of maintenance TMZ cycles until first tumour	6 (1-26)	6 (1-26)	4 (1-24)			musculoskeletal disorders	8 (8)	3 (3)	
							Metabolism and nutrition disorders	7 (3)	3 (3)	
							Fatigue	8 (4)	4 (4)	
							Infections	10 (5)	5 (5)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multi-centre Randomized Controlled Trial Aim of the study To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation	<table><tr><td>progression, median (range)</td><td></td><td></td><td></td></tr><tr><td>Duration of treatment with TTFields, median (range), mo</td><td>9 (1-58)</td><td>9 (1-58)</td><td></td></tr><tr><td>Adherence to TTFields therapy >75% during first 3 mo of treatment</td><td></td><td>157 (75)</td><td></td></tr></table> Carmustine wafers used in 2.4% of patients in the TTFields plus TMZ vs 2.9% of patients in the TMZ group Inclusion criteria Inclusion criteria: 1) Histologically confirmed supratentorial glioblastoma 2) Progression-free after having undergone maximal safe dubulking surgery when feasible or biopsy, or 3) Had completed standard concomitant chemoradiotherapy with TMZ. Other eligibility criteria were: 1) Age of 18 years or older 2) Karnofsky performance status (KPS) score of 70% or higher, and 3) Adequate bone marrow, liver, and renal function Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor		was offered per local practice. However, in the TTFields plus TMZ group, TTFileds could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months. Patient Surveillance and Follow-up Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance TMZ with or without TTFields. A complete physical examination with collection of laboratory		: low risk (All MRIs were reviewed centrally by 2 blinded independent radiologists and were evaluated for tumor response and progression using the criteria developed by McDonald et al. In the cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
therapy for patients with glioblastoma Study dates July 2009-November 2014 Source of funding Novocure Ltd	location and severe comorbidities were excluded. Exclusion criteria Not specified		parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20). A mini-mental state examination also was administered. Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical		involved in 17% of the treatment group and in 18% of the control group)) Blinding (performance bias and detection bias): low risk (see above details) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported) Other information Patient enrollment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists and were evaluated for tumour response and progression using the criteria developed by McDonald et al. In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus TMZ group and in 18% of the cases in TMZ alone group. The results of the central review		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 radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognosis. Interim analysis from the first 315 patients with at least 18 months

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight pattients in the TTFields plus TMZ group (4%) compared with 6 patients in the TMZ group alone (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumour progresion. Patients were removed from the progression-free survival analysis at the date of treatment change when this is occurred before evidence of tumour		follow-up. However, for detailed and meaningful subgroup analysis, the mature data of the full data set will be needed (expected end of 2016).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			progression or when patients reached the cut-off date without tumour progression. Adverse events were recorded prospectively according to the National Cancer Institutes Common Terminology Criteria until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			in hours per day and information was reviewed and transferred at the monthly follow-up visit. Statistical Considerations The primary end point was progression free survival (PFS) in the ITT population assessed by an independent review panel (80% power, HR, 0.78, 2-sided alpha level of 0.05). This study wasa also designed to have 80% power (HR, 0.76, 2-sided alpha level of 0.05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			statistically only if the primary end point was met. The prespecified interim analysiswas to be performed after the first 315 randomised patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard alpha spending function. The protocol prespecified that overall survival would be analysed in an as-treated population, excluding all patients in both treatment group who 1) never started maintenance TMZ, 3) crossed overto the other treatment group,		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			or 4) received TTFields outside the protocol setting. The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an alpha level of 0.01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus TMZ GROUP using a stratified log-rank test with an alpha level of		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			0.006. The confidence intervals that go with the HRs are prsented as 1 minus the prespecified alpha level for each analysis. For example, the alpha level in the per-protocol interim analysis for overall survival was 0.006. There fore, the corresponding interval used for presenting the HRs was 1.000-0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safetymonitoring committeewas chartered to stop the trial if the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns. In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2). Multiple imputation analyses also		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.23 The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespecified subgroup analyses and additional secondary end points, including quality of life.		
Full citation	Sample size At baseline: Allocated to BEV + RT/TMZ, n= 458	Interventions	Details HRQoL assessment was	Results Time to deterioration (TTD) and Disease free survival (DFS) ≥10 points deterioration in scores	Limitations Methodological

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Taphoorn, Mj, Henriksson, R, Bottomley, A, Cloughesy, T, Wick, W, Mason, Wp, Saran, F, Nishikawa, R, Hilton, M, Theodore-Oklota, C, Ravelo, A, Chinot, Ol, Health-Related Quality of Life in a Randomized Phase</td>
<td>Allocated to Plb + RT/TMZ, n= 463
Characteristics
<table>
<tr><td>Median age, years(range)</td><td>57 (20-84)</td><td>50 (18-79)</td></tr>
<tr><td>Gender (%)</td><td>Male = 276 (61%)
Female = 179 (39%)</td><td>Male = 291 (64%)
Female = 161 (36%)</td></tr>
<tr><td>KPS at baseline, no (%)</td><td>50-80: 145 (32%)
90-100: 304 (68%)</td><td>50-80: 136 (30%)
90-100: 315 (70%)</td></tr>
</table>
Inclusion criteria
Patients 18 years of age or older with newly diagnosed, histologically confirmed, supratentorial glioblastoma, World Health Organization (WHO) performance status of 2 or lower (on a scale of 0 to 5, with higher numbers indicating decreasing performance); the use of stable or decreasing glucocorticoid doses within the 5 days before randomization; adequate healing of craniotomy or cranial-biopsy site; adequate hematologic, hepatic, and renal function; and acceptable blood coagulation levels.

Exclusion criteria
Disease and treatment history:
Evidence of recent hemorrhage on postoperative MRI of the brain. However, patients with clinically asymptomatic presence</td>
<td>Patients received RT (total of 60 Gy, administered in 2 Gy fractions per day, 5 days per week, for 6 weeks) and TMZ (75 mg/m2) plus bevacizumab (10mg/kg) or placebo every 2 weeks. A 28-day treatment break followed. Then patients received TMZ (150 mg/ m2) per day [cycle 1] and 200mg/m2 per day [subsequent cycles if</td>
<td>considered part of the overall study assessment; therefore, participation was required. Patients completed the EORTC QLQ-C30 and the EORTC QLQ-BN20 (20-item questionnaire that supplements the QLQC30); for which local site language translations were available to minimize bias. Questionnaires were completed at baseline (after surgery and before treatment), after the concurrent phase treatment break (week 10), during the maintenance phase at the end of cycles 2, 4, and 6 (weeks 18, 26, and 34), during the monotherapy phase at the end of cycles 3 and 6 (weeks 43 and</td>
<td>in quality of life score according to intervention arm. HR [95% CI], P
<table>
<tr><td></td><td>DFS</td><td>TTD</td></tr>
<tr><td>Cognitive functioning</td><td>0.62 [0.54 to 0.72], P < 0.0001</td><td>0.74 [0.6 to 0.89], P = 0.0018</td></tr>
<tr><td>Role functioning</td><td>0.67 [0.58–0.78], P < 0.0001</td><td>0.82 [0.68 to 0.99], P = 0.0435</td></tr>
<tr><td>Emotional functioning</td><td>0.65 [0.56 to 0.75], P < 0.0001</td><td>0.78 [0.63 to 0.97], P = 0.0246</td></tr>
<tr><td>Difficulty with bladder control</td><td>0.59 [0.51 to 0.68], P < 0.0001</td><td>0.71 [0.55 to 0.92], P = 0.0082</td></tr>
<tr><td>Weakness in both legs</td><td>0.65 [0.56 to 0.75], P < 0.0001</td><td>0.81 [0.66 to 0.99], P = 0.0396</td></tr>
<tr><td>Visual disorder</td><td>0.65 [0.56 to 0.75], P < 0.0001</td><td>0.80 [0.65 to 0.99], P = 0.0433</td></tr>
<tr><td>Appetite loss</td><td>0.78 [0.67 to 0.89], P = 0.0004</td><td>1.13 [0.94 to 1.35], P = 0.1958</td></tr>
<tr><td>Headaches</td><td>0.78 [0.67 to 0.90], P = 0.0006</td><td>1.05 [0.84 to 1.31], P = 0.6519</td></tr>
</table>
</td>
<td>limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk of bias
Allocation concealment: low risk of bias
Blinding of participants and personnel: low risk of bias (study sponsor, investigators and patients were unaware of the study-group assignments. Unblinding was</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
III Study of Bevacizumab, Temozolomide, and Radiotherapy in Newly Diagnosed Glioblastoma, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 33, 2166-75, 2015 Ref Id 556973	of hemosiderin, resolving hemorrhagic changes related to surgery, and presence of punctate hemorrhage in the tumor are permitted entry into the study. Previous centralized screening for MGMT status for enrolment into a clinical trial Any prior chemotherapy (including carmustine-containing wafers (Gliadel®) or immunotherapy (including vaccine therapy) for glioblastomas and low grade astrocytomas Any prior radiotherapy to the brain or prior radiotherapy resulting in a potential overlap in the radiation field Bevacizumab related Exclusion Criteria Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 m Hg) Prior history of hypertensive crisis or hypertensive encephalopathy New York Heart Association (NYHA) Grade II or greater congestive heart failure History of myocardial infarction or unstable angina within 6 months prior to randomization History of stroke or TIAs within 6 months prior to randomization Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to randomization History of ≥ grade 2 hemoptysis according to the NCI-CTC criteria within 1 month prior to randomization	toxicity permitted]) on days 1 through 5 of six 4-week cycles and bevacizumab (10 mg/kg) or placebo on days 1 and 15 of each cycle (maintenance phase). Finally, patients received bevacizumab (15 mg/kg every 3 weeks) or placebo (every 3 weeks) until progressive disease (PD) or unacceptable toxicity (monotherapy phase).	52), and at the end of every third cycle thereafter until PD (ie, every 9 weeks starting at week 61; a total of 16 assessments during treatment). Five scales were preselected in the statistical analysis plan as important to glioblastoma (global health status, physical functioning, social functioning, motor dysfunction, and communication deficit), of which three were different from the original preselection in the protocol (emotional functioning, cognitive functioning, and visual disorder [motor dysfunction and communication deficit remained in the final	Nausea and vomiting	0.77 [0.66 to 0.88], P = 0.0002	1.10 [0.90 to 1.35], P = 0.3301	allowed at any time for safety reasons or at the time of disease progression if deemed necessary by the investigator) Blinding of outcome assessment : low risk of bias Blinding (performance bias and detection bias): low risk of bias Incomplete outcome data: low risk of bias Selective reporting: I ow risk of bias
				Constipation	0.69 [0.60 to 0.80], P < 0.0001	0.95 [0.77 to 1.18], P = 0.6524	
				Fatigue	0.64 [0.55 to 0.74], P < 0.0001	0.74 [0.62 to 0.89], P = 0.0013	
				Pain	0.76 [0.66 to 0.87], P = 0.0001	1.05 [0.86 to 1.27], P = 0.6351	
				Dyspnea	0.65 [0.56 to 0.76], P < 0.0001	0.85 [0.69 to 1.05], P = 0.1390	
				Insomnia	0.73 [0.63 to 0.85], P < 0.0001	1.09 [0.87 to 1.36], P = 0.4665	
				Diarrhea	0.73 [0.63 to 0.84], P < 0.0001	1.10 [0.87 to 1.40], P = 0.4129	
				Financial difficulties	0.61 [0.52 to 0.70], P < 0.0001	0.80 [0.63 to 1.00], P = 0.0487	
				Future uncertainty	0.66 [0.57 to 0.77], P < 0.0001	0.83 [0.66 to 1.04], P = 0.1051	

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
Country/ies where the study was carried out Netherlands Study type RCT Aim of the study To ensure that addition of bevacizumab to standard-of-care therapy was not associated with HRQoL detrime	Evidence of bleeding diathesis or coagulopathy (in the absence of therapeutic anticoagulation) Major surgical procedure, open biopsy, intracranial biopsy, ventriculoperitoneal shunt or significant traumatic injury within 28 days prior to randomization Core biopsy (excluding intracranial biopsy) or other minor surgical procedure within 7 days prior to randomization. Placement of a central vascular access device (CVAD) if performed within 2 days prior to bevacizumab/placebo administration History of abdominal fistula or gastrointestinal perforation within 6 months prior to randomization History of intracranial abscess within 6 months prior to randomization Serious non-healing wound, active ulcer or untreated bone fracture Pregnant or lactating females Fertile women < 2 years after last menstruation and men (surgically sterilized or of childbearing potential) unwilling or unable to use effective means of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) General Exclusion Criteria Any other malignancy within 5 years prior to randomization, except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix		selection]). The updated preselected scales were based on more recent clinical insights, and the change to the statistical analysis plan was made before unblinding of the data. The collection of HRQoL data was not required after PD because the scope of the study design was to measure HRQoL for patients during treatment.	Seizures	0.62 [0.53 to 0.72], P < 0.0001	0.86 [0.65 to 1.15], P = 0.3084	
				Drowsiness	0.72 [0.62 to 0.83], P < 0.0001	0.95 [0.78 to 1.15], P = 0.5781	
				Hair loss	0.67 [0.58 to 0.77], P < 0.0001	0.81 [0.66 to 0.98], P = 0.0337	
				Itchy skin	0.69 [0.59 to 0.79], P < 0.0001	0.91 [0.75 to 1.10], P = 0.3331	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nt in the AVAglio study (Chinot 2014) Study dates June 2009-March 2011 Source of funding F.Hoffman La Roche Ltd. The sponsor was involved in trial design, coordination of data collection, data analysis and interpr	Evidence of any active infection requiring hospitalization or IV antibiotics within 2 weeks prior to randomization Patients who have any other disease, either metabolic or psychological, or who have any evidence on clinical examination or special investigations (including a laboratory finding) which gives reasonable suspicion of a disease or condition that contraindicates the use of the investigational drug, or that may affect the patient's compliance with study requirements, or would place the patient at higher risk of potential treatment complications Current or recent (within 30 days of enrolment) treatment with another investigational drug or participation in another investigational study Known hypersensitivity to any excipients of bevacizumab formulation or to the chemotherapy regimen (temozolomide) Any contraindication to temozolomide listed in the local label Hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibody Unable to comply with the administration of the study treatment				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
etation, the writing of the manuscript, and the provision of bevacizumab					
Full citation Taphoorn, M. J., van den Bent, M. J., Mauer, M. E., Coens, C., Delattre, J. Y., Brandes, A. A., Sillevis Smitt, P. A., Bernsen, H. J.,	Sample size N= 368 AO or AOA RT + PCV n=185 RT only n=183 Characteristics RT + PCV vs. RT Age, median (range), years: 48.6 (18.6-68.7) vs 49.8 (19.2-68.7) Gender: male, female: 102,83 vs 110,73 WHO performance status 0-1 (%), 2 (%): 155 (84%), 30 (16%) vs 153 (84%), 30 (16%) Inclusion criteria Diagnosed by the local pathologist with an anaplastic mixed oligoastrocytoma with at least 25% oligodendroglial elements, had at least three of five anaplastic characteristics (high cellularity, mitosis, nuclear abnormalities, endothelial proliferation, and necrosis);were between 16 and 70 years old; had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; had provided written informed consent; had not	Interventions RT: dose of 45 Gy to be delivered to the planning target volume (PTV-1) in 25 daily fractions of 1.8 Gy, 5fractions a week. Thereafter, a boost of 14.4 Gy (up to a cumulative dose of 59.4 Gy) was delivered to	Details 368 patients were randomly assigned by 40 institutions; 138 patients were randomly assigned to the control arm (RT only) and 185 were assigned to RT + PCV. Median follow-up was 62.6 monts in the RT/PCV arm and 59 months in the RT arm.	Results Mean (SD) change from baseline to end of RT of fatigue Health-related quality of life scale RT: 1 (17.5) RT+PCV: 1.9 (17.3) Mean (SD) change from baseline to end of RT + 1 year of fatigue Health- related quality of life scale RT: -5.9 (11.3) RT+PCV: -5.4 (12.3) Mean (SD) change from baseline to end of RT + 2.5 years of fatigue Health- related quality of life scale RT: -4.9 (8.9) RT+PCV: -6.9 (10.9) Mean (SD) change from baseline to end of RT of nausea/vomiting health related quality of life scale RT: 1.2 (8.2)	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk of bias (patients were randomly assigned) Allocation concealment: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Frenay, M., Tijssen, C. C., Lacombe, D., Allgeier, A., Bottomley, A., European Organisation for, Research, Treatment of, Cancer, Health-related quality of life in patients treated for anaplastic oligodendroglioma with	undergone prior chemotherapy or RT to the skull; had no diseases interfering with follow-up; and had adequate hematologic, renal, and hepatic function (WBC count 3.0 109 /L, platelets 100 109 /L, serum creatinine 120 mol/L, and serum bilirubin 25mol/L). Exclusion criteria Not reported	the PTV-2 in eight fractions of 1.8 Gy, 1 fraction a day, 5 fractions a week. PCV: consisted of six cycles of standard PCV chemotherapy and had to start within 4 weeks after the end of RT. Each cycle consisted of lomustine 110 mg/m2 orally on day 1 with antiemetics (domperidone or metoclopramide, and if necessary, ondansetron or a similar agent),		RT+PCV: 3.5 (8.24) Mean (SD) change from baseline to end of RT + 1 year of nausea/vomiting health related quality of life scale RT: -1.4 (5.7) RT+PCV: 0.4 (6.09) Mean (SD) change from baseline to end of RT + 2.5 years of nausea/vomiting health related quality of life scale RT: -0.8 (4.5) RT+PCV: -1.5 (5.4) Mean (SD) change from baseline to end of RT of physical functioning health-related quality of life scale RT: -2.7 (18.16) RT+PCV: 5.8 (18.7) Mean (SD) change from baseline to end of RT + 1 year of physical functioning health-related quality of life scale RT: 0.5 (12.7) RT+PCV: -2 (13.7) Mean (SD) change from baseline to end of RT + 2.5 years of physical functioning health-related quality of life scale	(”Patients were stratified by age (< 40 v ≥ 40 years), extent of resection (biopsy v resection), WHO ECOGPS (0 or 1 v 2), and possible prior surgery for low-gradeoligodendrogliom a (yes v no). Treatment was assigned using the minimization technique of Simon and Pocockto ensure balance with respect to the stratification factors.”

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial, Journal of Clinical OncologyJ Clin Oncol, 25, 5723-30, 2007 Ref Id 556976 Country/ies		procarbazine 60mg/m2orally on days 8 to 21, and vincristine 1.4mg/m2 intravenous on days 8 and 29 (with amaximum dose of 2mg).Cycleswere to be repeated every 6 weeks, with dose reductions as previously described		RT: 1.5(10) RT+PCV: 3.7 (12.2)	Blinding of participants and personnel: High risk (not blinded) Blinding of outcome assessment: High risk (not blinded) Incomplete outcome data: Unclear risk (no mention of loss to follow-up) Selective reporting: Low risk (outcomes reported adequately) Other information Original trial conducted by van den Bent 2006

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
where the study was carried out Multicenter European study Study type RCT Aim of the study To study the impact of combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
after radiotherapy (RT) compared with RT alone on HRWOL in the randomised European Organisation for Research and Treatment of Cancer (EORTC) 26951 tial Study dates 13, 1996 and March 3, 2002					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported					
Full citation Thomas, D., Stenning, S., Lantos, P., Ironside, J., Moss, T., Whaley, J., Bleehen, N. M., Roberts, J. T., Senanayake, L. F. N., Abram, W. P., Brada, M., Gullan, R.,	Sample size n = 674 (n= 113 Grade III Anaplastic astrocytoma, other participants were Grade IV GBM) Characteristics Patient Characteristics for whole trial population grade IV GBM and grade III AA were defined, however not specifically for AA Inclusion criteria Adult patients of either sex, up to 70 years of age, with pathologically proven supratentorial astrocytoma grade 3 or 4 (AA and GBM), provided their neurologi and mental function was not so seriously impaired as to make RT undesirable. The exact interpretation of this criterion was left to the treating clinician, to reflect their usual practice. Exclusion criteria Not specified	Interventions RT + PCV vs RT RT schedule:45 Gy in 20 fractions, each of 2.25 Gy over4 weeks, or 60Gy in 30 fractions, each of 2 Gy over 6 weeks. Median received dose was 60 Gy, an interquartile range of 45 Gy to 60 Gy in each arm. PCV schedule:	Details Randomisation Randomised after neurosurgery by a telephone call to the MRC Cancer Trials Office. Treatment, RT alone or RT followed by chemotherapy (RT-PCV), was allocated using the minimisation method, balancing on treatment center and age group. Neuropathology Review A panel of 3 neuropathologists was set up to review the eligibility of all patients randomised onto the trial. Each	Results Overall Survival PCV + RT vs RT HR 0.86 (95% CI, 0.58 to 1.30) No other subgroup analyses done for AA, other analyses are GBM and AA	Limitations Cochrane Risk of Bias Assessment Random sequence generation (selection bias): Unclear risk (no details on method of randomisation) Allocation concealment (selection bias): Low risk (randomisation done centrally at MRC Cancer Trials office by

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Murrell, D. S., McIntosh, J., Tobias, J., Godlee, J. N., Guthrie, D., Bradford, R., Campbell, D., Sarkar, T., Watson, J. V., Lamont, A., Stone, J., Mantell, B., Plowman, P. N., Hope-Stone, H., Hoskin, P., Ritchie, D., Pigott,		Procarbazine 100mg/m2, lomustine 100mg/m2, vincristine 1.5mg/m2	member of the panel reviewed slides independently of the other members and without knowledge of the patients outcome and graded them according to both the WHO classification grade and the Daumas Duport classification. A consensus view of the patients eligibility and tumour grade was established by taking the majority result of the 3 panel members. Statistical considerations Main endpoint: OS Secondary endpoint: PFS The trial was designed to detect a 10% increase in survival at 2 years, from		telephone call and allocation done via minimization method) Blinding (performance bias and detection bias) All Outcomes: High risk (not blinded) Incomplete outcome data (attrition bias) All outcomes: Low risk (Analysed by ITT principle, 19% drop out from PCV arm, however all accounted for and described) Selective reporting (reporting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
K., Hawkins, R., Baillie-Johnson, H., Lindup, R., Adab, F., Hurman, D., Gaze, M., Collis, C., Neave, F., Thomas, G., Robinson, A., Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of			approximately 15%-25%, with 90% power at a significance level of 5% (two-sided). This approximately required 550 patients to be randomised to observe 434 events. Because there was a pre-planned subgroup analysis of those eligible on neuropathology review, a minimum target of 600 patients was set, anticipating a 10% ineligibility rate. All randomised patients were included in the main analyses, which were carried out on an ITT principle. Survival rates were estimated using the Kaplan Meier method and were compared using the log rank		bias): Low risk (outcomes reported adequetely) Other information AA only 16% of whole trial population

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
high-grade astrocytoma: A Medical Research Council Trial, Journal of Clinical OncologyJ Clin Oncol, 19, 509-518, 2001 Ref Id 554134 Country/ies where the study was carried out United Kingdom			test. Multivariate analyses used Cox's proportional hazards regression model.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised Controlled Trial Aim of the study To assess the value of adjuvant PCV chemotherapy on survival in patients with high grade astrocytoma. A further aim was the evaluation of					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the prognostic value of in vitro chemosensitivity testing. Study dates December 1988 - May 1997 Source of funding Not reported					
Full citation van den Bent, M. J., Baumert, B., Erridge, S. C., Vogelbaum,	Sample size n= 475. n=187 in the RT alone group; n= 185 in the ocncurrent RT and TMZ group; n=185 in the RT with adjuvant TMZ; and n=188 in the concurrent RT and TMZ + adjuvant TMZ group. Characteristics Baseline characteristics	Interventions Arm 1: RT (59.4-Gy in 33 fractions of 1.8 Gy) and further treatment including chemotherapy if indicated	Details Adults were "stratified by institution, performance status score (>0 vs 0), age (>50 vs ≤50 years), 1p loss of heterozygosity (yes vs no), the presence of	Results OS in adults receiving adjuvant TMZ adjusted by baseline stratification factors - Cox proportional hazards model - HR (95% CI) Adjuvant TMZ: 32/373 had died - HR 0.65 (0.45-0.93), p = 0.00014 Age (>50 y/o vs ≤ 50 y/o): HR 4.04 (2.78 -5.87), p<0.0001 WHO performance stats score (>0 vs 0): HR 1.36 (0.94 - 1.96), p=0.0273	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>M. A., Nowak, A. K., Sanson, M., Brandes, A. A., Clement, P. M., Baurain, J. F., Mason, W. P., Wheeler, H., Chinot, O. L., Gill, S., Griffin, M., Brachman, D. G., Taal, W., Ruda, R., Weller, M., McBain, C., Reijneveld, J., Enting,</td>
<td>
<table>
<tr><th></th><th>Age - median (range)</th><th>WHO performance status (0)</th><th>WHO performance status (>0)</th></tr>
<tr><td>RT alone</td><td>42.2 (19-81.2)</td><td>110 (59%)</td><td>77 (41%)</td></tr>
<tr><td>Concurrent RT and TMZ</td><td>43.2 (20.1-77.1)</td><td>109 (59%)</td><td>76 (41%)</td></tr>
<tr><td>RT with adjuvant TMZ</td><td>39.9 (20-82.3)</td><td>108 (58%)</td><td>77 (42%)</td></tr>
<tr><td>Concurrent RT and TMZ + adjuvant TMZ</td><td>42.8 (18.3-80.1)</td><td>112 (60%)</td><td>76 (40%)</td></tr>
</table>
MGMT promoter methylation (available before randomisation) *(see other comments below)
<table>
<tr><th></th><th>Methylated</th><th>Non-methylated</th><th>Indeterminate or invalid</th></tr>
<tr><td>RT alone</td><td>29 (16%)</td><td>40(21%)</td><td>118 (63%)</td></tr>
<tr><td>Concurrent RT</td><td>27(15%)</td><td>40(22%)</td><td>118 (64%)</td></tr>
</table>
</td>
<td>at progression
Arm 2: RT (59.4-Gy in 33 fractions of 1.8 Gy) and concurrent TMZ
Arm 3: RT (59.4-Gy in 33 fractions of 1.8 Gy) + adjuvant TMZ for 12 cycles
Arm 4: RT (59.4-Gy in 33 fractions of 1.8 Gy) and concurrent TMZ + adjuvant TMZ for 12 cycles</td>
<td>oligodendroglial elements on microscopy (yes vs no) and MGMT promoter methylation status (methylated vs non-methylated and indeterminate or invalid vs non-methylated). The randomisation schedule was generated centrally with the electronic EORTC web-based ORTA system, which was accessed by study physicians via the Internet. Patients were assigned in equal numbers (1:1:1:1) " (van den Bent 2017)</td>
<td>1p loss of heterozygosity (yes vs no): HR 1.56 (0.84 -2.88), p=0.2230
MGMT promoter before randomisation
Methylated vs non-methylated: HR 0.49 (0.26 - 0.93), p= 0.0031
Indeterminate or invalid vs non-methylated: HR 0.81 (0.54-1.21), p= 0.1606</td>
<td>Random sequence generation: Low risk (randomisation was generated centrally with the ORTA system)
Blinding of participants and personnel: This consisted of an open-label study. Low risk for OS, and high risk for PFS and quality of life.
Blinding of outcome assessment: This consisted of an open-label study. Low risk for OS, and high risk for PFS</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
R. H., Weber, D. C., Lesimple, T., Clenton, S., Gijtenbeek, A., Pascoe, S., Herrlinger, U., Hau, P., Dhermain, F., van Heuvel, I., Stupp, R., Aldape, K., Jenkins, R. B., Dubbink, H. J., Dinjens, W. N. M., Wesseling, P.,	<table><tr><td>and TMZ</td><td></td><td></td><td></td></tr><tr><td>RT with adjuvant TMZ</td><td>29 (16%)</td><td>40 (22%)</td><td>116 (63%)</td></tr><tr><td>Concurrent RT and TMZ + adjuvant TMZ</td><td>29 (15%)</td><td>41(22%)</td><td>118 (63%)</td></tr></table> Inclusion criteria Adults above 18 years old, with newly diagnosed anaplastic glioma without 1p/19q co-deletion, had WHO performance status scores 0-2 and adequate haematological, renal, and liver function. To be included, adults also had to be taking stable or decreasing doses of corticosteroids, start of TMZ within 8 days from randomisation, start of RT within 7 weeks from surgery, no prior chemotherapy, no prior RT to the brain. If patients had previously presented with a LGG, surgery was allowed, provided histological confirmation of an anaplastic tumour is present at the time of progression. Exclusion criteria Presence of any other serious medical condition that can interfere with follow-up or with oral medication intake.				and quality of life. Incomplete outcome data: Low risk (all pre-specified outcomes have been reported). Selective reporting: Low risk (please note that in the protocol it was stated that QoL will be assessed with the MMSE, and it was finally assessed with the EORTC QLQC30) Other bias: Low risk Other information *MGMT methylation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nuyens, S., Golfinopoulos, V., Gorlia, T., Wick, W., Kros, J. M., Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-					promoter testing was not available for 63% of the patients at the time of randomisation. This was mainly due to limited time before starting the randomisation.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study, Lancet Lancet, 08, 08, 2017 Ref Id 676690 Country/ies where the study was carried out Multicentre study Study type					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Phase III RCT Aim of the study To assess the use of RT with concurrent and adjuvant TMZ in adults with non-codeleted anaplastic gliomas Study dates 4th December 2007 to 19th of September 2015					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Schering Plough and MSD by an unrestricted grant and by the provision of TMZ. Also supported by theEORTC Cancer Research Funf, NRG, Cancer research UK, and Cancer Australia.					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Westphal, M., Heese, O., Steinbach, J. P., Schnell, O., Schackert, G., Mehdorn, M., Schulz, D., Simon, M., Schlegel, U., Senft, C., Geletneky, K., Braun, C., Hartung, J. G., Reuter, D., Metz, M. W., Bach, F.,</td>
<td>Sample size
n = 250
(n=236 included in analysis)
Characteristics
<table>
<tr><th></th><th>Sitimagene ceredenovec group (n=119)</th><th>Standard care group (n=117)</th></tr>
<tr><td>Age years</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>55.8 (10.28)</td><td>55.1 (9.90)</td></tr>
<tr><td>Median (range)</td><td>58.0 (20-70)</td><td>57.0 (26-70)</td></tr>
<tr><td>Age years</td><td></td><td></td></tr>
<tr><td><40</td><td>8 (7%)</td><td>12 (10%)</td></tr>
<tr><td>41-50</td><td>23 (19%)</td><td>25 (21%)</td></tr>
<tr><td>51-60</td><td>46 (39%)</td><td>43 (37%)</td></tr>
<tr><td>61-70</td><td>42 (35%)</td><td>37 (32%)</td></tr>
<tr><td>Karnofsky Score</td><td></td><td></td></tr>
<tr><td>70</td><td>18 (15%)</td><td>11 (9%)</td></tr>
<tr><td>80</td><td>22 (18%)</td><td>23 (20%)</td></tr>
<tr><td>90</td><td>49 (41%)</td><td>47 (40%)</td></tr>
</table>
</td>
<td>Interventions
Intervention
I.V. Nimotuzumab 400mg weekly for 12 weeks and I.V. Nimotuzumab 400mg every 2/52 thereafter until progression added to standard radiation 60Gy in 30 fractions with concomitant TMZ (75 mg/m2) followed by 6 cycles of adjuvant TMZ therapy (150 mg/m2)

Control
standard radiation</td>
<td>Details
Randomisation by fax took place after histological diagnosis of glioblastoma by local neuropathological review which was later confirmed by centralised review.

End points
PFS based on centralised image review of MRIs. Overall survival was a major secondary end point. In addition, toxicity, tumor response and quality of life were evaluated.

Sample size
Sample size considerations were based mainly on the European Organisation for Research and Treatment of</td>
<td>Results
Overall Survival and PFS
<table>
<tr><th></th><th>Experimental</th><th>Control</th><th>HR (CI)</th><th>P Value</th></tr>
<tr><td>Median Overall Survival (95 % CI)</td><td>22.3 months (17.2-26.5)</td><td>19.6 months (14.8-24.0)</td><td>0.862 (0.568 - 1.308)</td><td>0.4856</td></tr>
<tr><td>Median Progression Free Survival (95% CI)</td><td>7.7 months (4.7-8.8)</td><td>5.8 months (3.6-8.6)</td><td>0.953 (0.669 - 1.359)</td><td>0.7898</td></tr>
</table>
Methylated and Non-Methylated Overall Survival and PFS Sub-Analysis
<table>
<tr><th></th><th>Median Progression Free Survival (months)</th><th>Progression Free at 12 Months %</th><th>Median Overall Survival (months)</th><th>Alive at 12 months %</th></tr>
<tr><td>MGMT methylated</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Experimental (95% CI) n=15</td><td>8.9 (7.9-12.7)</td><td>38.9</td><td>Not reached</td><td>93.3</td></tr>
</table>
</td>
<td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: unknown risk of bias (insufficient detail regarding process, only randimisation by fax was described)
Allocation concealment: unknown risk of bias (insufficient detail regarding process, only randimisati</td>
</tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results					Comments
Pietsch, T., A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma, European Journal of Cancer Eur J	100	30 (25%)	36 (31%)	60Gy in 30 fractions with concomitant TMZ (75 mg/m2) followed by 6 cycles of adjuvant TMZ therapy (150 mg/m2)	Cancer (EORTC)/National Cancer Institute of Canada (NCIC) study (RT plus Temozolomide) [15] with a median progression-free survival of 6.9 months in glioblastoma patients and included results from a phase I/II study of nimotuzumab plus Radiation Therapy (RT) in high grade glioma [19], where the 16 GBM patients reached an overall survival of 17.4 months. The Type I error rate was specified as a = 0.05 for two-sided comparisons and the power for showing a significant difference between the two 12 months PFS rates was chosen as 80% = 1b,				(24.8-33.8)		on by fax was described) Blinding of participants and personnel: high risk of bias (open label) Blinding of outcome assessment: unknown risk of bias (central neurological review for PFS, however no details as to whether blinded or not) Blinding (performance bias and detection bias): high risk of bias Incomplete outcome data: unclear risk
	Gender, n (%)					Control (95% CI) n=16	12.7 (8.4-25.7)	53.6	33.8 (22.1-19.5)	100	
	Male	70 (59%)	76 (59%)						HR = 0.864 (0.273-2.734)		
	Female	49 (41%)	41 (35%)						P-value 0.8034		
	Histopathology diagnosis					MGMT non-methylated					
	Glioblastoma multiforme	112 (94%)	111 (95%)			Experimental (95% CI) n=33	8.3 (5.8-11.2)	23.8	19.5 (14.7-25.6)	78.8	
	Other high-grade glioma	4 (3%)	4 (3%)			Control (95% CI) n=32	5.8 (3.4-9.2)	13.6	15.5 (13.8-24)	70.9	
	Other	3 (3%)	2 (2%)						HR = 0.807 (0.457-1.425)		
	Location of tumor								p-value 0.4578		
	Right	71 (60%)	60 (51%)								
	Frontal	18 (15%)	11 (9%)								
	Parietal	16 (13%)	13 (11%)								
	Temporal	26 (22%)	27 (23%)								
	Other	11 (9%)	9 (8%)								
	Left	48 (40%)	57 (49%)								
	Frontal	13 (11%)	15 (13%)								

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Cancer, 51, 522-32, 2015
Ref Id 557237
Country/ies where the study was carried out
Europe
Study type
International, open-label, randomised, open label, phase 3 trial
Aim of the study
Assess the efficacy of a</td>
<td>
<table>
<tr><td>Parietal</td><td>10 (8%)</td><td>12 (10%)</td></tr>
<tr><td>Temporal</td><td>14 (12%)</td><td>22 (19%)</td></tr>
<tr><td>Other</td><td>11 (9%)</td><td>8 (7%)</td></tr>
<tr><td>Ventricular opening</td><td></td><td>5 (5)</td></tr>
<tr><td>Yes</td><td>27 (23%)</td><td>18 (15%)</td></tr>
<tr><td>Time since clinical diagnosis (days)</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>9.5 (9.89)</td><td>12.5 (13.99)</td></tr>
<tr><td>Median (rannge)</td><td>7.0 (1-76)</td><td>8.5 (0-115)</td></tr>
<tr><td>Estimate of resection during surgery n (%)</td><td></td><td></td></tr>
<tr><td>Radical</td><td>99 (83%)</td><td>95 (81%)</td></tr>
<tr><td>Partial</td><td>20 (17%)</td><td>22 (19%)</td></tr>
<tr><td>Estimated extent of tumour resected from posoperative MRI</td><td></td><td></td></tr>
<tr><td><50%</td><td>2 (2%)</td><td>3 (3%)</td></tr>
</table>
</td>
<td></td>
<td>where b = 0.20 denotes the Type II error rate. From Stupp et al. [15] and from the study of Ramos et al. [19] we had the interesting estimates 0.269 for pC and 0.50 for pE, respectively, where and pE stand for the true 12 months PFS rates, respectively. Considering a possible dropout rate of about 5%, the enrolment for the study was calculated as N = 150 patients to reach a per protocol cohort of at least 140 patients, equally distributed between the two study arms. As EGF-R status was not used for eligibility, there was accordingly no stratification.</td>
<td>Pre-specified ARDs
<table>
<tr><td></td><td>Exp. Arm</td><td>Cont.arm</td><td>Total</td></tr>
<tr><td>Fatigue</td><td>39 (55%)</td><td>31 (44%)</td><td>70 (49%)</td></tr>
<tr><td>Memory Impairment</td><td>4 (6%)</td><td>8 (11%)</td><td>12 (8%)</td></tr>
</table>
Grade 3 and 4 ADRs
<table>
<tr><td></td><td>Exp. Arm</td><td>Cont.arm</td></tr>
<tr><td>Thrombocytopenia</td><td>10</td><td>0</td></tr>
<tr><td>Pulmonary Embolism</td><td>3</td><td>0</td></tr>
<tr><td>Leukopenia</td><td>2</td><td>1</td></tr>
<tr><td>Neutropenia</td><td>2</td><td>1</td></tr>
<tr><td>Lymphopenia</td><td>2</td><td>0</td></tr>
<tr><td>Pneumonia</td><td>1</td><td>1</td></tr>
<tr><td>Alveolitis</td><td>1</td><td>0</td></tr>
<tr><td>Convulsions</td><td>0</td><td>1</td></tr>
<tr><td>Deep Vein Thrombosis</td><td>1</td><td>0</td></tr>
<tr><td>Diarrhoea</td><td>0</td><td>1</td></tr>
<tr><td>Nausea</td><td>0</td><td>1</td></tr>
<tr><td>Platelet Count Increased</td><td>1</td><td>0</td></tr>
<tr><td>Urinary Tract Infection</td><td>0</td><td>1</td></tr>
</table>
</td>
<td>of bias (low drop out rate, all drop-outs acounted for, however, analysed as per protocol cohort with drop outs including poor compliance)
Selective reporting: low risk of bias (all pre-specified outcomes reported, however additional unplanned subgroup analysis included in the results section which wasn't pre-empted)</td>
</tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results			Comments
locally applied adenovirus-mediated gene therapy with a prodrug converting enzyme (herpes-simplex-virus thymidine kinase: sitimagene ceradenovec) followed by intravenous ganciclovir in patients with newly diagno	50-69%	5 (4%)	8 (7%)			Vomiting	0	1	
	70-89%	30 (25%)	22 (19%)						
	>90%	80 (67%)	80 (68%)						
	Not done	2 (2%)	4 (3%)						
	MGMT Analysis								
	Methylated	34/98 (35%)	19/79 (24%)						
	Non-methylated	64 /98 (65%)	60/79 (76%)						
	Inclusion criteria Adult patients (aged 18-70) with a Karnofsky score of 70 or more at screening and newly diagnosed supratentorial glioblastoma multiforme that were deemed by the treating neurosurgeon to be amenable to complete resection from 38 sites in nine countries in Europe. Exclusion criteria Patients with bihemispheric or multifocal tumours, recurrent glioma, other clinically significant concomitant disease(including renal or liver disease), hypersensitivity to ganciclovir, or patients who had received chemotherapy within 6 weeks of randomisation were excluded from the study								

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
sed resectable glioblastoma Study dates Nov 3, 2005-April,16 2007 Source of funding None reported However, under conflicts of interest authors are employers and shareholders of Ark Therapeutics					
Full citation	Sample size n = 250	Interventions Intervention	Details Randomisation	Results Overall Survival in ITT Population	Limitations Methodological

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Westphal, M., Yla-Herttuala, S., Martin, J., Warnke, P., Menei, P., Eckland, D., Kinley, J., Kay, R., Ram, Z., Aspect Study Group, Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous</td>
<td>(236 patients were included in the ITT population and 241 in the safety population)
Characteristics
<table>
<tr><th></th><th>Sitimagene ceradenovec group (n=119)</th><th>Standard care group (n=117)</th></tr>
<tr><td>Age (years)</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>55.8 (10.28)</td><td>55.1 (9.90)</td></tr>
<tr><td>Median (range)</td><td>58.0 (20-70)</td><td>57.0 (26-70)</td></tr>
<tr><td>Age (years)</td><td></td><td></td></tr>
<tr><td><40</td><td>8 (7%)</td><td>12 (10%)</td></tr>
<tr><td>41-50</td><td>23 (19%)</td><td>25 (21%)</td></tr>
<tr><td>51-60</td><td>46 (39%)</td><td>43 (37%)</td></tr>
<tr><td>61-70</td><td>42 (35%)</td><td>37(32%)</td></tr>
<tr><td>Sex (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>70 (59%)</td><td>76 (65%)</td></tr>
<tr><td>Female</td><td>49 (41%)</td><td>41 (35%)</td></tr>
<tr><td>Histopathology Diagnosis</td><td></td><td></td></tr>
</table>
</td>
<td>Sitimagene ceradenovec + Ganciclovir + standard care
Control
Standard care</td>
<td>The randomisation sequence was generated centrall by covance laboratories using a computerised interactive voice response system. Randomisation was done within 24hrs of planned surgery by the investigator telephoning the computerised interactive voice response system, which then automatically allocated patients to study treatment. Patients were randomised in a 1:1 to emperimental or control groups in blocks of 4. The block size was not stratified by site or region because we thought small numbers of patients would be recruited by</td>
<td>
<table>
<tr><th></th><th>Intervention (n=119)</th><th>Control (117)</th></tr>
<tr><td>Overall Survival</td><td></td><td></td></tr>
<tr><td>6 months</td><td>101</td><td>100</td></tr>
<tr><td>12 months</td><td>70</td><td>76</td></tr>
<tr><td>18 months</td><td>54</td><td>51</td></tr>
<tr><td>24 months</td><td>30</td><td>25</td></tr>
<tr><td>30 months</td><td>20</td><td>18</td></tr>
<tr><td>36 months</td><td>6</td><td>5</td></tr>
<tr><td>42 months</td><td>0</td><td>0</td></tr>
</table>
Hazard ratio 0.31 (95% CI 0.86-1.61)
p value=0.31

Overall Survival in Patients with Unmethylated MGMT
<table>
<tr><th></th><th>Intervention</th><th>Control</th></tr>
<tr><td>Overall Survival (median)*</td><td>497 days</td><td>452 days</td></tr>
</table>
</td>
<td>limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk of bias (The randomisation sequence was generated centrally by covance laboratories using a computerised interactive voice response system)
Allocation concealment: low risk of bias (Randomisation was done within 24hrs of</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial, Lancet OncologyLancet Oncol, 14, 823-33, 2013
Ref Id 557243
Country/ies where the study was carried out</td>
<td>
<table>
<tr><td>Glioblastoma Multiforme</td><td>112 (94%)</td><td>111 (95%)</td></tr>
<tr><td>Other high-grade glioma</td><td>4 (3%)</td><td>4 (3%)</td></tr>
<tr><td>Other</td><td>3 (3%)</td><td>2 (2%)</td></tr>
<tr><td>Location of tumour</td><td></td><td></td></tr>
<tr><td>Right</td><td>71 (60%)</td><td>60 (51%)</td></tr>
<tr><td>Frontal</td><td>18 (15%)</td><td>11 (9%)</td></tr>
<tr><td>Parietal</td><td>16 (13%)</td><td>13 (11%)</td></tr>
<tr><td>Temporal</td><td>26 (22%)</td><td>27 (23%)</td></tr>
<tr><td>Other</td><td>11 (9%)</td><td>9 (8%)</td></tr>
<tr><td>Left</td><td>48 (40%)</td><td>57 (49%)</td></tr>
<tr><td>Frontal</td><td>13 (11%)</td><td>15 (13%)</td></tr>
<tr><td>Parietal</td><td>10 (8%)</td><td>12 (10%)</td></tr>
<tr><td>Temporal</td><td>14 (12%)</td><td>22 (19%)</td></tr>
<tr><td>Other</td><td>11 (9%)</td><td>8 (7%)</td></tr>
<tr><td>Ventricular Opening</td><td></td><td></td></tr>
<tr><td>Yes</td><td>27 (23%)</td><td>18 (15%)</td></tr>
</table>
</td>
<td></td>
<td>individual sites. Neither the patients nor the investigators were masked to treatment during the course of the study.
Proceedures
Patients allocated to the experimental group received a one-time treatment of sitimagene ceradenovec given as a series of injections (between 30-70) into the wall of the resection cavity at the end of the completed resection, using a blunt needle which was advanced up to 2cm (tissue depth permitting) slowly administered 100uL per injection site which could later be seen on MRI as small</td>
<td>
<table>
<tr><td>95% CI</td><td>369-574</td><td>437-558</td></tr>
<tr><td>p value</td><td>0.11</td><td></td></tr>
<tr><td>HR (95% CI)</td><td>1.40 (0.92-2.12)</td><td></td></tr>
</table>
*Only in patients witH unmethylated MGMT
<table>
<tr><td></td><td>Intervention (n=64)</td><td>Control (n=60)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Overall Survival</td><td></td><td></td></tr>
<tr><td>6 months</td><td>56</td><td>50</td></tr>
<tr><td>12 months</td><td>38</td><td>36</td></tr>
<tr><td>18 months</td><td>26</td><td>18</td></tr>
<tr><td>24 months</td><td>14</td><td>5</td></tr>
<tr><td>30 months</td><td>10</td><td>3</td></tr>
<tr><td>36 months</td><td>3</td><td>0</td></tr>
<tr><td>42 months</td><td>0</td><td>0</td></tr>
</table>
Hazard ratio 1.40 (0.92-2.12)
</td>
<td>planned surgery by the investigator telephoning the computerised interactive voice response system, which then automatically allocated patients to study treatment)
Blinding of participants and personnel: high risk of bias (open-label)
Blinding of outcome assessment: low risk of bias (3-D images of scans were masked and assessed by</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Europe
Study type
Randomised, Open-label, parallel group, multicentre Phase III Controlled Trial

Aim of the study
Investigate the efficacy and safety of sitimagene cerade novec with subsequent ganciclo</td>
<td>
<table>
<tr><td>Time Since Clinical Diagnosis (days)</td><td></td><td></td></tr>
<tr><td>Mean (SD)</td><td>9.5 (9.89)</td><td>12.5 (13.99)</td></tr>
<tr><td>Median (range)</td><td>7.0 (1-76)</td><td>8.5 (0-115)</td></tr>
<tr><td>Karnofsky Score</td><td></td><td></td></tr>
<tr><td>70</td><td>18 (15%)</td><td>11 (9%)</td></tr>
<tr><td>80</td><td>22 (18%)</td><td>23 (20%)</td></tr>
<tr><td>90</td><td>49 (41%)</td><td>47 (40%)</td></tr>
<tr><td>100</td><td>30 (25%)</td><td>36 (31%)</td></tr>
<tr><td>Estimate of resection during surgery n (%)</td><td></td><td></td></tr>
<tr><td>Radical</td><td>99 (83%)</td><td>95 (81%)</td></tr>
<tr><td>Partial</td><td>20 (17%)</td><td>22 (19%)</td></tr>
<tr><td>Estimated extent of tumour resected from postoperative MRI</td><td></td><td></td></tr>
<tr><td>< 50%</td><td>2 (2%)</td><td>3 (3%)</td></tr>
</table>
</td>
<td></td>
<td>cavitations. After allowing for 5 days for transduction, ganciclovir 5mg/kg was given IV twice a day (from day 5-19 after operation).
During the course of the study, standard care was heterogenous, particularly with regardsto the use of TMZ. Surgery and RT (60 Gy in 30 fractions to the tumour volume with a 2cm margin) was the protocol-prescribed standard, by RT according to the Stupp protocol was an option depending on whether TMZ was available at the study site. All sites complied with the protocol-defined radiation therapy regimen in terms of dose</td>
<td>p value = 0.11

Adverse events (safety population)
<table>
<tr><td></td><td>Intervention</td><td>Control</td></tr>
<tr><td>Number of patients with one or more adverse event</td><td></td><td></td></tr>
<tr><td>Maximum CTC Grade</td><td></td><td></td></tr>
<tr><td>1</td><td>2 (2%)</td><td>5 (4%)</td></tr>
<tr><td>2</td><td>6 (5%)</td><td>36 (29%)</td></tr>
<tr><td>3</td><td>39 (31%)</td><td>25 (20%)</td></tr>
<tr><td>4</td><td>33 (27%)</td><td>22 (18%)</td></tr>
<tr><td>5</td><td>39 (31%)</td><td>34 (27%)</td></tr>
<tr><td>Number of patients with one or more study-intervention-related adverse events</td><td></td><td></td></tr>
</table>
</td>
<td>members of steerring committee)
Incomplete outcome data: low risk of bias (ITT analysis)
Selective reporting: low risk (all pre-specified outcomes reported)</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>ovir for the treatment of operable, newly diagnosed glioblastoma compared with standard treatment

Study dates
Nov 3, 2005 - April 16, 2007

Source of funding
DE and JK were employees of Ark</td>
<td>
<table>
<tr><td>50-69%</td><td>5 (4%)</td><td>8 (7%)</td></tr>
<tr><td>70-89%</td><td>30 (25%)</td><td>22 (19%)</td></tr>
<tr><td>>90%</td><td>80 (67%)</td><td>80 (68%)</td></tr>
<tr><td>Not done</td><td>2 (2%)</td><td>4 (3%)</td></tr>
<tr><td>MGMT analysis</td><td></td><td></td></tr>
<tr><td>Methylated</td><td>34/98 (35%)</td><td>19/79 (24%)</td></tr>
<tr><td>Non-methylated</td><td>64/98 (65%)</td><td>60/79 (76%)</td></tr>
</table>
Inclusion criteria
Adult patients (aged 18-70) with a Karnofsky score or more at screening and newly diagnosed supratentorial glioblastoma multiforme that were deemed by the treating neurosurgeon to be amenable to complete resection.
Exclusion criteria
Bihemispheric or multifocal tumours, recurrent glioma, other significant concomitant disease (including renal or liver disease), hypersensitivity to ganciclovir, or patients who had received chemotherapy within 6 weeks of randomisation were excluded from the study.
</td>
<td></td>
<td>and timing after surgery, aiming at beginning RT within 8 weeks of surgery.
As the study progressed, TMZ was becoming more frequently, although not universally, used for the treatment of patients with glioblastoma. A protocol ammendment allowed the use of TMZ after surgery at the discretion of the investigator.
Central imaging analysis was done according to a pre specified imaging assessment plan by bio-image technologies SAS collecting MRI obtained with a standardised volumetric protocol with an without contrast at diagnosis, early postoperatively (within 48hrs),</td>
<td>
<table>
<tr><td>Maximum CTC Grade</td><td></td><td></td></tr>
<tr><td>1</td><td>11 (9%)</td><td>13 (10%)</td></tr>
<tr><td>2</td><td>24 (20%)</td><td>27 (21%)</td></tr>
<tr><td>3</td><td>31 (25%)</td><td>7 (6%)</td></tr>
<tr><td>4</td><td>17 (14%)</td><td>1 (1%)</td></tr>
<tr><td>5</td><td>5 (4%)</td><td>3 (2%)</td></tr>
<tr><td>Number of patients who discontinued due to an adverse event</td><td>2 (2%)</td><td>0</td></tr>
<tr><td>Number of patients who died due to a treatment-emergent adverse event</td><td>65 (52%)</td><td>52 (41%)</td></tr>
</table>
CNS-related adverse events
<table>
<tr><td></td><td>Intervention</td><td></td><td></td><td>Control</td><td></td><td></td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Therapeutics Ltd during the conduct of the study. SY-H and Ark Therapeutics LTD. JM are shareholders of Ark Therapeutics Ltd. MW, PW, PM, and ZR were compensated by Ark Therapeutics Ltd for their involvement in the			and on day 19, month 3, and every 3 months thereafter. On the basis of a 3-D image registration algorithm enhancing tumour volumes were assessed discounting haemorrhage, cysts and necrosis. Because of an unexpected increase of enhancement at day 19 in the experimental group, further assessment of these scans in a masked manner by members of the steering committee suggested that this observation was probably due to an injection and ganciclovir-related so-called pseudoprogression, which is an increase in tumour size that		

	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Brain and cerebral oedema						
0-4 days	6	0	1	3	0	1
5-19 days	2	0	0	0	0	0
20-56 days	3	1	0	0	0	0
Hydrocephalus						
0-4 days	0	0	0	0	0	0
5-9 days	0	0	0	0	0	0
20-56 days	0	0	1	1	0	0
Cognitive disorder						
0-4 days	0	0	0	0	0	0
5-19 days	0	1	0	0	0	0
20-56 days	1	0	0	0	0	0

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>steering committee. JM was a consultant to Ark Therapeutics Ltd.</td>
<td></td>
<td></td>
<td>regresses spontaneously, as described elsewhere.
Statistical analysis
The ITT population was used for efficacy and all randomly allocated patients for safety analyses. The ITT population was defined as all randomised patients who had a glioma (high or low grade) as confirmed by a central histology review.
The prespecified primary analysis was a triangular test, using the log-rank test adjusted for intention to use TMZ and based on the ITT population. Each interim analysis was based on a log-rank statistic Z, stratified for intended TMZ use</td>
<td>
<table>
<tr><td>Increased intracranial pressure</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-4 days</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>5-19 days</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>20-56 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Decreased consciousness</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-4 days</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>5-19 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>20-56 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Encephalitis</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>0-4 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>5-19 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>20-56 days</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			at a specified at time of randomisation. In accordance with this prespecified assessment plan, because of a change in the actual use of TMZ, the data and safety monitoring board recommended at the 3rd interim analysis to stop the study due to futility.		

Hyponatraemia and low blood sodium						
0-4 days	0	1	0	4	0	0
5-19 days	4	5	0	0	0	0
20-56 days	1	0	0	4	0	0
Seizures						
0-4 days	8	0	0	7	0	0
5-19 days	11	2	0	3	0	0
20-56 days	4	1	0	2	0	1
Hemiparesis						
0-4 days	7	5	0	6	1	0
5-19 days	1	1	1	2	1	0
20-56 days	4	1	0	2	0	1
Aphasia						
0-4 days	4	5	0	5	2	0

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td><table>
<tr><td>5-19 days</td><td>1</td><td>1</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>20-56 days</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
</table></td><td></td></tr>
<tr><td>Full citation
Wick, W., Platten, M., Meisner, C., Felsberg, J., Tabatabai, G., Simon, M., Nikkhah, G., Papsdorf, K., Steinbach, J. P., Sabel, M., Combs, S. E., Vesper, J., Braun,</td><td>Sample size
N=373
Characteristics<table>
<tr><td></td><td>Temolozomide</td><td>Radiotherapy</td></tr>
<tr><td>Gender = n, %</td><td>Female = 107, 55%
Male = 88, 45%</td><td>Female = 90, 51%
Male = 88, 49%</td></tr>
<tr><td>Median KPS, % Overall (Range)</td><td>80 (60-100)</td><td>80 (60-100)</td></tr>
<tr><td>Resection = n, %</td><td>Complete= 53, 27%
Partial= 61, 31%
Biopsy= 80, 41%
Missing= 1, <1%</td><td>Complete=51, 20%
Partial=62, 35%
Biopsy=65, 37%
Missing=0</td></tr>
</table>Inclusion criteria
De-novo anaplastic astrocytoma or gliobastoma that was histologically confirmed</td><td>Interventions
Temolozomide: 1 week on/ 1 week off schedule, 100 mg/m2 on days 1-7, with increases or decreases og 25 mg/m2 depending on blood counts and tolerability.
Radiotherapy: to gross tumour volume plu a 2cm margin over 6-7 weeks in fractions</td><td>Details
Randomised phase III trial. Randomisation was performed centrally by an independent contract research organisation. A list was generated electronically in block of variable length without stratification with allocation 1:1 before the start of the study.</td><td>Results
Tumour response was defined by the Macdonald criteria. MGMT promotor methylation was assessed by two distinct methylation-specific PCR assays.
Primary endpoint: overall survival
Secondary endpoints: event-free survival, best response, QOL and safety

Overall survival
HR= 1.09 , 95% CI 0.84-1.42

Overall survival for those who presented with MGMT methylated versus unmetylated status
HR=0.62, 95% CI 0.42-0.91

Grade 3-4 fatigue
Temozolomide group: 24/195
Radiotherapy group: 20/178</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: Low risk (central independent randomisation by an independent organisation)
Allocation concealment: Low risk</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
C., Meixensberger, J., Ketter, R., Mayer-Steinacker, R., Reifenberger, G., Weller, M., N. O. A. Study Group of Neuro-oncology Working Group of German Cancer Society, Temozolomide chemotherapy alone	locally after biopsy or resection: age older that 65 years; and a Karnofsky Performance Score of 60 or more. Exclusion criteria Patients having undergone previous systemic chemotherapy or radiotherapy to the brain; inadequate bone marrow reserve, liver function or renal function	of 1.8-2.0 Gy to a total of 60.0 Gy according to preoperative MRI and dedicated CT or three-dimensional planning systems.			(allocation were revealed by fax transmission to a project manager) Blinding of participants and personnel: High risk (not blinding or placebo used) Blinding of outcome assessment: High risk (not blinding or placebo used) Blinding (performance bias and detection bias): High risk (not blinding or placebo used)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial, Lancet OncologyLancet Oncol, 13, 707-15, 2012 Ref Id 557264 Country/ies where the study was					Incomplete outcome data: High risk (analysis was on an intention-to-treat basis with all withdrawals and protocol violations clearly specified. There was a high rate of drop Selective reporting: low risk of bias (All pre-specified outcomes were reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
carried out Germany and Switzerland Study type RCT Aim of the study To compare the efficacy and safety of dose-dense temozolomide alone versus radiotherapy alone in elderly patients with anaplastic astrocy					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
toma or gliobla stoma Study dates May 15, 2005 to Nov 2, 2009 Source of funding Merck Sharp & Dohme . Conflict s of interest : WW, JPS, GR, and MW have					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
received consulting and lecture fees, and WW and MW have received research support from Merck Sharp & Dohme. The other authors declare that they have no conflicts of interest.					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wick, W, Â , Hartmann C, Â , Engel C, Â , Stoffels, Â , Felsberg J, Â , Stockhammer F, NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and	Sample size Arm A (RT); n= 139 Arm B1 (PCV); n= 54 Arm B2 (TMZ); n= 53 Characteristics RT + PCV or TMZ on progression vs. PCV or TMZ + RT on progression Age median (range), years: 44 (23-74) vs. 42 (20-77) AA, local, central: 65, 70 vs 66,74 AOA, local, central: 41,47 vs 41,44 AO, local, central: 33, 22 vs 27,17 KPS median (range): 90 (70-100) vs 90 (70-100) Inclusion criteria Adult patients with centrally confirmed diagnosis of a WHO grade 3 anaplastic glioma, KPS of ≥70, no prior systemic chemotherapy or radiotherapy to the brain, and adequate bone marrow reserve, liver and renal functions, and stable or decreasing corticosteroid dose within 14 days before random assignment. Exclusion criteria Not reported	Interventions Arm A Radiotherapy consisted of fractioned focal irradiation to gross tumour volume (GTV) plus a 2-cm margin in 6-week courses of 1.8- to 2 Gy fractions to a total of 60 Gy dose based on preoperative magnetic resonance imaging (MRI) with dedicated computed tomography or three-dimensional planning systems.	Details Patients were randomly assigned 2:1:1 to Radiotherapy or chemotherapy (PCV or TMZ) as initial therapy. At first disease progression, patients treated initially with radiotherapy (63% patients with AA treated in arm A, 41% AO and 43% with AOA) crossed over to the treatment with chemotherapy and were randomly assigned 1:1 to PCV (arm A1) or TMZ (arm A2). Patients who experienced disease progression after being treated with chemotherapy (60% of patients with AA reated in arms B1/B2, 35% of patients with AO and 48% of	Results FIRST ANALYSIS (median follow-up = 5.4 years) All patients in arm A (RT) completed treatment. In arm B1 (PCV) the median number of completed cycles was 4 (range 1-5 cycles) and in arm B1 (TMZ) was 8 (range: 0- 12). TTF, OS and PFS - Arm B1/B2 vs Arm A [HR, 95% CI]: TTF, HR= 1.2 ; 95% CI, 0.8 to 1.8, p= 0.2805 OS, HR= 1.2 ; 95% CI, 0.8 to 1.9 PFS, HR = 1; 95% CI 0.7 to 1.3, p = 0.87 Prognostic factors as determines in a Univariate Cox Regression Analysis for TTF [HR, 95% CI]: Anaplastic astrocytoma vs anaplastic oligoastrocytoma, HR = 3.2; 95% CI 2 to 5.1 Anaplastic astrocytoma vs anaplastic oligodendroglioma, HR = 3.3; 95% CI 1.7 to 6.4, p< 0.0001 Anaplastic oligoastrocytoma vs anaplastic oligodendroglioma, HR = 1; 95% CI 0.5 to 2.2 IDH1, wild-type vs mutated, HR = 2.5; 95% CI 1.6 to 3.9, p< 0.0001 1p/19q retained vs 1p/19q deleted, HR = 3.1; 95% CI 1.8 to 5.2, P<0.0001 MGMT promoter, unmethylated vs methylated, HR= 2.4; 95% CI 1.6 to 3.7, p<0.0001 Age, > 50 y/o vs ≤50 y/O, HR= 2.7; 95% CI 1.9 to 3.9, p< 0.0001 Prognostic factors as determines in a Univariate Cox Regression Analysis for PFS [HR, 95% CI]:	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk of bias Allocation concealment: unclear risk (no indication of stratification, but baseline characteristics indeed well balances between treatment groups) Blinding of participants and personnel:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
vincristine or temozolomide, Journal of Clinical OncologyJ Clin Oncol, 27, 5874-80, 2009 Ref Id 557249 Country/ies where the study was carried out Germany Study type RCT Aim of the study To compar		Arm B1 chemotherapy PCV consisted of four 8-week cycles of lomustine (110mg/m2 on day 1), vincristine (2 mg on days 8 and 29), and procarbazine (60mg/m2 on days 8 through 21). Dose modifications were based on weekly blood cell counts and polyneuropathy. Arm B2 chemotherapy TMZ consisted of eight 4-week cycles of temozolomide (200 mg/m2 on	patients with AOA crossed over to second-line treatment with radiotherapy. The primary end point was time from operation to treatment failure stratified for therapy in the ITT population. Treatment failure (TTF) was defined as withdrawal from therapy before second progression because of toxicity or poor general condition, second progression, or death. Patients without one of these events were censored at the end of their follow-up. Secondary end points included response rate, PFS (calculated as time between operation and first	Anaplastic astrocytoma vs anaplastic oligoastrocytoma, HR = 2.7; 95% CI 1.9 TO 3.8, P<0.0001 Anaplastic astrocytoma vs anaplastic oligodendroglioma, HR = 3; 95% CI 1.7 to 5.1 Anaplastic oligoastrocytoma vs anaplastic oligodendroglioma, HR = 1.1; 95% CI 0.6 to 2.0 IDH1, wild-type vs mutated, HR = 2.4; 95% CI 1.7 to 3.5, p< 0.0001 1p/19q retained vs 1p/19q deleted, HR = 3.2; 95% CI 2.0 to 5, P<0.0001 MGMT promoter, unmethylated vs methylated, HR= 2; 95% CI 1.4 to 2.9, p<0.0001 Age, > 50 y/o vs ≤50 y/O, HR= 1.7; 95% CI 1.2 to 2.3, p< 0.0022 No information of the prognostic factors for OS LONG TERM ANALYSIS (Extracted from Wick 2016) Median follow-up time for this analysis is 9.5 years (95% CI 8.6 - 10.2), 78% (arm A) and 79% (arms B1/B2) progression events have been observed. The primary endpoint TTF has been reached by 66% and 67% of patients, respectively. About half of the patients have died in both arms (48% in arm A and 53% in arms B1/B2). TTF, HR= 0.99 ; 95% CI, 0.75 to 1.33, p= 0.97 OS, HR= 1.11 ; 95% CI, 0.8 to 1.55, p=0.53 PFS, HR = 0.97; 95% CI 0.74 to 1.26, p = 0.8	high risk of bias (no blinding of participants or personnel) Blinding of outcome assessment : low risk of bias (not blinded, but unlike to introduce any type of bias) Blinding (performance bias and detection bias): high risk of bias (not blinded) Incomplete outcome data: unclear risk (not mention of loss to follow-up) Selective reporting: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
e the efficacy and safety or radiotherapy versus chemotherapy with either PCV or temozolomide as initial therapy in patients with newly diagnosed, supratentorial anaplastic gliomas and examined the clinical relevance of 1p/19q		days 1 though 5) with dose modifications based on blood cell counts. If toxicity in arms B1 and B2 resulted in delays longer than 4 weeks, radiotherapy was commenced. Treatment was stopped at disease progression or for unacceptable toxicity. At disease progression after completion of primary treatment, patients in arm A were treated with PCV or	progression during or after either chemotherapy or radiotherapy), overall survival, time to treatment failure (TTF) stratified for histtology, 1p/19q codeletion, MGMT promoter methylation status and safety. Analyses were performed with SAS on a modified ITT basis. Because the treatment-related documentation in he 2 groups was quite different, patients who changed their therapy were analysed in the group they were randomly assigned.	Multivariate Cox regression of histology and molecular classification for time-to-treatment failure Histology, AO(A) vs AA, HR = 0.75; 95% CI 0.48 to 1.02, p= 0.65 CIMPNon-Codel vs CIMPneg, , HR= 0.5 (95% CI 0.34 to 0.75), p = 0.001 CIMPCodel vs CIMPneg. , HR = 0.25 (0.15 to 0.40_, p<0.001	(outcomes reported adequately)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
codeletion, MGMT promoter methylation, and IDH1 mutations in codon 132 in these tumours. Study dates June 1999 to February 2005 Source of funding Supported by the AKF program of the Medical Faculty		temozolomide (1:1 random assignment). Patients in arms B1 or B2 who achieved an initial response or stable disease and completed the full course of chemotherapy were re-treated with the same chemotherapy for 2 (arm B1) or four (arm B2) additional cycles before radiotherapy was given at further progression. Progression in the protocol			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of the University of Tubingen and an unrestricted grant from Essex Pharma. The translational investigations reported in this study were supported by a collaborative grant within the program of molecular diagnostics of the		and in this specific article, was defined as progression after chemotherapy or after radiotherapy, indicating the time point to switch treatments between these modalities			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
German Federal Ministry for Science and Technology.					
Full citation Wick, W., Roth, P., Hartmann, C., Hau, P., Nakamura, M., Stockhammer, F., Sabel, M. C., Wick, A., Koeppen, S., Ketter, R.,	This trial was extracted as part of Wick 2009				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vajkoczy, P., Eyupoglu, I., Kalff, R., Pietsch, T., Happold, C., Galldiks, N., Schmidt-Graf, F., Bamberg, M., Reifenberger, G., Platten, M., von Deimling, A., Meisner, C., Wiestler, B., Weller, M., Neurooncology Working					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Group of the German Cancer, Society, Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. [Erratum appears in Neuro Oncol.					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>2016 Nov;18 (11):e1 ; PMID: 27738185], Neuro-OncologyNeuro-oncol, 18, 1529-1537, 2016</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Zhu, J. J., Demireva, P., Kanner, A. A., Pannullo, S., Mehdorn, M., Avgeropoulos, N., Salmaggi, A., Silvani, A., Goldlu</td><td>Sample size
N=280
Characteristics<table><tr><td></td><td>Age - median (range)</td><td>KPS - median (range)</td></tr><tr><td>TTFields/TMZ</td><td>57 (20-83)</td><td>90 (60-90)</td></tr><tr><td>TMZ</td><td>58 (21-80)</td><td>90 (70-100)</td></tr></table>Inclusion criteria
See Stupp 2015
Exclusion criteria
See Stupp 2015</td><td>Interventions
See Stupp 2015</td><td>Details
Adults completed the MMSE, EORTC QLQ-C30, Version 3, supplemented by the brain cancer module (BN 20). Afterwards, MMSE and KPS assessments were repeated monthly during clinic visits. HRQoL questionnaires were completed every 3 months until progression</td><td>Results
Functional status (KPS) - mean percentage change from baseline*
TTFields/TMZ group: -1.6 (month 1) and -4.3 (month 7) (no SD were reported/these were reported in graphs and were not possible to interpret numerically)
TMZ alone group: -0.4 (month 2) and -4.2 (month 8)
This reflected relative stability
Cognitive status (as measure by the MMSE) - mean percentage change from baseline*

TTFields/TMZ group:-2.4 (month 1) and 4.8 (month 7)

TMZ alone group: -0.5 (month 2) and 3.8 (month 8)
This reflects relative stability</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: unclear risk of bias (the authors do not provide sufficient detail to</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
st, S., David, C., Benouaich-Amiel, A., Zvi Ram on behalf of the, E. F. Trial Investigators, Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields			or withdrawal from the trial.	Health-related quality of life (HRQoL)* At 3 and 6 months: TTFields/TMZ vs TMZ: change from baseline at 3 moths (CFB3) was 24% and CFB6 was 13% in the TTFields/TMZ group vs CFB3: -7% and CFB6:-17% This reflects and improvement in the TTFields/ TMZ group At 9 months: TTFields/TMZ vs TMZ: change from baseline at 9 months CFB: 0.42 in the TTFields/TMZ and 0 in the TMZ group No significant group differences were reported fro any of the functional scales from the EORTC QLQ-C30 measure. Group differences were found for "itchy skin" in the TTFields/TMZ group. Self-reported neurologic symptomatology did not differ between the 2 groups	allow an assessment of whether allocation was randomised using appropriate methods) Allocation concealment: low risk of bias (central interactive voice response system) Blinding of participants and personnel: high risk of bias (open label study) Blinding of outcome assessment: high risk of bias (open label study) Blinding (performance bias and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma, Journal of Neuro OncologyJ Neurooncol, 28, 28, 2017 Ref Id 676722 Country/ies where the study was carried out					detection bias): high risk of bias (open label study) Incomplete outcome data: high risk of bias (per protocol analysis with all drop-outs/discontinuations clearly accounted for, however very high drop-out rate of 90%) Selective reporting: low risk (all pre-specified outcomes reported) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multicentre study Study type Phase III RCT Aim of the study To assess the health related quality of life, cognitive and functional status of adults treated with TTF in combination with TMZ or TMZ alone Study dates					Please note that Stupp 2015 was analysed as the ITT and Zhu 2017 per protocol *(no SDs were reported/these were reported in graphs and were not possible to interpret numerically)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Stupp 2015 Source of funding Novocure					

1 Evidence tables for review 2d - Management of recurrent high-grade glioma

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation 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., Gattamane	Sample size N=325 Cediranib, n=131 Cediranib + lomustine, n=129 Lomustine + placebo, n =65 Characteristics Median age, years: 54 / 54 / 54 KPS <70: 0 / 1 (0.8%) / 1 (1.6%) KPS 70-80: 65 (50%) / 62 (48%) / 23 (36.2%) KPS 90-100: 65 (50%) / 66 (51.2%) / 40 (62.5%) (Cediranib / Cediranib + lomustine / Lomustine + placebo)	Interventions Experimental: Cediranib alone Cediranib + lomustine (30 mg daily, n=131; 20 mg oral daily + lomustine 110mg/m2 q6w (n=129) Control: Lomustine alone: 110mg/m2 q6w	Details Patients were randomised in a 2:2:1 ratio. The primary endpoint of the study was PFS based on centralised, radiographic review. Secondary endpoints	Results PFS HR (95% CI) Cediranib alone vs Cediranib + lomustine HR 1.05 (0.74 - 1.50), P=0.90 Cediranib + lomustine vs lomustine + placebo HR 0.76 (0.53-1.08), P=0.16 OS HR (95% CI) Cediranib alone vs Cediranib + lomustine HR 1.43 (0.96-2.13), p = 0.10 Cediranib + lomustine vs lomustine + placebo HR 1.15 (0.77 - 1.72), p=0.50 Any adverse events, ≥ grade 3 Cediranib, n= 78/128 (60.9%) Cediranib + lomustine, n= 98/123 (79.7%)	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: Low risk (randomisation was computer programme) Allocation concealment: Low risk (double blinded) Blinding of participants and personnel: Low risk (double blinded) Blinding of outcome assessment: Low risk (outcomes were assessed using centralised radiographic review, with masking to study arm)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ni, 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	Inclusion criteria Confirmation of recurrent glioblastoma, life expectancy ≥12 weeks and patients who received only 1 prior systemic chemotherapy regimen, and this regimen must contain temozolomide. Exclusion criteria Patients taking enzyme-inducing antiepileptic drugs within 3 weeks before randomisation, poorly controlled hypertension and previous antiangiogenesis (e.g. bevacizumab, sorafenib, sunitinib) therapy		were OS, response rate in patients with measurable disease, APF6, time to deterioration in neurologic status, mean change in average daily dosage of corticosteroids, and average number of progression and corticosteroids- free days.	Placebo + lomustine, n= 39/64 (60.9%) Fatigue Cediranib, n= 21/128 (60.9%) Cediranib + lomustine, n= 19/123 (79.7%) Placebo + lomustine, n= 6/64 (60.9%)	Incomplete outcome data: Low risk (dropout rate was very low (10 participants in total), making attrition bias less significant. Follow-up was similar across all study groups Selective reporting: Low risk (All pre-specified outcomes were reported and confirmed on registration at clinicaltrials.gov)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
OncologyJ Clin Oncol, 31, 3212-8, 2013 Ref Id 554440 Country/ies where the study was carried out Multicenter Study type RCT Aim of the study To investigate the efficacy of cediranib, as monotherapy and in combination with the synthetic alkylating agent lomustine (1-(2-chloroethyl) - 3-cyclohexyl - 1-					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
nitrosuera) versus lomustine in patients with recurrent glioblastoma Study dates October 2008-September 2009 Source of funding AstraZeneca, Milenium, Pfizer, Novartis, Merck, Celgene, Genetech Oncology, ImmunoCellular Therapeutics, Diffusion Pharmaceutical, Med-Immune, Boehringer					

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Ingelheim, Myrexis, Sanofi-Aventis, EMD-Serono, Roche, Dyax.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Brem, H., Piantadosi, S., Burger, P. C., Walker, M., Selker, R., Vick, N. A., Black, K., Sisti, M., Brem, S., Mohr, G., et al.,, Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of</td><td>Sample size
All patients (GBM, AA, AOA, ODs)
N=222
Carmustine polymer; n= 110
Placebo polymer; n=112
GBM patients only
N=148
Carmustine polymer; n= 75
Placebo polymer; n=73
Characteristics
<table>
<tr><td></td><td>Carmustine</td><td>Placebo</td></tr>
<tr><td>Mean age (SD)</td><td>48.1 (12.3)</td><td>47.6 (13.6)</td></tr>
<tr><td>Gender (male)</td><td>74 (67%)</td><td>69 (62%)</td></tr>
<tr><td>Mean (SD) KPS</td><td>11 (13.1)</td><td>74.6 (12.1)</td></tr>
<tr><td>Median interval from first operation</td><td>12.9 months</td><td>11.3 months</td></tr>
<tr><td>Glioblastoma**</td><td>75 (65.5%)</td><td>73 (65.2%)</td></tr>
</table></td><td>Interventions
Carmustine discs: BIODEL, the polyanhydride polymer used, is a copolymer of poly-cerboxyphenoxy propane and sebacic acid prepared in a 20/80 ratio. The polymer and carmustine were co-dissolved in methylene chloride and spray dried into microspheres, which were compressed into discs of 1.4 cm diameter and 1 mm thickness, and sterilised by 2.2 x 104 Gy</td><td>Details
Patients underwent a craniotomy for maximum resection of tumour. The final admission criterion for the study was either the pathologist's report of malignant glioma or the report of recurrent tumour in a patient with a previously</td><td>Results
Effect of carmustine polymer adjusted for prognostic factors for grade IV patients only (n=145) univariate regressions
Carmustine polymer vs placebo polymer: HR 0.83 (0.63-1.09); p = 0.19
Karnofsky ≥70 vs < 70: HR 0.53 (0.40-0.70); p <0.001
Overall survival AA vs GBM: HR 0.60 (0.40 – 0.90)
Overall survival – oligodendroglioma vs glioblastoma HR 0.39 (0.26 – 0.59)

Effect of carmustine polymer adjusted for prognostic factors for grade III patients only (n=145) univariate regressions
HR= 0.31 (0.13-0.70), P=0.005</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk of bias
Allocation concealment: unclear risk of bias
Blinding of participants and personnel: low risk (placebo wafers appeared similar to Gliadel although some subtle differences may remain)
Blinding of outcome assessment: unclear risk of bias
Incomplete outcome data: low risk of bias
Selective reporting: low risk of bias</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group, LancetLancet, 345, 1008-12, 1995 Ref Id 554609 Country/ies where the study was carried out USA Study type RCT Aim of the study To evaluate the effectiveness of biodegradable polymers impregnate	<table><tr><td>Anaplastic astrocytoma</td><td>15 (13.6%)</td><td>16 (14.3%)</td></tr><tr><td>Anaplastic Oligodendroglioma</td><td>4 (3.6%)</td><td>5 (4.5%)</td></tr><tr><td>Oligodendroglioma</td><td>2 (1.8%)</td><td>2 (1.8%)</td></tr><tr><td>Other glial tumours</td><td>16 (14.5%)</td><td>16 (14.5%)</td></tr><tr><td>Necrosis</td><td>1 (0.9%)</td><td>0</td></tr></table> Only glioblastoma results have been reported for the purpose of the analysis Inclusion criteria Presence of a unilateral single focus of tumour in the cerebrum showing at least 1 cm3 enhancing volume on computed tomography scan or magnetic resonance imaging: a KPS score of at least 60 (ie ability to function independently); completion of external beam radiation therapy; and no nitrosureas for 6 weeks and no other systemic chemotherapeutic agent for 4 weeks before enrolment. In addition, patients' surgeons made an independent determination that another tumour resection would be done irrespective of the study. Exclusion criteria Not reported	gamma irradiation. Loading with 50µg carmustine/mm3 of polymer (3.85% carmustine loading) tielded 7.7 mg of carmustine oer wafer for a maximum patient dose of 62 mg (dose previously utilised in a phase I trial).	established malignant glioma. After removal of the tumour, up to 8 discs were applied to the resection cavity surface. Sheets of oxidised regenerated cellulose were used occasionally to secure the polymers against the brain. All patients were clinically and radiologically reassesse		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
d with carmustine to treat recurrent malignant gliomas Study dates March 1989 - January 1992 Source of funding Guildors Pharmaceuticals Ins, Baltimore; Scios-Nova Corporation, Mountain View; and by the National Cooperative Drug Discovery Groups of the National Cancer Institute if the			d at least every 2 months. Patients were eligible to receive systemic chemotherapy 2 weeks after the implant surgery. Pathological evaluation: The tissue section of the recurrent tumours were reviewed without any knoeledge of patients' treatment or outcome. Fibrillary astrocytic		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>National Institutes of Health.</td><td></td><td></td><td>tumours were classified by a modofoed Ringertz system.</td><td></td><td></td></tr>
<tr><td>Full citation
van den Bent, M. J., Brandes, A. A., Rampling, R., Kouwenhoven, M. C., Kros, J. M., Carpentier, A. F., Clement, P. M., Frenay, M., Campone, M., Baurain, J. F., Armand, J. P., Taphoorn, M. J., Tosoni, A.,</td><td>Sample size
N=110; n= 56 TMZ/BCNU and n=54 in the Erlotinib arm
Characteristics
<table>
<tr><td></td><td>TMZ/BCNU</td><td>Erlotinib</td></tr>
<tr><td>Age, median (range)</td><td>54.2 (19.5-78.8)</td><td>54.7 (18.7-71.4)</td></tr>
<tr><td>Female,n (%)</td><td>19 (33.9%)</td><td>19 (35.2%)</td></tr>
<tr><td>KPS 70-80</td><td>26 (46.4%)</td><td>24 (44.4%)</td></tr>
<tr><td>KPS 90-100</td><td>30 (53.6%)</td><td>30 (55.6%)</td></tr>
</table>
Inclusion criteria
Patients were eligible if they had a histologically proven GBM recurrent disease after previous radiation therapy documented by magnetic resonance imaging; no prior chemotherapy for recurrent disease or a maximum of only 1 prior chemotherapy regimen given as adjuvant treatment;</td><td>Interventions
Erlotinib was started at 150mg daily, with dose scalation to 200mg daily if no or minimal toxicity was experienced, in patients who were not on enzyme-inducing anticonvulsants (EIADS), and at 300 mg daily, with dose escalation in 50-mg increments up to 500 mg daily if no or minimal toxicity, for patients on EIAEDs. Four weeks of erlotinib treatment comprised one cycle.</td><td>Details
Patients were randomly assigned by internet or by phone</td><td>Results
PFS and OS summary statistics
<table>
<tr><td></td><td>Erlotinib</td><td>BCNU/TMZ</td></tr>
<tr><td>Median PFS, moths</td><td>1.8</td><td>2.4</td></tr>
<tr><td>6-month PFS, % (95%CI)</td><td>11.4 (4.6 to 21.5)</td><td>24.1</td></tr>
<tr><td>1 year PFS, %</td><td>5.7</td><td>4.0</td></tr>
<tr><td>Median OS, months</td><td>7.7</td><td>7.3</td></tr>
</table></td><td>Limitations
Limitations assessed with the Cochrane Risk of bias Assessment tool:
Random sequence generation (selection bias): low risk Patients were randomly assigned by internet or by phone)
Blinding of outcome assessment (Detection bias): Unclear (not reported)
Incomplete outcome data (attrition bias): low risk (no missing data)
Selective reporting (reporting bias): very high risk (study reports ranges only for the primary end point and not for the remaining outcomes)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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 OncologyJ Clin Oncol, 27, 1268-74, 2009 Ref Id 557077 Country/ies where the study	completion of all prior chemotherapy at least 4 weeks (or 6 weeks if nitrosurea treatment) before registration into the study; no receipt of radiotherapy in the past 3 months; at least one bidimensionally measurable target lesion with one diameter of at least 2 cm, a KPS ≥70; and adequate bone marrow, renal, and hepatic function Exclusion criteria Not reported	Patients randomly in the control arm received either TMZ—or carmustine (BCNU) if TMZ was part of initial treatment. TMZ was started at 200 mg/m2 on days 1 to 5 every 4 weeks in chemotherapy-naïve patients or at 150 mg/m2 on days 1 to 5 every 4 weeks after prior adjuvant chemotherapy, with dose escalation to 200 mg/m2 in the absence of significant toxicity (Common Terminology Criteria of Adverse Events) in cycle 1. BCNU was given initially at a dose level of 80mg/m2 on days 1 to 3 every 8 weeks for a		6 months OS, % 57.6 58.5 1 year OS, % 21.9 26.7	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
was carried out Multicenter study Study type Randomised phase II trial Aim of the study To assess the efficacy of erlotining versus temozolomide or carmustine in recurrent glioblastoma Study dates Not reported Source of funding Hoffman-la Roche Ltd, Basel, Switzerland; by Grants		maximum of five cycles. Because of the BCNU-induced myelosuppression observed after chemoradiotherapy with TMZ, the dose was reduced to 60 mg/m2 on days 1 to 3 every 8 weeks.			

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>from the European Organisation of Cancer headquarters is supported by Fonds Cancer</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Friedman, Hs, Prados, Md, Wen, Py, Mikkelsen, T, Schiff, D, Abrey, Le, Yung, Wk, Paleologos, N, Nicholas, Mk, Jensen, R, Vredenburgh, J, Huang, J, Zheng, M, Cloughesy, T, Bevacizumab alone</td><td>Sample size
N= 167 patients, n=85 for BEV group and n=82 for BEV+CPT-11 group
Characteristics<table><tr><td></td><td>BEV</td><td>BEV+CPT</td></tr><tr><td>Age median (range)</td><td>54 (23-78)</td><td>57 (23-79)</td></tr><tr><td>KPS 90-100</td><td>44.7%</td><td>37.8%</td></tr><tr><td>KPS 70-80</td><td>55.3%</td><td>62.2%</td></tr><tr><td>IS: partial resection</td><td>49.9%</td><td>53.7%</td></tr><tr><td>IS: complete resection</td><td>42.9%</td><td>37.8%</td></tr><tr><td>IS: biopsy only</td><td>8.2%</td><td>8.5%</td></tr></table>Inclusion criteria
Histologically confirmed GBM in first or second relapse and disease progression confirmed by MRI ≤14 days before the study treatment. Contrast enhancing,</td><td>Interventions
All patients received BV 10mg/kg intravenously every other week. Patients in the BV +CPT-11 group received CPT-11 340mg/m2 (if taking enzyme-inducing antiepileptic drugs [EIAEDs]) or 125 mg/m2 (if not taking EIAEDs) intravenously over 90 minutes every other week. A treatment cycle was defined as 6 weeks of</td><td>Details
Eligible patients were randomly assigned to receive BV or BV + CPT-11 and were stratified by KPS (70% to 80%, 90% to 100%) and by first or second relapse.</td><td>Results
Efficacy:
BV
OS (median): 9.2 months (95% CI, 8.2 to 10.7)
PFS (median): 4.2 months (95% CI, 2.9 to 5.8)
BV + CPT-11
OS (median): 8.7 months (95% CI 7.8, to 10.9)
PFS (median): 5.6 months (95%CI, 4.4 to 6.2)
BV vs BV + CPT-11
OS, HR: 1.04 (0.85-1.28)*
PFS, HR:1.01 (0.83-1.22)*
Adverse events (grade ≥3):
Wound-healing complications
BV 2/84
BV + CPT-11 1/79
Aphasia
BV 3/84
BV + CPT-11 6/79</td><td>Limitations
Limitations assessed with the Cochrane Risk of bias Assessment tool:
1. Random sequence generation (selection bias): unclear risk (method not reported)
2. Blinding of outcome assessment (Detection bias): low risk (outcome assessors were blinded)
3. Incomplete outcome data (attrition bias): low risk (no missing data)
4. Selective reporting (reporting bias): low risk (all expected outcomes have been reported).</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and in combination with irinotecan in recurrent glioblastoma, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 27, 4733-40, 2009 Ref Id 555133 Country/ies where the study was carried out US Study type Phase II, multicentre, open-label, non-comparative trial.	bidimensionally measurable disease was required. Patients had been treated with standard RT and had received TMZ. KPS ≥ 70%; life expectancy greater than 12 weeks; and adequate hematologic, hepatic and renal function. Patients taking corticosteroids were required to be on stable or decreasing dose for 5 or fewer days before baseline MRI. Therapeutic systematic anticoagulation with low molecular weight heparin or warfarin was allowed. Exclusion criteria Previous treatment with prolifeprospan 20 with carmustine wafer, CPT-11, or anti-VEGF agents; MRI evidence of recent intracranial haemorrhage; history of bleeding diathesis or coagulopathy; clinically significant cardiovascular disease; arterial thromboembolism less than 6 months before the first study treatment; and uncontrolled hypertension.	therapy. Reduction in BV dose was not permitted. If toxicity necessitated holding BV, the dose level was not changed once treatment resumed. If a patient given BEV + CPT-11 dose was reduced by 25%. If no additional toxicity occurred, the reduced dose was maintained for all subsequent treatments. If grade 3 or 4 toxicity occurred at the reduced CPT-11 dose, the dose was reduced by an additional 25%. Additional dose reductions were not permitted. The maximum allowable length of treatment		Fatigue BV 3/84 BV + CPT-11 7/79 *values calculated by the NGA team using the calculator developed by Tieney et al. 2007	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with recurrent glioblastoma. Study dates 15th September 2007 to 15th November 2007 Source of funding Not reported		interruption was 30 days.			
Full citation Taal, W, Oosterkamp, Hm, Walenkam	Sample size N=153, N = 8 in the BEV/LOM group; N=50 in the in the BEV group; n=46 in the lomustine group; n=44 in the BEV/LOM group. Characteristics	Interventions Single-agent lomustine was given orally at a dose of 110 g/m2 (in 40 mg	Details Patients were randomly allocated by a web-	Results Efficacy: BEV/lomustine vs lomustine* OS, HR:0.68 (0.42-1.10) PFS, HR: 0.58 (0.37-0.90)	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
p, Am, Dubbink, Hj, Beerepoot, Lv, Hanse, Mc, Buter, J, Honkoop, Ah, Boerman, D, Vos, Fy, Dinjens, Wn, Enting, Rh, Taphoorn, Mj, Berkmortel, Fw, Jansen, Rl, Brandsma, D, Bromberg, Je, Heuvel, I, Vernhout, Rm, Holt, B, Bent, Mj, Single-agent bevacizumab or lomustine versus a combination of bevacizum	<table><tr><td></td><td>BEV/LOM</td><td>BEV</td><td>Lomustine</td><td>BEV/LOM</td></tr><tr><td>Age range</td><td>29-62</td><td>37-77</td><td>28-73</td><td>24-73</td></tr><tr><td>WHO 0 (N,%)</td><td>3, 38%</td><td>13, 26%</td><td>15, 33%</td><td>11, 25%</td></tr><tr><td>WHO 1 (N,%)</td><td>4, 50%</td><td>32, 64%</td><td>25, 54%</td><td>28, 64%</td></tr><tr><td>WHO 2 (N, %)</td><td>1, 13%</td><td>5, 10%</td><td>6, 13%</td><td>5, 11%</td></tr><tr><td>Days since last RT median (range)</td><td>259 (133, 699)</td><td>254 (101, 2087)</td><td>298 (106,1092)</td><td>272 (69,1337)</td></tr></table> Inclusion criteria Histologically proven glioblastoma with a first progression after previous chemo-radiotherapy with TMZ, documented by MRI with at least one bi-dimensionally measurable target lesion with one diameter of at least 10 mm, visible on 2 or more axial slices 5 mm apart; had not received previous chemotherapy for recurrent disease; has not	capsules, up to a maximum dose of 200 mg) on day 1 every 6 weeks with prophylactic anti-emetic drugs, foe a maximum of 6 treatment cycles (in which 1 treatment cycle was defined as 6 weeks). Single-agent bevacizumab was given intravenously at a dose of 10mg/kg every 6 weeks, with a maximum lomustine dose of 200 mg per cycle of 6 weeks. After the preplanned safety review, the lomustine dose was reduced for the rest of the patients in the combination group to 90 mg/m2, with a maximum	based program o n a 1:1:1 basis to bevacizumab in combination with lomustine, single agent bevacizumab, or single-agent lomustine.	BEV/lomusitne vs BEV* OS, HR: 0.64 (0.40-1.02) PFS, HR:0.60 (0.38-0.95) Adverse events Fatigue (grade 3) Bevacizumab, n=2 (4%) Lomustine, n= 3 (7%) BEV/LOM, n=8 (18%) * Calculated using the calculator developed by Tierney 2007 (Tierney, Jayne F., et al. "Practical methods for incorporating summary time-to-event data into meta-analysis." Trials 8.1 (2007): 16.)	Random sequence generation (selection bias): low risk (web based program) Blinding of outcome assessment (Detection bias): high risk (open label) Incomplete outcome data (attrition bias): low risk (no missing data) Selective reporting (reporting bias): low risk (all expected outcomes have been reported).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial, The Lancet. Oncology, 15, 943-53, 2014 Ref Id 556931 Country/ies where the study was carried out The Netherlands Study type Randomised phase II study Aim of the study	previously received treatment with anti-VEGF agent or nitrosureas; were on a stable or decreasing dose of steroids for 7 days before the baseline MRI scan; has not received RT within the 3 months before the diagnosis of progression; had not received chemotherapy in the last 4 weeks; were at least 18 years of age; had WHO performance status of 0-2; and had adequate bone marrow, renal, and hepatic function. Exclusion criteria Uncontrolled hypertension (systolic blood pressure>150 mm Hg or diastolic blood pressure > 100 mm Hg), any arterial or venous thrombosis up to 6 months before registration, evidence of recent haemorrhage on brain MRI, substantial cardiac disease, or use of therapeutic doses of oral or parenteral anticoagulants or thrombolytic drugs. Re-operated patients could not start the treatment until 4 weeks after surgery.	lomustine dose of 160 mg per cycle of 6 weeks.			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the efficacy of bevacizumab in recurrent glioblastoma Study dates Dec 11, 2009 and Nov 10, 2011 Source of funding Roche Nederland and the Dutch Cancer Society. Roche Nederland provided bevacizumab free of charge					
Full citation Field, K. M., Simes, J., Nowak, A. K., Cher, L.,	Sample size N= 122; n=60 BEV + carboplatin and n= 62 on BEV Characteristics BEV + carboplatin / BEV	Interventions Patients received BEV 10 mg/kg every 2 weeks plus carboplatin AUC 5 every 4 weeks (4 weeks	Details Patients were randomised 1:1. Study therapy	Results Efficacy The median follow-up was 32 months. Median PFS was 3.5 months (95%CI 2.2-3.7 mo)	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool: Random sequence generation (selection bias): unclear risk (randomisation was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Wheeler, H., Hovey, E. J., Brown, C. S., Barnes, E. H., Sawkins, K., Livingstone, A., Freilich, R., Phal, P. M., Fitt, G., Cabaret Cogno investigators, Rosenthal, M. A., Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma, Neuro-OncologyNeuro-oncol, 17, 1504-13, 2015 Ref Id 555069	<table><tr><td>Age (y)</td><td>55 (32-79)</td><td>55 (25-82)</td></tr><tr><td>KPS 90-100</td><td>21 (35%)</td><td>22 (35%)</td></tr><tr><td>KPS 70-80</td><td>28 (47%)</td><td>28 (45%)</td></tr><tr><td>KPS <70</td><td>11 (18%)</td><td>10 (16%)</td></tr><tr><td>IS: biopsy</td><td>6 (10%)</td><td>9 (15%)</td></tr><tr><td>IS: debulking</td><td>21 (35%)</td><td>16 (26%)</td></tr><tr><td>IS: resection</td><td>33 (55%)</td><td>37 (60%)</td></tr></table>IS: initial surgery Inclusion criteria Adults > 18 yeas with Eastern Cooperative Group (ECOG) performance status ≤2 and a histological diagnosis of GBM following resection or biopsy, who had received treatment with both radiotherapy and temozolomide (concurrently and/or sequentially). Patients with first or subsequent recurrences were eligible, provided that prior therapy had only included RT and TMZ. At least 12 weeks must have elapsed since the cessation of RT. Recurrent or progressive disease had to be confirmed by MRI showing measurable disease according to RANO criteria or surgical resection of recurrent disease. The baseline or eligibility MRI was performed within 14 days prior to randomisation. The craniotomy or biopsy site had to be healed. Other key inclusion criteria were adequate renal function (including <2 + urine protein or dipstick or urine/ protein creatinine ratio ≤ 1.0)	in the length of a cycle), or BEV monotherapy at the same dose	continued until progressive disease, unacceptable toxicity, participant withdrawal, noncompliance with protocol guidelines, or death. Following disease progression, participants considered suitable for further treatment, and who consented to further treatment on the trial, were the randomised to cease or continue	(combination) and 3.5 months (95%CI 1.9 -3.7 mo) (monotherapy), HR: 0.92, 95% CI: 0.64-1.32, P=0.66 Median OS was 6.9 months (combination) versus 7.5 months (monotherapy), HR: 1.18, 95% CI: 0.82 -1.69, p=.38 Progression was determined clinically for 30 of the 118 participants who had completed part 1 (25%) without radiological confirmation at time of progression. For the remaining participants, central radiological confirmation of disease progression included increased enhancement on the postcontrast T1-weighted images, T1/FLAIR increase, a new lesi on, or a combination of these radiologic findings, with no single imaging technique predominant in terms of determining disease progression. Adverse events (NCI- CTCTA) Any grade ≥ grade 3 adverse event : 37 (64%) for combination and 36 (58%) for monotherapy Wound healing complication grade ≥ 3: nil	performed, method not reported) Blinding of outcome assessment (Detection bias): high risk (open label study) Incomplete outcome data (attrition bias): low risk (no missing data) Selective reporting (reporting bias): low risk (all expected outcomes have been reported). Other information *Only results of the part 1 of this trial have been reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia Study type Multicenter, sequential, stratified, nonblinded, randomised phase 2 study in 2 parts Aim of the study To compare combination therapy with bevacizumab (BEV) monotherapy Study dates Source of funding Investigator-driven study	and adequate haematological parameters (including neutrophil count ≥1.5 x 109/L and platelets ≥ 100 x 109/L). Anticoagulation was permitted if required; low molecular-weight heparin was the preferred approach. Exclusion criteria Prior chemotherapy other than TMZ, prior bevacizumab or other investigative agent for the treatment of glioma, surgery within 4 weeks before treatment commencement, evidence of recent haemorrhage on MRI with the exception of asymptomatic punctuate hemorrhage on MRI with the exception of asymptomatic punctuate haemorrhage or resolving postsurgical change, inability to undergo MRI, inadequately controlled hypertension, clinically significant cardiovascular disease, history of coagulation disorder, prior or concurrent malignancy (except nonmelanomatous skin cancer or malignancy treated and disease-free for > 5 years), pregnancy or lactation, or other concurrent physical, psychological, or sociological condition that could jeopardize patient safety or compliance.		BEV using the same dose and schedule, in addition to further chemotherapy dependent on clinician preference (part 2). PFS was defined as time from randomisation to disease progression based on centrally reviewed modified RANO criteria or death from any cause OS was defined as the time from randomisation to the	Fatigue: 5/58 for combination ans 4/62 for monotherapy	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
funded by Roche Products Australia Pty Ltd			date of death from any cause. Response evaluation was determined by MRI, clinical and neurological examination, and steroid use, which are incorporated in the RANO criteria.		
Full citation Gilbert, M. R., Pugh, S. L., Aldape, K., Sorensen, A. G., Mikkelsen, T., Penas-Prado, M., Bokstein, F., Kwok,	Sample size N= 123; n=63 (N=60 analysed) allocated to BEV + TMZ and n= 60 (n=57 analysed) allocated to BEV+CPT-11 Characteristics BEV + TMZ: Age <50: 14 (23%); Age ≥ 50: 46 (77%) BEV + IRINOTECAN: Age <50: 22 (39%); Age ≥ 50: 35 (61%)	Interventions All patients received bevacizumab (BEV) at a dose of 10mg/kg every 2 weeks. Patients randomised to receive irinotecan (CPT) received this agent at	Details Patients were stratified according to age (<50 years vs ≥ 50 years) and KPS (70-80 vs 90-100) then	Results BEV + TMZ vs BEV + CPT PFS 1.03 (0.81-1.30) OS 0.86 (0.64-1.15) Neurologic adverse events: 6/60 in the bevacizumab + irinotecan group and 3/57 in the bevacizumab + DD TMZ group	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool: Random sequence generation (selection bias): low risk (randomisation was done according to the permuted block design) Blinding of outcome assessment (Detection bias): unclear risk (not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Y., Lee, R. J., Mehta, M., NRG oncology RTOG 0625: a randomized phase II trial of bevacizumab with either irinotecan or dose-dense temozolomide in recurrent glioblastoma, Journal of Neuro-OncologyJ Neurooncol, 1-7, 2016 Ref Id 555234 Country/ies where the study was carried out USA Study type	<table><tr><td>KPS 70-80</td><td>30 (50%)</td><td>31 (54%)</td></tr><tr><td>KPS 90-100</td><td>30 (50%)</td><td>26 (46%)</td></tr></table> Inclusion criteria Eligible patients had recurrent or progressive GBM or gliosarcoma. All patients were required to provide written informed consent. There were no limits placed on the number of prior treatment regimens, although patients with prior treatment with interstitial brachytherapy, stereotactic radiosurgery or Gliadel wafers (polifeprosan 20 with carmustine implant) were required to have histologic evidence of recurrent tumor. Measurable tumor was not required if the patient underwent a repeat tumor resection prior to enrollment. Patients must have had completed radiation treatment more than 42 days prior to enrollment. Other important inclusion criteria included age ≥18 years, Karnofsky performance status ≥70, systolic blood pressure ≤160 mg Hg or diastolic pressure ≤90 mg Hg, adequate hematologic function [white blood cell count (WBC) ≥3000/μL, absolute neutrophil count (ANC) ≥1500/μL, platelet count ≥100,000 cells/μL, and hemoglobin ≥10 gm/μL] renal and hepatic function. Patients must have been on a stable or decreasing dose of corticosteroids for the 5 days prior to study enrollment.	125mg/m2 very 2 weeks along with bevacizumab. Patients randomised to receive temozolomide were treated with a dose-dense schedule starting at 75mgg/m2 on days 1-21 of a 28-day cycle. Patients who did not develop grade 2 or higher myelotoxicity had the temozolomide (TMZ) dose increased to 100mg/m2 for subsequent cycles. A ctycle wasd eifned by 4 weeks of treatment and patients were permitted to continue treatment for up to 24 cycles as long as the treatment was tolerated and there was no	randomised in a 2:1 ratio between the BEV and the TMZ arm. The primary endpoint for the BEV + CPT arm was the 6-month PFS rate. The primary endpoint for the TMZ + DD TMZ was safety and treatment toxicity.		Incomplete outcome data (attrition bias): low risk (no missing data) Selective reporting (reporting bias): low risk (all expected outcomes have been reported). Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised phase II study Aim of the study To determine the efficacy and safety of bevacizumab with either irinotecan or dose-dense TMZ in recurrent glioblastoma Study dates March 2007 Source of funding National Cancer Institutes (NCI)	Systemic anticoagulation with either warfarin or low molecular weight heparin was permitted. Exclusion criteria Ongoing treatment with a hepatic enzyme-inducing anticonvulsant; an acute intratumoral hemorrhage on MR imaging; an active comorbid condition including recent (<6 months) myocardial infarction, unstable angina, uncontrolled hypertension or history of recent (<6 months) stroke or transient ischemic attack; major surgical procedure or history of abdominal abscess or fistula or gastrointestinal perforation within 28 days of study enrolment.	evidence of tumour progression. In case of toxicity, there were no dose modifications allowed for bevacizumab. If adverse events that required holding treatment with bevacizumab did not resolve within 8 weeks, bevacizumab treatment was discontinued. For irinotecan, grade 3 or 4 toxicities required holding treatment until these resolved to grade 1 or less. The dose was then reduced to 100mg/m2. If grade 3 or 4 toxicities were noted at the lower dose, then a final dose reduction of 75mg/m2 was			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		permitted. Subsequent grade 3 or 4 toxicities mandated cessation of treatment. For temozolomide, grade 3 or 4 toxicities resulted in a dose reduction to 50mg/m2 if the patient did not have the initial cycle 2 dose escalation or a dose reduction to 75mg/m2 if the dose had previously been increased to 100mg/m2. An additional dose reduction to 35mg/m2 was possible, but toxicity at this lowest dose level mandated treatment cessation. For both irinotecan and temozolomide, if			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		treatment delays exceeded 4 weeks, the treatment was stopped.			
Full citation Weathers, S. P., Han, X., Liu, D. D., Conrad, C. A., Gilbert, M. R., Loghin, M. E., O'Brien, B. J., Penas-Prado, M., Puduvalli, V. K., Tremont-Lukats, I., Colen, R. R., Yung, W. K., de Groot, J. F., A randomized phase II trial of standard dose bevacizumab versus	Sample size N= 69; n= 33 in the Bevacizumab + CCNU and n=35 in the Bevacizumab alone group Characteristics Bevacizumab + CCNU / Bevacizumab alone 1st recurrence: 25 (71.4%) / 24 (66.7%) 2nd recurrence: 10 (28.7%) / 12 (33.3%) ≤50: 13 (37.1%) / 13 (36.1%) ≥50: 22 (62.9%) / 23 (69.9%) KPS 60-80: 11 (31.4%) / 13 (36.1%) KPS 90-100: 24 (68.6%) / 23 (69.9%) Female: 24 (68.8%) / 24 (66.7%)	Interventions Single agent bevacizumab was given intravenously at a dose of 10mg/kg every 2 weeks until disease progression or unacceptable toxicity. In the combination group, bevacizumab was given intravenously at a dose of 5 mg/kg every 3 weeks Lomustine was initially given at 90 mg/m2 every 6 weeks but was later reduced ro 75mg/m2 following the occurrence of 17 grade 3 and 7	Details Patients were randomised to either treatment using a 1:1 randomisation scheme. The primary measure of efficacy was PFS, which was determined in patients based on gadolinium enhanced, T1 weighted and T2/FLAIR MRI scans	Results Bevacizumab + CCNU vs Bevacizumab (All patients) HR= 0.71 (95%ci 0.43-1.17) Bevacizumab + CCNU vs Bevacizumab (patients with 1st recurrence) HR= 0.58 (0.31-1.08) Median OS (patients with 1st recurrence) Bevacizumab + CCNU vs Bevacizumab BEV + CCNU, 13.05 (7.08 to 17.82) BEV alone 8.8 (0.42 to 20.22) Adverse events (grade 3) Bev + lomustine 90mg/m2 = 0/12 Bev + lomustine 75mg/m2 = 1/21 Bev alone = 4/35	Limitations Limitations assessed with the Cochrane Risk of bias Assessment tool: Random sequence generation (selection bias): low risk Blinding of outcome assessment (Detection bias): low risk Incomplete outcome data (attrition bias): low risk (no missing data) Selective reporting (reporting bias): high risk (OS only reported for patients at 1st recurrence and not reported in HR).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
low dose bevacizumab plus lomustine (CCNU) in adults with recurrent glioblastoma, Journal of Neuro-OncologyJ Neurooncol, 129, 487-94, 2016 Ref Id 557184 Country/ies where the study was carried out USA Study type Phase II RCT Aim of the study To evaluate the efficacy of low dose bevacizumab in	Inclusion criteria Age ≥18 years, histologically confirmed GBM in 1st 2nd or 3rd relapse, prior treatment with TMZ and KPS ≥60, an adequate hematologic, renal and hepatic function. Exclusion criteria Prior treatment with antiangiogenic agent or a nitrosurea	grade 4 hematologic adverse events observed in 12 patients and 27 cycles of treatment. For those patients randomised to the combination group, lomustine was given on day 3 of each 6-week cycle. After every 6-week cycle, patients underwent clinical evaluation and radiographic tumour assessment with MRI. Lomustine was given up to a maximum of 6 cycles. In the setting of hematologic toxicity from lomustine, the lomustine dose could be reduced a maximum of 2 times. Further reduction in dose	assessed separately by a neuro-radiologist and treating physicians (treatment-arm blinded). For patients with a measurable disease at study entry (defined as bi-dimensionally measurable disease with a minimum measurement of 1 cm on MRI), PFS was defined as either: 1) 25% increase in the sum		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
combination with lomustine (CCNU) compared to standard dose bevacizumab in patients with recurrent glioblastoma Study dates January 2010 - December 2014 Source of funding National Institutes of Health		was not permitted, and the patient was removed from the protocol.	of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline; 2) clear worsening of any evaluable diasease; 3) appearance of any new lesion/site; 4) clear clinical worsening or failure to return for evaluation due to		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>death or deteriorating condition (unless clearly unrelated to this cancer)</td><td></td><td></td></tr>
<tr><td>Full citation
Stupp, R., Wong, E. T., Kanner, A. A., Steinberg, D., Engelhard, H., Heidecke, V., Kirson, E. D., Taillibert, S., Lieberman n, F., Dbaly, V., Ram, Z., Villano, J. L., Rainov, N., Weinberg, U., Schiff, D., Kunschner</td><td>Sample size
Tumour treating filds (n=120)
Active control (n=117)
Characteristics<table><tr><td></td><td>TTF (n=120)</td><td>Active control (n=117)</td></tr><tr><td>Age, median (range)</td><td>54 years (24-80)</td><td>54 years (29-74)</td></tr><tr><td>Gender</td><td>Male: 92 (77%)
Female: 28 (23%)</td><td>Male: 73 (62%)
Female: 44 (38%)</td></tr><tr><td>Histology</td><td>Glioblastoma: 100%
Prior LGG: 10 (8%)</td><td>Glioblastoma: 100%
Prior LGG: 9 (8%)</td></tr></table></td><td>Interventions
For patients assigned to the TTF group, 4 transducer arras were placed on the patient´s shaved scalp and connected to a portable battery or power supply operate device which was set to generate 200 kHz electric fields within the brain in 2 perpendicular directions 8operated sequentially). Field intensity was set at >0.7 V/cm at the centre of the</td><td>Details
Patients were randomised at 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician´s choice (active control). Randomis</td><td>Results
OS for TTF vs active control chemotherapy
HR 0.86 (0.66-1.23), p=0.27
PFS for TTF vs active control chemotherapy
HR 0.81(0.60-1.09)
Safety and toxicity
Cognitive disorder (≥grade 2) was reported by n=2 (1%) of the patients treated with TTF and by 2 (1%) of patients in the active control group</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: Low risk (Randomisation was performed using random block sizes and was stratified by centre according to whether patients underwent surgery for their latest recurrence prior to trial entry)
Allocation concealment: unclear risk of bias (the authors report the method used, but they do not provide sufficient detail to determine whether intervention allocations should have been foreseen</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
, L., Raizer, J., Honnorat, J., Sloan, A., Malkin, M., Landolfi, J. C., Payer, F., Mehdorn, M., Weil, R. J., Pannullo, S. C., Westphal, M., Smrcka, M., Chin, L., Kostron, H., Hofer, S., Bruce, J., Cosgrove, R., Paleologous, N., Palti, Y., Gutin, P. H., NovoTTF-100A versus physician's choice chemotherapy in	<table><tr><td>Prior therapy</td><td>1st recurrence: 11 (9%) 2nd recurrence: 58 (48%) 3rd recurrence: 51 (43%)</td><td>1st recurrence:17 (15%) 2nd recurrence: 54 (46%) 3rd recurrence: 46 (39%)</td></tr></table> Inclusion criteria Patients 18 years or older with histologically confirmed glioblastoma were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients who had a KPS score ≥70% and adequate hematologic, renal and hepatic function (absolute neutrophil count ≥1000/m3; haemoglobin ≥100g/L platelet count, ≥100000/mm3; serum creatinine level ≤1.7 mg/dL (< 150 µmol/L); total serum bilirubin level ≤ the upper limit of normal and liver function values, < 3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temolozomide). There was no limit on number or type of prior therapies or recurrences Exclusion criteria Patients with infra-tentorial tumour location, and implanted medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt).	brain. Patients were trained on how to operate the device and then continued treatment at home. Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.	ation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.		in advance of, or during, enrolment) Blinding of participants and personnel: High risk (not blinded) Blinding of outcome assessment: High risk (not blinded) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
recurrent glioblastoma: a randomised phase III trial of a novel treatment modality, European Journal of CancerEur J Cancer, 48, 2192-202, 2012 Ref Id 556904 Country/ies where the study was carried out Multicenter study Study type RCT Aim of the study To assess the efficacy and safety of NovoTTF-100A					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
monotherapy (TTF) compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma multiforme Study dates September 2006 until May 2009 Source of funding Novocure Ltd					
Full citation Socha, J., Kepka, L., Ghosh, S., Roa, W., Kumar, N., Sinaika, V., Matiello, J.,	Sample size All treatments ; N= 79 BSC, n=47 Active treatment, n=32 of which: 21 received TMZ 8 received surgery 2 received surgery + TMZ	Interventions Patients were randomised to receive active treatment only (RT, surgery or chemotherapy) or best supportive care.	Details After a median follow-up of 30 weeks after randomisation (range 3-84), 84	Results Multivariate cox regression analysis of prognostic factors HR (95%CI) (Any) active treatment vs BSC PPS, HR 0.34 (0.19-0.60), P < 0.0001 OS, HR 0.31 (0.17-0.57), P<0.0001 Age <65 versus ≥ 65 years	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: Low risk (An independent statistician at the coordinating centre (Cross Cancer Institute)

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Lomidze, D., de Castro, D. G., Hentati, D., Fidarova, E., Outcome of treatment of recurrent glioblastoma multiforme in elderly and/or frail patients, Journal of Neuro-OncologyJ Neurooncol, 126, 493-8, 2016
Ref Id
556799
Country/ies where the study was carried out
Multicenter study
Study type
RCT</td>
<td>1 received surgery +RT
3 received RT only
for 5 patients there was no data available.

Characteristics
<table>
<tr><td></td><td>Active treatment (n, %)</td><td>BSC (n, %)</td></tr>
<tr><td>KPS ≤60%</td><td>19 (59.4%)</td><td>24 (51.1%)</td></tr>
<tr><td>KPS ≥70%</td><td>12 (37.5%)</td><td>15 (31.9%)</td></tr>
<tr><td>No data</td><td>1 (3.1%)</td><td>8 (17%)</td></tr>
<tr><td>Gender - male</td><td>16 (50%)</td><td>25 (53.2%)</td></tr>
<tr><td>Gender - female</td><td>16 (50%)</td><td>26 (55.3%)</td></tr>
<tr><td>Age <65</td><td>16 (50%)</td><td>21 (44.7%)</td></tr>
<tr><td>Age ≥ 65</td><td>16 (50%)</td><td>26 (55.3%)</td></tr>
</table>
Inclusion criteria
The principal eligibility criteria included age > 60 years, histologically confirmed GBM, and KPS > 50.
Exclusion criteria
Previous cranial RT, concomitant or prior invasive cancer (except nonmelanomatous skin cancer and carcinoma in situ), failure to commence RT for GBM within 6 weeks of surgical diagnosis, and inability to comply with follow up requirements. Patients were</td>
<td></td>
<td>out of 98 patients enrolled in the initial study (Roa 2015) experienced a relapse.</td>
<td>PPS HR 0.75 (0.45 - 1.26), p= 0.28
OS HR 0.91 (0.54-1.53), p = 0.71
KPS at relapse ≤50% vs ≥60%
PPS, HR 0.31 (0.17-0.56), P <0.0001
OS 1.60 (0.94-2.75), p=0.008</td>
<td>produced computer-generated randomization lists)
Allocation concealment: Low risk (See random sequence generation, also strata-specific, sequentially numbered, sealed opaque envelopes containing the treatment assignment were supplied by the statistician to the research nurse at the coordinating center. Once patient eligibility had been determined and consent was obtained, participating centers contacted the coordinating nurse by fax to request randomization.)
Blinding of participants and personnel: High risk (open-label study)
Blinding of outcome assessment: High risk (open label study)
Incomplete outcome data: Low risk (all drop outs were clearly explained)
Selective reporting: Low risk (All pre-specified outcomes were reported)
Other information
This study represents the same patients as in Roa</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the impact of different treatment methods on post-progression survival (PPS) and overall survival (OS) of elderly and /or frail patients. Study dates Not reported Source of funding Alberta Cancer Board	also ineligible if pre- and postoperative imaging studies were unavailable for review.				2015 on post-progression survival. Post - progression survival was defined as the time from the date of relapse to the date of death from any cause, censored at the last follow-up Overall survival was defined as the time from randomisation to the date of death from any cause, censored as the last follow-up.
Full citation Kesari, S., Ram, Z., E. F. Trial Investigators, Tumor-treating	Sample size N= 204 (TTFIelds + second-line chemotherapy n = 144 ; second- line chemotherapy alone n= 60) Characteristics TTFIelds+ second line Second-line	Interventions For patients assigned to the TTF group, 4 transducer arras were placed on the patient´s shaved scalp	Details Patients were randomised at 2:1 ratio to receive either TTF	Results OS for TTFields + chemotherapy vs chemotherapy alone HR =0.70 (0.48-1.02), p = 0.049 TTFIelds + bevacizumab vs bevacizumab alone	Limitations Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial, CNS oncology, 6, 185-193, 2017 Ref Id 676593 Country/ies where the study was carried out USA Study type Sub analysis of an RCT Aim of the study To assess the effectiveness of	<table><tr><td></td><td>chemotherapy</td><td>chemotherapy alone</td></tr><tr><td>Median age, years (range)</td><td>57 (29-83)</td><td>58 (22-75)</td></tr><tr><td>% male</td><td>75</td><td>75</td></tr><tr><td>median KPS</td><td>90 (60-100)</td><td>90 (70-100)</td></tr><tr><td>MGMT methylated, n(%)</td><td>35 (24)</td><td>14 (23)</td></tr><tr><td>MGMT unmethylated, n(%)</td><td>59 (41)</td><td>25 (42)</td></tr><tr><td>MGMT unknown/invalid, n(%)</td><td>50 (35)</td><td>21 (35)</td></tr></table> Inclusion criteria Patients 18 years or older with histologically confirmed glioblastoma were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients who had a KPS score ≥70% and adequate haematologic, renal and hepatic function (absolute neutrophil count ≥1000/m3; haemoglobin ≥100g/L platelet count, ≥100000/mm3; serum creatinine level ≤1.7 mg/dL (< 150 µmol/L); total serum bilirubin level ≤ the upper limit of normal and liver function values, < 3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temolozomide). There was	and connected to a portable battery or power supply operate device which was set to generate 200 kHz electric fields within the brain in 2 perpendicular directions 8operated sequentially). Field intensity was set at >0.7 V/cm at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed	+chemotherapy or TMZ alone (active control). Following TMZ treatment and after recurrence, patients received second-line chemotherapy. 13 patients out of 73 in the TMZ group crossed over and received second-line therapy after disease progression in combination with TTFIelds. In total, 60	Since bevacizumab was the most frequent second-line treatment of choice, OS was evaluated in that subset of patients HR= 0.61 (0.37-1.01), p=0.043 Grade 3/4 adverse events TTFields + chemotherapy group = 70 (49%), total n= 144 Second-line chemotherapy alone = 20 (33%), total n= 60	Random sequence generation: Low risk (Randomisation was performed using random block sizes and was stratified by centre according to whether patients underwent surgery for their latest recurrence prior to trial entry) Allocation concealment: unclear risk of bias (the authors report the method used, but they do not provide sufficient detail to determine whether intervention allocations should have been foreseen in advance of, or during, enrolment) Blinding of participants and personnel: low risk for OS and high risk for adverse events (not blinded) Blinding of outcome assessment: low risk for OS and high risk for adverse events (not blinded) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
TTFields when added to second-line treatment according to physician's best choice after first disease recurrentce. Study dates September 2006 Source of funding Novocure Ltd	no limit on number or type of prior therapies or recurrences Exclusion criteria Patients with infra-tentorial tumour location, and implanted medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt).	according to local practice and depending on prior treatment exposure.	patients were trated with second line chemotherapy alone and 144 with TTFields + second-line chemotherapy after first disease progression.		Other information
Full citation Dirven, L., van den Bent, M. J., Bottomley, A., van der Meer, N., van der Holt, B.,	Sample size See Taal 2014 Characteristics See Taal 2014 Inclusion criteria	Interventions See Taal 2014	Details To measure QOL, the EORTC quality of life questionnaire C30 (QLQ-C30) and	Results Mean changes from baseline of health related quality of life score at 3 different time points (SDs not reported) Time point | 2 | 4 | 6 Lomustine | -5.8 | 3.5 | 5.3	Limitations See Taal 2014

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vos, M. J., Walenkamp, A. M., Beerepoot, L. V., Hanse, M. C., Reijneveld, J. C., Otten, A., de Vos, F. Y., Smits, M., Bromberg, J. E., Taal, W., Taphoorn, M. J., Dutch Neuro-Oncology, Group, The impact of bevacizumab on health-related quality of life in patients treated for recurrent glioblastoma: results of the	See Taal 2014 Exclusion criteria See Taal 2014		brain cancer module (QLQ-BN20) were selected. All items were rated in a 4-point Likert Scale, except for the 'global health' and 'overall quality of life' items in the QLQ-C30, which are scored on a 7-point Likert scale. Raw scores were linearly transformed to 0-100 scales. if at least	Bevacizumab 0.6 -0.9 -15.5 Bevacizumab/lomustine -4.5 1.1 5.1	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomised controlled phase 2 BELOB trial, European Journal of CancerEur J Cancer, 51, 1321-30, 2015 Ref Id 554937 Country/ies where the study was carried out The Netherlans Study type Quality of life results for the BELOB trial (randomised phase II study by Taal 2014) Aim of the study To report the health-			half of the items of a scale were completed, scale score was calculated based on the available values. For functional scales, and the 'global health' and 'overall quality of life' items, a higher score represents better functioning and quality of life, respectively. Conversely, for symptom items/scal		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
related quality of life results of the BELOB trial, a secondary endpoint Study dates 11 Dec 2009 - Nov 10 2011 Source of funding Roche Netherlands and by the Dutch Cancer Society			es a higher score indicated a higher level of symptomatology/problems. Differences in the mean value of HRQoL parameters ≥ 10 points are classified as being clinically meaningful, whereas changes of >20 points represent a very large effect. HRQoL forms were administered by paper at baseline		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			(after randomisation), and then every 6 weeks until disease progression. For all analyses, progression as determined by the local investigator was used, but one analysis (HRQoL during progression-free time) also included a central review of date of first progression. A time window for acceptabl		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			e HRQoL fo rms was applied to allocate forms to a specific treatment cycle and set a four-week period interval: from 2 weeks before until 2 weeks after the start of a new six-week treatment cycle or the assessme nt of progressio n.		
Full citation Wefel, Js, Cloughesy, T, Zazzali,	Sample size See Friedman 2009 (phase II BRAIN trial) Characteristics See Friedman 2009 (phase II BRAIN trial) Inclusion criteria	Interventions See Friedman 2009 (phase II BRAIN trial)	Details For the neurocog nitive testing,	Results Change from baseline to end point (18-months) for the	Limitations See Friedman 2009 (phase II BRAIN trial)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Jl, Zheng, M, Prados, M, Wen, Py, Mikkelsen, T, Schiff, D, Abrey, Le, Yung, Wk, Paleologos, N, Nicholas, Mk, Jensen, R, Vredenburgh, J, Das, A, Friedman, Hs, Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab, Neuro-OncologyNeuro-oncol, 13, 660-8, 2011 Ref Id 557191	See Friedman 2009 (phase II BRAIN trial) Exclusion criteria See Friedman 2009 (phase II BRAIN trial)		memory, visuomotor scanning speed, and executive function were evaluated using 3 valid test: the Hopkins verbal Learning est-Revised (HVLT-R), The Trail Making Test (TMT) and the Controlled oral Word Association (COWA). The maximum time to complete each test ranged from 3 to 5 minutes,	bevacizumab group (values are standardised scores) HVL-T-R-TR: -2.2 HVL-T-R-DE:-2.0 HVL-T-R-RECOG: -1.6 TMTA: -2.24 TMTB:-1 COWA: -2.24 Change from baseline to end point (18-months) for the bevacizumab +CPT-11(values are standardised scores) HVL-T-R-TR: -1.9 HVL-T-R-DE:-2.6 HVL-T-R-RECOG: -0.5 TMTA: -2.14 TMTB:-1.2 COWA: -1.2	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type QoL results for Friedman 2009 (phase II BRAIN trial) (Bevacizumab vs Bevacizumab + irinotecan) Aim of the study To report the neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab			for a total evaluation time of approximately 25 minutes. For each neurocognitive test, raw scores and standardized scores (mean=0, SD=1) using published normative data from a healthy population were calculated for analyses. At each assessment, change in raw test score relative to baseline was calculated, and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates June 2006 - February 2007 Source of funding Not reported			neurocognitive status was categorized as improved, stable or decline using the Reliable Change Index (RCI). The RCI is derived from the standard error of each test and represents the 90% confidence interval for the difference in raw score from baseline to the next assessment that would be expected		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			if no real change occurred. Changes that did not meet the RCI threshold for improvement or decline were categorised as stable performance. Changes (i.e. improvement, decline) from baseline neurocognitive status were confirmed at the next neurocognitive assessment, when available.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			85 to 98% of all patients completed the neurocognitive tests at baseline; and the majority of patients who remained on study completed tests at each assessment.		

Evidence tables for review 3a - Managing inoperable, incompletely excised or recurrent meningioma

Study details	Participants	Interventions	Methods/risk of bias	Results
Full citation Alghamdi, M., Li, H., Olivotto, I., Easaw, J., Kelly, J., Nordal, R., Lim, G., Atypical Meningioma: Referral Patterns, Treatment and Adherence to	83 patients (characteristics only reported for group as a whole): 34 males/49 females; median (range) age = 57 (27-89) years; Meningioma locations: convexity / parasagittal / olfactory groove / skull base / posterior fossa / other: N = 58 / 11 / 3 / 4 / 4 / 3;	Subtotal resection + / - RT (delivered in daily (Monday-Friday) fractions of 2 Gy to total doses of 54 Gy (N = 4), 55.8 Gy (N = 1), and 60	-Bias due to confounding: unclear risk of bias (patient characteristics not reported split by group, no relevant adjusted analyses) -Bias in selection of participants into the study: low risk of bias	Recurrence rate: STR-RT: 19/30 STR+RT: 2/6 (p = 0.21, Fisher's exact test)

Study details	Participants	Interventions	Methods/risk of bias	Results
Guidelines, Canadian Journal of Neurological Sciences, 44, 283-287, 2017 Ref Id 670844 Country/ies where the study was carried out Canada Study type Retrospective cohort study Aim of the study “to document population-based care and outcomes for patients with AM and to determine whether CPG [clinical practice guideline] influenced RO [radiation oncology] referral or the use of PORT in southern Alberta.” (p. 284) Study dates 2003-2013	divided into 4 groups: - Gross total resection (NOS): N = 44. Not in PICO so no more details about this group reported. - Unknown extent of resection: N = 3. Not in PICO so no more details about this group reported. - Subtotal resection, no RT (STR-RT): N = 30 - Subtotal resection with RT (STR+RT): N = 6 Inclusion criteria Patients aged > 18 years and treated for intracranial atypical meningioma with maximum safe resection first-line. Exclusion criteria None reported	Gy (N = 2)). Please note one of these 7 patients received GTR. Unclear what the dosing regimen was for that person. Follow up: Median (range) = 29 (4.3-121) months	-Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders, small sample) Other information:	

Study details	Participants	Interventions	Methods/risk of bias	Results
Source of funding "The Al Baha University (Al Baha, Saudi Arabia) sponsored MA for his residency training at the University of Calgary." (p. 286)				
Full citation Bagshaw, H. P., Burt, L. M., Jensen, R. L., Suneja, G., Palmer, C. A., Couldwell, W. T., Shrieve, D. C., Adjuvant radiotherapy for atypical meningiomas, Journal of Neurosurgery, 126, 1822-1828, 2017 Ref Id 670847 Country/ies where the study was carried out USA Study type Retrospective cohort study	59 patients of whom 42 received surgery alone and 17 received surgery + adjuvant RT (characteristics only reported for these groups as a whole): - Surgery alone: 20 males/22 females; median (range) age = 54 (not reported) years; initial KPS 100-90 / 80 / 70 / <70: N = 7 / 7 / 2 / 1; extent of resection Simpson grade I/II/III/IV: N = 37 / 2 / 1 / 2 - Surgery + adjuvant RT: 7 males/10 females; median (range) age = 52 (not reported) years; initial KPS 100-90 / 80 / 70 / <70: N = 14 / 15 / 10 / 3; extent of resection Simpson grade I/II/III/IV: N = 10 / 1 / 1 / 9 Meningioma locations (only reported for the sample as a whole): convexity / parasagittal / sphenoid ridge / suprasellar / olfactory groove / middle fossa / posterior fossa / cerebellopontine	Subtotal resection (Simpson grade IV) + / - RT (18/21 tumors treated with fractionated radiation therapy [median (range) dose = 54 (45–59.4) Gy]; 3/21 tumours treated with stereotactic radiosurgery [median (range) dose = 15 (12.5–15) Gy]. Follow up: Median (range) = 26 (3-111) months	-Bias due to confounding: unclear risk of bias (patient characteristics not reported split by group, no relevant adjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders, small sample) Other information:	Initial treatment: Recurrence rate: STR-RT: 2/2 STR+RT: 5/9 (p = 0.41) Survival: STR-RT: 6/9 STR+RT: 2/2 (p = 1, Fisher's exact test) Recurrent meningioma (first local failure): 26/59 patients recurred and received the following treatment: - Surgery + RT: N = 4 - RT alone: N = 12 - Surgery alone: N = 10 Local failure in these patients: - Surgery + RT: N = 3/4 - RT alone: N = 9/12 - Surgery alone: N = 9/10 (p = 0.87) LC after salvage:

Study details	Participants	Interventions	Methods/risk of bias	Results
Aim of the study To investigate the role of adjuvant radiotherapy in patients treated for AM "comparing outcomes of patients treated with combined modality therapy (surgery followed by radiotherapy) to those treated with a single modality (surgery alone)" (p. 1823) Study dates 1991-2014 Source of funding Not reported	angle / periventricular: N = 27 / 10 / 6 / 4 / 6 / 1 / 6 / 3 / 2; Inclusion criteria Patients treated 1991-2014 for atypical meningioma. Exclusion criteria None reported			Time to local failure: RT alone and surgery + RT groups (median = 25 months) = surgery alone (median = 35 months; p = 0.96). LC after RT salvage: SRS (50% of RT salvage patients) = fractionated RT (50% RT salvage patients; p = 0.26).
Full citation Frostell A, Hakim R, Dodoo E, Sinclair G, Ohlsson M, Förander P, Milovac B, Brundin L, Svensson M. Adjuvant Stereotactic Radiosurgery Reduces Need for Retreatments in Patients with Meningioma	119 patients divided into 3 groups: - Radical total resection, no RT: N = 79. Not in PICO so no more details about this group reported. - Near total resection (NOS), no adjuvant stereotactic radiosurgery (NTR-aSRS): N = 19; 9 males/10 females; median age (range) = 56 (41-77) years; multiple meningioma (4). Tumour	Near total resection + / - adjuvant SRS (using stereotactic Leksell frame, MRI, and GammaKnife Perfexion). NTR+aSRS: Received aSRS after a median of 0.6 (range 0.3-2.6) years	-Bias due to confounding: low risk of bias -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias	Retreatment for growth of remnant: NTR-aSRS: 14/19 NTR+aSRS: 3/21 Mortality: NTR-aSRS: 4/19 NTR+aSRS: 0/21

Study details	Participants	Interventions	Methods/risk of bias	Results
Residuals. World neurosurgery. 2016 Apr 30;88:475-82. Ref Id 509172 Country/ies where the study was carried out Sweden Study type Retrospective cohort study Aim of the study “To evaluate the effect of adjuvant stereotactic radiosurgery (aSRS) on the time to significant growth of meningioma residuals requiring retreatment.” (p. 475) Study dates 2004-2013 Source of funding Torsten and Ragnar Soederberg Foundation, the	characteristics: Proliferation, Mib-1/Ki-67 median (range) = 10 (2-40); WHO grade 1/2/3 N = 12/5/2; largest tumour diameter median = 4 cm. - Near total resection, adjuvant stereotactic radiosurgery (NTR+aSRS): N = 21; 3 males/18 females; median age (range) = 54 (27-69) years; multiple meningioma (5). Tumour characteristics: Proliferation, Mib-1/Ki-67 median (range) = 5 (0-15); WHO grade 1/2/3 N = 19/5/5; largest tumour diameter median = 3 cm. Inclusion criteria Patients who had primary surgical treatment for cerebral meningioma which was located in proximity to a venous structure (parasagittal, transverse, and sigmoid sinus), at Karolinska University Hospital 2004-2013. Exclusion criteria Patients with neurofibromatosis type 2.	after NTR. SRS characteristics, Gy median, (range): Min dose: 15 (10-15); max dose: 31 (22-38); prescription dose: 15 (0-16); tumour volume: 1.07 (0-6) cm3. NTR-aSRS: Monitored with MRI/CT and treated when necessary due to residual tumour growth. Received second treatment (which seems to be either surgery or SRS) after a median of 1.4 (range 0.4-4.8) years after NTR. SRS characteristics, Gy median (range): Min dose: 15 (10-18); max dose: 32 (30-38); prescription dose: 15 (14-22); tumour volume: 1.68 (0-4) cm3. Follow up: NTR-aSRS: median 5.3 (range 0.5-9.3) years;	-Bias in the selection of the reported results: low risk of bias -Overall bias: moderate (small sample/low event rates relative to the number of covariates); OS result not adjusted Other information:	Progression-free survival (interval from primary surgery to either 3rd overall treatment or death): NTR-aSRS: 9 events NTR+aSRS: 3 events Time to first retreatment: Unadjusted/univariate: NTR-aSRS < NTR+aSRS, p < 0.001; Multivariate/adjusted for age at primary surgery, gender, size, atypical meningioma, and multiple meningiomas: NTR-aSRS < NTR+aSRS, HR = 7.35 (95% CI 2.08-25.93), p = 0.001 Progression-free survival: Unadjusted/univariate: NTR-aSRS = NTR+aSRS, p = 0.07; Multivariate/adjusted for age at primary surgery, gender, size, atypical meningioma, and multiple meningiomas: NTR-aSRS = NTR+aSRS, p = 0.055 Overall survival: Unadjusted/univariate: NTR-aSRS < NTR+aSRS, p < 0.05; None of the patients in either group had oedema or necrosis after SRS.

Study details	Participants	Interventions	Methods/risk of bias	Results
Swedish Research Council, and Karolinska Institutet		NTR+aSRS: median 4.7 (range 0.9-9) years.		
Full citation Han, M. S., Kim, Y. J., Moon, K. S., Lee, K. H., Yang, J. I., Kang, W. D., Lim, S. H., Jang, W. Y., Jung, T. Y., Kim, I. Y., Jung, S., Lessons from surgical outcome for intracranial meningioma involving major venous sinus, Medicine (United States), 95, no pagination, 2016 Ref Id 598030 Country/ies where the study was carried out South Korea Study type Retrospective cohort study Aim of the study	14 of 107 patients received STR: - STR-RT: N = 7; major venous sinus involvement no lumen invasion / lumen invasion [patent sinus / occluded sinus]: N = 3 / 4 [4 / 0] - STR + RT: N = 7; SRS / RT: N = 5 / 2; major venous sinus involvement no lumen invasion / lumen invasion [patent sinus / occluded sinus]: N = 3 / 4 [3 / 1] Inclusion criteria Patients with intracranial meningioma involving the major venous sinus Exclusion criteria None reported	Subtotal resection + / - RT (consisting of radiation therapy or gamma knife radiosurgery NOS) Follow up: Median (range) = 60.2 (6.2-218.2) months	-Bias due to confounding: unclear risk of bias (patient characteristics not reported split by group, no relevant adjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders, small sample) Other information:	Recurrence rate: STR-RT: 3/7 STR+RT: 0/7 (p = 0.19)

Study details	Participants	Interventions	Methods/risk of bias	Results
"to retrospectively review the morbidity/mortality and long-term outcome and analyze the predictive factors for recurrence in our experience and finally discuss management strategy for intracranial meningiomas involving the MVS [major venous sinus]." (p. 2) Study dates 1993-2011 Source of funding grant (HCRI15014–21) of Chonnam National University Hospital Biomedical Research Institute South Korea				
Full citation Hardesty DA, Wolf AB, Brachm DG, McBride HL, Youssef E, Nakaji P, Porter RW, Smith KA, Spetzler RF,	228 unique patients undergoing 257 operations of which 42% were sub-total resections (total resections defined as Simpson grades I-II) and of which 11% reported a history of radiotherapy of some type (either SRS or IMRT) prior to craniotomy for	Subtotal resection + / - adjuvant RT given within 6 months of surgery before any clinical or radiographic tumour recurrence and consisted of either	-Bias due to confounding: serious risk of bias (unadjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias	Progression-free survival: - STR+SRS = STR-RT (RR = 0.567, p = 0.16). - STR+IMRT = STR-RT (RR = 1.27, p = 0.55).

Study details	Participants	Interventions	Methods/risk of bias	Results
Sanai N. The impact of adjuvant stereotactic radiosurgery on atypical meningioma recurrence following aggressive microsurgical resection. J Neurosurg 119:475–481, 2013 Ref Id 509268 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “to define the long-term recurrence rate of atypical meningiomas and identify the value of SRS in affecting outcome.” (p. 475)	tumour resection, and of which 32 patients received adjuvant SRS (of which 22 patients had received SRT) and 39 (of which 20 patients had received SRT) adjuvant intensity modulated RT. Patient details not reported for patients who received SRT +/- RT separately. RT details in next cell given for the full 32 and 39 patient respectively. Inclusion criteria “all patients who underwent operations for atypical meningiomas between 1992 and 2011 at the Barrow Neurological Institute” (p. 476) Exclusion criteria None reported	SRS with 19 patients treated using Gamma Knife surgery and 13 patients treated with CyberKnife technology; Target volume mean = 11.4 cm3 (range 1.8-45). Median (range) radiation dose = 14 (11–16) Gy to the 50% isodose line for Gamma Knife-treated patients; for CyberKnife-treated patients the radiation dose ranged from 14–16 Gy in 1 fraction, to 21–27 Gy in 3 fractions, to 25 Gy in 5 fractions. or IMRT: Median (range) radiation dose = 54 (54–59) Gy in standard fractionation of 1.8–2 Gy per day. Follow up: Median (for the whole group) = 52 months; median = 23 months for the IMRT patients	-Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders)	There were no periprocedural complications associated with radiosurgical therapy. There was 1 patient who suffered cranial wound breakdown due to IMRT, requiring operative reconstruction.

Study details	Participants	Interventions	Methods/risk of bias	Results
Study dates 1992-2011 Source of funding Not reported. Authors have some conflicts of interest				
Full citation Lee, Kangmin D., DePowell, John J., Air, Ellen L., Dwivedi, Alok K., Kendler, Ady, McPherson, Christopher M., Atypical meningiomas: is postoperative radiotherapy indicated?, Neurosurgical Focus, 35, E15, 2013 Ref Id 509543 Country/ies where the study was carried out USA Study type Retrospective cohort study	90 patients (patient characteristics only given for whole group: mean (SD)age 56.9 (13.4) years, 34 males/56 females; tumour locations: convexity, falx/ parasagittal, sphenoid wing, midline anterior skull base, or other, with the most common being convexity (47.8%) and falx/ parasagittal (21.1%); mean (SD) tumour size = 4.8 (1.5) cm) divided into 3 groups: - Gross total resection (Simpson grade I-III): N = 71. Not in PICO so no more details about this group reported. - Subtotal resection (Simpson grade IV), no RT (STR-RT): N = 5 - Subtotal resection with RT (STR+RT): N = 14. 14 of the 19 STR patients had also received pre-operative RT. Inclusion criteria	Subtotal resection + / - RT “All patients who received radiation therapy postoperatively underwent fractionated stereotactic radiotherapy by linear accelerator (median dose 59.4 Gy, range 50.4–60.0 Gy) delivered to the tumor bed in 1.8- to 2.0-Gy fractions.” (p. 2) Follow up: Median (range) = 48.7 (12-108) months.	-Bias due to confounding: serious risk of bias (patient characteristics not reported split by SRT group, but results unadjusted) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders) Other information:	Recurrence rate: STR-RT: 100% (5/5) STR+RT: 7.1% (1/14) 5-year recurrence-free survival: STR-RT (20%) < SRT+RT (91%), p = 0.0016.

Study details	Participants	Interventions	Methods/risk of bias	Results
Aim of the study To “examine the recurrence rates for atypical meningiomas after resection (with or without adjuvant radiotherapy) and identify which factors were associated with recurrence” (p. 1) Study dates 1999-2009 Source of funding Not reported	Patients who had resection of intracranial pathology-confirmed Grade II atypical meningiomas at the University of Cincinnati Medical Center 1999-2009, who had at least 1 year of follow-up. Exclusion criteria Not reported			
Full citation McCarthy BJ, Davis FG, Freels S, Surawicz TS, Damek DM, Grutsch J, Menck HR, Laws ER. Factors associated with survival in patients with meningioma. J Neurosurg 88:831–839, 1998 Ref Id NA	9827 patients with benign, atypical, or malignant meningioma. Of these the following treatment groups are included: Benign meningioma: Subtotal resection, no RT (STR-RT): N = 4577. - Subtotal resection with RT (STR+RT): N = 238 Atypical meningioma: Subtotal resection, no RT (STR-RT): N = 86. - Subtotal resection with RT (STR+RT): N = 20 Malignant meningioma:	Subtotal resection + / - RT (any form of RT; NOS) Follow up: Median (range) = 10 (0-93) months for benign meningiomas, 12 (0-79) months for atypical meningiomas, and 12 (0-90) months for malignant meningiomas.	-Bias due to confounding: serious risk of bias (patient characteristics by intervention group not reported, unadjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias, although all aspects of RT given is unclear -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias	Benign meningioma: Overall survival: STR-RT (5-year OS: 75.3% of 4577 patients) = STR+RT (5-year OS: 65.3% of 238 patients; non-significant). Malignant meningioma: Overall survival: STR-RT (5-year OS: 63.8% of 279 patients) > STR+RT (5-year OS: 44.7% of 169 patients; favour surgery alone; p = 0.02). Atypical meningioma: 5-year overall survival: STR-RT: 88% of 86 patients; STR+RT:49.7% of 20 patients.

Study details	Participants	Interventions	Methods/risk of bias	Results
Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “To explore factors affecting the survival rate in patients with meningiomas.” (p. 831) Study dates 1985-1988 and 1990-1992 Source of funding “This work was conducted under contract to the Central Brain Tumor Registry of the United States, and supported by the Pediatric Brain Tumor Foundation of the United States through the Ride for Kids Fundraising Program sponsored by the American	Subtotal resection, no RT (STR-RT): N = 279. - Subtotal resection with RT (STR+RT): N = 169 Patient characteristics not reported split by these groupings. Inclusion criteria “Data on individuals with brain and central nervous system tumors were obtained from the NCDB, a non-random voluntary sample of cancer cases in the United States compiled by the Commission on Cancer of the American College of Surgeons and the American Cancer Society International Classification of Diseases for Oncology (ICDO) codes 9530 to 9537 were used to select 9827 cases of meningioma from the larger NCDB data set.20 from the data set. There was no case of an asymptomatic meningioma diagnosed at autopsy in the current study.” (p. 832) Exclusion criteria Papillary meningiomas (ICDO 9538/1; N = 13); meningeal sarcomatoses (ICDO 9539/3; N = 3)		-Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders) Other information:	

Study details	Participants	Interventions	Methods/risk of bias	Results
Honda Motor Company, Motorcycle Division." (p. 839)				
Full citation Park, H. J., Kang, H. C., Kim, I. H., Park, S. H., Kim, D. G., Park, C. K., Paek, S. H., Jung, H. W., The role of adjuvant radiotherapy in atypical meningioma, Journal of Neuro-Oncology, 115, 241-247, 2013 Ref Id 509986 Country/ies where the study was carried out Korea Study type Retrospective cohort study Aim of the study "to analyze treatment outcomes and to identify the prognostic factors, with a focus on the	83 patients divided into 3 groups: - Gross total resection: N = 55. Not in PICO so no more details about this group reported. - Subtotal resection, no RT (STR-RT): N = 18. - Subtotal resection with RT (STR+RT): N = 10 3 patients had unknown extent of resection. They are included in the STR groups, but unclear whether they received RT or not. Patient characteristics not reported split by these groupings, but the tumours were located in the following 5 categories (numbers are for the whole population): convexity (43), parasagittal/falx (20), skull base/ sphenoid ridge (10), sella/ parasella (6), and other (4). Inclusion criteria Patients referred 1997-2011 who had pathologically diagnosed atypical meningioma ((WHO grade II) according to the WHO 2000/2007 classification) at Seoul National University Hospital, Korea. Exclusion criteria	Subtotal resection + / - RT "median dose was 61.2 Gy (range 40–61.2 Gy) over 7 weeks with photon. All the patients except one with poor performance status were treated with over 54 Gy. Conventional RT until 2002 and three-dimensional conformal RT thereafter were used in 9 and 27 patients, respectively. Neither fractionated stereotactic RT nor intensity-modulated RT was applied. Clinical target volume (CTV) encompassed residual enhancing lesions, if existed, and the entire resection cavity with a 1.5 cm margin for the large field and with a 0.5 cm margin	-Bias due to confounding: serious risk of bias (patient characteristics by intervention group not reported, unadjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders) Other information:	Progression-free survival: STR-RT < STR+RT ($p < 0.001$). Complications: - No severe acute side effects during treatment period. - Transient mild side effects (e.g., fatigue, headache, intermittent nausea, dizziness and skin irritation at portals) seen in most patients. - Late toxicity (categorized according to the Common Terminology Criteria for Adverse Events v3.0 score): Cognitive disturbance and motor neuropathy most common late side effects, with others (e.g, memory disturbance, speech impairment, encephalopathy, seizures, and aemorrhage) occurring less often. This is for GTR + STR. Not reported for STR group only.

Study details	Participants	Interventions	Methods/risk of bias	Results
role of adjuvant radiotherapy (ART), predicting disease progression in atypical meningiomas." (p. 241) Study dates 1997-2011 Source of funding Not reported	Patients with < 6 months follow-up period due to follow-up loss; without resection; with preoperative radiotherapy or postoperative adjuvant radiosurgery, which did not target the whole surgical bed; with spinal cord meningioma; with recurrent atypical meningioma after treatment of previous benign meningioma; with multiple intracranial meningiomas, although one patient who had one benign lesion in the right convexity and another discrete atypical lesion in the left was included.	for the cone-down field adhering to the anatomical borders. To account for setup inaccuracy, a 0.3 cm margin was added to CTV for planning target volume." (p. 242) Follow up: Median = 43 (range 6.2-160) months.		
Full citation Peele, K. A., Kennerdell, J. S., Maroon, J. C., Kalnicki, S., Kazim, M., Gardner, T., Malton, M., Goodglick, T., Rosen, C., The role of postoperative irradiation in the management of sphenoid wing meningiomas. A preliminary report, Ophthalmology, 103, 1761-6; discussion 1766-7, 1996	- Subtotal resection, no RT (STR-RT): N = 44 (38 primary subtotal excisions; 9 males/29 females; mean age (range) = 50 (10-73) years; N = 22 were stable without evidence of recurrent disease (mean follow-up, 3.5 years) and 16 patients had a recurrence (mean interval to recurrence, 4.4 years AND 6 recurrent tumours: 6 females, with N = 1 stable after 1 year of follow-up and five have had recurrences again (mean interval to recurrence, 14 months). - Subtotal resection with RT (STR+RT): N = 42; 11 males/31 females; mean age (range) = 49 (17-72) years. N = 31 underwent	Subtotal resection + / - RT usually started 1-2 months after surgery; "The radiation target volume included the residual or recurrent tumor, the resection bed, and at least a l-cm safety margin." (p. 1762) "Multiple radiation protocols with edge-compensating filters were used to deliver a mean dose of 180 cGy per fraction (range, 150-200 cGy)	-Bias due to confounding: serious risk of bias (few patient characteristics reported, unadjusted analyses) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders)	Recurrence: - Primary sphenoid wing meningiomas: STR-RT: 42% (16/38) > STR+RT: 0% (0/31), p < 0.00005 - Recurrent sphenoid wing meningiomas: STR-RT: 83% (5/6) > STR+RT: 0% (0/11), p < 0.0012 Operative complications: - most common was third cranial nerve palsy (N = 4), then fifth cranial nerve dysfunction (N = 1), ptosis (N = 1), central retinal artery occlusion (N = 1), cerebrospinal fluid leak (N = 1), and pulmonary embolism (N = 1).

Study details	Participants	Interventions	Methods/risk of bias	Results
Ref Id 509908 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “To determine whether postoperative radiation therapy decreases recurrence rates in subtotally excised and recurrent sphenoid wing meningiomas.” (p. 1761) Study dates 1981-1994 Source of funding Not reported	primary subtotal excisions, N = 11 underwent surgery for recurrent tumours; the mean follow-up interval was 4.3 years for the patients with primarily subtotal excisions and 3.5 years (overall range of follow-up, 5-204 months) for the patients with recurrent tumours. Inclusion criteria Patients who underwent a frontotemporal craniotomy between 1981 to 1995 for primary sphenoid wing meningiomas who were treated with subtotal excision (n = 69) or for recurrent sphenoid wing meningiomas (n = 17) Exclusion criteria Patients with complete gross excision confirmed by postoperative neuroimaging or with histopathologically malignant meningiomas; tumours believed to arise from sites other than the sphenoid bone; recurrent lesions approached transphenoidally or by frontal craniotomy.	to a total dose of 4500 cGy (range, 4350-4850 cGy) with 6-MV photon beams. Patients were treated 5 days a week, one fraction per day. Special attention was given to the doses delivered to critical structures such as the retina/optic nerve (maximum, 5000 cGy), and optic chiasm/pituitary gland (maximum, 4500 cGy) to minimize toxicity.” (p. 1762) Follow up: See “Participants”	Other information: Patients treated 1981-1994, unclear how many treated 1981-1985, that is, outside of our inclusion criterion of 1985 onwards.	Serious morbidity (N = 0) or mortality (N = 0) Anterior ischemic optic neuropathy (N = 3), central retinal vein occlusion (N = 1). “All events occurred at least 2 years postoperatively but ipsilateral to tbe previous frontotemporal craniotomy.” Radiation therapy (temporary) adverse events: Commonly mild skin erythema and lateral brow alopecia, but no retinal or optic nerve complications, except possibly N = 1.
Full citation Sun SQ, Cai C, Murphy RKJ, DeWees T, Dacey	- Subtotal resection, no RT (STR-RT): N = 27; 13 males/14 females; mean age at initial resection = 58.3 years; tumour	Subtotal resection + / - adjuvant	-Bias due to confounding: serious risk of bias (unadjusted analyses apart from for	Local control: - STR+RT (SRS or EBRT) > STR-RT (favours STR+RT, p = 0.02)

Study details	Participants	Interventions	Methods/risk of bias	Results
RG, Grubb RL, Rich KM, Zipfel GJ, Dowling JL, Leuthardt EC, Leonard JR, Evans J, Simpson JR, Robinson CG, Perrin RJ, Huang J, Chicoine, MR, Kim AH. Management of Atypical Cranial Meningiomas, Part 2: Predictors of Progression and the Role of Adjuvant Radiation After Subtotal Resection. Neurosurgery 75:356–363, 2014 Ref Id 510226 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “to identify clinical and pathological	location convexity (2), parasagittal (15), anterior fossa skull base (1), middle fossa skull base (5), posterior fossa skull base (4); 37% received near total resection. - Subtotal resection with SRS (STR+SRS): N = 7; 2 males/5 females; mean age at initial resection = 51.6 years; tumour location convexity (2), parasagittal (4), anterior fossa skull base (0), middle fossa skull base (0), posterior fossa skull base (1); 43% received near total resection. - Subtotal resection with EBRT (STR+EBRT): N = 25; 10 males/15 females; mean age at initial resection = 52.1 years; tumour location convexity (2), parasagittal (8), anterior fossa skull base (3), middle fossa skull base (10), posterior fossa skull base (2); 16% received near total resection. Inclusion criteria Patients whose initial resection for cranial atypical meningiomas was performed at the authors’ institution between 1993 and 2012; patients with multiple meningiomas without known syndromic association Exclusion criteria	RT (delivered before any signs of radiographic progression) consisting of either SRS (median dose = 18 Gy; range = 14-18 Gy) or EBRT (median dose = 54 Gy; range, 52-60 Gy) delivered in 1.8- to 2.0-Gy fractions. Follow up: Median (range) = 67 (7-246) months after STR	progression, low N for the adjusted analyses though) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders)	Progression-free survival: - STR+RT (SRS or EBRT) > STR-RT (favours STR+RT, p = 0.007) - 2-, 5-, and 10-year PFS = 96%, 65%, and 45% for STR+EBRT and 60%, 30%, and 26% for STR-RT - Multivariate analysis controlling for age, sex and spontaneous necrosis showed a significant effect of adjuvant RT: HR = 0.3 (95% CI 0.2-0.8, p = 0.006 (favouring RT). Overall survival: - STR+RT (SRS or EBRT) > STR-RT (favours STR+RT, p = 0.049) - 0/32 STR+SRS/EBRT patients died over a follow-up time of 56 months (range, 7-149 months), and 5/27 STR-RT patients died at a median time of 45 months (range, 20-159 months). Four of the 5 patients had significant comorbidities that may have contributed to their deaths (e.g., coronary artery disease, metastatic prostate cancer, VE). RT was not complicated by any morbidity or mortality.

Study details	Participants	Interventions	Methods/risk of bias	Results
features associated with radiographic progression in AM patients after STR and to clarify the relative benefit of adjuvant radiation." (p. 356-7) Study dates 1993-2012 Source of funding "The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article." (p. 362) although some of the authors have received some financial support for collecting the data on which the study is based.	Patients with neurofibromatosis type 2, meningomatosis, satellite tumors, undergoing biopsy only, patients who died perioperatively after STR and patients with short follow-up if the extent of resection could not be deduced from their operative records or postoperative imaging.			
Full citation Wang, Y. C., Chuang, C. C., Wei, K. C., Hsu, Y. H., Hsu, P. W., Lee, S. T., Wu, C. T., Tseng, C. K., Wang, C. C., Chen, Y. L., Jung, S.	28 patients divided into 3 groups: - Gross total resection (NOS): N = 14. Not in PICO so no more details about this group reported. - Subtotal resection, no RT (STR-RT): N = 5 - Subtotal resection with RT (STR+RT): N = 9	Subtotal resection + / - RT (given within 6 months of surgery, before any clinical or radiographic signs of tumour recurrence) consisting of a total	-Bias due to confounding: unclear risk of bias (patient characteristics not reported split by group, but no relevant adjusted analyses) -Bias in selection of participants into the study: low risk of bias	Recurrence rate: STR-RT: 100% STR+RT: NR, but not significantly different from SRT-RT (p = 0.074) One complication observed after STR (facial palsy; tumour location petroclivus).

Study details	Participants	Interventions	Methods/risk of bias	Results
M., Chen, P. Y., Skull base atypical meningioma: Long term surgical outcome and prognostic factors, Clinical Neurology and Neurosurgery, 128, 112-116, 2015 Ref Id 510361 Country/ies where the study was carried out Taiwan Study type Retrospective cohort study Aim of the study “to examine the clinical outcomes of treating atypical meningioma at the skull base region following surgical resection and adjuvant radiotherapy, and to analyze the association between clinical characteristics	Characteristics only reported for STR group as a whole: 6 males/8 females; mean (SD) age = 59.9 (3.2) years. Meningioma locations: sphenoid ridge (5), olfactory groove (2), sella region (2), petroclivus (3), other (2), Inclusion criteria Patients treated for atypical meningioma between June 2001 and November 2009 at Chung Gang Memorial Hospital, with tumours located in the skull base area. Exclusion criteria “Four patients with recurrent atypical meningioma after being treated previously for benign meningioma, or who multiple intracranial meningiomas were excluded because of the difficulty in evaluating the treatment response. Other three patients were either lost to follow-up or had incomplete records and were excluded from this evaluation” (p. 113)	dose of 54–60 Gy, delivered in 27–30 fractions. Follow up: Mean = 57.4 (range 16-144) months	-Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders, small sample) Other information:	No severe acute side effects after radiotherapy, but some self-limiting symptoms were observed (e.g., dizziness, headache, and skin irritation).

Study details	Participants	Interventions	Methods/risk of bias	Results
and progression free survival." (p. 112) Study dates 2001-2009 Source of funding National Science Council, Taiwan (No. 102-2334-B-182A-068-MY3), and Chang- Gung Memorial Hospital, Taiwan (No. CMRPG3C0041).				
Full citation Yoon, H., Mehta, M. P., Perumal, K., Helenowski, I. B., Chappell, R. J., Akture, E., Lin, Y., Marymont, M. A. H., Sejpal, S., Parsa, A., Chandler, J., Bendok, B. R., Rosenow, J., Salamat, S., Kumthekar, P., Raizer, J., Baskaya, M. K., Atypical meningioma: Randomized trials are required to resolve contradictory retrospective results regarding the role of	158 patients (patient characteristics only given for whole group: median (range) age 58 (19-90) years, 72 males/86 females; tumour locations: cerebral convexity (105), skull base or sphenoid (34), falx/ parasagittal (13), suprasellar/parasellar (4), or other (2) divided into 4 groups: - Gross total resection (Simpson grade I-III): N = 109. - Unknown extent of resection: N = 7. Not in PICO so no more details about these groups reported. - Subtotal resection (Simpson grade IV), no RT (STR-RT): N = 30	Subtotal resection + / - RT "Of the 23 patients [some with GTR] who received adjuvant radiation, the mean adjuvant EBRT dose in 7 patients was 57 Gy, and the mean adjuvant SRS dose in 11 patients was 14 Gy; complete dosimetric information was not available for 5 patients." (p. 62)	-Bias due to confounding: serious risk of bias (patient characteristics not reported split by SRT group, but results unadjusted) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: unclear risk of bias -Overall bias: serious (uncontrolled confounders)	Recurrence rate: STR-RT (27% [8/30]) = STR+RT (25% [3/12]), p = 0.99 Median progression-free survival: STR-RT (47 months) = SRT+RT (59 months), p = 0.4 5-year overall survival: STR-RT (83%) = SRT+RT (83%), p = 0.98

Study details	Participants	Interventions	Methods/risk of bias	Results
adjuvant radiotherapy, Journal of Cancer Research and Therapeutics, 11, 59-66, 2015 Ref Id 510409 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study To review the outcome for grade 2 meningiomas (using the updated WHO 2000 classification system) treated with or without adjuvant RT; to determine factors predictive for recurrence. Study dates 2000-2010 Source of funding	- Subtotal resection with RT (STR+RT): N = 12. Inclusion criteria “data from 2 institutions were gathered in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner for patients with grade 2 meningiomas diagnosed between 2000 and 2010.” (p. 60) Exclusion criteria Patients aged ≤18 years; multiple meningiomas; meningiomatosis; extra-cranial meningiomas; radiation-induced meningiomas; and inoperable patients.	Follow up: Median (range) = 32 (0-157) months.	Other information:	

Study details	Participants	Interventions	Methods/risk of bias	Results
Not reported				

Evidence tables for review 3b - Techniques for radiotherapy for meningioma

Study details	Participants	Interventions	Methods/risk of bias	Results
Full citation Correa, S. F., Marta, G. N., Teixeira, M. J.Neurosymptomatic carvenous sinus meningioma: a 15-years experience with fractionated stereotactic radiotherapy and radiosurgery Radiation Oncology 2014 9 p.27 Ref Id 629785 Country/ies where the study was carried out Brazil Study type Retrospective cohort study Aim of the study “to present the results of the	N = 89 (some patient characteristics only given for whole group, not split by type of RT): males / females: N = 16 / 73; previous biopsy / resection: N = 18 / 8 Divided into 2 groups, based on radiotherapy treatment: - SRS: N = 32 (mean (SD) age = 61.03 (16.38) years; mean (SD) KPS = 90 (5.08)%; mean (SD) duration of symptoms = 15.74 (23.03) months; mean (SD) tumour volume = 8.25 (10.88) cc). - SRT: N = 57 (mean (SD) age = 57.12 (15.87) years; mean (SD) KPS = 89.12 (5.44)%; mean (SD) duration of symptoms = 19.04 (24.62) months; mean (SD) tumour volume = 25.39 (9.91) cc). KPS, age and duration of symptoms did not differ significantly between the groups, but tumour volume did ($p < 0.001$). Inclusion criteria Patients treated with SRS or SRT for symptomatic cavernous sinus	“Patients with tumors larger than 3 cm diameter, with volume higher than 14 cc, or very close to the visual pathways were treated with SRT.” (p. 2) - SRS (performed with 6MV linear accelerator; median total dose (range) = 14 (13-15) Gy) versus - SRT (performed with 6MV linear accelerator; median total dose (range) = 50.4 (45-54) Gy; delivered in median (range) fractions of 1.8 (1.8- 2) Gy). The doses of both treatments covered ≥	-Bias due to confounding: serious risk of bias (significantly larger tumours in the SRT group) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (uncontrolled confounders) Other information: Please note SRS had significantly smaller tumours than SRT.	Disease-free survival: SRS (5, 10 and 15 year = 100%, 95.7% and 90.3%) = SRT (5, 10 and 15 year = 98.1%, 90.3% and 90.3%; p = 0.567). Epilepsy improvement: SRS (2/32 patients) = SRT (0/57 patients; p = 0.13). Cognitive/dysthymic [persistent depressive disorder] alteration improvement: SRS (3/32 patients) = SRT (1/57 patients; p = 0.13). Steroid-use and adverse events: SRT (N = 0 treated with dexamethasone); SRS (N = 7 experienced temporary morbidity and were treated with dexamethasone, with 5/7 recovering spontaneously and 2/7 having “trigeminal neuropathy (CTC grade 2), also regressing rapidly with steroid use. One patient had total occlusion of the internal carotid artery with no neurological repercussions (CTC grade 2).”, p. 6)

Study details	Participants	Interventions	Methods/risk of bias	Results
treatment with SRS or SRT of 89 patients with Grade I symptomatic CSMs. [cavernous sinus meningioma]" (p. 2) Study dates 1994-2009 Source of funding Not reported.	meningiomas with ≥ 3 years follow up, Exclusion criteria Unable to attend the follow up consultations; ≤ 3 years of follow up; WHO stage II and III.	95% of the tumour volume treated at the 80-90% of the dose curve. Follow up: Median (range) = 73 (36-129) months		- No fatal treatment complications - No radiation-induced malignancies during the 15-year follow-up.
Full citation Fokas, E., Henzel, M., Surber, G., Hamm, K., Engenhart-Cabillic, R. Stereotactic radiation therapy for benign meningioma: long-term outcome in 318 patients. International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys 2014 89 p.569-75 Ref Id 670901	318 patients (patient characteristics only given for whole group): median (range) age 66 (13-85) years, male / female: 104/214; median tumour volume (range): 14 (0.6-191) cm3; diagnosis of WHO grade I meningioma based on previous surgery/no previous surgery: 142/176; location olfactory (3), optic (14), sphenopid wing (100), cavernous sinus (69), petroclival (39), temporal (13), falx cerebri (27), tentorium (8), frontobasal (15), occipital (4),cerebellar/cerebellopontine angle (8), overlapping (multiple) sites (18); divided into 3 groups, based on type of radiotherapy: - FSRT: N = 253 - hFSRT: N = 49	FSRT (tumor size >4 cm3 , distance to critical structures <2 mm; median (range?) dose = 55.8 (50.4/50-55.8/56) Gy in fractions of 1.8-2.0 G; target volume (range) = 16.0 (0.6-191) cm3). versus hFSRT (tumor size >4 cm3 , distance >2 mm to critical structures; administered as 10 fractions of 4 Gy (cumulative dose 40 Gy) or 5-7 fractions	-Bias due to confounding: serious risk of bias (patient characteristics not reported split by radiotherapy group, but clear that at least target volume differ between the treatment groups) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: Serious (confounders) Other information: Some patients aged below 16 years, unclear how many.	Local control: FSRT = hFSRT (both in univariate (p = 0.12) and multivariate analysis (HR = 1.568; p = 0.27) - No new neurologic deficits, radiation necrosis, or radiation-induced tumorigenesis - No treatment-related mortality.

Study details	Participants	Interventions	Methods/risk of bias	Results
Country/ies where the study was carried out Germany Study type Retrospective cohort study Aim of the study “investigated the long-term clinical outcome and toxicity in 318 patients with either histology- or imagingdefined benign (World Health Organization grade 1) intracranial meningiomas treated with stereotactic-based radiation therapy.” (p. 570) Study dates 1997-2010 Source of funding Not reported	- SRS: N = 16 (please note N < 30 so no further information will be reported about this group) Inclusion criteria Patients treated with stereotactic-based radiation therapy at Philipps University Marburg and the HELIOS Klinikum Erfurt for benign meningioma. “Stereotactic-based radiation therapy was considered for: (1) patients with meningiomas that were unresectable or incompletely resectable owing to their proximity to high-risk functional areas; (2) patients considered unsuitable for surgery owing to reduced general health status; and (3) patients who had electively opted for radiation therapy instead of surgical resection.” (p. 570) Exclusion criteria None reported	of 5 Gy (cumulative dose 25-35 Gy; target volume (range) = 6.11 (1.9-35.7) cm3). Follow up: Median (range) = 50 (12-167) months.		
Full citation Han, J., Girvigian, M. R., Chen, J. C., Miller, M. J., Lodin, K., Rahimian, J.,	N = 213 patients divided into 3 groups based on radiotherapy treatment: - SRS: N = 55 (Median age (range) = 60 (28-83) years; males	SRS (median total dose = 1250 cGY; median maximum tumor dose (range)	-Bias due to confounding: serious risk of bias (baseline differences in tumour volume) -Bias in selection of participants into the study: low risk of bias	Progression-free survival: - SRS (88%; median (range) time to tumour progression: 17 (5-32) months) = FSRT (92%, p = 0.53; median time

Study details	Participants	Interventions	Methods/risk of bias	Results
Arellano, A., Cahan, B. L., Kaptein, J. S. A comparative study of stereotactic radiosurgery, hypofractionated, and fractionated stereotactic radiotherapy in the treatment of skull base meningioma. American Journal of Clinical OncologyAm J Clin Oncol 2014 37 p.255-60 Ref Id 657257 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study to “directly compare 3 treatment techniques that is, stereotactic radiosurgery (SRS),	/ females: N = 16 / 39; mean/median? tumour volume: 2.8 (0.1-16.94) cm3; optic nerve involved yes / no / unknown: N = 5 / 49 / 1; optic chiasm involved yes / no / unknown: N = 0 / 51 / 4; prior surgery yes / no: N = 21 / 34; WHO grade I / II / III / unknown (surgical patients): N = 12 / 3/ 3 / 3) - FSRT: N = 143 (Median age (range) = 59 (30-84) years; males / females: N = 32 / 111; mean/median? tumour volume: 11.1 (0.43-214) cm3; optic nerve involved yes / no / unknown: N = 46 / 97 / 0; optic chiasm involved yes / no / unknown: N = 34 / 108 / 2; prior surgery yes / no: N = 48 / 95; WHO grade I / II / III / unknown (surgical patients): N = 38 / 4 / 0 / 6) - hFSRT: N = 22 (as N < 30 no further details will be included about this group) Inclusion criteria Patients treated for basal meningiomas with SRS (single fraction), hFSRT (5 fractions), or FSRT (> 5 fractions) who had sufficient follow up. Exclusion criteria Patients without sufficient follow up	= 1581 (1432-2020) cGy) versus FSRT (median total dose = 5040 cGY; median number of fractions = 28; median dose per fraction = 180 cGY; median maximum tumor dose (range) = 204 (184-241) cGy) “A strict tumor volume cut off was not employed to determine candidacy for SRS. In general, tumors located in the CPA < 3 cm in maximum diameter were treated with SRS. In the anterior skull base, SRS was used if the tumor was <3 cm in diameter and at least >2mm from the optic apparatus.” (p. 256) “Patients with tumor causing optic nerve/chiasm dysfunction, or	-Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: Serious (baseline differences) Other information: Tumour volume significantly larger in FSRT group than SRS group	to tumour progression: 18 (6-64) months) Symptomatic oedema requiring steroids: - SRS: N = 6 patients (11%; median (range) time to symptomatic oedema: 8 (3-23) months) - FSRT: N = 6 patients (4%, p = 0.1; median (range) time to symptomatic oedema: 4 (2-9) months) Adverse events: - SRS: Worsened trigeminal neuralgia in 4 patients with tumors at the CPA, cavernous sinus, and petroclival region. New syndrome of inappropriate antidiuretic hormone secretion in 1 patient. - FSRT: Treatment for progressive trigeminal neuralgia with tumor locations in the cavernous sinus and petroclival region in 4 patients. New endocrine dysfunction requiring hormone replacement in 3 patients - No treatment-related deaths

Study details	Participants	Interventions	Methods/risk of bias	Results
hypofractionated stereotactic radiotherapy (hFSRT), and fractionated stereotactic radiotherapy (FSRT) as primary or combined treatment for skull base meningiomas. (p. 255) Study dates 2003-2010 Source of funding Not reported		<2mm from the optic structures or large tumor diameter (> 3 cm) were treated with fully fractionated radiotherapy. Patients with tumor size between 3 cm and 5 cm in diameter and >2mm from the optic apparatus were treated with hFSRT. Oftentimes these patients qualified for fully fractionated therapy, but were unable to comply with the longer treatment schedule" (p. 256) Follow up: Median (range) = 32 (7-97) months		
Full citation Hardesty, D. A., Wolf, A. B., Brachman, D. G., McBride, H. L., Youssef, E., Nakaji, P., Porter, R. W., Smith, K. A., Spetzler, R. F., Sanai, N. The impact of adjuvant	- Adjuvant SRS: N = 32; (mean (SD) age: 55 (19) years; males / females: N = 14 / 18; tumour location convexity / parasagittal / skull base / other: N = 3 / 12 / 17 / 3; subtotal resection (STR) / gross total resection (GTR): N = 22 / 8. - Adjuvant IMRT: N = 39; (mean (SD) age: 55 (14) years; males /	Adjuvant radiotherapy given within 6 months of surgery - SRS (Gamma knife surgery (N = 19; median (range) dose = 14 (11–16) Gy to the 50% isodose	-Bias due to confounding: unclear risk of bias (tumour volume not reported, and target volume only reported for SRS) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias	Progressive disease: SRS: N = 8 IMRT: N = 7 Progression free-survival: SRS = IMRT (RR = 0.715 no CI reported, p = 0.52). Adverse events:

Study details	Participants	Interventions	Methods/risk of bias	Results
stereotactic radiosurgery on atypical meningioma recurrence following aggressive microsurgical resection. Journal of NeurosurgeryJ Neurosurg 2013 119 p.475-481 Ref Id 509268 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study “To define the risk factors associated with postoperative atypical meningioma recurrence and further clarify the role of adjuvant SRS in the management of these lesions” (p. 476)	females: N = 17 / 22; tumour location convexity / parasagittal / skull base / other: N = 10 / 14 / 9 / 2; STR / GTR: N = 20/15. Inclusion criteria Patients with atypical meningiomas for which they received surgery. Exclusion criteria None reported	line) or Cyberknife technology (N = 13; median doses ranged from 14–16 Gy in 1 fraction, to 21–27 Gy in 3 fractions, to 25 Gy in 5 fractions); versus - IMRT (median (range) dose = 54 (54–59) Gy in 1.8–2 Gy daily fractions). Follow up: Median = 72 and 23 months, for SRS and IMRT, respectively	-Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: Serious (tumour volume not reported) Other information: Unequal lengths of follow up between the treatment groups	SRS: No periprocedural complications IMRT: Cranial wound breakdown requiring operative reconstruction in N = 1.

Study details	Participants	Interventions	Methods/risk of bias	Results
Study dates 1992-2011 Source of funding Not reported				
Full citation Kaul, D., Budach, V., Wurm, R., Gruen, A., Graaf, L., Habbel, P., Badakhshi, H. Linac-based stereotactic radiotherapy and radiosurgery in patients with meningioma. Radiation Oncology 2014 9 p.78 Ref Id 670928 Country/ies where the study was carried out Germany Study type Retrospective cohort study Aim of the study	N = 297 patients (patient characteristics only given for whole group, not split by type of RT): Mean age (range) = 59 (20-87) years; males / females: N = 95 / 202; mean (range) tumour volume: 15.01 (0.26-190.85); tumour location skull base / falx-parasagittal / convexity: N = 254 / 20 / 23; WHO grading NA / I / II / III: N = 215 / 50 / 20 /12; adjuvant RT / primary RT: N = 153 / 144; peritumoural oedema: N = 13 (of 197); multiple meningioma: N = 58; divided into 3 groups, based on type of RT: - nFSRT: N = 179 - hFSRT: N = 92 - SRS: N = 26 (as N < 30 no further information will be reported about this treatment group) Inclusion criteria Patients with an intracranial meningioma for which they received FSRT and had adequate follow up.	"1.6-2.2 Gy were considered normo-fractionated (nFSRT), 2.2-5 Gy were considered hypofractionated (hFSRT) and high single doses delivered in less than 5 sessions were considered stereotactic radiosurgery (SRS). Tumors in close proximity to critical structures were assigned to nFSRT, while large tumors (> 2 cm) distant to critical structures underwent hFSRT and small tumors (< 2 cm) were treated by SRS." (p. 2) nFSRT (mean (SD?) total dose = 57.31 (5.82)) versus	-Bias due to confounding: serious risk of bias (tumour size not reported split by treatment group, but likely to differ between them) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (uncontrolled confounders) Other information: None	Progression-free survival: nFSRT (3-year = 92.7%; 5-year = 88.9%; 10-year = 86.9%) = hFSRT (3-year = 92.4%; 5-year = 80.9%; 10-year = NA; p = 0.81) Acute toxicity: - nFSRT (67.1%) > hFSRT (47.9%), mainly due to Grade I reactions: FSRT: (50.3%) > hFSRT (31% p < 0.001), - Grade II and III reactions: nFSRT = hFSRT

Study details	Participants	Interventions	Methods/risk of bias	Results
"to analyze long-term clinical outcome and to identify prognostic factors after Linac-based fractionated stereotactic radiotherapy (Linac-based FSRT) and stereotactic radiosurgery (SRS) in patients with intracranial meningiomas" (p. 1) Study dates 1995-2009 Source of funding Not reported.	Exclusion criteria Patients receiving reirradiation due to a secondary meningioma; patients with a questionable diagnosis; patients with incomplete follow up; patients for whom the fractionation scheme was not determinable.	hFSRT (mean (SD?) total dose = 37.6 (4.4)) Follow up: Mean (range) = 35 (1-132) months		
Full citation Metellus, P., Regis, J., Muracciole, X., Fuentes, S., Dufour, H., Nanni, I., Chinot, O., Martin, P. M., Grisoli, F. Evaluation of fractionated radiotherapy and gamma knife radiosurgery in cavernous sinus meningiomas: treatment strategy Neurosurgery 2005	- FR: N = 38; mean age (SD; range) = 53 (6.4; 33-77) years; males / females: N = 7 / 31; median (range) tumour volume = 12.7 (5.6-33.6) cm3; primary / recurrent lesions: N = 32 / 6; RT as adjuvant / first line treatment: N = 17 / 15. - GKS: N = 36; mean age (SD; range) = 51 (6.2; 17-71) years; males / females: N = 7 / 29; median (range) tumour volume = 5.9 (1.1-15.6) cm3; primary / recurrent lesions: N = 35 /1; RT as adjuvant / first line treatment: N = 13 / 23.	"External beam radiotherapy was chosen as the recommended therapy before the availability of gamma knife radiosurgery (1992 in our center) or because of lesion size, shape, and location (proximity to the optic apparatus). Indeed, tumors larger than 3 cm, showing cranial base dural spreading or too	-Bias due to confounding: serious risk of bias (tumour volumes differed between the treatment groups) -Bias in selection of participants into the study: high risk of bias (different time periods for the treatment groups) -Bias in classification of interventions: low risk of bias -Bias due to missing data: low risk of bias -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias	Progression-free survival: - FR: 5- and 10-year = 94.7%; 2 patients progressed. - GKS: 5- and 10-year = 94.4%; 2 patients progressed Clinical outcome: - FR: Improved / unchanged / worsened: N = 24 / 13 / 1 - GKS: Improved / unchanged / worsened: N = 21 / 13 / 2. Complications: FR:

Study details	Participants	Interventions	Methods/risk of bias	Results
57 p.873-86; discussion 873-86 Ref Id 670962 Country/ies where the study was carried out France Study type Retrospective cohort study Aim of the study “To investigate the respective role of fractionated radiotherapy (FR) and gamma knife stereotactic (GKS) radiosurgery in cavernous sinus meningioma (CSM) treatment.” (p. 873) Study dates FR: 1986-1999 GKS: 1994-1997 Source of funding Not reported	Inclusion criteria Patients with cavernous sinus meningioma. Exclusion criteria Not reported	close to the optic tractus, were not treated by gamma knife surgery, even after 1992.” (p. 874) “criteria for GKS treatment were less than 3 cm in size, at least 3 mm distant from the optic nerve, and the absence of dural spreading on the cranial base.” (p. 873) - FR (median total dose (range) = 53 (50–55) Gy; median dose per fraction (range) = 1.9 (1.6-2.5) Gy, delivered 4-5 days per week over 5-6 weeks) versus - GKS (median central total? dose (range) = 30 (12-50) Gy; median peripheral total? dose (range) = 15 (6-25) Gy; median number of isocentres (range) = 8 (4-18))	-Overall bias: serious (uncontrolled confounders) Other information: The time frames covering the two treatment groups differed; tumour volume differed between the treatment groups.	- No severe complications; - short-term course of corticotherapy (< 3 months) in 6% of patients; - no radiation-induced optic neuropathy or radiation-induced encephalopathy. - no increased intracranial pressure detected caused by post-radiation therapy perifocal oedema. - no benign or malignant radiation-induced central nervous system tumour. - moderate, progressive, short-term memory loss (8 months after FR) in 1 patient, but patients not tested for neuropsychologicaldeficits. GKS: - transient ischemic stroke in 1 patient during the follow-up period, who then 1 year later presented a transient contralateral central facial palsy. - no other complications observed

Study details	Participants	Interventions	Methods/risk of bias	Results
		Follow up: Mean (range) = 88.6 (42-168) months for FR and 63.6 (48-92) months for GKS		
Full citation Torres, R. C., Frighetto, L., De Salles, A. A., Goss, B., Medin, P., Solberg, T., Ford, J. M., Selch, M. Radiosurgery and stereotactic radiotherapy for intracranial meningiomas. Neurosurgical FocusNeurosurg 2003 14 p.e5 Ref Id 510285 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study	128 patients: Mean age (range) = 57.2 (18–87) years; males / females: N = 40 / 88; RT adjuvant / primary treatment: N = 84 / 44; divided into 2 groups based on type of RT: - SRS: 63 patients with 79 meningiomas; mean volume (range) = 12.7 (1.1–43) ml. - SRT: 72 patients with 77 meningiomas; mean volume (range) = 16.1 (1.25–57) ml. (Please note, patient numbers don't quite add up) Inclusion criteria "Between 1991 and 2002, 161 patients with 194 intracranial meningiomas underwent SRS or fractionated SRT at UCLA Medical Center……. Clinical and radiological follow-up data were obtained in 128 patients (79.5%) harboring 156 meningiomas (80.4%)." (p. 2) Exclusion criteria None reported	"Stereotactic radiotherapy was indicated for tumors involving the optic apparatus, substantially compressing the brainstem, or those deemed too large for SRS treatment. Its selection was also based on the UCLA classification of sellar and parasellar meningiomas" (p. 2) SRS (mean no of fractions = 1; mean prescribed dose (range) = 1567 (1200–2285); mean max dose (range): 2456 (1500–4000)) versus SRT (mean no of fractions (range) = 26.85 (5-30); mean prescribed dose (range) = 4839 (2380–5400); mean	-Bias due to confounding: serious risk of bias (not many patient characteristics reported split by treatment group; tumour volume may differ between the groups) -Bias in selection of participants into the study: low risk of bias -Bias in classification of interventions: low risk of bias -Bias due to missing data: unclear risk of bias (data available for 128/161 patients) -Bias in measurement of outcomes: low risk of bias -Bias in the selection of the reported results: low risk of bias -Overall bias: serious (potential baseline differences between treatment groups, missing data) Other information: Unequal lengths of follow up for the treatment groups	Tumour control: SRS: -Tumour size decreased/ no change/ increased: N = 22 / 36 / 5 - Tumour control rate (decreased + no change): 92% (58/63) SRT: -Tumour size decreased/ no change/ increased: N = 24 / 46 / 2 - Tumour control rate (decreased + no change): 97.2% (70/72) Neurological findings: - SRS (N = 63): Improved/ unchanged/ worsened: N = 22 / 36 / 5 - SRT (N = 65): Improved/ unchanged/ worsened: N = 21 / 42 / 2 Complications: SRS: - 4 procedures / 5% (slight decrease in visual acuity (N = 2), decrease in facial sensation (N = 2)) - Imaging-detected abnormalities not proceeded by clinical symptoms (3 procedures - Radiation-induced changes in the pattern of contrast enhancement due

Study details	Participants	Interventions	Methods/risk of bias	Results
"to describe our experience at UCLA with the management of intracranial meningiomas, demonstrating the evolution of the treatment planning and radiation delivery in the last decade." (p. 2) Study dates 1991-2002 Source of funding Not reported		max dose (range): 5350 (4500–6000)) Follow up: Mean (range) = 40.6 (6-125) months and 23.8 (6-72) months for SRS and SRT respectively.		to disruption of the blood–brain barrier (N = 2 images); small area of radiation necrosis (N = 1 follow-up image). SRT: - 4 procedures / 5.2% (mild reduction in facial sensation (N = 3), subjective complaint of worsened diplopia (N = 1)). In both groups, no patients needed further surgical treatment due to complications, which were mild and did not interfere with the patients' activities of daily living.

1 Evidence tables for review 4a - Management for a single brain metastasis

Study details	Participants	Interventions	Outcomes and results	Comments
Full citation Andrews, D. W., Scott, C. B., Sperduto, P. W., Flanders, A. E., Gaspar, L. E., Schell, M. C., Werner-Wasik, M., Demas, W., Ryu, J., Bahary, J. P., Souhami, L., Rotman, M., Mehta, M. P., Curran, W. J., Jr., Whole brain radiation therapy with	Sample size 331 randomised: 164 WBRT and radiosurgery; 167 to WBRT alone Characteristics | | WBRT+stereotactic surgery (n-164) | WBRT alone (n=167) | | --- | --- | --- | | Age mean | 58.8 (19-82) | 59.9 (24-90) |	Interventions WBRT alone or WBRT with stereotactic radiosurgery boost. Details WBRT: All patients received	Results | | WBRT | WBRT +SRS | p-value/ statistical analyses | | --- | --- | --- | --- | | Mean overall survival | 6.5 (n=167) | 5.7 (N=164) | p=0.1356 |	Limitations Randomisation: Yes, randomisation within strata by permutated blocks was done by use of computerised techniques at RTOG headquarters

Study details	Participants	Interventions	Outcomes and results	Comments
or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial, LancetLancet, 363, 1665-72, 2004 Ref Id 497036 Country/ies where the study was carried out USA Study type RCT Aim of the study We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG). Study dates From January, 1996, to June, 2001	<table><tr><td>Primary tumour site</td><td></td><td></td></tr><tr><td>Breast</td><td>9%</td><td>11%</td></tr><tr><td>Lung</td><td>64%</td><td>63%</td></tr><tr><td>Skin/melanoma</td><td>4%</td><td>5%</td></tr><tr><td>Other</td><td>14%</td><td>10%</td></tr><tr><td>Kidney</td><td>1%</td><td>1%</td></tr><tr><td>Bladder</td><td>0</td><td>2%</td></tr><tr><td>Colon</td><td>2%</td><td>1%</td></tr><tr><td>Ovarian</td><td>1%</td><td>1%</td></tr><tr><td>Unknown primary</td><td>4%</td><td>0</td></tr><tr><td>Number of brain metastases</td><td></td><td></td></tr><tr><td>1</td><td>56%</td><td>56%</td></tr><tr><td>2</td><td>24%</td><td>28%</td></tr><tr><td>3</td><td>20%</td><td>16%</td></tr></table> Inclusion criteria	WBRT in daily 2·5 Gy fractions to a total of 37·5 Gy over 3 weeks. WBRT with stereotactic radiosurgery boost: Patients allocated stereotactic radiosurgery boost received this treatment within 1 week of completing WBRT. We treated metastases up to 2·0 cm in broadest diameter with a surface isodose prescription of 24·0 Gy; metastases larger than 2 cm but equal to or smaller than 3 cm with 18·0 Gy; and metastases larger than 3 cm and less	<table><tr><td></td><td></td><td></td><td>(Kaplan-Meier method)</td></tr><tr><td>Mean overall survival single</td><td>4.9 (n=94)</td><td>6.5 (n=92)</td><td>p=0.0390 (Kaplan-Meier method)</td></tr><tr><td>Mean overall survival multiple</td><td>6.7 (n=73)</td><td>5.8 (n=72)</td><td>p=0.9776 (Kaplan-Meier method)</td></tr><tr><td>Mean overall survival if had squamous/non small cell lung carcinoma</td><td>3.9 (n=29)</td><td>5.9 (n=27)</td><td>p=0.0508 (Kaplan-Meier method)</td></tr><tr><td>Mean overall time to intracranial tumour progression</td><td></td><td></td><td>p=0.1278</td></tr></table>	when member institutions telephoned to enrol eligible patients. Patients were stratified by number of brain metastases (single vs 2–3) and extent of extracranial disease (none vs present). Allocation concealment: Yes, RTOG headquarters when member institutions telephoned to enrol eligible patients Patient blinding: Unlikely no. Assessor blinding: Unclear

Study details	Participants	Interventions	Outcomes and results	Comments
Source of funding This publication was supported by grant number (RTOG U10 CA21661, CCOP U10CA37422, Stat U10 CA32115) from the National Cancer Institute. Contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.	All patients were aged 18 years or older with no previous cranial radiation. Entry criteria included a contrast-enhanced MRI scan showing one to three brain metastases with a maximum diameter of 4 cm for the largest lesion and additional lesions not exceeding 3 cm in diameter. Metastases were deemed unresectable if they were located in deep grey matter or in eloquent cortex. Patients with newly diagnosed cancer presenting with brain metastases or patients with unknown primaries were both considered to have unknown disease control and were included in the study. Exclusion criteria We excluded patients who had Karnofsky Performance Status (KPS) score of less than 70, haemoglobin concentration less than 80 g/L, absolute neutrophil count of less than 1000 cells/L, or platelet count less than 50 000 cells per uL. Patients with metastases in the brain stem, or within 1 cm of the optic apparatus were excluded since no safety data for these sites were available from the antecedent phase I study, RTOG 9005.10 Patients who had	than or equal to 4 cm with 15·0 Gy.		Investigator blinding: Unclear Reporting bias: A number of outcomes the SD was not reported. It could only be calculated by using p value Drop out: none lost to follow up Compliance: 133/164 in WBRT and surgery completed treatment; 167 in WBRT completed treatment ITT: yes Single metastases: 56% Prior treatments: No previous cranial

			(Kaplan-Meier method)
1 year control of treated lesion (unchanged or improved)	37 (71%)	41 (82%)	
Complete response (3 months)	6 (n=78)	12 (n=75)	
Partial response (3 months)	42 (n=78)	43 (n=75)	
Stable (3 months)	17 (n=78)	11 (n=75)	
Progression (3 months)	13 (n=78)	8 (n=75)	
Acute toxicities (<90 days) GRADE 3-4	0/166	5/160	
Late toxicities, GRADE 3-4	4/166	6/160	
Death due to brain metastases (single)	22/82	19/73	
Death due to brain metastases (multiple)	24/67	20/64	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>received treatment for systemic cancer within 1 month of enrolment were judged to have active disease and were excluded.</td>
<td></td>
<td>
<table>
<tr><td>Death due to brain metastases (mixture)</td><td>46/149</td><td>39/137</td><td></td></tr>
<tr><td>KPS improved</td><td>3/75</td><td>10/79</td><td></td></tr>
<tr><td>Steroids increased</td><td>6/75</td><td>7/76</td><td></td></tr>
</table>
</td>
<td>radiation. Post operative patients with either residual or distal brain metastases remained 3 or fewer.

Mean treatment duration: 4 weeks (3 weeks WBRT)

Time points for measurement: 3 months, 12 months, 24 months</td>
</tr>
<tr>
<td>Full citation
Brown, P. D., Ballman, K. V., Cerhan, J. H., Anderson, S. K., Carrero, X. W., Whitton, A. C., Greenspoon, J., Parney, I. F., Laack, N. N. I., Ashman, J. B., Bahary, J. P., Hadjipanayis, C. G., Urbanic, J. J., Barker, F. G., 2nd, Farace, E., Khuntia, D., Giannini, C., Buckner, J. C.,</td>
<td>Sample size
194 randomised: 98 to stereotactic radiosurgery; 98 to whole brain radiotherapy
Characteristics
<table>
<tr><th></th><th>Stereotactic radiosurgery (n = 96)</th><th>Whole brain radiotherapy (n = 98)</th></tr>
<tr><td>Age, median (IQR)</td><td>61 (54-66)</td><td>62 (54-68)</td></tr>
<tr><td>Sex, M:F (%)</td><td>46:52 (47:53)</td><td>50:46 (52:48)</td></tr>
</table>
</td>
<td>Interventions
SRS group: stereotactic radiosurgery with a prescribed dose determined by surgical cavity volume (20 Gy if cavity volume was less than 4.2ml; 18 Gy if 4.2 - 7.9ml; 17 Gy if 8.0 - 14.3ml; 15 Gy</td>
<td>Results
<table>
<tr><th></th><th>SRS group, n = 98</th><th>WBRT group, n = 96</th><th>Notes</th></tr>
<tr><td>Median cognitive-deterioration-free survival (95% CI)</td><td>3.7 months (3.45 to 5.06)</td><td>3.0 months (2.86 to 3.25)</td><td>p<0.0001. HR 0.47 (95% CI 0.35 to 0.63). Cognitive-deterioration-free survival defined as the time from</td></tr>
</table>
</td>
<td>Limitations
Allocation concealment: yes (due to dynamic allocation algorithm, users could not deduce the next assignment in the sequence)
Patient blinding: no
Assessor blinding:</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
Galanis, E., Roberge, D., Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial, Lancet OncologyLancet Oncol, 18, 1049-1060, 2017 Ref Id 676087 Country/ies where the study was carried out USA and Canada Study type RCT Source of funding Supported by the National Cancer Institute of the National Institutes of Health, and in collaboration with other cooperative groups including Canadian Cancer Trials Group and the	<table><tr><td>Number of brain metastases, n (%)</td><td></td><td></td></tr><tr><td>1</td><td>75 (77)</td><td>74 (77)</td></tr><tr><td>2-4</td><td>23 (23)</td><td>22 (23)</td></tr><tr><td>Primary tumour site, n (%)</td><td></td><td></td></tr><tr><td>Lung</td><td>58 (59)</td><td>56 (58)</td></tr><tr><td>Other</td><td>29 (30)</td><td>30 (31)</td></tr><tr><td>Radioresistant</td><td>11 (11)</td><td>10 (10)</td></tr><tr><td>Extent of resection, n (%)</td><td></td><td></td></tr><tr><td>Subtotal</td><td>8 (8)</td><td>13 (14)</td></tr><tr><td>Total</td><td>90 (92)</td><td>83 (86)</td></tr><tr><td>Period of systemic disease control, n (%)</td><td></td><td></td></tr><tr><td>≤3 months</td><td>54 (55)</td><td>54 (56)</td></tr><tr><td>>3 months</td><td>44 (45)</td><td>42 (44)</td></tr></table>Inclusion criteria Inclusion criteria were: adult patients (aged 18 years or over) with one resected metastatic brain lesion, and a resection cavity measuring less than 5.0cm in maximal extent. Up to three unresected metastases (each <3cm in maximal extent) were allowed. Eastern Cooperative Oncology Group	if 14.4 - 19.9ml; 14 Gy if 20.0 - 29.9ml and 12 Gy if 30.0ml or more up to the maximal surgical cavity extent of 5cm). The surgical cavity was treated with a 2mm margin. Any unresected metastases were treated with SRS with 24 Gy in a single fraction if lesions were less than 1.0cm; 22 Gy if 1.0 to 2.0cm and 20 Gy if lesions were 2.1 to 2.9cm in maximal diameter. WBRT: treated with either 30 Gy in ten fractions of 3.0 Gy, or 37.5 Gy in 15 fractions of 2.5 Gy, delivered five	<table><tr><td></td><td></td><td></td><td>randomisation to a drop of > 1SD from baseline in at least one of the six cognitive tests used in the study.</td></tr><tr><td>Median overall survival (95% CI)</td><td>12.2 months (9.7 to 16.0)</td><td>11.6 months (9.9 to 18.0)</td><td>p = 0.7. HR 1.07 (95% CI 0.76 to 1.50)</td></tr><tr><td>Time to intracranial tumour progression (95% CI)</td><td>6.4 months (5.16 to 8.90)</td><td>27.5 months (14.85 - not reached)</td><td>p<0.0001. HR 2.45 (95% CI 1.62 to 3.72)</td></tr><tr><td>Surgical bed control at 6 months</td><td>80.4%</td><td>87.1%</td><td>p = 0.00068</td></tr><tr><td>Median duration of stable or better functional independence (95% CI)</td><td>median not yet reached (17.6 months to not yet reached)</td><td>14.0 months (8.4 to 27.0)</td><td>p = 0.034. HR 0.56 (0.32 to 0.96)</td></tr><tr><td>Number of participants experiencing</td><td>47/93 (51%)</td><td>65/92 (71%)</td><td></td></tr></table>	neuropsychologists who conducted the cognitive tests were blinded to treatment allocation. All other outcome assessors were not. Investigator blinding: no Reporting bias: none Dropout: 4 patients were lost to follow up, all in the WBRT group Compliance: 5 patients in the SRS group and 4 patients in the WBRT group did not receive treatment. 1 patient assigned to SRS received WBRT instead. Additional treatment: not fully reported. Local salvage therapy used

Study details	Participants	Interventions	Outcomes and results				Comments
NRG Oncology Group, supported by the National Cancer Institute. Aim of the study To establish the effect of stereotactic radiosurgery on survival and cognitive outcomes compared to whole brain radiotherapy in patients with resected brain metastases. Study dates Recruitment took place from November 10th 2011 until November 16th 2015.	performance status of 0-2, and pathology from the resected brain metastasis consistent with a non-CNS primary site. Exclusion criteria Exclusion criteria were: pregnant or nursing women, men or women of childbearing potential unwilling to use adequate contraception, inability to complete an MRI scan with contrast, planned chemotherapy during the radiation, previous cranial radiotherapy, leptomeningeal metastases, lesion located within 5mm of the optic chiasm or within the brainstem, or metastases from primary germ-cell tumours, small-cell carcinoma or lymphoma. Previous treatment with systemic therapies (eg. chemotherapy) was permitted. Cytotoxic chemotherapy was not allowed during SRS or WBRT but could start immediately afterwards.	days a week. Sites predetermined the fractionation schedule, based on institutional preference, that would be used for all patients randomised at the site. Any unresected metastases were treated with SRS with 22 Gy in a single fraction if lesions were less than 1.0cm; 20 Gy if 1.0 to 2.0cm and 18 Gy if lesions were 2.1 to 2.9cm in maximal diameter. For both study groups, the SRS dose was prescribed to the highest isodose line encompassing the target.	toxic events (any grade)				in 31/98 of SRS group (20 of whom had WBRT as part of salvage therapy) and 20/96 in WBRT group ITT: yes Single metastasis: 77% of population had a single (resected) metastasis Prior treatments: all patients had received surgical resection of a single metastasis before entry to the trial. Other previous therapies are not reported. Mean treatment duration: WBRT regime took 2-3 weeks, depending on the choice of
			Number of participants experiencing toxic events (grade 3 or worse)	11/93 (12%)	17/92 (18%)		
			FACT-Br scores at 6 months				
			Physical well-being subscore	33/65 stable/improved	18/64 stable/ improved	Difference in change from baseline scores between groups: 16.7 (95% CI 7.8 to 25.5)	
			Social/family subscore	31/65 stable/improved	30/64 stable/improved	Difference in change from baseline scores between groups: -5.4 (95% CI -14.8 to 3.9)	
			Emotional well-being subscore	36/65 stable/improved	37/64 stable/improved	Difference in change from baseline	

Study details	Participants	Interventions	Outcomes and results				Comments
		Details Randomisation: electronic, web-based randomisation system. Group allocation 1:1 with stratification according to age, duration of extracranial disease, number of brain metastases, histology, maximal diameter of resection cavity and treatment centre				scores between groups: -9 (95% CI -20 to 1.2)	fractionation protocol Time points for measurement: 12 weeks, then 6, 9, 12, 16 and 24 months
			Functional well-being subscore	35/65 stable/improved	30/65 stable/improved	Difference in change from baseline scores between groups: 15.1 (95% CI 4.4 to 25.7)	
			Brain specific concerns	41/65 stable/improved	30/65 stable/improved	Difference in change from baseline scores between groups: 10 (95% CI 0.7 to 19.3)	
			LASA scores for overall quality of life at 6 months	35/65 stable/improved	25/64 stable/improved	Difference in change from baseline scores between groups: 14.9 (95% CI 3.5 to 26.2)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Kepka, L, Tyc-Szczepaniak, D, Bujko, K, Olszyna-Serementa, M, Michalski, W, Sprawka, A, Trabska-Kluch, B, Komosinska, K, Wasilewska-Tesluk, E, Czeremszynska, B, Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: results from a randomized trial, Radiotherapy and Oncology, 121, 217-224, 2016
Ref Id
654685
Country/ies where the study was carried out
Poland
Study type
RCT
Source of funding
The authors report that there was no funding source for the study.
Aim of the study</td>
<td>Sample size
60 participants were randomised. 30 participants allocated to tumour bed radiotherapy; 30 participants allocated to whole brain radiotherapy.
Characteristics
<table>
<tr><th></th><th>Stereotactic radiotherapy to the tumour bed
n = 29</th><th>Whole brain radiotherapy
n = 30</th></tr>
<tr><td>Age in years, median (range)</td><td>59.5 (30 - 77)</td><td>59.5 (43 - 78)</td></tr>
<tr><td>Sex, M:F (%)</td><td>11:18 (38:62)</td><td>15:15 (50:50)</td></tr>
<tr><td>Karnofsky Performance Score</td><td></td><td></td></tr>
<tr><td>90-100</td><td>24 (83%)</td><td>25 (83%)</td></tr>
<tr><td>70-80</td><td>5 (17%)</td><td>5 (17%)</td></tr>
<tr><td>Extracranial disease</td><td>14 (48%)</td><td>13 (43%)</td></tr>
<tr><td>Total resection of brain metastasis</td><td>24 (83%)</td><td>27 (90%)</td></tr>
<tr><td>Location of primary tumour</td><td></td><td></td></tr>
<tr><td>Lung</td><td>14 (48%)</td><td>15 (50%)</td></tr>
</table>
</td>
<td>Interventions
Stereotactic radiotherapy to the tumour bed: SRS-TB was linac based. Participants had post-gadolinium enhanced T1-weighted MRI (1.5mm slices) and CT with intravenous contrast performed for planning. Both sets of images were fused for target delineation. The clinical target volume was defined as the contrast-enhancing surgical cavity with exclusion of the surgical tract, postoperative changes and surrounding oedema. Contouring was performed</td>
<td>Results
<table>
<tr><th></th><th>SRS-TB group
n = 29</th><th>WBRT group
n = 30</th><th></th></tr>
<tr><td>Overall survival at 2 years</td><td>10% (5% CI 0 - 22)</td><td>37% (95% CI 19-55)</td><td>p = 0.046, HR 1.8 (95% CI 0.99 - 3.30)</td></tr>
<tr><td>Cumulative incidence of neurological/cognitive failure at 6 months</td><td></td><td></td><td>Defined as worsening of neurological status by one point or more within the five points MRC scale, a worsening of MMSE test score by three or more points, or neurological death. Difference at 6 months between the groups was -8% (95% CI +17 to -34% in favour of WBRT)</td></tr>
<tr><td>Cumulative incidence of neurological/cognitive failure at 2 years</td><td>21/29 75% (95%</td><td>19/30 62% (95%</td><td>p = 0.31, HR 1.32 (95% CI 0.74 to 2.36)</td></tr>
</table>
</td>
<td>Limitations
Allocation concealment: unclear
Patient blinding: unclear, unlikely
Assessor blinding: unclear, unlikely
Investigator blinding: unclear, unlikely
Reporting bias: none
Dropout: 1 participant in the SRS-TB group withdrew consent for the trial and was not included in the ITT analysis
Compliance: 21/29 received the allocated treatment in the SRS group: 5 received whole brain radiotherapy; 2</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
To evaluate whether neurological and cognitive outcomes differ between individuals who receive stereotactic radiotherapy to the tumour bed, and those who receive whole body radiotherapy, following surgical resection of a single brain metastasis. Study dates From December 2011 to September 2015.	<table><tr><td>Colorectal</td><td>7 (24%)</td><td>2 (6.5%)</td></tr><tr><td>Breast</td><td>1 (3.5%)</td><td>6 (20%)</td></tr><tr><td>Melanoma</td><td>1 (3.5)</td><td>3 (10%)</td></tr><tr><td>Kidney</td><td>2 (7%)</td><td>0</td></tr><tr><td>Other</td><td>4 (14%)</td><td>4 (13.5%)</td></tr></table>Inclusion criteria Inclusion criteria were: single brain metastasis found by pre-operative MRI of the brain, pathologically confirmed metastasis from the solid tumour in the resected brain tumour, total or subtotal resection in the surgeon's operative report, Karnofsky performance status ≥70, life expectancy > 6 months, no obstacle to perform MRI in the follow-up period, and signed informed consent. Exclusion criteria Exclusion criteria were: brain metastasis from small-cell lung cancer and haematological malignancies, dementia syndromes, and previous brain irradiation.	with the aid of a neuroradiologist wherever necessary. A 3mm margin was added to create the planned target volume. A dose of 15-18 Gy was prescribed at the isodose line, encompassing the PTV (no lower than 80% IDL, usually 90% IDL). For surgical cavities larger than 5cm, or those of irregular, complex shape, or in the proximity of critical structures for which dose limits with a single fraction would be exceeded, the prescribed	<table><tr><td></td><td>CI 58-93)</td><td>CI 43-80)</td><td></td></tr><tr><td>Toxicity events of Grade 3 or higher</td><td>0/29</td><td>0/30</td><td></td></tr><tr><td>Total intracranial progression (in the tumour bed and/or at new sites in the brain)</td><td>11/19 (58%)</td><td>10/28 (36%)</td><td>p = 0.133</td></tr><tr><td>Relapse in tumour bed</td><td>5/19 (26%)</td><td>7/28 (25%)</td><td>p = 1</td></tr><tr><td>Progression at new sites in the brain</td><td>8/19 (42%)</td><td>6/28 (21%)</td><td>p = 0.128</td></tr><tr><td>Salvage treatment of brain relapse</td><td>9/11 (81%)</td><td>6/10 (60%)</td><td></td></tr></table>	received radiosurgery for metastases identified on planning MRI; 1 did not receive the allocated treatment. 29/30 received the allocated treatment in the WBRT group: 1 received tumour bed radiotherapy. Additional treatment: not reported ITT: yes Single metastasis: 93.3% (2 participants were identified as having additional metastases on their planning MRI) Prior treatments: not reported Mean treatment duration:

Study details	Participants	Interventions	Outcomes and results	Comments
		dose was 25 Gy given in 5 fractions over 5 days. Whole brain radiotherapy: Participants in this group had no MRI, and CT was conducted without contrast. The WBRT dose was 30 Gy in 10 fractions, delivered 5 times per week at the linear accelerator. Details Randomisation : Randomisation based on the minimization method was performed by telephone to a central datacentre. Participats were stratified according to the institution,		WBRT was conducted over two weeks. For the majority of participants in the SRS arm they received a single fraction for treatment. However 6/29 participants received five fractions, given over five days (for reasons as specified in the methods) Time points for measurements : 8 weeks, then every 3 months

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>the presence of extracranial disease, Karnofsky performance score and "radioresistant disease" histology (melanoma or renal cancer) versus others)</td><td></td><td></td></tr>
<tr><td>Full citation
Kepka, L., Tyc-Szczepaniak, D., Osowiecka, K., Sprawka, A., Trabska-Kluch, B., Czeremszynska, B., Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial, Clinical and Translational Oncology, 1-10, 2017
Ref Id
676193
Country/ies where the study was carried out
Poland</td><td>Sample size
60 participants were randomised; 30 were allocated to stereotactic radiotherapy to the tumour bed; 30 were allocated to whole brain radiotherapy
Characteristics
See entry for Kepka 2016
Inclusion criteria
See entry for Kepka 2016
Exclusion criteria
See entry for Kepka 2016</td><td>Interventions
See entry for Kepka 2016
Details
See entry for Kepka 2016, except:
ITT analysis was not performed for this publication.
Participants who received initial treatment with stereotactic radiotherapy to the tumour bed (n = 24) were compared to those who received whole</td><td>Results<table><tr><th></th><th>SRS-TB group n = 24</th><th>WBRT group n = 34</th><th>Notes/p value</th></tr><tr><td>Global quality of life scores at 2 months</td><td>65.9 (±24.6)</td><td>61.4 (±25.7)</td><td>p = 0.60
Mean scores of QLQ-C30 and BN-20 questionnaire measures.</td></tr><tr><td>Global quality of life scores at 5 months</td><td>55.7 (±26.9)</td><td>67.1 (±23.7)</td><td>p =0.19</td></tr></table></td><td>Limitations
See Kepka 2016</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Study type
RCT
Source of funding
None reported.
Aim of the study
To compare the health related quality of life for people who receive stereotactic radiotherapy to the tumour bed, as compared with whole brain radiotherapy, following surgical resection of a single brain metastasis.
Study dates
December 2011 to September 2015</td><td></td><td>brain radiotherapy (n = 34).</td><td></td><td></td></tr>
<tr><td>Full citation
Mintz, A. H., Kestle, J., Rathbone, M. P., Gaspar, L., Hugenholtz, H., Fisher, B., Duncan, G., Skingley, P., Foster, G., Levine, M., A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis, CancerCancer, 78, 1470-1476, 1996</td><td>Sample size
N=84 (n=43 radiation alone and n=41 surgery plus radiation)
Characteristics<table><tr><th></th><th>Radiation alone (n=43)</th><th>Radiation plus surgery (n=41)</th></tr><tr><td>Age (years SD)</td><td>58 (9.86)</td><td>58.9 (8.98)</td></tr><tr><td>Location of primary tumour</td><td></td><td></td></tr><tr><td>No known primary tumour</td><td>2</td><td>2</td></tr></table></td><td>Interventions
Radiation: Radiation therapy was initiated within 3 weeks of the qualifying CT scan. Patients assigned to both treatment arms received 3000 centigray (cGy) of whole brain radiation therapy over 2 weeks (300</td><td>Results<table><tr><th></th><th>Radiation</th><th>Radiation and surgery (n=41)</th><th>Narrative</th></tr><tr><td>Deaths within 30 days of surgery</td><td>4</td><td>3</td><td></td></tr><tr><td>Deaths within 1 year of treatment</td><td>30</td><td>36</td><td></td></tr><tr><td>Median survival (months)</td><td>6.28 (3-11.4)</td><td>5.62 (3.9-7.2)</td><td></td></tr><tr><td>Mean proportion of days spent functionally independent - Karnofsky</td><td>0.32 (0.3)</td><td>0.32 (0.3)</td><td>same</td></tr></table></td><td>Limitations
Randomisation: yes, unclear methods (central telephone randomisation)
Allocation concealment: Unclear
Patient blinding: Unlikely
Assessor blinding: Unclear</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id
498664
Country/ies where the study was carried out
Canada
Study type
Randomised controlled trial
Source of funding

Funded by the National Cancer Institute of Canada and the Ontario Clinical Oncology Group.

Aim of the study
We now report the results of a randomized multicentred trial of surgery plus radiation therapy compared with radiation alone in patients with a single brain metastasis.
Study dates</td>
<td>
<table>
<tr><td>Lung (non small cell)</td><td>22</td><td>23</td></tr>
<tr><td>Breast</td><td>8</td><td>2</td></tr>
<tr><td>Colon or rectum</td><td>3</td><td>10</td></tr>
<tr><td>Skin</td><td>2</td><td>2</td></tr>
<tr><td>Renal</td><td>2</td><td>1</td></tr>
<tr><td>Head and neck</td><td>1</td><td>0</td></tr>
<tr><td>Other</td><td>3</td><td>1</td></tr>
<tr><td>Dose of dexamethasone</td><td>11.3 (6.5)</td><td>12.2 (8)</td></tr>
<tr><td>Time between brain metastases and randomisation (days/SD)</td><td>8 (6.83)</td><td>9.7 (14.05)</td></tr>
<tr><td>After treatment of brain metastases: Chemotherapy and Hormone treatment</td><td>6/2</td><td>4/1</td></tr>
</table>
Inclusion criteria
Patients younger than 80 years of age who had a lesion consistent with a single brain metastasis on computed
</td>
<td>cGy X 10 fractions). Surgery plus radiation: Patients allocated to surgery plus radiation underwent craniotomy under general anesthesia to achieve gross total removal of the metastases or lobectomy.Radiotherapy began no later than 4 weeks after surgery.</td>
<td>
<table>
<tr><td>performance scores ≥ 70</td><td></td><td></td><td></td></tr>
<tr><td>Quality of life (Spitzer score) 3 months</td><td>5.36 (2.19)</td><td>6.38 (2.64)</td><td></td></tr>
<tr><td>Quality of life (Spitzer score) 4-6 months</td><td>6.15 (1.9)</td><td>6.32 (2.03)</td><td></td></tr>
</table>
</td>
<td>Investigator blinding: Unclear
Reporting bias: None
Drop out: None of the patients were lost to follow-up
Compliance: Surgery 83% N who did not comply n= 7/ 41 (4 died prior, 2 withdrew, 1 type of cancer) Radiation 63%; N who did not comply n= 16/43 (1 died, 10 had surgery, 5 later required surgery)
ITT: yes
Multiple metastases: none
Prior treatments: No previous cranial irradiation. Some patients received other</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td>tomography (CT) scan and pathologic confirmation of cancer within the previous 5 years were potentially eligible
Exclusion criteria
Patients were excluded from the study if they had a Karnofsky performance status" of less than 50; had leukemia, lymphoma, small cell lung cancer, or skin cancer other than melanoma; had signs of meningeal carcinomatosis; had previous cranial irradiation; had an underlying medical illness or comorbid condition that precluded adequate follow-up; had a lesion in the brainstem or basal ganglia; required emergency decompression due to increased intracranial pressure (other than relief of obstructive hydrocephalus); or had previous brain metastases.</td><td></td><td></td><td>treatments for their primary tumor, e.g., chemotherapy after treatment of the brain metastasis
Mean treatment duration: NR
Time points for measurement: All patients were seen monthly after completion of treatment for 6 months and every 3 months thereafter. At least 18 months
Other information</td></tr>
<tr><td>Full citation
Muacevic, A., Wowra, B., Siefert, A., Tonn, J. C., Steiger, H. J., Kreth, F. W., Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single</td><td>Sample size
N=64 (n=31 radiosurgery, n=33 surgery + WBRT)
Characteristics<table><tr><td></td><td>Surgery (n=33)</td><td>Radiosurgery (n=31)</td></tr><tr><td>Age years</td><td>58.3 (9.6)</td><td>54.3 (11.7)</td></tr></table></td><td>Interventions
Radiosurgery:
Surgery + WBRT:

WBRT was started within the first 14 days after tumor resection</td><td>Results<table><tr><td></td><td>Radiosurgery (n=31)</td><td>Resectory (Surgery) + WBRT (n=33)</td><td>Narrative</td></tr><tr><td>Died by 12 months follow-up</td><td>19</td><td>17</td><td></td></tr><tr><td>Complete response</td><td>9</td><td>33</td><td></td></tr></table></td><td>Limitations
Details
Randomisation: yes, using a minimisation programme with a random element. Randomization was performed centrally at the</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
metastases to the brain: a randomized controlled multicentre phase III trial, Journal of Neuro-OncologyJ Neurooncol, 87, 299-307, 2008 Ref Id 498710 Country/ies where the study was carried out Study type Prospective randomized multi-center trial Source of funding Elekta Research Foundation. Aim of the study The current randomized trial was conducted, to analyze and compare for the first time the effectiveness of surgery plus WBRT with that of Gamma Knife surgery alone.	<table><tr><td>Tumour location</td><td></td><td></td></tr><tr><td>Supratentorial</td><td>26</td><td>23</td></tr><tr><td>Infratentorial</td><td>7</td><td>8</td></tr><tr><td>Site of primary tumour</td><td></td><td></td></tr><tr><td>Lung/other primaries</td><td>12/21</td><td>10/21</td></tr></table> Inclusion criteria Patients were considered eligible for the study if they had a single untreated brain metastasis with a diameter B3 cmin an operable site, were aged between 18 and 80 years, had a historically proven cancer at a site outside the central nervous system, presented with a KPS greater than or equal to 70, and were thought to have stable systemic disease with a life expectancy of at least 4 months. Exclusion criteria Patients were excluded if they had documented or suspected meningeal metastases, had a history of previous cranial radiotherapy, were in need of immediate brain tumor resection or were known to have a radiosensitive primary tumor type, such as small cell lung cancer, lymphoma, leukemia, myeloma, or germ cell tumor.	using lateral ports covering the brain and meninges to the foramen magnum. Patients received 40 Gray (Gy) over 4 weeks (2 Gy 9 20 fractions). Tumor resection: Tumor resection was performed using microsurgical techniques. Navigational devices were applied according to the decision of the treating surgeon. Gadolinium enhanced MRI scans of the head were done within the first 3 days after surgery to confirm that the brain metastases had been	<table><tr><td>(complete resolution)</td><td></td><td></td><td></td></tr><tr><td>Partial response (tumour volume reduction >50%)</td><td>15</td><td>0</td><td></td></tr><tr><td>Stable disease (tumour control)</td><td>6</td><td>0</td><td></td></tr><tr><td>Progressive disease (any tumour V increase >25%)</td><td>1</td><td>0</td><td></td></tr><tr><td>Freedom from local recurrence</td><td>30</td><td>27</td><td></td></tr><tr><td>Local recurrence (complete resolution and any reappearance of new enhanced lesion in same location)</td><td></td><td></td><td></td></tr><tr><td>Steroid use</td><td>22</td><td>28</td><td></td></tr><tr><td>Health related quality of life</td><td></td><td></td><td>No data provided only a narrative and p value</td></tr><tr><td>Acute toxicity (<90 days) (unclear if patient is represented more than 1 x)</td><td>16</td><td>32</td><td></td></tr></table>	data center by telephone Allocation concealment: Unclear. No detail of what happened to schedule with 3rd party Patient blinding: No, unlikely Assessor blinding: Unclear Investigator blinding: Unclear Reporting bias: SD nor CI were reported for median survival, mean/SD not reported for Quality of life Drop out: None reported Compliance: All complied but some had additional treatment. Surgery group n=6/33 additional

Study details	Participants	Interventions	Outcomes and results	Comments
Study dates		completely resected. Radiosurgery: Gamma Knife surgery was administered using stereotactic MRI guidance. The treatment was performed on an outpatient basis. The mean dose applied to the tumor margin (prescribed tumor dose) was 21 Gy (range: 14–27 Gy). The prescribed tumor dose was in the range of 20–27 Gy for radio-resistant tumors. The mean maximum dose was 41 Gy (range: 28–54 Gy), and on average, the 50% isodose (range: 35–	Pulmonary embolism | 0 | 1 |	treatment (4 had surgical re-treatment or gamma knife surgery, 2 had supportive treatment (not defined); Radiosurgery n=6/31 additional treatment (5 had new radiosurgery; 1 WBRT) ITT: yes Single metastases: 100% Prior treatments: No history of previous cranial radiotherapy Mean treatment duration: NR Time points for measurement: 12 months follow up

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>85%) was used to irradiate the tumor margin. Conformal multiple isocenter Gamma Knife surgery (mean number of isocenters per patient: 7) was performed in all patients</td><td></td><td></td></tr>
<tr><td>Full citation

Mulvenna, P., Nankivell, M., Barton, R., Faivre-Finn, C., Wilson, P., McColl, E., Moore, B., Brisbane, I., Ardron, D., Holt, T., Morgan, S., Lee, C., Waite, K., Bayman, N., Pugh, C., Sydes, B., Stephens, R., Parmar, M. K., Langley, R. E., Dexamethasone and supportive care with or without whole brain radiotherapy in</td><td>Sample size

538 patients (269 to WBRT and OSC; 269 to OSC alone)

Characteristics<table><tr><td></td><td>WBRt+OSC (n=269)</td><td>OSC (N=269)</td></tr><tr><td>Age (years) median</td><td>66 (38-84)</td><td>67 (45-85)</td></tr></table></td><td>Interventions

OSC (Optimal Supportive Care) + WBRT vs. WBRT

Details

Optimal Supportive Care: OSC included oral dexamethasone given with a proton pump inhibitor with</td><td>Results<table><tr><td></td><td>WBRT+OSC (n=269)</td><td>OSC (N=269)</td><td>p value/notes</td></tr><tr><td>Any serious adverse event</td><td>89 (33%)</td><td>82 (30%)</td><td></td></tr><tr><td>Cardiac</td><td>2</td><td>1</td><td></td></tr><tr><td>Infection</td><td>17</td><td>16</td><td></td></tr><tr><td>Quality of life (EQ-5D) 12 weeks</td><td></td><td></td><td></td></tr></table></td><td>Limitations

Randomisation: yes, unclear methods.

Allocation concealment: unclear. All ocation to treatment group was done by a phone call from the hospital to the Medical Research</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial, LancetLancet, 2, 2, 2016 Ref Id 498722 Country/ies where the study was carried out UK, Australia Study type Non-inferiority, phase 3 randomised trial Source of funding Funding was provided by Cancer Research UK (C17956/A6414). The trial sponsor was	<table><tr><td>Brain metastases status</td><td></td><td></td></tr><tr><td>Newly diagnosed</td><td>83%</td><td>82%</td></tr><tr><td>Progressive disease</td><td>17%</td><td>18%</td></tr><tr><td>N brain mets</td><td></td><td></td></tr><tr><td>1</td><td>80</td><td>82</td></tr><tr><td>2</td><td>56</td><td>56</td></tr><tr><td>3</td><td>28</td><td>22</td></tr><tr><td>4</td><td>15</td><td>20</td></tr><tr><td>5+</td><td>85</td><td>89</td></tr><tr><td>NSCLC</td><td>100%</td><td>100%</td></tr></table> **Inclusion criteria** Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted (with predefi ned washout periods of 4 weeks for chemotherapy and 1 week for TKIs). Participants were aged 18 years or older. Patients with histologically proven NSCLC and brain metastases (confirmed by CT or MRI).	the dose of steroid determined by the patients' symptoms and titrated downwards if symptoms improved, as well as support from a named specialist nurse and immediate access to specialised clinicians and palliative care teams. WBRT was defined as 20 Gy in five daily fractions ideally given over 5–8 days with a 4–8 MV linear accelerator with two parallel opposed fields, commenced as soon as was practical	<table><tr><td>Maintained or improved quality of life</td><td>24/54</td><td>21/43</td><td></td></tr><tr><td>KPS changes at 12 weeks</td><td></td><td></td><td>p=0.0724</td></tr><tr><td>Mean (SD)</td><td>18 (15.53)</td><td>13.4 (13.66)</td><td></td></tr><tr><td>Overall survival HR 1 met</td><td>79/80</td><td>82/82</td><td>HR 1.00 (0.73 to 1.36)</td></tr><tr><td>2</td><td>56/56</td><td>56/56</td><td>HR 1.11 (0.76 to 1.62)</td></tr><tr><td>3</td><td>29/28</td><td>22/22</td><td>HR 1.11 (0.63 to 1.95)</td></tr><tr><td>4</td><td>15/15</td><td>20/20</td><td>HR 0.70 (0.35 to 1.40)</td></tr><tr><td>>5</td><td>84/85</td><td>89/89</td><td>HR 1.37 (1.01 to 1.86)</td></tr><tr><td>All patients</td><td>267/269</td><td>269/269</td><td>HR 1.10 (0.93 to 1.31)</td></tr></table>	**Council Clinical Trials Unit** **Patient blinding: No** **Assessor blinding: Unclear** **Investigator blinding: No** **Reporting bias: unclear** **Lost to follow up: None appeared to withdraw. ITT was used.** **Compliance: WBRT+OSC= 30 did not receive WBRT (10 died before starting treatment); 19 received <20 Gy 88% compliance; OSC = 100%** **ITT: yes, ITT**

Study details	Participants	Interventions	Outcomes and results	Comments
the Medical Research Council in the UK, and the Trans Tasman Radiation Oncology Group in Australia. Funding for Australia sites was provided by the National Health and Medical Research Council Australia (NHMRC 441402). Aim of the study We aimed to establish whether WBRT could be omitted without a signifi cant eff ect on survival or quality of life. Study dates March 2, 2007, and Aug 29, 2014,	**Exclusion criteria** Exclusion criteria included previous radio therapy to the brain, or previous or current illness thought likely to interfere with protocol treatment.	after randomisation	Median survival weeks: 8.5 (7.1 to 9.9); 9.2 (7.2 to 11.1) Use of dexamethasone 4 weeks: 16/245; 11/233 8 weeks: 30/245; 24/233	**Single metastases: 30%** **Prior treatments: Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted (with predefined washout periods of 4 weeks for chemotherap y and 1 week for TKIs)** **Mean treatment duration: mean survival up to 11·1 weeks** **Time points for measurement**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>: 4, 8 or 12 weeks</td></tr>
<tr>
<td>Full citation
Patchell, R. A., Tibbs, P. A., Regine, W. F., Dempsey, R. J., Mohiuddin, M., Kryscio, R. J., Markesbery, W. R., Foon, K. A., Young, B., Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial, Journal of the American Medical Association, 280, 1485-1489, 1998
Ref Id
498897
Country/ies where the study was carried out
USA
Study type
RCT
Source of funding
Not reported.
Aim of the study
To assess the impact of whole brain radiotherapy in addition to surgical</td>
<td>Sample size
95 participants were randomised: 49 were allocated to the radiotherapy group; 46 were allocated to the observation group (surgery only, without post-operative radiotherapy)
Characteristics
<table>
<tr><th></th><th>Observation group (surgery only) n = 46</th><th>Radiotherapy group (surgery followed by radiotherapy) n = 49</th></tr>
<tr><td>Sex, M:F (%)</td><td>27:19 (59:41)</td><td>28:21 (57:43)</td></tr>
<tr><td>Age in years, median (range)</td><td>58 (38-80)</td><td>60 (42-78)</td></tr>
<tr><td>Karnofsky score, median (range)</td><td>90 (70 - 100)</td><td>90 (70 - 100)</td></tr>
<tr><td>Primary tumour location, n (%)</td><td></td><td></td></tr>
<tr><td>Lung (non-small cell)</td><td>28 (61)</td><td>29 (59)</td></tr>
<tr><td>Breast</td><td>4 (9)</td><td>5 (10)</td></tr>
<tr><td>Other</td><td>14 (30)</td><td>15 (31)</td></tr>
</table>
</td>
<td>Interventions
Both groups had received surgical resection of the metastasis prior to entry to the trial. At the time of randomisation, all patients not taking corticosteroids began treatment with 4mg dexamethasone sodium phosphate every 6 hours. Whole brain radiotherapy group: patients received 50.4 Gy over 5.5 weeks (1.8 Gy x 28 fractions) prescribed ot the cranial midline. Radiotherapy was started</td>
<td>Results
<table>
<tr><th></th><th>Observation group n = 46</th><th>WBRT group n = 49</th><th></th></tr>
<tr><td>Overall survival</td><td>7/46 (15%)</td><td>6/49 (12%)</td><td></td></tr>
<tr><td>Median survival, weeks</td><td>43</td><td>48</td><td>p = 0.39. RR of death 0.91 (95% CI 0.59 to 1.40)</td></tr>
<tr><td>No brain recurrence</td><td>14/46 (30%)</td><td>40/49 (82%)</td><td></td></tr>
<tr><td>Recurrence at site of original metastasis</td><td>15/46 (33%)</td><td>2/49 (4%)</td><td></td></tr>
<tr><td>Recurrence at original site and distant brain sites</td><td>6/46 (13%)</td><td>3/49 (6%)</td><td></td></tr>
<tr><td>Distant brain recurrence only</td><td>11/46 (24%)</td><td>4/49 (8%)</td><td></td></tr>
<tr><td>Time to any brain recurrence, median weeks</td><td>26</td><td>220</td><td>RR of any brain recurrence 4.94 (95% CI 2.36 - 10.35)</td></tr>
</table>
</td>
<td>Limitations
Details
Randomisation: computer generated random numbers at a central site were used to assign patients to the treatment groups. Participants were stratified by the extent of disease and primary tumour type.
Allocation concealment: unclear
Patient blinding: unclear, unlikely
Assessor blinding: unclear, unlikely</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments

resection of a single brain metastasis as compared with surgical resection alone.
Study dates
Trial ran from September 1989 to March 1997. Follow up continued until November 1997.

unknown	4 (9)	5 (10)
genitourinary	5 (11)	3 (6)
gastrointestinal	4 (8)	4 (8)
head and neck	0	2 (4)
melanoma	1 (2)	1 (2)
Extent of disease, other than brain metastasis, n (%)		
None	16 (35)	18 (37)
Primary tumour only	18 (39)	19 (39)
Disseminated	12 (26)	12 (24)
Time from diagnosis of primary tumour and development of brain metastasis, median (range, weeks	29 (0 - 1111)	39 (0 - 843)
Location of brain metastasis		
Supratentorial	33 (72)	32 (65)
Infratentorial	13 (28)	17 (35)

Inclusion criteria
The inclusion criteria were: participants over 18 years of age with tissue-proven diagnosis of metastatic brain tumour,

within 28days following surgery. Use of corticosteroids was continued without tapering through the first 2 weeks of radiation therapy and then tapered and stopped, if tolerated. WBRT was given using lateral ports covering the brain and meninges to the foramen magnum. Observation group: received surgery only, with no further treatment for the brain metastasis. Corticosteroids were tapered and use was discontinued within 2 weeks following

Time to distant brain recurrence, median weeks	53	220	RR of distant brain recurrence 2.77 (95% CI 1.16 to 6.59)
Median time to deterioration in Karnofsky score (<70), weeks	35	37	p = 0.61. RR 0.84 (95% CI 0.61 to 1.17)

Investigator blinding: unclear, unlikely
Reporting bias: none
Dropout: no withdrawals from the trial

Study details	Participants	Interventions	Outcomes and results	Comments
	obtained from a complete resection of a single brain metastasis. Exclusion criteria Exclusion criteria were: brain metastases that had not been completely removed by surgery, evidence of leptomeningeal metastases, history of previous cranial radiotherapy, a need for immediate treatment to prevent neurological deterioration, concomitant second malignancies, Karnofsky performance scores < 70% or certain radiosensitive primary tumours (small-cell lung cancer, germ cell tumours, lymphoma, leukaemia and multiple myeloma).	surgery, when possible. Compliance: two participants assigned to the radiotherapy groups received non-protocol doses (30 Gy and 36 Gy instead of 50.4 Gy). One patient who was assigned to receive no radiotherapy was instead given WBRT (30 Gy). Additional treatment: not reported ITT: yes Single metastasis: 100% Prior treatments: not reported, other than surgical resection for metastasis Mean treatment duration:		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>WBRT was of 5.5 weeks duration
Time points for measurements : MRI scans were repeated at 3-month intervals for the first year, and every 6 months thereafter.</td><td></td><td></td></tr>
<tr><td>Full citation
Patchell, R. A., Tibbs, P. A., Walsh, J. W., Dempsey, R. J., Maruyama, Y., Kryscio, R. J., Markesbery, W. R., Macdonald, J. S., Young, B., A randomized trial of surgery in the treatment of single metastases to the brain, New England Journal of MedicineN Engl J Med, 322, 494-500, 1990
Ref Id
498898
Country/ies where the study was carried out
USA</td><td>Sample size
N=48 (n=25 surgery+WBRT; n=23 WBRT)
Characteristics
<table>
<tr><th></th><th>Surgery+WBRT (n=25)</th><th>Radiation (WBRT) n=23</th></tr>
<tr><td>Age Median (Range)</td><td>59 (44-74)</td><td>60 (49-73)</td></tr>
<tr><td>Primary tumour</td><td></td><td></td></tr>
<tr><td>Lung (non small cell)</td><td>17</td><td>19</td></tr>
<tr><td>Breast</td><td>2</td><td>1</td></tr>
</table></td><td>Interventions
Surgical group + WBRT: surgical treatment was undertaken within 72 hours of entry into study. All underwent craniotomy and goal was removal of metastasis. All underwent CT 2-5 days post-op to determine if surgical removal of tumour was complete. Within 14 days</td><td>Results
<table>
<tr><th></th><th>Surgery + WBRT (n=25)</th><th>WBRT (n=23)</th><th>Narrative</th></tr>
<tr><td>Local control of tumour</td><td></td><td></td><td></td></tr>
<tr><td>No recurrence of brain tumour</td><td>18</td><td>10</td><td></td></tr>
<tr><td>Recurrence distant only</td><td>2</td><td>0</td><td></td></tr>
<tr><td>Recurrence original only</td><td>2</td><td>10</td><td></td></tr>
<tr><td>Recurrence original and distant</td><td>3</td><td>2</td><td></td></tr>
<tr><td>Recurrence original all types</td><td>5</td><td>12</td><td></td></tr>
<tr><td>Median survival length</td><td>40 weeks (no CI)</td><td>15 weeks (no CI)</td><td></td></tr>
</table></td><td>Limitations Details
Randomisation : Yes, computer generated random numbers
Allocation concealment: Unclear
Patient blinding: Unclear (unlikely)
Assessor blinding: Unclear
Investigator blinding: Unclear
Reporting bias: median</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
Study type Randomised prospective trial Source of funding None reported Aim of the study To determine whether surgical removal of single brain metastases resulted in improved survival and quality of life compared with surgery plus postoperative radiotherapy Study dates October 1985 to December 1988	<table><tr><td>Gastrointestional</td><td>2</td><td>1</td></tr><tr><td>Genitourinary</td><td>1</td><td>1</td></tr><tr><td>Melanoma</td><td>2</td><td>1</td></tr><tr><td>Location of brain metastases</td><td></td><td></td></tr><tr><td>Supratentorial</td><td>18</td><td>17</td></tr><tr><td>Infratentorial</td><td>7</td><td>6</td></tr><tr><td>Prior treatment for primary tumour</td><td></td><td></td></tr><tr><td>Radiation</td><td>5</td><td>7</td></tr><tr><td>Surgery</td><td>12</td><td>8</td></tr><tr><td>Chemotherapy</td><td>5</td><td>3</td></tr></table>Inclusion criteria Patients at least 18 years who had radiographic evidence of a single metastases to the brain were eligible if they had documented systemic cancer (not originating from CNS) that had been	after surgery, the patients began receiving 36 Gy (3600 rad) of whole brain radiation therapy. A dose fraction of 3 Gy of cobalt-60 per day was given at a rate of 1 to 2 Gy per minute. A total of 12 dose fractions were given. WBRT (Radiation group): Patients with supratentorial lesions underwent stereotaxic needle biopsies of the suspected metastasis within 72 hours after entering study. Patients with infratentorial lesions did not undergo	<table><tr><td>Relative risk of death higher in WBRT:</td><td></td><td></td><td>2.2 (1.2 to 4.1)</td></tr><tr><td>Relative risk of Kanofsky score <70% developing</td><td></td><td></td><td>2.4 (1.3 to 4.6)</td></tr><tr><td>Quality of life</td><td></td><td></td><td>no raw data only p values</td></tr><tr><td>Mortality rate - 30 days</td><td>1</td><td>1</td><td></td></tr><tr><td>Morbidity rate - 30 days</td><td>2</td><td>4</td><td></td></tr><tr><td>Death due to systemic causes</td><td>15</td><td>11</td><td></td></tr></table>	survival had no SD or CI. Quality of life only p values. Drop out: No patients were lost to follow up Compliance: All complied to treatment. Additional treatment: Radiation group n=5 had additional treatment for recurrence (1 surgery + radiation: 4 radiotherapy); Surgery 4 additional treatment (1 surgery, 4 radiotherapy) ITT: yes Single metastases: 100% Prior treatments: Yes for primary tumour (not for brain metastases).

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td>diagnosed by examination of tissue within 5 years of treatment of the brain metastases. Had to be capable fo caring for themselves independently (Karnofsky performance scores >=70%).
Exclusion criteria
If had brain lesions that were not potentially surgically resectable; evidence of leptomeningeal metastases; a history of cranial radiotherapy; a need for immediate treatment to prevent acute neurological deterioration; or certain radiosensitive primary tumors.</td><td>biopsy because of the increased risk in that area. Within 48 hours of biopsy or study entry, patients received radiotherapy according to the same schedule and dosage used in the surgery group</td><td></td><td>No history of cranial radiotherapy
Mean treatment duration: 15 weeks in radiation and 40 weeks in surgical group
Time points for measurement: Patients were evaluated every 3 months</td></tr>
<tr><td>Full citation
Roos, D. E., Wirth, A., Burmeister, B. H., Spry, N. A., Drummond, K. J., Beresford, J. A., McClure, B. E., Whole brain irradiation following surgery or radiosurgery for solitary brain metastases: Mature results of a prematurely closed randomized Trans-Tasman Radiation Oncology Group trial (TROG 98.05),</td><td>Sample size
N = 19 randomised; n = 10 allocated to whole brain radiotherapy, n = 9 allocated to observation only.
Characteristics
<table>
<tr><th></th><th>Whole brain radiotherapy n = 10</th><th>Observation only n = 9</th></tr>
<tr><td>Sex, M:F</td><td>7:3</td><td>7:2</td></tr>
<tr><td>Age in years, median (range)</td><td>51.5 (27 - 71)</td><td>65 (34 - 74)</td></tr>
<tr><td>Primary cancer</td><td></td><td></td></tr>
<tr><td>Non-small cell lung</td><td>6</td><td>3</td></tr>
</table></td><td>Interventions
All participants underwent complete surgical or radiosurgical excision of the metastasis prior to the start of the trial.
Whole brain radiotherapy: radiotherapy was to commence within 2 weeks of randomisation.</td><td>Results
<table>
<tr><th></th><th>WBRT arm n = 10</th><th>Observation arm n = 9</th><th>Notes</th></tr>
<tr><td>Acute radiation toxicity ≥grade 3</td><td>2 (20%)</td><td>0</td><td>Grade 3 anorexia in 2 patients</td></tr>
<tr><td>Median CNS failure-free survival</td><td>5.7 months</td><td>4.5 months</td><td>p = 0.74. HR 1.18 (95% CI 0.45 to 3.07). Defined as time to CNS relapse (either radiological or symptomatic) or CNS toxicity (new or</td></tr>
</table></td><td>Limitations
Details
Randomisation: described as randomised trial, but no further information given about the process of randomisation.
Patient blinding: unclear, unlikely
Assessor blinding: unclear, unlikely</td></tr>
</table>

Study details	Participants			Interventions	Outcomes and results				Comments
Radiotherapy and Oncology, 80, 318-322, 2006 Ref Id 499143 Country/ies where the study was carried out Australia Study type RCT Source of funding Not reported. Aim of the study To assess the effect of adjuvant whole brain irradiation after surgery or radiosurgery for solitary brain metastases. Study dates August 1998 to April 2000. Trial was suspended by the Trial MAnagement Committee on 31 July 2000 due to slow accrual.	Melanoma	1	2	The initial protocol specified a mid-plane does of 36 Gy in 18 fractions (3 Gy/fraction, 5 fractions per week) using opposed lateral megvoltage photon beams to cover the entire intracranial contents with a 2cm margin. The fractionation was amended 11 months after trial activation to 30 Gy in 10 fractions over 2 weeks in an attempt to improve accrual. Observation group: underwent surgery/radiosurgery only for metastasis,				worsening cognitive dysfunction with new/progressive generalised atrophy and/or diffuse white matter change on CT/MRI) or death from any cause.	Investigator blinding: unclear, unlikely Reporting bias: none Dropout: no loss to follow up. Compliance: all patients allocated to the WBRT arm received treatment as per protocol (5 received 36 Gy in 18 fractions, five received 30 Gy in 10 fractions). In addition, one participant in the observation group received WBRT after declining observation alone. Additional treatment: not reported. ITT: yes
	Colorectal	1	2						
	Unknown primary	1	1						
	Kidney	1	0						
	Parotid	0	1						
	Site of brain metastasis								
	Supratentorial	8	7						
	Cerebellum	2	2						
	WHO performance status								
	0	7	4						
	1	3	4						
	2	0	1						
	Overall health/ QOL score, mean (range)	62.5 (50 - 83)	66.7 (33 - 100)						
	Mini-mental state score, mean (range)	28.3 (26 - 30)	27.3 (21 - 30)						
	Inclusion criteria Inclusion criteria were: MRI prior to surgery or radiosurgery which showed a solitary (presumed) brain metastasis from an extra-cranial primary malignancy, with complete surgical excision or radiosurgery within 6 weeks of registration. Post				CNS relapse	3/10 (30%)	7/9 (78%)	p = 0.12. HR 2.81 (95% CI 0.72 to 10.9) Defined as either radiological (≥25% increase in the product of diameters of an enhancing lesion at the index site and/or new enhancing lesions on brain imaging) or symptomatic (new or progressive symptoms of intracranial disease associated with radiological	

Study details	Participants	Interventions	Outcomes and results				Comments
	surgery/radiosurgery WHO performance status ≤2 and age ≥18 years. Exclusion criteria Exclusion criteria were: primary brain tumour, small cell lung cancer, seminoma, lymphoma, myeloma or leukaemia, macroscopic residual disease following surgery, meningeal disease, life expectancy due to extra-cranial disease presumed to be less than 6 months, or prior brain radiation.	and no irradiation. Dexamethasone and anti-convulsants were prescribed as required throughout the study. Subsequent treatment for intracranial or extra-cranial relapse was at the investigators discretion. .				relapse or treated with surgery or radiosurgery despite a lack of diagnostic radiological changes or occurring in the terminal phase).	Single metastasis: 100% Prior treatments: not reported, no previous cranial radiotherapy Mean treatment duration: WBRT took between 2 and 4 weeks, depending on the fractionation schedule used. Time points for measurement: radiation toxicity scores were recorded at months 1 and 2. Patients were evaluated clinically at month 2 following randomisation and 3 monthly thereafter. Brain CT or MRI was
			CNS toxicity	2/10 (20%)	0/9	Defined as new or worsening cognitive dysfunction with new/progressive generalised atrophy and/or diffuse white matter change on CT/MRI. Radiological evidence of CNS relapse had to be absent, and no intercurrent cause of cognitive dysfunction could be present. Focal	

Study details	Participants	Interventions	Outcomes and results				Comments
						CNS toxicity was identified in the presence of a new/persistent neurological deficit clinically compatible with a focal area of atrophy, a negative thallium/SPECT scan in the presence of an enhancing lesion, or an excised solitary mass lesion of necrotic tissue.	performed at 2 and 5 months and when required to evaluate new symptoms/signs. Quality of life was assessed at 2 months, 5 months and 6 monthly thereafter. Mini mental state examinations were performed annually
			Median progression-free survival	4.3 months	4.5 months	p = 0.64. HR 1.27 (95% CI 0.46 to 3.54)	
			Median overall survival	9.2 months	6.2 months	p = 0.99. HR 1.01 (95% CI 0.36 to 2.79)	
			Time to deterioration of performance status to WHO >1	not reported	not reported	p = 0.80. HR 1.16 (95% CI 0.38 to 3.48)	

1 Evidence tables for review 4b - Management for multiple brain metastases

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr>
<td>Full citation
Cao, K. I., Lebas, N., Gerber, S., Levy, C., Le Scodan, R., Bourgier, C., Pierga, J. Y., Gobillion, A., Savignoni, A., Kirova, Y. M., Phase II randomized study of whole-brain radiation therapy with or without concurrent temozolomide for brain metastases from breast cancer, Annals of OncologyAnn Oncol, 26, 89-94, 2015
Ref Id
497343
Country/ies where the</td>
<td>Sample size
100 patients were enrolled in the study (50 in the WBRT + TMZ arm, 50 in the WBRT arm).

Characteristics
<table>
<tr><th></th><th>WBRT (n=50)</th><th>WBRT + TMZ (n=50)</th></tr>
<tr><td>Age (years)</td><td>57.8 (38-79)</td><td>53.6 (29-78)</td></tr>
<tr><td>Adjuvant chemotherapy (yes)</td><td>32 (64%)</td><td>29 (58%)</td></tr>
<tr><td>Adjuvant hormonotherapy (yes)</td><td>13 (26%)</td><td>12 (24%)</td></tr>
<tr><td>Isolated brain metastases</td><td>8 (16%)</td><td>7 (14%)</td></tr>
<tr><td>Mean number of brain metastases</td><td>4.6</td><td>3.6</td></tr>
<tr><td>Primary tumour breast cancer</td><td>100 %</td><td>100%</td></tr>
</table>
Inclusion criteria
Eligible women were aged >18 years with ECOG Performance Status 0–2, and had at least one brain lesion from histologically documented primary breast cancer. BM were either unresectable or unsuitable for radiosurgery, or the patient refused surgery

Exclusion criteria</td>
<td>Interventions
WBRT - All patients received hypofractionated conformal WBRT to a dose of 30 Gy in ten equal daily fractions, given 5 days a week. WBRT was delivered using a linear accelerator, with two opposed photon beams.

WBRT + temozolomide (TMZ) arm, oral TMZ was administered continuously at a dose of 75 mg/m2/day (in a way similar to the prescribed dosage in the treatment of glioblastoma) on an empty stomach each morning during</td>
<td>Details
Randomisation: yes, unclear methods
Allocation concealment: unclear
Drop outs: WBRT 3/50 (6%) WBRT+TMZ 13/50 (26%) (13 died before 1st assessment at 6 weeks)
Patient blinded: unclear
Assessor blinded: yes, blinded radiologist
Investigator Blinded: unclear
ITT: yes
Reporting bias: confidence interval not provided for one outcome
Treatment duration: 14 days of treatment
Previous treatments: Mean number of prior chemotherapy regimines WBRT: 2.5 WBRT + TMZ 2.9
Number of single metastases: WBRT: 16% WBRT+TMZ 14%</td>
<td>Results
<table>
<tr><th></th><th>WBRT (n=50)</th><th>WBRT + TMZ (n=50)</th></tr>
<tr><td>Median OS survival (months)</td><td>11.1 (8.3-15.3)</td><td>9.4 (7.3-13.4)</td></tr>
<tr><td>Median progression free survival (months)</td><td>7.4 (5.3-13.1)</td><td>6.8 (4.6-8.6)</td></tr>
<tr><td>Complete response</td><td>0</td><td>0</td></tr>
<tr><td>Partial response</td><td>18 (36)</td><td>15 (30)</td></tr>
<tr><td>Stable disease</td><td>26 (32)</td><td>18 (36)</td></tr>
<tr><td>Progressive disease</td><td>3 (6)</td><td>4 (8)</td></tr>
<tr><td>Neurological symptoms (6 weeks)</td><td>22 (44)</td><td>12 (24%)</td></tr>
<tr><td>Treatment-related morbidity. Radionecrosis Oedema Postop infection Stroke Steroid (e.g dexamethasone) use (duration and dose)</td><td>NR</td><td>NR</td></tr>
</table>
</td>
</tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
study was carried out France Study type Phase II randomised control trial Aim of the study The aim of this study was to assess the efficacy and safety of WBRT with concomitant TMZ in treatment of BM especially from breast cancer. Study dates 2008-2010 Source of funding This work was supported by Schering-Plough, France	Patients with leptomeningeal metastases or prior cranial irradiation including stereotactic radiosurgery were excluded	the brain irradiation period also on weekends for a total of 14 days. Preventive oral administration of sulfamethoxazole-trimethoprim was planned in this arm. No additional doses of TMZ were administered. Corticosteroids and antiepileptic drugs were prescribed at the lowest dosage, when necessary. Antiemetics were prescribed at the physician's discretion. Follow-up: mean 9.4 months (1-68.1 months)		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr>
<td>Full citation
Chabot, P., Hsia, T. C., Ryu, J. S., Gorbunova, V., Belda-Iniesta, C., Ball, D., Kio, E., Mehta, M., Papp, K., Qin, Q., Qian, J., Holen, K. D., Giranda, V., Suh, J. H., Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: results of a randomized, global, placebo-controlled study, Journal of Neuro OncologyJ</td>
<td>Sample size
N=307 (n=102 WBRT + placebo BID; n=103 WBRT+ veliparib 50 mg BID; WBRT+veliparib 200 mg BID)

Characteristics
<table>
<tr><th></th><th>Placebo + WBRT (n=102)</th><th>Veliparib 50mg + WBRT (n=103)</th><th>Veliparib 200mg + WBRT (n=102)</th></tr>
<tr><td>Age median (range)</td><td>60 (41-86)</td><td>60 (33-83)</td><td>62 (39-81)</td></tr>
<tr><td>EGFR epidermal growth factor receptor, yes</td><td>19 (36%)</td><td>14 (29%)</td><td>18 (34%)</td></tr>
<tr><td>ALK anaplastic lymphoma kinase, yes</td><td>0</td><td>1 (4%)</td><td>1 (4%)</td></tr>
<tr><td>N brain mets n (%)</td><td></td><td></td><td></td></tr>
<tr><td>1</td><td>18 (18%)</td><td>22 (22%)</td><td>14 (14%)</td></tr>
<tr><td>2-3</td><td>22 (22%)</td><td>26 (26%)</td><td>29 (19%)</td></tr>
<tr><td>>3</td><td>58 (59%)</td><td>53 (51%)</td><td>56 (57%)</td></tr>
<tr><td>Unknown/missing</td><td>4</td><td>2</td><td>3</td></tr>
</table>
Inclusion criteria Eligible patients had cytologically or histologically confirmed NSCLC</td>
<td>Interventions

The treatment period began on the first day of WBRT and continued for 45 days.
WBRT: All patients received 30.0 Gy of WBRT in ten daily fractions of 3.0 Gy, given 5 days per week (excluding holidays and weekends).
Oral veliparib: Oral veliparib BID (50 or 200 mg) or placebo BID was self-administered starting on day 1 of WBRT and continued until 1 day after completion of WBRT</td>
<td>Details
Randomisation: yes, no details
Allocation concealment: unclear
Patient blinding: yes (double blinded)
Assessor blinding: Unclear
Investigator blinding: yes (double blind)
Reporting bias: no raw data on neurocognitive function. Unclear what objective response rate is.
Drop out: There was only one patient who was lost to follow-up for survival information,
Compliance: Not reported
ITT: yes, During the treatment period, if a patient discontinued veliparib/placebo and WBRT due to both radiographic and clinical brain metastases progression, the patient continued to be followed for survival and posttreatment</td>
<td>Results
<table>
<tr><th></th><th>Placebo +WBRT (n-102)</th><th>Velipa rib 50 mg + WBRT (n=103)</th><th>Veliparib 200 mg + WBRT (N=102)</th><th>Narrative</th></tr>
<tr><td>Median overall survival, days</td><td>185 (137 - 251)</td><td>109 (169 - 264)</td><td>209 (138 - 255)</td><td></td></tr>
<tr><td>Objective response rates</td><td>42 (41.2%)</td><td>38 (36.9 %)</td><td>43 (42.2%)</td><td></td></tr>
<tr><td>Median time to clinical brain metastases progression days</td><td>348 (216 - NR)</td><td>286 (192 - NR)</td><td>255 (204 - 342)</td><td></td></tr>
<tr><td>Median time to radiographic brain metastases progression days</td><td>259 (184, NR)</td><td>226 (147, 360)</td><td>224 (137, 358)</td><td></td></tr>
<tr><td>Neurocognitive tests</td><td></td><td></td><td></td><td>no difference in change from baseline in neurocog</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr>
<td>Neurooncol, 21, 21, 2016
Ref Id 497369
Country/ies where the study was carried out
Study type Phase 2, randomized, double blinded, multicentre study

Aim of the study To evaluate the efficacy and safety of WBRT administered in combination with veliparib BID (50 or 200 mg) versus placebo BID. Velipari b (ABT-888) is a potent, orally bioavailable, PARP-1 and</td>
<td>and brain metastases demonstrated via magnetic resonance imaging (MRI) brain scan. Total number of brain metastases was not a part of inclusion criteria. Patients had to be over the age of 18 years and be eligible for WBRT treatment (per investigator), with Karnofsky performance status (KPS) scores ≥70, and have adequate hematologic, renal, and hepatic function. Patients could not have been diagnosed with brain metastases >28 days before commencing treatment or have received prior cranial radiation or undergone resection for brain metastases

Exclusion criteria To exclude patients who might be more likely to die from systemic disease as opposed to neurologic disease, additional exclusion criteria included more than two sites of metastases from NSCLC (excluding the brain, bone, and thorax) and evidence of liver metastases. Due to the very poor outcomes for patients with leptomeningeal metastases and subarachnoid spread of the tumor, these patients were excluded.</td>
<td></td>
<td>therapy data for up to 36 months.
Single metastases: 19%
Prior treatments: No prior cranial radiation or undergone resection for brain metastases. About 32% currently taking EGFR
Mean treatment duration: 45 days treatment (followed up to 36 months for survival)
Time points for measurement: Monthly (30-day intervals) for 9 months, and every 3 months thereafter for up to 24 months.</td>
<td>
<table>
<tr><td></td><td></td><td></td><td></td><td>nitive tests measured by z-score across all scheduled visits between either veliparib dose groups (50 mg versus 200 mg) and placebo group.</td></tr>
<tr><td>Any AE</td><td>91 (90%)</td><td>90 (87%)</td><td>90 (98%)</td><td></td></tr>
<tr><td>Brain edema</td><td>6</td><td>1</td><td>0</td><td></td></tr>
<tr><td>Stroke</td><td></td><td></td><td></td><td>NR</td></tr>
<tr><td>Post-op infection</td><td></td><td></td><td></td><td>NR</td></tr>
</table>
Radiographic response or progression was modeled after the Macdonald criteria with response evaluation criteria in solid tumors (RECIST) definitions of measurable lesions and non-target lesions. Four response categories are proposed: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Response in this
</td>
</tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
-2 inhibitor that has the ability to cross the blood–brain barrier. In preclinical models, veliparib potentiated the antitumor activity of fractionated radiation an d inhibited PARP levels in patient tumors in a phase 0 biopsy trial at doses as low as 25 mg. Poly (adenosine diphosphate -ribose) polymerase (PARP) is a family of enzymes involved in a number of cellular processes,				scheme is based on major changes in tumor size on the enhanced computed tomographic (CT) or magnetic resonance imaging (MRI) scan

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
including DNA replication, transcription, and cell death. Increased PARP activity has been observed in numerous cancers, and is thought to be one possible mechanism of resistance to cell-death by DNA-damaging therapeutics. There is evidence that the absence of PARP-1 and -2, which are both activated by DNA damage and facilitate DNA repair, results in				

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
hypersensitivity to ionizing radiation. Therefore, the inhibition of PARP-mediated DNA damage repair can help sensitize cells to DNA-damaging agents. Study dates Not reported Source of funding: bbVie Inc, provided financial support for this study and participated in the design, study conduct, analysis,				

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr><td>and interpretation of the data as well as the writing, review, and approval of this manuscript</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Knisely, J. P. S., Berkey, B., Chakravarti, A., Yung, A. W. K., Curran Jr, W. J., Robins, H. I., Movsas, B., Brachman, D. G., Henderson, R. H., Mehta, M. P., A Phase III Study of Conventional Radiation Therapy Plus Thalidomide Versus Conventiona</td><td>Sample size
N=183, n=93 to WBRT; 90 to WBRT + thalidomide

Characteristics<table><tr><td></td><td>WBRT</td><td>WBRT+Thalidomide</td></tr><tr><td>Age median (years)</td><td>59 (33-78)</td><td>58.5 (31-83)</td></tr><tr><td>Primary tumour site</td><td></td><td></td></tr><tr><td>Breast</td><td>15</td><td>16</td></tr><tr><td>Lung</td><td>56</td><td>53</td></tr><tr><td>Skin/melanoma</td><td>10</td><td>9</td></tr><tr><td>Other</td><td>9</td><td>6</td></tr><tr><td>Unknown</td><td>2</td><td>0</td></tr><tr><td>Number of brain mets</td><td></td><td></td></tr><tr><td>1</td><td>3</td><td>5</td></tr><tr><td>2</td><td>6</td><td>1</td></tr><tr><td>3</td><td>10</td><td>10</td></tr></table></td><td>Interventions
Radiation therapy: all patients received WBRT to a dose of 37.5 Gy in 15 equal daily fractions, with photon energies between 1.25 to 10 MV. No cone-down or boost treatments were permitted. Drug therapy: patients randomised to thalidomide started at a dose of 200 mg per os every night and had a weekly dose</td><td>Details
Randomisation: yes, permuted block design
Allocation concealment: yes, randomised centrally
Patient Blinding:No
Assessor blinding: unclear
Investigator blinding: unclear
Randomised/ final numbers
numbers: WBRT: 90/92 WBRT+Thalidomide: 93/84
Compliance: WBRT: n=88/92 (96%) completed treatment WBRT+thalidomide: n=77/84 (92%) completed WBRT; 64/84 (76%) stopped taking drug < 2 months (may not have been adequate to</td><td>Results<table><tr><td></td><td>WBRT</td><td>WBRT+Thalidomide</td></tr><tr><td>Median survival years</td><td>3.9 (no CI)</td><td>3.9 (no CI)</td></tr><tr><td>Rates of CNS progression (3 months) (time to CNS progression from first day of treatment until deterioration as documented by the individual investigator)</td><td>18.7%</td><td>13.1%</td></tr><tr><td>Adverse events (Grade 3-4 = definitely related to treatment)</td><td></td><td></td></tr><tr><td>Infection (not necessarily post-op)</td><td>0</td><td>0</td></tr><tr><td>Lymphatics (oedema)</td><td>0</td><td>0</td></tr><tr><td>Cardiovascular (arrhythmia, stroke)</td><td>0</td><td>2</td></tr><tr><td>Death due to brain metastases</td><td>34%</td><td>27%</td></tr></table></td></tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
l Radiation Therapy for Multiple Brain Metastases (RTOG 0118), International Journal of Radiation Oncology Biology Physics, 71, 79-86, 2008 Ref Id 498253 Country/ies where the study was carried out USA Study type Phase III randomised control trial Aim of the study To compare whole brain radiotherapy with WBRT combined with thalidomide for patients	>3 | 73 | 69 Inclusion criteria Patients >18 years if they had an anticipated survival of >8 weeks, a Zubrod performance status of 0-1, and required WBRT for MRI-documented brain metastases that were inappropriate for radiosurgery because of size (>4 cm) number (>3) or location (midbrain). Exclusion criteria Prior cranial radiotherapy or radiosurgery, prior thalidomide therapy, ongoing anticoagulant therapy or a history of deep venous thrombosis, a grade >=2 sensory neuropathy, AIDS, pregnancy, breast-feeding, or other medical or psychiatric conditions. Chemotherapy could not have been performed within 2 weeks of protocol entry.	escalation of 200 mg per day during the WBRT. Post WBRT thalidomide dose escalation occured on an every-toerh week basis to a max dose of 1200 mg continuing for a maximum of 2 years. Systemic chemotherapy was deferred for 6 weeks after protocol enrollment unless documented tumour progression required earlier slot Follow-up: assessments every 2 months after treatment start for 1 year, then every 4 months for a year, every 6 months for 2	have an effect), 2 (2%) never took the drug Reporting bias: Quality of life measured but not reported. CI's were not provided for mean survival Single metastases: 4% Prior treatments: No prior radiotherapy or radiosurgery, no prior thalidomide Treatment duration: 2 years Duration: Median duration of thalidomide:30 days (1 to 269) Measurements: assessments every 2 months from treatment start for year 1, then every 4 months for a year, every 6 months for 2 years, and annually for the patient's lifetime	Rate of Grade 3-4 treatment related AE | 11/92 | 39/84

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
with brain metastases not amenable to resection or radiosurgery Study dates 2001 Source of funding None stated		years and annually for patient's lifetime.		
Full citation Corn, B. W., Moughan, J., Knisely, J. P. S., Fox, S. W., Chakravarti, A., Yung, W. K. A., Curran Jr, W. J., Robins, H. I., Brachman, D. G., Henderson, R. H., Mehta, M. P., Movsas, B., Prospective Evaluation of Quality of	Sample size See Knisely 2008 Characteristics See Knisely 2008 Inclusion criteria See Knisely 2008 Exclusion criteria See Knisely 2008	Interventions See Knisely 2008 Details See Knisely 2008	Limitations See Knisely 2008	Results Quality of life as measured with the Spitzer Quality of life Index (SQLI) Mean change from baseline to endpoint (6 months) in the WBRT alone group: -0.53 Mean change from baseline to endpoint (6 months) in the WBRT+thalidomide alone group: 0.33 No SDs deviations were reported

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
Life and Neurocognitive Effects in Patients With Multiple Brain Metastases Receiving Whole-Brain Radiotherapy With or Without Thalidomide on Radiation Therapy Oncology Group (RTOG) Trial 0118, International Journal of Radiation Oncology Biology Physics, 71, 71-78, 2008 Ref Id 497469 Country/ies where the study was carried out				

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
Multicentre study Study type Sub-analysis of a RCT reporting quality of life Source of funding Not reported Aim of the study To report the quality of life of the adults with brain metastases receiving WBRT with or without thalidomide included in the radiation therapy oncology group				

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr><td>(RTOG) 0118 (Knisely 2008)

Study dates

See Knisely 2008</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Kondziolka, D., Patel, A., Lunsford, L. D., Flickinger, J. C., Decision making for patients with multiple brain metastases: radiosurgery, radiotherapy, or resection?, Neurosurgical FocusNeurosurg, 9, e4, 2000
Ref Id 498284</td><td>Sample size
27 randomised (14 to whole brain radiation therapy WBRT and 13 to WBRT and radiosurgery)

Characteristics
<table><tr><td></td><td>WBRT</td><td>WBRT + Radiosurgery</td></tr><tr><td>Age</td><td>58 (33-77)</td><td>59 (46-74)</td></tr><tr><td>N tumours</td><td></td><td></td></tr><tr><td>2</td><td>11</td><td>8</td></tr><tr><td>3</td><td>1</td><td>3</td></tr><tr><td>4</td><td>2</td><td>2</td></tr><tr><td>Lung carcinoma</td><td>7</td><td>5</td></tr><tr><td>Melanoma</td><td>3</td><td>2</td></tr><tr><td>Renal cell carcinoma</td><td>2</td><td>2</td></tr><tr><td>Breast carcinoma</td><td>2</td><td>2</td></tr></table></td><td>Interventions
WBRT =were treated with megavoltage beams with a source axis distance no less than 80 cm. Fraction sizes of 2.5 Gy were used. A midplane dose of 30 Gy in 12 fractions was delivered. WBRT/radiosurgery group = underwent gamma knife radiosurgery (Elekta Instruments, Atlanta, GA) administered using</td><td>Details
Randomisation: Yes, coin-toss
Allocation concealment: Unclear
Participant blinding: No
Assessor blinding: Yes (interpretation of serial MRI images)
Investigator blinding: Yes, data collated and reviewed by an investigator independent of treatment arm
Drop outs: none reported
Reporting bias: all outcomes reported, except no real data on local control. Few outcomes
Time points: The primary outcome was</td><td>Results
<table><tr><td></td><td>WBRT (n=14)</td><td>WBRT/radiosurgery (n=13)</td><td></td></tr><tr><td>Median time of survival (months)</td><td>7.5 (4.6-10.4)</td><td>11 (3.8-18.2)</td><td></td></tr><tr><td>Rate of local failure (including patients who died)</td><td>100%</td><td>8%</td><td></td></tr><tr><td>Local tumor control rate</td><td>NR</td><td>NR</td><td>Favoured WBRT/Radiosurgery</td></tr><tr><td>Median time to progression of initial tumor or development of new tumor (months)</td><td>5 (3.2-6.8)</td><td>34 (CI NR)</td><td></td></tr></table></td></tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
Country/ies where the study was carried out USA Study type Randomised control trial Aim of the study The authors conducted a randomized trial in which they compared radiosurgery combined with WBRT with WBRT alone. Study dates Source of funding National Institutes of Health Grant No. K08 NS01723.	<table><tr><td>Other</td><td>0</td><td>2</td></tr><tr><td>Single tumours</td><td>0</td><td>0</td></tr></table> Inclusion criteria Eligible patients met the following criteria: 1) histological confirmation of tumor type at the primary site or at a site of metastatic disease had been obtained in each patient; 2) all brain metastases were less than or equal to 25 mm in mean diameter and were located more than 5 mm from the optic chiasm; 3) only two, three, or four tumors were visualized on contrast-enhanced MR imaging prior to randomization; and 4) patients had a Karnofsky performance scale score less than or equal to 70. Histological tumor types could include lung, breast, colon, renal cell, melanoma, bladder, ovarian, and uterine carcinomas. Number with single tumors: none Exclusion criteria Patients were considered ineligible if they did not meet one or more of the aforementioned criteria or could not undergo MR imaging.	stereotactic MR guidance. Dose planning was performed using an imageintegration on a computer workstation. All known tumors were irradiated. The 50% or greater isodose (16 Gy) was used to irradiate the tumor margin in all patients. Radio surgery could precede, follow, or be performed within the time course of WBRT. The maximum time interval between WBRT and radiosurgery in patients randomized to radiosurgery was 1 month.	defined by the change in size and number of tumors at 1.5, 3, 6, 9, 12, 15, and 18 months following completion of radiotherapy or radiosurgery with serial MR images. Previous treatments: Unclear Single metastases: 0%	<table><tr><td>Complications from treatment.</td><td>There was no neurologic or systemic morbidity related to stereotactic radiosurgery. After whole brain irradiation, patients developed mild scalp erythema and hair loss.</td></tr></table>
Full citation	Sample size	ventions	Details	Results

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr>
<td>Pesce, G. A., Klingbiel, D., Ribi, K., Zouhair, A., von Moos, R., Schlaeppi, M., Caspar, C. B., Fischer, N., Anchisi, S., Peters, S., Cathomas, R., Bernhard, J., Kotrubczik, N. M., D'Addario, G., Pilop, C., Weber, D. C., Bodis, S., Pless, M., Mayer, M., Stupp, R., Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell</td>
<td>N=59 (Gefitnib GFT n=16; temozolomide TMZ n=43)

Characteristics
<table>
<tr><td></td><td>TMZ (n=43)</td><td>GFT (n=16)</td></tr>
<tr><td>Age years</td><td>63 (45-79)</td><td>57 (46-82)</td></tr>
<tr><td>N brain metastases</td><td></td><td></td></tr>
<tr><td>1</td><td>4</td><td>3</td></tr>
<tr><td>2</td><td>6</td><td>4</td></tr>
<tr><td>3</td><td>8</td><td>1</td></tr>
<tr><td>≥4</td><td>25</td><td>8</td></tr>
<tr><td>Administration of steroids</td><td>40</td><td>15</td></tr>
</table>
Inclusion criteria
Adult patients with multiple BM from NSCLC were eligible. Patients had to be on a stable or decreasing dose of corticosteroids for at least 4 days. Staging with MRI/CT of the brain, chest and upper abdomen was required within 6 weeks. Other inclusion requirements were a WHO performance status 0–2, adequate haematological (haemoglobin P100 g/l, neutrophils P1.5 · 109/l, thrombocytes P100 · 109/l), hepatic (bilirubin 61.5 · ULN, ASAT, ALAT, and alkaline phosphatase 62.5 · ULN) and renal (calculated creatinine clearance P40 ml/min) function. No prior irradiation to the brain was allowed, prior hemotherapy was allowed except GFT or TMZ</td>
<td>WBRT + Gefitnib GFT
WBRT + Temozolomide TMZ
Radiotherapy
WBRT consisted in standard cranial irradiation (6–10 MV photons) of 10 · 3 Gy, without cone down or boost. Central axis dose calculations were considered sufficient for dosimetry. The reference dose was the isodose ICRU point (ICRU-62). Minimum and maximum doses had to be defined according to ICRU-62 recommendations.
Gefitinib Patients</td>
<td>Randomisation: yes, unclear methods. Randomisation was performed using the minimisation method. Patients were stratified according to the number of BM (1–3 versus multiple (P4)), prior chemotherapy, WHO performance status (0–1 versus 2) and institution.
Allocation concealment: unclear
Patient blinding: no, open label
Assessor blinding: no, open label
Investigator blinding: no, open label
Reporting bias: did not report SD for quality of life, cognitive function.
Drop out: TMZ n=8; GFT n=4 (toxicity and other)
ITT: yes
Discontinuation: TMZ + radiotherapy n=43/43 (progression n=31, toxicity n=3, death n=4; other n=5); Gefitinib + radiotherapy n=16/16 (Progression n=11,</td>
<td>
<table>
<tr><td></td><td>WBRT +Gefitinib (n=16)</td><td>WBRT + Temozolomide (n=43)</td></tr>
<tr><td>Median overall survival (months)</td><td>6.3 (2.1 - 14.6)</td><td>4.9 (2.3-5.6)</td></tr>
<tr><td>Median time to progression (months)</td><td>1.8 (1.1 - 3.9)</td><td>1.8 (1.5-1.8)</td></tr>
<tr><td>1 year survival rates</td><td>37.5% (15.4 - 59.8%)</td><td>20.9% (10.4-34.0)</td></tr>
<tr><td>Withdrew due to toxicity</td><td>3</td><td>4</td></tr>
<tr><td>Lymphopaenia</td><td>0</td><td>4</td></tr>
</table>
</td>
</tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03), European Journal of CancerEur J Cancer, 48, 377-84, 2012 Ref Id 498936 Country/ies where the study was carried out Switzerland Study type Multicentre, randomised, open-label,	Exclusion criteria Patients receiving hepatic enzyme inducing drugs (e.g. antiepileptics) were not eligible	randomised to GFT (Iressa, Astra Zeneca, Macclefield, UK) received 250 mg p.o. daily from day 1 of radiotherapy without interruption until disease progression. Temozolomide TMZ (Temodal, Temodar, Schering-Plough, Kenilworth, NJ) was prescribed at a daily dose of 75 mg/m2 p.o. daily for 21 days continuously every 28 days (1 cycle), beginning on day 1 of radiotherapy.	toxicity n=3, death n=1, other n=1) Single metastases: yes, 14% Prior treatments: no prior irradiation to brain, yes prior chemotherapy (except GFT or TMZ). Mean duration of treatment: Median follow up of 34 months. The median duration of chemotherapy was 1.6 (range 0.3–7.6) months in the TMZ arm, and 1.8 (range 0.3–10.5) months in the GFT arm.	

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
2-stage phase II trial Aim of the study Our trial aimed at evaluating the addition of a chemotherapeutic or targeted agent with single agent activity to standard hypofractionated radiotherapy; and to evaluate the benefits and limitations of standard WBRT in the management of BM from NSCLC. Study dates April 2005 until April 2009				

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
Source of funding The trial was supported with free drug supply and an unrestricted educational grant by Essex Chemie (subsidiary of Schering-Plough), Switzerland and AstraZeneca (Switzerland). It has also been funded by the Swiss State Secretariat for Education and Research (SER).				
Full citation Suh, J. H., Stea, B., Nabid, A.,	Sample size 515 (efaproxiral n=265; control n=250) Characteristics	Interventions WBRT All patients received a	Details Randomisation: yes, unclear methods (only	Results WBRT+ Control / WBRT+ Efaproxiral / Narrative

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods/Limitations</th><th>Outcomes and Results</th></tr>
<tr>
<td>Kresl, J. J., Fortin, A., Mercier, J. P., Senzer, N., Chang, E. L., Boyd, A. P., Cagnoni, P. J., Shaw, E., Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases, Journal of Clinical OncologyJ Clin Oncol, 24, 106-114, 2006
Ref Id 499463
Country/ies where the study was carried out
Canada, USA and other countries
Study type</td>
<td>
<table>
<tr><td></td><td>Control+WBRT (n=250)</td><td>Etaproxiral + WBRT (N=265)</td></tr>
<tr><td>Age <65 years</td><td>73</td><td>72</td></tr>
<tr><td>Age ≥65 years</td><td>27</td><td>28</td></tr>
<tr><td>Primary site</td><td></td><td></td></tr>
<tr><td>Non-small cell lung cancer</td><td>58%</td><td>66%</td></tr>
<tr><td>Breast</td><td>20%</td><td>22%</td></tr>
<tr><td>Other</td><td>22 %</td><td>23%</td></tr>
<tr><td>Number of brain metastases</td><td></td><td></td></tr>
<tr><td>1</td><td>20%</td><td>17%</td></tr>
<tr><td>2-3</td><td>32%</td><td>30%</td></tr>
<tr><td>>3</td><td>47%</td><td>52%</td></tr>
<tr><td>Prior brain resection</td><td></td><td></td></tr>
<tr><td>yes</td><td>10%</td><td>8%</td></tr>
<tr><td>no</td><td>90%</td><td>92%</td></tr>
</table>

Inclusion criteria
Enrollment was open to RPA class I or II patients with brain metastases originating from solid tumors, excluding small-cell lung cancer, germ cell tumors, and lymphomas. Additional eligibility criteria included no prior treatment for</td>
<td>standard 2-week course of WBRT (3 Gy/fraction for 10 days) plus supplemental oxygen (4 L/min via nasal cannula). Oxygen as administered beginning 35 minutes before, during, and for at least 15 minutes after daily WBRT.

Efaproxiral: For the efaproxiral arm, administration began on the first day of WBRT and continued every day (Monday through Friday) of the 2-week WBRT course for a total of 10 doses. Efaproxiral was administered intravenously</td>
<td>stated they used permuted blocks within strata)
Allocation concealment: unclear
Patient blinding: unclear, unlikely
Assessor blinding: yes, neuroradiologists who reviewed the scans were blinded.
Investigator blinding: unclear
Reporting bias: no CI or SD for mean survival time
Drop out: 0%
Compliance: 95% in the efaproxiral arm and 97% of patients in the control arm received all 10 doses of intended WBRT. 82% in the efaproxiral arm received at least seven doses of efaproxiral, and the mean daily dose of efaproxiral was 83.6 mg/kg.

ITT: yes, no patients were lost to follow up in survival analysis of Jan 31, 2003</td>
<td>
<table>
<tr><td>Death at 30 days</td><td>16/250</td><td>13/265</td><td></td></tr>
<tr><td>Death at 6 months</td><td>151/250</td><td>142/265</td><td></td></tr>
<tr><td>Death at 30 months</td><td>206/250</td><td>215/265</td><td></td></tr>
<tr><td>Median survival time (MST)</td><td>4.4 months</td><td>5.4 months</td><td>HR=0.87; p=0.16</td></tr>
<tr><td>Radiographic progression 1 year</td><td>18%</td><td>21%</td><td></td></tr>
<tr><td>Clinical progression at 1 year</td><td>51%</td><td>49%</td><td></td></tr>
<tr><td>Response rate (complete+partial response)</td><td>96 (38%)</td><td>121 (46%)</td><td></td></tr>
<tr><td>Complete response (N)</td><td>14</td><td>28</td><td></td></tr>
<tr><td>N patients with stable or improving QoL, Spitzer Questionnaire 6 months (N)</td><td>38</td><td>43</td><td></td></tr>
<tr><td>N patients with stable or improving neurocognitive function, Karnofksy performance status (N)</td><td>36</td><td>48</td><td></td></tr>
<tr><td>Survival</td><td></td><td></td><td>HR 0.87</td></tr>
</table>
</td>
</tr>
</table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
Randomised control trial Aim of the study To determine whether efaproxiral, an allosteric modifier of hemoglobin, improves survival in patients with brain metastases when used as an adjunct to whole-brain radiation therapy (WBRT). Study dates Source of funding Allos Therapeutics Inc, Westminster, CO.	brain metastases (other than resection with measurable lesion remaining), age 18 years, and adequate hematologic, hepatic, and renal function as defined by hemoglobin10 g/dL, WBC count2,000 cells/L, platelet count 75,000 cells/L, creatinine ——————————— 2.0 mg/dL, bilirubin ——————————— 2.0 mg/dL, and transaminases 3 the upper limit of normal. Patients were required to have no other concurrent active malignancy, no planned therapy for brain metastases through the 1-month post-WBRT follow-up visit, and standard pulse oximetry (SpO2) measurement (resting and exercise) 90%. Women could not be breastfeeding or pregnant, and females of childbearing potential and all nonsterile males were required to use contraception. Exclusion criteria Patients were excluded if they had prior exposure to efaproxiral, had received chemotherapy within 7 days, or had used investigational agents within 28 days before WBRT.Informed consent was obtained from all patients .Human experimentation guidelines of the appropriate regulatory authorities and the guidelines of the investigators' institutions were followed in the conduct of clinical research.	via a central venous access device over 30 minutes; the infusion was completed no more than 30 minutes before WBRT. The intended daily dose of efaproxiral was 75 or 100 mg/kg. Control The control arm received the same treatment without administration of efaproxiral; no placebo was administered. Efaproxiral (Efaproxyn, RSR13; Allos Therapeutics Inc, Westminster,CO) is an allosteric modifier of hemoglobin and the first of a new class of	Single metastases: 18.5% Prior treatments: yes, 9% had prior brain tumor resection> no other prior brain treatment for brain metastases, no chemo in past 7 days or prior efaproxiral treatment Mean treatment duration: 15.2 months Time points for measurement: baseline, 1 month after WBRT, 3 months after WBRT, and every 3 months thereafter until progression or death.	<table><tr><td></td><td></td><td></td><td>(0.71 to 1.05)</td></tr><tr><td>Multivariable analysis</td><td></td><td></td><td>HR 0.74 (0.61 to 0.90)</td></tr><tr><td>Grade 4 adverse events</td><td>28/263</td><td>33/266</td><td></td></tr></table>

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
		pharmaceutical agents. Efaproxiral binds noncovalently in the central water cavity of the hemoglobin tetramer and affects the conformational structure of hemoglobin. T his leads to a reduction in hemoglobin oxygen-binding affinity and thereby facilitates the release of oxygen. By this mechanism, efaproxiral increases wholeblood pO2 for 50% hemoglobin saturation (p50), resulting in enhanced tumor oxygenation and radiation sensitivity. Unli ke other agents		

Study details	Participants	Interventions	Methods/Limitations	Outcomes and Results
		that have been used to improve the effectiveness of WBRT, efaproxiral does not need to enter cancer cells to increase radiosensitivity because oxygen readily diffuses across the blood-brain barrier to decrease tumor hypoxia. Theoretically, efaproxiral has the potential to increase the effectiveness of WBRT.		

1

2 # Evidence tables for review 4c – Management of brain metastases with a mixed population

Study details	Participants	Interventions	Outcomes and results	Comments
Full citation Andrews, D. W., Scott, C. B., Sperduto, P. W.,	Sample size 331 randomised: 164 WBRT and radiosurgery; 167 to WBRT alone Characteristics	Interventions WBRT alone or WBRT with stereotactic radiosurgery boost.	Results WBRT | WBRT+SRS	Limitations Randomisation: Yes, randomisation within

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Flanders, A. E., Gaspar, L. E., Schell, M. C., Werner-Wasik, M., Demas, W., Ryu, J., Bahary, J. P., Souhami, L., Rotman, M., Mehta, M. P., Curran, W. J., Jr., Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial, LancetLancet, 363, 1665-72, 2004
Ref Id 497036</td>
<td>
<table>
<tr><td></td><td>WBRT+ SRS (n-164)</td><td>WBRT alone (n=167)</td></tr>
<tr><td>Age mean</td><td>58.8 (19-82)</td><td>59.9 (24-90)</td></tr>
<tr><td>Primary tumour site</td><td></td><td></td></tr>
<tr><td>Breast</td><td>9%</td><td>11%</td></tr>
<tr><td>Lung</td><td>64%</td><td>63%</td></tr>
<tr><td>Skin/melanoma</td><td>4%</td><td>5%</td></tr>
<tr><td>Other</td><td>14%</td><td>10%</td></tr>
<tr><td>Kidney</td><td>1%</td><td>1%</td></tr>
<tr><td>Bladder</td><td>0</td><td>2%</td></tr>
<tr><td>Colon</td><td>2%</td><td>1%</td></tr>
<tr><td>Ovarian</td><td>1%</td><td>1%</td></tr>
<tr><td>Unknown primary</td><td>4%</td><td>0</td></tr>
<tr><td>Number of brain metastases</td><td></td><td></td></tr>
<tr><td>1</td><td>56%</td><td>56%</td></tr>
<tr><td>2</td><td>24%</td><td>28%</td></tr>
<tr><td>3</td><td>20%</td><td>16%</td></tr>
</table>
Inclusion criteria

All patients were aged 18 years or older with no previous cranial radiation. Entry criteria included a contrast-enhanced MRI scan showing one to three brain metastases with a maximum diameter of 4 cm for the largest lesion and additional lesions not exceeding 3 cm in diameter.
</td>
<td>Details
WBRT: All patients received WBRT in daily 2·5 Gy fractions to a total of 37·5 Gy over 3 weeks.
WBRT with stereotactic radiosurgery boost: Patients allocated stereotactic radiosurgery boost received this treatment within 1 week of completing WBRT. We treated metastases up to 2·0 cm in broadest diameter with a surface isodose prescription of 24·0 Gy; metastases larger than 2 cm but equal to or smaller than 3 cm with 18·0 Gy; and metastases larger than 3 cm and less than or equal to 4 cm with 15·0 Gy.</td>
<td>
<table>
<tr><td>Mean overall survival</td><td>6.5 (n=167)</td><td>5.7 (N=164)</td><td>p=0.1356</td></tr>
<tr><td>Mean overall survival single</td><td>4.9 (n=94)</td><td>6.5 (n=92)</td><td>p=0.0390</td></tr>
<tr><td>Mean overall survival multiple</td><td>6.7 (n=73)</td><td>5.8 (n=72)</td><td>p=0.9776</td></tr>
<tr><td>Mean overall survival if had squamous/non-small cell lung carcinoma</td><td>3.9 (n=29)</td><td>5.9 (n=27)</td><td>p=0.0508</td></tr>
<tr><td>Overall time to intracranial tumour progression</td><td></td><td></td><td>p=0.1278</td></tr>
<tr><td>1 year control of treated lesion (unchanged or improved)</td><td>37 (71%)</td><td>41 (82%)</td><td></td></tr>
<tr><td>Complete response (3 months)</td><td>6 (n=78)</td><td>12 (n=75)</td><td></td></tr>
<tr><td>Partial response (3 months)</td><td>42 (n=78)</td><td>43 (n=75)</td><td></td></tr>
<tr><td>Stable (3 months)</td><td>17 (n=78)</td><td>11 (n=75)</td><td></td></tr>
</table>
</td>
<td>strata by permutated blocks was done by use of computerised techniques at RTOG headquarters when member institutions telephoned to enrol eligible patients. Patients were stratified by number of brain metastases (single vs 2–3) and extent of extracranial disease (none vs present).

Allocation concealment: Yes, RTOG headquarte</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results				Comments
Country/ies where the study was carried out USA Study type RCT Source of funding This publication was supported by grant number (RTOG U10 CA21661, CCOP U10CA37422, Stat U10 CA32115) from the National Cancer Institute. Contents are solely the responsibility of the authors and do not necessarily represent the official views of the National	Metastases were deemed unresectable if they were located in deep grey matter or in eloquent cortex. Patients with newly diagnosed cancer presenting with brain metastases or patients with unknown primaries were both considered to have unknown disease control and were included in the study. Exclusion criteria We excluded patients who had Karnofsky Performance Status (KPS) score of less than 70, haemoglobin concentration less than 80 g/L, absolute neutrophil count of less than 1000 cells/L, or platelet count less than 50 000 cells per uL. Patients with metastases in the brain stem, or within 1 cm of the optic apparatus were excluded since no safety data for these sites were available from the antecedent phase I study, RTOG 9005.10 Patients who had received treatment for systemic cancer within 1 month of enrolment were judged to have active disease and were excluded.		Progression (3 months)	13 (n=78)	8 (n=75)		rs when member institutions telephoned to enrol eligible patients Patient blinding: Unlikely no. Assessor blinding: Unclear Investigator blinding: Unclear Reporting bias: A number of outcomes the SD was not reported. It could only be calculated by using p value Drop out: none lost to follow up Compliance: 133/164 in WBRT and surgery
			Acute toxicities (<90 days) GRADE 3-4	0/166	5/160		
			Late toxicities, GRADE 3-4	4/166	6/160		
			Death due to brain metastases (single)	22/82	19/73		
			Death due to brain metastases (multiple)	24/67	20/64		
			Death due to brain metastases (mixture)	46/149	39/137		
			KPS improved	3/75	10/79		
			Steroids increased	6/75	7/76		

Study details	Participants	Interventions	Outcomes and results	Comments
Cancer Institute. Aim of the study We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG). Study dates From January, 1996, to June, 2001				completed treatment; 167 in WBRT completed treatment ITT: yes Single metastases: 56% Prior treatments: No previous cranial radiation. Postoperative patients with either residual or distal brain metastases remained 3 or fewer. Mean treatment duration: 4 weeks (3 weeks WBRT) Time points for measurement: 3 months, 12

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>months, 24 months
Other information</td></tr>
<tr><td>Full citation
Antonadou, D., Paraskevaidis, M., Sarris, G., Coliarakis, N., Economou, I., Karageorgis, P., Throuvalas, N., Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases, Journal of Clinical OncologyJ Clin Oncol, 20, 3644-50, 2002
Ref Id
497058</td><td>Sample size
52 were randomised. TMZ + RT = 27, RT =25
n=48 analysed (4 refused treatment, 2 in each group)
Characteristics
<table>
<tr><th></th><th>TMZ+RT (n=25)</th><th>RT (n=23)</th></tr>
<tr><td>Median age</td><td>61</td><td>62</td></tr>
<tr><td>Primary tumour site</td><td></td><td></td></tr>
<tr><td>Lung (non-small cell)</td><td>16 (64%)</td><td>15 (65%)</td></tr>
<tr><td>Lung (small cell)</td><td>5 (20%)</td><td>4 (17%)</td></tr>
<tr><td>Breast</td><td>2 (8%)</td><td>3 (13%)</td></tr>
<tr><td>Unknown</td><td>2 (8%)</td><td>1 (4%)</td></tr>
<tr><td>Brain metastases</td><td></td><td></td></tr>
<tr><td>Solitary</td><td>6 (24%)</td><td>7 (30%)</td></tr>
<tr><td>Multiple</td><td>19 (76%)</td><td>15 (70%)</td></tr>
</table>
Inclusion criteria
Patients (18 years of age) with histologically proven cancer at the primary site (either lung or breast) and from an unknown primary tumor with brain metastases assessable by contrast-enhanced computed tomographic (CT) scan or gadolinium-enhanced magnetic resonance imaging (MRI) were eligible for the study. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status 2; a</td><td>Interventions
TMZ + RT group: oral TMZ plus conventional fractionated external-beam radiotherapy
RT group: RT alone
Details
TMZ + RT: Planned conventional WBRT was administered with two opposed lateral fields from the supraorbital ridge to the mastoid. The daily dose was 2 Gy 5 days each week for 4 weeks to a total dose of 40 Gy. The 2-Gy fraction was chosen in order to minimize the side effects of the radiation treatment. The total dose of 40 Gy was designed to enhance the efficacy of RT. Patients were</td><td>Results
<table>
<tr><th></th><th>TMZ + RT (n=24)</th><th>RT (n=21)</th></tr>
<tr><td>Complete response (3 months after RT)</td><td>9</td><td>7</td></tr>
<tr><td>Partial response (3 months after RT)</td><td>14</td><td>7</td></tr>
<tr><td>Objective response (complete + partial) (3 months after RT)</td><td>23</td><td>14</td></tr>
<tr><td>Stable disease (3 months after RT)</td><td>1</td><td>5</td></tr>
<tr><td>Progressive disease (3 months after RT)</td><td>0</td><td>2</td></tr>
<tr><td>Neurological functional status level I (fully functional)</td><td>11 (25)</td><td>9 (23)</td></tr>
<tr><td>Neurological functional status level II (fully functional but not able to work)</td><td>11 (25)</td><td>10 (23)</td></tr>
<tr><td>Neurological function status level III (stays in bed and needs help half the time)</td><td>2 (25)</td><td>4 (23)</td></tr>
<tr><td>Neurological function status IV (requires help all of the time)</td><td>NA</td><td>NA</td></tr>
<tr><td>Required anticonvulsants (2 months post RT)</td><td>29%</td><td>38%</td></tr>
</table></td><td>Limitations
Randomisation: yes, unclear methods
Allocation concealment: unclear
Patient blinding: unclear/unlikely
Assessor blinding: Yes. All CT and MRI scans were centrally reviewed by blinded radiologist
Investigator blinding: unclear
Reporting bias: unclear,
Drop out: TMZ + RT (n=27) (2</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results			Comments
Country/ies where the study was carried out Greece Study type Phase II randomised study Source of funding None reported Aim of the study To evaluate the efficacy and safety of continuous daily dosing with temozolomide concurrent with conventional external-beam radiotherapy in patients with previously untreated brain metastases from solid tumors	life expectancy of 3 months; and adequate hematologic, renal, and hepatic function (including absolute neutrophil count 1,500/mm3, platelet count 100,000/mm3, serum creatinine and total serum bilirubin 1.5 times the upper limit of normal, and AST and ALT 3 times the upper limit of normal). Eligible patients must have fully recovered from all ongoing toxicities (except alopecia) resulting from previous therapy, and were also required to have given written informed consent. Exclusion criteria Any patient who had received prior chemotherapy or radiotherapy for brain metastases, or had any uncontrollable, life-threatening systemic disease was ineligible. Pregnant or lactating women were also ineligible.	irradiated with a linear accelerator and a 12-MV photon beam. TMZ was administered orally at a dosage of 75 mg/m2/d during radiation treatment and 200 mg/m2/d 5 days every 28 days after RT to fasting patients for a maximum of six additional cycles.	Required corticosteroids (2 months post RT)	67%	91%	dropped out) RT (n=25) (2 dropped out, 1 lost to follow) Compliance: 93% in TMZ+RT; 88% RT ITT: no, ACA Single metastases: 27% Prior treatments: None Mean treatment duration: WBRT = 4 weeks. TMZ = during radiation treatment and every 28 days after RT for a maximum of six additional cycles. Time points for measurem
			Overall survival (months) median	8.6	7.0	
			Myelosuppression GRADE 3 (decrease in production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes)	0/24	0/21	
			Death from systemic disease	20/24	19/21	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Study dates
October 1999 and June 2000</td><td></td><td></td><td></td><td>ent: monthly
Other information</td></tr>
<tr><td>Full citation
Aoyama, H., Shirato, H., Tago, M., Nakagawa, K., Toyoda, T., Hatano, K., Kenjyo, M., Oya, N., Hirota, S., Shioura, H., Kunieda, E., Inomata, T., Hayakawa, K., Katoh, N., Kobashi, G., Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled</td><td>Sample size
n=132 (65 WBRT+SRS, 67 SRS)
Characteristics
<table>
<tr><td></td><td>WBRT+SRS (n=65)</td><td>SRS (n=67)</td></tr>
<tr><td>Age mean</td><td>62.5 (36-78)</td><td>62.1 (33-86)</td></tr>
<tr><td>N, brain metastases</td><td></td><td></td></tr>
<tr><td>1</td><td>31 (48%)</td><td>33 (49%)</td></tr>
<tr><td>2-4</td><td>34 (52%)</td><td>34 (51%)</td></tr>
<tr><td>Primary tumour site</td><td></td><td></td></tr>
<tr><td>Breast</td><td>6 (9%)</td><td>3 (4%)</td></tr>
<tr><td>Lung</td><td>46 (66%)</td><td>45 (67%)</td></tr>
<tr><td>Colorectal</td><td>5 (8%)</td><td>6 (9%)</td></tr>
<tr><td>Kidney</td><td>5 (8%)</td><td>5 (7%)</td></tr>
<tr><td>Other</td><td>6 (9%)</td><td>8 (12%)</td></tr>
</table>
Inclusion criteria

Patients were eligible who were aged 18 years or older with 1 to 4 brain metastases, each with a maximum diameter of no more than 3 cm on contrastenhanced magnetic resonance imaging (MRI) scans, derived from a histologically confirmed systemic cancer. Eligible patients had a</td><td>Interventions
SRS + WBRT
SRS
Details

SRS + WBRT: the WBRT dosage schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The WBRT treatment visit proceeded to SRS

SRS: The SRS dose was prescribed to the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22 to 25 Gy and those larger than 2 cm were treated with doses of 18 to 20 Gy. The dose was reduced by 30% when the treatment was combined with</td><td>Results
<table>
<tr><td></td><td>WBRT+SRS</td><td>SRS</td><td>p value</td></tr>
<tr><td>Survival Time (median, months)</td><td>7.5 (0.8-58.7)</td><td>8.0 (0.5-57)</td><td>0.42</td></tr>
<tr><td>Brain tumour recurrence at distal sites (median months)</td><td>16.2 (n=31)</td><td>5.5 (n=31)</td><td>0.003</td></tr>
<tr><td>Death neurological causes</td><td>13/57</td><td>12/62</td><td></td></tr>
<tr><td>Acute toxic effects GRADE 3-4</td><td>1/65</td><td>2/67</td><td></td></tr>
<tr><td>Acute Seizure GRADE 1-4</td><td>1/65</td><td>4/67</td><td></td></tr>
<tr><td>Late toxic effects GRADE 3-4</td><td>4/65</td><td>2/67</td><td></td></tr>
<tr><td>Late radiation necrosis GRADE 1-4</td><td>3/65</td><td>1/67</td><td></td></tr>
<tr><td>Leukoencephalopathy GRADE 1-4</td><td>3/65</td><td>0/67</td><td></td></tr>
<tr><td>Brain tumour distal or local</td><td>23</td><td>40</td><td></td></tr>
<tr><td>12 month actuarial brain tumour recurrence rate %</td><td>46.8 (29.7 to 63.9)</td><td>76.4 (63.3 to 89.5)</td><td><0.001</td></tr>
<tr><td>New brain metastases at distal sites</td><td>21</td><td>34</td><td></td></tr>
</table></td><td>Limitations
Randomisation: was performed at the Hokkaido University Hospital Data Center. A permuted-blocks randomization algorithm was used with a block size of 4. A randomization sheet was created for each institution. Patients were stratified based on number of brain metastases</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>trial, JAMAJama, 295, 2483-91, 2006
Ref Id 497062
Country/ies where the study was carried out
Japan
Study type

Prospective, multi-institutional, randomized controlled trial

Source of funding
None reported
Aim of the study

To determine if WBRT combined with SRS results in improvements in survival, brain tumor control,</td>
<td>Karnofsky Performance Status (KPS) score of 70 or higher.

Exclusion criteria
Patients with metastases from small cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded.</td>
<td>WBRT because the optimal combination of WBRT and SRS had not been studied in well-conducted, prospective, phase 1 dose escalation trials.</td>
<td>
<table>
<tr><td>12 month actuarial brain tumour recurrence %</td><td>41.5 (49 to 78.4)</td><td>63.7 (49 - 78.4)</td><td>p=0.003</td></tr>
<tr><td>Local tumour control rate (actuarial) 12 months, %</td><td>88.7 (80.1to 97.3)</td><td>72.5 (60.3 to 84.7)</td><td>p=0.002</td></tr>
<tr><td>KPS score >=70 at 12 months</td><td>33.9 (22.2-45.4)</td><td>26.9 (16.3 to 37.5)</td><td>p=0.53</td></tr>
<tr><td>Neurological preservation at 12 months</td><td>72.1 (58.8 - 85.4)</td><td>70.3 (55.6 - 85)</td><td>p=0.99</td></tr>
<tr><td>Neurocognitive function (mini-mental state examination MMSE), who lived >12 months, final FU</td><td>27 (21 to 30)) (n=16)</td><td>28 (18-30) (n=12)</td><td>(0.5-57)</td></tr>
</table>
Note: they provided data on outcomes for single and multiple mets but not comparing the two treatment arms, rather 1 vs. multiple mets;
Leukoencephalopathy: damage to white matter in brain
</td>
<td>(single vs 2-4), extent of extracranial disease (active vs stable), and primary tumor site (lung vs other sites).

Allocation concealment: unclear
Patient blinding: unclear, unlikely
Assessor blinding: no, were scored by physicians who treated the patients
Investigator blinding: no
Reporting bias:
Drop out: 0 lost to follow-up
Compliance: 88%</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
functional preservation rate, and frequency of neurologic death. Study dates October 1999 and December 2003				57/65 WBRT+SRS; 97% 65/67 SRS ITT: yes Single metastases: 49% Prior treatments: unclear Mean treatment duration: 2.5 weeks Time points for measurement: clinical evaluations and MRI scans 1 and 3 months after treatment and every 3months thereafter up to 60 months Other information
Full citation	Sample size	Interventions	Results	Limitations

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Brown, P. D., Jaeckle, K., Ballman, K. V., Farace, E., Cerhan, J. H., Keith Anderson, S., Carrero, X. W., Barker, F. G., Deming, R., Burri, S. H., Menard, C., Chung, C., Stieber, V. W., Pollock, B. E., Galanis, E., Buckner, J. C., Asher, A. L., Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases a randomized clinical trial, JAMA -</td>
<td>213 randomized participants (SRS alone, n = 111; SRS plus WBRT, n = 102)

Characteristics
<table>
<tr><td></td><td>SRS alone (n-111)</td><td>SRS plus WBRT (n=102)</td></tr>
<tr><td>Age mean</td><td>59.8 (10.4)</td><td>61.4 (10.6)</td></tr>
<tr><td>N of brain metastasis</td><td></td><td></td></tr>
<tr><td>1</td><td>55</td><td>56</td></tr>
<tr><td>2</td><td>39</td><td>36</td></tr>
<tr><td>3</td><td>17</td><td>10</td></tr>
<tr><td>Primary brain tumour site</td><td></td><td></td></tr>
<tr><td>Breast</td><td>11</td><td>7</td></tr>
<tr><td>Colorectal</td><td>7</td><td>4</td></tr>
<tr><td>Lung</td><td>80</td><td>66</td></tr>
<tr><td>Skin/melanoma</td><td>3</td><td>9</td></tr>
<tr><td>Bladder</td><td>1</td><td>1</td></tr>
</table>
</td>
<td>SRS vs. SRS plus WBRT
Details

SRS = received 24 Gy in a single fraction if lesions were less than 2.0 cmor 20 Gy if lesions were 2 to 2.9 cmin maximum diameter.
SRS plus WBRT = received 22 Gy in a single fraction if lesionswere less than 2.0 cmor 18 Gy if lesions were 2 to 2.9 cm in maximum diameter. The dose was prescribed to the highest isodose line encompassing the target, ranging from 50% to 80% of the maximum dose. Patients randomly assigned to SRS plusWBRT received 30 Gy in 12 fractions of 2.5-Gy WBRT delivered 5 days a week. Whole brain radiotherapy began</td>
<td>
<table>
<tr><td></td><td>SRS</td><td>SRS plus WBRT</td><td>MD p value</td></tr>
<tr><td>Local control 3 months</td><td>94/105</td><td>92/95</td><td>NA</td></tr>
<tr><td>Local control 12 months</td><td>75/103</td><td>82/91</td><td>NA</td></tr>
<tr><td>Distal brain control 3 months</td><td>86/105</td><td>92/95</td><td>NA</td></tr>
<tr><td>Distal brain control 12 months</td><td>72/103</td><td>84/91</td><td>NA</td></tr>
<tr><td>Cognitive deterioration 3 months</td><td>40/63</td><td>44/48</td><td>NA</td></tr>
<tr><td>Quality of life 3 months (change from baseline) points</td><td>-0.1 (-4.8 to 4.5) n=65</td><td>-12 (-17.4 to 6.6) n=50</td><td>- 11.9 95% CI (48-19-17.71 to -6.09) p=0.001</td></tr>
<tr><td>Barthel ADL Index scores, functional assessment</td><td>-1.5 (n=65)</td><td>-4.2 (n=50)</td><td>2.7 (-2.0 to 7.4) p=0.26</td></tr>
</table>
</td>
<td>Randomisation: yes
Allocation concealment: yes
Patient blinding: no
Assessor blinding: yes
Investigator blinding: no
Reporting bias: no
Drop out: SRS 18% and WBRT plus SRS 27%
Compliance: SRS: 78% vs. WBRT plus SRS: 94%
ITT: yes for survival analysis
Single metastases: 52%
Prior treatments: No prior resection, cranial radiotherap</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Journal of the American Medical Association, 316, 401-409, 2016
Ref Id 497307
Country/ies where the study was carried out
USA
Study type
RCT
Source of funding

NCCTG (Alliance for Clinical Trials in Oncology) in collaboration with other cooperative groups including the Radiation Therapy Oncology Group, and was supported by grants NCI. There were</td>
<td>
<table>
<tr><td>Kidney</td><td>1</td><td>4</td></tr>
<tr><td>Gynaecologic</td><td>2</td><td>3</td></tr>
<tr><td>Other</td><td>6</td><td>7</td></tr>
</table>
Inclusion criteria

Adult patients (≥18 years of age) with 1 to 3 brain metastases, all smaller than 3 cmin diameter,were eligible for the trial. Eligibility criteria included Eastern Cooperative OncologyGroup performance status (score of 0, no symptoms; 1, mild symptoms; 2, symptomatic, <50%in bed during the day), and pathologic confirmation of tracerebral tumor site (eg, lung, breast, prostate) from either the primary site or a metastatic lesion.

Exclusion criteria

Exclusion criteria included pregnant or nursingwomen, men or women of childbearing potential unwilling to use adequate contraception, inability to complete a magnetic resonance imaging scan with contrast, prior resection of cerebral metastasis, chemotherapywithin 7 days of preregistration or planned chemotherapy during the radiotherapy, prior cranial radiotherapy, leptomeningeal metastases, lesion locatedwithin 5 mm of the optic chiasm or within the brainstem, or metastases from primary germ cell tumor, small cell carcinoma, or lymphoma.
</td>
<td>within 14 days of SRS.</td>
<td>
<table>
<tr><td>Time to intracranial failure HR (favours SRS+WBRT)</td><td></td><td></td><td>HR3.6 (2.2 to 5.9) p=0.001</td></tr>
<tr><td>Median overall survival</td><td>10.4</td><td>7.4</td><td>HR: 1.02 (0.75 to 1.38) p=0.92</td></tr>
<tr><td>CNS necrosis</td><td>5/111</td><td>3/102</td><td>NA</td></tr>
<tr><td>At least one GRADE 3+AE</td><td>46/111</td><td>44/102</td><td>NA</td></tr>
<tr><td>Edema limbs</td><td>4/111</td><td>0/102</td><td>NA</td></tr>
<tr><td>Lymphocyte count decreased</td><td>2/111</td><td>2/102</td><td>NA</td></tr>
<tr><td>Leukocyte count decreased```</td><td>0/111</td><td>3/102</td><td>NA</td></tr>
<tr><td>Infection grade, 1,2 ANC</td><td>0/111</td><td>1/102</td><td>NA</td></tr>
</table>
</td>
<td>y, no chemo <7 days
Mean treatment duration: 2 weeks
Time points for measurement: 62 months
Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>no commercial sponsors of this study.

Aim of the study

To determine whether there is less cognitive deterioration at 3 months after SRS alone vs SRS plus WBRT.

Study dates

February 2002 and December 2013,</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Brown, P. D., Pugh, S., Laack, N. N., Wefel, J. S., Khuntia, D., Meyers, C., Choucair, A., Fox, S., Suh,</td><td>Sample size
N=554 (278 Memantine + WBRT; 276 WBRT+Placebo)
Characteristics<table><tr><td></td><td>Memantine+WBRT (n=256)</td><td>Placebo+WBRT (n=252)</td></tr><tr><td>Age median</td><td>60 (31-84)</td><td>59 (29-86)</td></tr></table></td><td>Interventions
WBRT+placebo
WBRT+Memantine
Memantine is a noncompetitive, low-affinity, openchannel blocker that has been shown to be</td><td>Results<table><tr><td></td><td>WBRT plus Memantine</td><td>WBRT plus placebo</td><td>p value</td></tr><tr><td>Cognitive function failure 3 months</td><td>43.6% (total evaluated, n=75)</td><td>51.9% (total evalu</td><td></td></tr></table></td><td>Limitations
Randomisation: yes, unclear methods
Allocation concealment: unclear</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
J. H., Roberge, D., Kavadi, V., Bentzen, S. M., Mehta, M. P., Watkins-Bruner, D., Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial, Neuro-OncologyNeuro-oncol, 15, 1429-1437, 2013 Ref Id 497309 Country/ies where the study was carried out USA Study type	<table><tr><td>Primary disease site</td><td></td><td></td></tr><tr><td>Lung</td><td>70.7%</td><td>69%</td></tr><tr><td>Breast</td><td>12.5%</td><td>17.1%</td></tr><tr><td>Colon</td><td>1.2%</td><td>0.8%</td></tr><tr><td>Other</td><td>15.6%</td><td>13.1%</td></tr><tr><td>Prior surgery/surgical resection</td><td>26.2%</td><td>27%</td></tr><tr><td>Prior chemotherapy</td><td>41.8%</td><td>47.6%</td></tr><tr><td>Receiving steroids at time of study</td><td>68.4%</td><td>61.5%</td></tr></table>* No information on the number of brain metastases Inclusion criteria Adult patients with a pathologically proven diagnosis of solid malignancy within 5 years of registration and with brain metastases visible on contrast-enhanced MRI (or a contrast-enhanced CT for patients unable to have an MRI) were eligible. Eligibility criteria included a Karnofsky performance status of ≥70, stable systemic disease in the 3 months prior to study entry, serum creatinine ≤3 mg/dL, creatinine clearance ≥30 mL/min, total bilirubin ≤2.5 mg/dL, blood urea nitrogen (BUN), 20 mg/dL, Mini Mental State Exam (MMSE) score 18, negative serum pregnancy test, no memantine allergy, no current alcohol or drug abuse, no chronic use of benzodiazepines, and no severe active	neuroprotective in preclinical models. Details WBRT: Patients received 37.5 Gy of WBRT (15 fractions of 2.5 Gy). Study drug administration was to commence no later than the third day of WBRT. Memantine or Placebo: Orally for 24 weeks and escalating doses over the first 4 weeks. Week 1 was a single 5-mg morning dose followed by the addition of a 5-mg dose in the evening during week 2. In week 3, the morning dose was increased to 10 mg. The target dose for weeks 4 through 24 was 10 mg in the morning and 10 mg in the evening, for a total dose of 20 mg daily. The dose was lowered to 5 mg orally twice daily if	<table><tr><td></td><td></td><td>ated, n=66)</td><td></td></tr><tr><td>Cognitive function 15 months</td><td>56.4% (total evaluated, n=9)</td><td>67.1% (total evaluated, n=9)</td><td></td></tr><tr><td>Progression free survival (median months)</td><td>4.7</td><td>5.5</td><td>HR 1.06 (0.87 to 1.30) p =0.27</td></tr><tr><td>Overall survival (median, months)</td><td>6.7</td><td>7.8</td><td>HR 1.06 (0.86 to 1.31) p =0.28</td></tr><tr><td>Time to cognitive failure (first cognitive failure on any neurological test)</td><td></td><td></td><td>HR 0.78 (0.62 to 0.99) p=0.1 favoured memantine</td></tr><tr><td>Grade 3-4 events attributed to treatment</td><td>14%</td><td>14%</td><td>fatigue, alopecia, nausea, headache</td></tr></table>Cognitive failure for each test was defined as a posttreatment score that met one of the following criteria: follow-up score that was at least 2 SD worse than the patient's personal baseline score or the patient's raw score change greater than the reliable change index RCI.	Patient blinding: yes to drug Assessor blinding: unclear Investigator blinding: yes Reporting bias: No Drop out: Patient refusal, adverse events, other and non-specified. N=94/278 Memantine; n=90/276 Placebo. Compliance: 93% completed WBRT; 31% memantine; 33% placebo ITT: yes (Patients missing assessments due to

Study details	Participants	Interventions	Outcomes and results	Comments
Randomised, double-blind, placebo-controlled trial Source of funding Radiation Therapy Oncology Group (RTOG) and was supported by RTOG grant U10 CA21661 and Community Clinical Oncology Program grant U10 CA37422 from the National Cancer Institute (NCI) and by Forest Pharmaceuticals Aim of the study	comorbidity. Patients could have received prior therapy for brain metastasis, including radiosurgery and surgical resection (but no prior cranial external beam radiotherapy). Patients receiving systemic therapy were eligible if such therapy was given .14 days prior to study entry, and they could not receive chemotherapy for at least 14 days after completing radiotherapy. Exclusion criteria None listed	creatinine clearance fell below 30 mL/min and was held if the creatinine clearance was less than 5 mL/min with a weekly recheck of laboratory values		neurologic disability were assigned the worst score) Single metastases : unclear Prior treatments: Patients could have received prior therapy for brain metastasis, including radiosurgery and surgical resection (but no prior cranial external beam radiotherapy). Mean treatment duration: 24 weeks Time points for measurem

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>To determine the protective effects of memantine on cognitive function in patients receiving whole brain radiotherapy (WBRT).

Study dates March 2008 and July 2010</td><td></td><td></td><td></td><td>ent: At baseline and 8, 16, 24, and 52 weeks after the start of the study drug

Other information</td></tr>
<tr><td>Full citation
Chang, E. L., Wefel, J. S., Hess, K. R., Allen, P. K., Lang, F. F., Kornguth, D. G., Arbuckle, R. B., Swint, J. M., Shiu, A. S., Maor, M. H., Meyers, C. A., Neurocognition in patients with brain</td><td>Sample size
After 58 patients were recruited (n=30 in the SRS alone group, n=28 in the SRS plus WBRT group), the trial was stopped by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%)
Characteristics<table><tr><td></td><td>Stereotactic radiosurgery (n=30)</td><td>Stereotactic radiosurgery plus WBRT (n=28)</td></tr><tr><td>Age Median</td><td>63 (35–82)</td><td>64 (40–78)</td></tr></table></td><td>Interventions
SRS vs. SRS plus WBRT
Details
SRS: All patients received initial SRS for one to three brain metastases detected with screening brain MRI within 1 month before enrolment. SRS dose was prescribed in general accordance to the Radiation Therapy Oncology</td><td>Results<table><tr><td></td><td>SRS</td><td>SRS+WBRT</td><td>P value</td></tr><tr><td>Median survival (months)</td><td>15.2</td><td>5.7</td><td>p=0.003</td></tr><tr><td>1 year survival</td><td>63%</td><td>21%</td><td></td></tr><tr><td>Local tumour control</td><td>67%</td><td>100%</td><td>p=0.012</td></tr><tr><td>Distant tumour control</td><td>45% (14-51)</td><td>73% (46-100)</td><td>p=0.02</td></tr><tr><td>1 year freedom from CNS recurrence</td><td>27%</td><td>73%</td><td>p=0.0003</td></tr><tr><td>Median KPS (4 months)</td><td>80</td><td>70</td><td></td></tr></table></td><td>Limitations
Randomisation: yes, randomisation was done by computer in a 1:1 fashion between group 1 (SRS plus WBRT) and group 2 (SRS alone) using a</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial, Lancet OncologyLancet Oncol, 10, 1037-44, 2009 Ref Id 497382 Country/ies where the study was carried out USA Study type Randomiised control trial Source of funding No external funding was received Aim of the study We propose that the learning and memory	<table><tr><td>Number of brain metastases</td><td></td><td></td></tr><tr><td>1</td><td>18 (60)</td><td>15 (54)</td></tr><tr><td>2</td><td>7 (23)</td><td>8 (28)</td></tr><tr><td>3</td><td>5 (17)</td><td>5 (18)</td></tr><tr><td>Primary tumour site</td><td></td><td></td></tr><tr><td>Breast</td><td>4 (13)</td><td>4 (14)</td></tr><tr><td>Lung</td><td>16 (53)</td><td>16 (57)</td></tr><tr><td>Renal</td><td>2 (7)</td><td>2 (7)</td></tr><tr><td>Melanoma/ Skin</td><td>4 (13)</td><td>3 (11)</td></tr><tr><td>Other</td><td>4 (13)</td><td>3 (11)</td></tr></table> Inclusion criteria Eligibility requirements were: age 18 years or greater; recursive partitioning analysis (RPA) class one or two (Karnofsky Performance Status [KPS] ≥70); one to three newly diagnosed brain metastases eligible for SRS; brain MRI within 1 month of enrolment; and signed written informed consent. Exclusion criteria Patients were excluded if they had undergone prior brain surgery, SRS, or WBRT; if they were diagnosed with leukaemia, lymphoma, germ-cell tumour, small-cell lung cancer, leptomeningeal disease, or unknown primary tumour; if they were RPA class three (KPS <70); and if they were pregnant. After meeting eligibility criteria, patients	Group (RTOG) 90-05 guidelines.13 WBRT was prescribed to a total dose of 30 Gy given in 12 daily fractions of 2·5 Gy per day. SRS plus WBRT group received SRS fi rst, followed by WBRT given within 3 weeks. SRS was given before WBRT (as is standard practice at the University of Texas MD Anderson Cancer Center) to ensure that intracranial metastases identified at enrolment could be localised and therefore treated with SRS. (If WBRT was given first, a robust or complete response could preclude subsequent targeting with SRS). WBRT was delivered from a	<table><tr><td>Systemic death</td><td>10</td><td>16</td><td></td></tr><tr><td>Neurological death</td><td>8</td><td>7</td><td>plus n=2 deaths due to unknown causes in each group</td></tr><tr><td>Deaths 4 months</td><td>4</td><td>8</td><td></td></tr><tr><td>HR for death SRS+WBRT vs. SRS</td><td></td><td></td><td>HR: 2.47 (1.34 to 4.54) p=0.0036</td></tr><tr><td>Grade 3 toxicity (due to radiation)</td><td>1</td><td>1</td><td>seizures, motor neuropathy, depressed consciousness versus aphasia</td></tr><tr><td>Grade 4 toxicity</td><td>2</td><td>0</td><td>radiation necrosis</td></tr><tr><td>Neurocognitive function</td><td></td><td></td><td></td></tr><tr><td>Total recall</td><td>52% (7/11)</td><td>24% (4/20)</td><td></td></tr></table>	standard permutated block algorithm in which block sizes were randomly chosen from 2, 4, 6, or 8. Allocation concealment: yes, The sequence was concealed until interventions were assigned by the Clinical Oncology Research (CORE) database computer. Patient blinding: no, revealed after treatment assignment Assessor blinding: n

Study details	Participants	Interventions	Outcomes and results	Comments
functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction. Study dates Jan 2, 2001 to Sept 14 2007	were randomly assigned to SRS alone or SRS plus WBRT.	linear accelerator by using 6 MV photons, opposed lateral technique, and standard whole-brain fields.	Delayed recall: 22% (2/11); 6% (1/20) Delayed recognition: 11% (1/11); 0% (0/20)	o, revealed after treatment assignment Investigator blinding: no, revealed after treatment assignment Reporting bias: none Drop out: 0% SRS+WBRT; n=1 SRS alone Compliance: WBRT n=1 refused WBRT treatment assignment. 57 out of 58 (98%) of the enrolled patients completing their assigned treatment. ITT: This patient remained in

Study details	Participants	Interventions	Outcomes and results	Comments
				the SRS plus WBRT group and was analysed according to his original assignment. Single metastases: 57% Prior treatments: Yes, received systemic therapy. SRS+WBRT: 21 (75%) patients SRS: 21 (70%) patients Mean treatment duration: 4 weeks (WBRT given within 3 weeks of SRS, 12 days of treatment).

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Time points for measurement: Median follow-up 9·5 months (range 0·3–66) for the entire study.
Other information</td></tr>
<tr><td>Full citation
Chua, D., Krzakowski, M., Chouaid, C., Pallotta, M. G., Martinez, J. I., Gottfried, M., Curran, W., Throuvalas, N., Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell</td><td>Sample size
95 patients (n=47 WBRT + temozolomide arm and n=48 WBRT)
Characteristics<table><tr><td></td><td>WBRT+TMZ (n=47)</td><td>WBRT (N=48)</td></tr><tr><td>Age, median</td><td>59 (38-78)</td><td>62 (43-79)</td></tr><tr><td>Median KPS</td><td>90 (70-100)</td><td>90 (70-100)</td></tr><tr><td>Extracranial metastases</td><td></td><td></td></tr><tr><td>NO</td><td>21 (45%)</td><td>20 (42%)</td></tr><tr><td>YES</td><td>26 (55%)</td><td>28 (58%)</td></tr></table></td><td>Interventions
WBRT plus Temozolomide versus WBRT
Details
WBRT (30 Gy in 10 fractions) completed over days 1-14; Temozolomide 75 mg/m2 orally daily on days 1-28 followed by 7-day rest period (days 29-35). Two schedules of 21 or 28 days.
WBRT (30 Gy in 10 fractions) completed over days 1-14 followed by 7-day rest period (days 15-21)</td><td>Results<table><tr><td></td><td>WRT+TMZ</td><td>WBRT</td><td>p value</td></tr><tr><td>Median overall survival (ITT)</td><td>4.4</td><td>5.7</td><td>HR 1.14 (0.71 to 1.83) p =0.59</td></tr><tr><td>Median time to CNS progression *</td><td>3.1</td><td>3.8</td><td>HR 1.01 (0.64 to 1.62) p =0.95</td></tr><tr><td>Adverse events ≥3</td><td>3</td><td>0</td><td>Lead to discontinuation: 1 deep vein thrombosis and pneumonitis. 1 chest pain and dyspnea; 1 sudden death</td></tr></table></td><td>Limitations
Randomisation: yes, unclear
Allocation concealment: unclear
Patient blinding: no (changed from double blind, phase III to open label phase II trial)
Assessor blinding: no
Investigator blinding: no</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
lung cancer: a randomized, open-label phase II study, Clinical Lung CancerClin Lung Cancer, 11, 176-81, 2010 Ref Id 497431 Country/ies where the study was carried out 14 countries Study type Randomised control trial. Phase II Source of funding All authors report no relevant financial conflicts of interest. Aim of the study This study sought to confirm the benefit of	<table><tr><td>NSCLC diagnosed within 30 days</td><td>30%</td><td>13%</td></tr><tr><td>Previous chemotherapy</td><td>81%</td><td>58%</td></tr></table> Inclusion criteria Adult patients (≥ 18 years of age) were eligible if they had histologically or cytologically confirmed NSCLC and ≥ 1 newly diagnosed brain metastasis (diagnosed ≤ 30 days before randomization). Patients with postcraniotomy incomplete resection and those with extracranial metastases in up to two anatomic sites were eligible. Eligible patients may have received previous radiation therapy to the primary tumor and/or systemic metastatic sites but no previous WBRT or radiosurgery for brain metastases. Exclusion criteria Patients were excluded if they (1) had known leptomeningeal or meningeal metastases; (2) had received > 1 previous regimen of cytotoxic chemotherapy for metastatic NSCLC; (3) had received any investigational drugs, chemotherapy, immunotherapy, or hormonal therapy within 7 days of randomization; (4) had received any previous treatment with temozolomide; or (5) had received radiation therapy to ≥ 50% of their bone marrow.		<table><tr><td>Lymphocyte count <0.5x109/L</td><td>31%</td><td>18%</td><td></td></tr></table> * radiologic CNS progression or death,	Reporting bias: no Drop out: WBRT+TMZ n=8/47; WBRT n=4/48 (discontinued treatment, adverse event, lost to follow-up, patient request (not treatment related) Compliance: 91% WBRT+TMZ; 96% WBRT ITT: yes Single metastases: unclear Prior treatments: previous chemotherapy (81% in the WBRT + temozolomide arm vs.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>adding temozolomide to WBRT in patients with non–small-cell lung cancer (NSCLC) with brain metastases. Study dates March 31, 2004, and March 31,2006</td><td></td><td></td><td></td><td>58% in the WBRT) Mean treatment duration: WBRT 1-14 days; TMZ 1-28 days Time points for measurement:Following the final 6-week follow-up visit, survival of patients was documented every 8 weeks until death Other information</td></tr>
<tr><td>Full citation El Gantery, M. M., El Baky, H. M. A., El Hossieny, H. A., Mahmoud, M., Youssef, O.,</td><td>Sample size

n=60 ; 21 patients received WBRT +SRS, 21 patients received WBRT and 18 patients received SRS.
Characteristics
<table><tr><td></td><td>WBRT+SRS</td><td>WBRT</td><td>SRS</td></tr></table></td><td>Interventions
WBRT + SRS versus SRS versus WBRT
Details
WBRT + SRS: The WBRT treatment preceded SRS when patients were assigned to the</td><td>Results
<table><tr><td></td><td>WBRT+SRS</td><td>WBRT</td><td>SRS</td><td>p value/notes</td></tr><tr><td>Best local control at 1 year</td><td>9/21</td><td>4/21</td><td>4/18</td><td>p=0.04</td></tr><tr><td>Median local</td><td>10</td><td>6</td><td>5</td><td>p=0.04</td></tr></table></td><td>Limitations Randomisation: yes, unclear methods Allocation concealment: unclear</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both, Radiation OncologyRadiat, 9 (1) (no pagination), 2014
Ref Id 497637
Country/ies where the study was carried out
Egypt
Study type

Prospective randomized study

Source of funding
Aim of the study

To evaluate the role of</td>
<td>
<table>
<tr><td>Single metastases</td><td>15 (71.4%)</td><td>13 (62%)</td><td>14 (77.8%)</td></tr>
<tr><td>2</td><td>5</td><td>5</td><td>4</td></tr>
<tr><td>3</td><td>1</td><td>3</td><td>0</td></tr>
</table>

Inclusion criteria

The present work involved 60 patients with 1 to 3 brain metastases, each with a maximum diameter of no more than 4 cm on contrast-enhanced MRI scans, derived from a histologically confirmed systemic cancer. Age ≤ 70 years, KPS ≥ 70%, Ensured adequate organ function (Haemogram, Kidney and Liver function), no previous treatment for brain metastases.

Exclusion criteria
None provided
</td>
<td>WBRT + SRS group and the whole treatment duration was within 1 month. The prescribed dose of SRS in the WBRT + SRS arm ranged from 14 to 20 Gy (mean = 14.6 Gy, median = 14 Gy)
SRS: The prescribed dose in the SRS alone arm ranged from 18 to 20 Gy (mean = 19.5 Gy, median dose = 20 Gy). The dose choice was dependant on the size, number of the brain lesion and proximity to critical structures.
WBRT: The WBRT dosage schedule is 30 Gy in 10 fractions over 2 weeks delivered using megavoltage machines with photon beams of energy 6 MV. Treatments were delivered through</td>
<td>
<table>
<tr><td>control (months)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Overall survival</td><td>NA</td><td>NA</td><td>NA</td><td>in graph form only no number or p value</td></tr>
<tr><td>Acute toxicity</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Neurological worsening without CNS progression</td><td>2</td><td>1</td><td>0</td><td></td></tr>
<tr><td>Seizures</td><td>0</td><td>0</td><td>1</td><td></td></tr>
<tr><td>Late toxicity</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Radionecrosis</td><td>1</td><td>0</td><td>1</td><td></td></tr>
<tr><td>Brain oedema</td><td>1</td><td>1</td><td>1</td><td></td></tr>
<tr><td>Neurological worsening without CNS progression</td><td>2</td><td>1</td><td>2</td><td></td></tr>
</table>
* Multiple and single mets were analysed but not per treatment type
</td>
<td>Patient blinding: unclear
Assessor blinding: unclear
Investigator blinding: unclear
Reporting bias: yes, they didn't provide the numbers for overall survival
Drop out: unclear, appears none
Compliance: 100%
SRS:
ITT: appears to be yes
Single metastases: 70%
Prior treatments: no previous treatment for brain metastases.</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
WBRT + SRS compared to SRS alone and to WBRT alone in improvement of overall survival, brain local control and neurologic manifestations Study dates January 2008 until March 2011		parallel opposed fields that cover the entire cranial contents		Mean treatment duration: 2 weeks to 1 month Time points for measurement: The follow-up included neurologic examinations and magnetic resonance imaging 3 months after start of treatment and in 3 months intervals to evaluate response or failure criteria and to evaluate treatment morbidity. Mean follow up duration was 10 months and

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the median follow up duration was 8.5 months (range 0–34 months).

Other information</td></tr>
<tr><td>Full citation
Gamboa-Vignolle, C., Ferrari-Carballo, T., Arrieta, O., Mohar, A., Whole-brain irradiation with concomitant daily fixed-dose temozolomide for brain metastases treatment: a randomised phase II trial, Radiotherapy & OncologyRadiother</td><td>Sample size
N=55 randomised (28 patients WBI plus TMZ; 27 patients WBI alone)
Characteristics
<table><tr><td></td><td>TMZ + WBI (n-28)</td><td>WBT (n=27)</td></tr><tr><td>Age median</td><td>49.5 (20-74)</td><td>53.8 (28-73)</td></tr><tr><td>No. metastases</td><td></td><td></td></tr><tr><td>≤4</td><td>11 (39%)</td><td>16 (59%)</td></tr><tr><td>>4</td><td>17 (61%)</td><td>11 (41%)</td></tr><tr><td>Histology</td><td></td><td></td></tr><tr><td>Breast cancer</td><td>20 (71%)</td><td>14 (52%)</td></tr><tr><td>NSCLC and others</td><td>8 (29%)</td><td>13 (48%)</td></tr></table>Inclusion criteria
Eligible patients were 18–80 years of age with a KPSP50 life expectancy P12 weeks, and had at least one BM. Patients with extracranial metastases or an uncontrolled primary tumour were eligible</td><td>Interventions
TMZ plus whole brain irradiation vs. control
Details
TMZ plus whole brain irradiation (WBI) vs. WBI (control).
WBI at a dose of 30 Gy in 10 daily fractions over 2 weeks and concomitant TMZ, without adjuvant cycles of TMZ. WBI was applied with two parallel and opposing fields using a 1.25- or 6-Mv photon beam. The dose was calculated in the</td><td>Results
<table><tr><td></td><td>WBI + TMZ</td><td>WBI</td><td>P value/ notes</td></tr><tr><td>Objective response rates (ORR) 4 weeks</td><td>78.6% (63.4-93.8)%</td><td>48.1 (29.2-66.9)%</td><td>p =0.019</td></tr><tr><td>Progression free survival, months</td><td>11.8 (4.7 to 18.9)</td><td>5.6 (4.9 to 6.2)</td><td>p=0.014</td></tr><tr><td>Overall survival, months</td><td>8 (4.9 to 11.1)</td><td>8.1 (5.9 to 10.1)</td><td>p=0.84</td></tr><tr><td>Neurological symptoms improved or disappeared, day 140</td><td>96.4%</td><td>70.4%</td><td>p=0.012</td></tr><tr><td>Adverse events GRADE 3 to 4</td><td></td><td></td><td></td></tr><tr><td>Leukopenia 2 weeks</td><td>1/28</td><td>0/27</td><td></td></tr><tr><td>Neutropenia 2 weeks</td><td>1/28</td><td>1/27</td><td></td></tr><tr><td>Lymphopenia 2 weeks</td><td>11/28</td><td>6/27</td><td></td></tr><tr><td>Total Grade 3-4 2 weeks</td><td>17/28</td><td>7/28</td><td></td></tr></table></td><td>Limitations
Randomisation: yes, unclear
Allocation concealment: unclear
Patient blinding: no, open trial
Assessor blinding: yes, radiologist blinded who evaluated brain MRIs
Investigator blinding: no, open trial</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
Oncol, 102, 187-91, 2012 Ref Id 497802 Country/ies where the study was carried out Mexico Study type Randomised phase II clinical trial Source of funding Merck Sharp and Dome (México City) provided Temozolomide as a donation without interference in the trial design or results analysis. Aim of the study	Exclusion criteria Patients were ineligible if they had received radiotherapy or surgery for a primary brain tumour or brain metastasis. Additionally, patients who had received systemic chemotherapy 3 weeks prior or oral chemotherapy 2 weeks prior to protocol entry were deemed ineligible. Patients with meningeal carcinomatosis, an allergy to iodinated contrast media, those unable to swallow, and pregnant or nursing women were ineligible for this study	midplane along the central axis. TMZ was administered 1 h before each WBI fraction, with the patients having fasted for 1 h, at a fixed dose of 200 mg on Mondays, Wednesdays and Fridays and at a fixed dose of 300 mg on Tuesdays and Thursdays.	<table><tr><td>Complete response 4 weeks</td><td>2/28</td><td>0/27</td><td></td></tr><tr><td>Partial response 4 weeks</td><td>20/28</td><td>13/27</td><td></td></tr><tr><td>Stable disease 4 weeks</td><td>5/28</td><td>12/27</td><td></td></tr><tr><td>Progressive disease 4 weeks</td><td>1/28</td><td>2/27</td><td></td></tr><tr><td>Objective response 4 weeks</td><td>22/28</td><td>13/27</td><td></td></tr></table>ORR encompassed complete response and partial response at 4 weeks	Reporting bias: no Drop out: TMZ + WBI = 1/28 (1 had thrombocytopenia/(1 died not included)) WBI = 1/27 (Lost to follow up due to progressive disease) Compliance: TMZ + WBI = 96%; WBI = 100% ITT: yes Single metastases: unclear ≤4 vs. >4 Prior treatments: Patients excluded if received radiotherapy or surgery for a primary brain

Study details	Participants	Interventions	Outcomes and results	Comments
This study assessed whether a regimen of a high daily fixed dose TMZ concomitant with WBI and without cycles of adjuvant TMZ was able to obtain a higher ORR than WBI alone in patients with brain metastases. Study dates January 2006 to September 2008				tumour or brain metastasis Mean treatment duration: 2 weeks Time points for measurement: first follow-up visit was 2 weeks after completion of the protocol treatment and every 2 months thereafter until loss of follow up or death of the patient. At least 15.4 months Other information
Full citation Kocher, M., Soffietti, R., Abacioglu,	Sample size N=359 (N=100 radiosurgery+ observation; n=99 radiosurgery + WBRT; n=79 surgery + observation; n=81 surgery + WBRT)	Interventions Surgery + WBRT Surgery + Observation	Results Overall survival: HR 0.98, 95% CI 0.78 to 1.23	Limitations Other information

Study details	Participants	Interventions	Outcomes and results	Comments
U., Villa, S., Fauchon, F., Baumert, B. G., Fariselli, L., Tzuk-Shina, T., Kortmann, R. D., Carrie, C., Ben Hassel, M., Kouri, M., Valeinis, E., van den Berge, D., Collette, S., Collette, L., Mueller, R. P., Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study, Journal of Clinical OncologyJ	Characteristics <table><tr><td></td><td>Observation (n=179)</td><td>WBRT (n=180)</td><td>Total (n=347)</td></tr><tr><td>Age (median, range)</td><td>61 (37-80)</td><td>60 (26-81)</td><td></td></tr><tr><td>Localization of primary tumour</td><td></td><td></td><td></td></tr><tr><td>Lung (NSCLC)</td><td>52%</td><td>54%</td><td></td></tr><tr><td>Breast</td><td>11%</td><td>12%</td><td></td></tr><tr><td>Kidney</td><td>7%</td><td>9%</td><td></td></tr><tr><td>Colorectal</td><td>9%</td><td>8%</td><td></td></tr><tr><td>Melanoma</td><td>5%</td><td>6%</td><td></td></tr><tr><td>Other</td><td>8%</td><td>7%</td><td></td></tr><tr><td>Cancer of unknown primary tumour</td><td>8%</td><td>5%</td><td></td></tr><tr><td>Number of lesions</td><td></td><td></td><td></td></tr><tr><td>1</td><td></td><td></td><td>81%</td></tr><tr><td>2</td><td></td><td></td><td>14%</td></tr><tr><td>3</td><td></td><td></td><td>8%</td></tr></table> Inclusion criteria Age 18 years; WHO performance status 2; 1-3 brain metastases; Radiosurgery: single metastasis 3.5 cm, multiple metastases 2.5 cm in diameter; Surgery: complete surgical resection; Radiosurgery: histologic confirmation of primary tumor or other; metastases 4 years ago, stereotactic biopsy of the brain metastasis otherwise; Stable systemic cancer for 3 months and/or asymptomatic synchronous primary tumor	Radiosurgery + WBRT Radiosurgery + Observation Details Surgery: Complete resection of the brain metastases, judged either by the surgeon's impression or early (24 hours) postoperative contrast-enhanced computed tomography and/or MRI. There were no limitations regarding size of the metastases. Radiosurgery: Both linear accelerators and gamma-knife devices were allowed. The planning target volume consisted of the gross tumor volumes of all (up to three) metastases surrounded by a margin of 1 to 2	Intracranial progression: WBRT :87 events Observation: 139 events Adverse events: WBRT: 180 events Observation: 146 events Serious side effects: WBRT: 13 events Observation: 3 events Serious infection: WBRT: 2 events Observation: 3 events Serious radionecrosis: WBRT: 2 events Observation: 1 event	

Study details	Participants	Interventions	Outcomes and results	Comments
Clin Oncol, 29, 134-41, 2011 Ref Id 498260 Country/ies where the study was carried out Study type Randomized phase III trial Source of funding Grants No. 2U10 CA11488-25 through 5U10 CA011488-40 from the National Cancer Institute (Bethesda, MD) and by a donation from the Deutsche Krebshilfe from Germany through the	without metastases outside the CNS or unknown primary tumor Exclusion criteria Brain metastasis of small-cell lung cancer, lymphoma, leukemia, myeloma, germ cell tumors; Brain stem metastases; Leptomeningeal metastases; Recurrent brain metastases after surgery and/or radiosurgery and/or brain irradiation; Inability to interrupt chemotherapy during whole-brain radiotherapy	mm around each metastasis. A dose of 25 Gy was prescribed to the center of each metastasis. The minimum dose at the surface of each planning target volume had to be 20 Gy. For the gamma-knife, a peripheral dose of 20 Gy to the 50% isodose was allowed. Size limits were 35 mm (maximal diameter) for singular metastases and 25 mm for multiple metastases. Dose limits for organs at risk were as follows: brainstem, 8 Gy; optic chiasm or optic nerves, 8 Gy;other cranial nerves, 12 Gy; and sensorimotor cortical areas, 18 Gy. Within 4 weeks after surgery or within 2 weeks before		

Study details	Participants	Interventions	Outcomes and results	Comments
EORTC Charitable Trust. Aim of the study This European Organisation for Research and Treatment of Cancer phase III trial assesses whether adjuvant whole-brain radiotherapy (WBRT) increases the duration of functional independence after surgery or radiosurgery of brain metastases. Study dates November 1996 to		radiosurgery, patients were allocated to WBRT or OBS WBRT: was applied using standard techniques. Observation.		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>November 2007</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Lee, S. M., Lewanski, C. R., Counsell, N., Ottensmeier, C., Bates, A., Patel, N., Wadsworth, C., Ngai, Y., Hackshaw, A., Faivre-Finn, C., Randomized trial of erlotinib plus whole-brain radiotherapy for NSCLC patients with multiple brain metastases, Journal of the National Cancer InstituteJ Natl Cancer Inst, 106, 2014
Ref Id 498409</td><td>Sample size
N=80 (N=40 WBRT+ Placebo; N=40 WBRT+erlotinib)
Characteristics<table><tr><td></td><td>WBRT+placebo (n=40)</td><td>WBRT+erlotinib (N=40)</td></tr><tr><td>Age median, range</td><td>62.2 (41-73)</td><td>61.3 (48-75)</td></tr><tr><td>Brain metastastes</td><td></td><td></td></tr><tr><td>≤3</td><td>26 (65%)</td><td>23 (57.5%)</td></tr><tr><td>>3</td><td>14 (35%)</td><td>17 (42.5%)</td></tr><tr><td>NSCLC</td><td>100%</td><td>100%</td></tr></table>Inclusion criteria
Inclusion criteria were: histologically or cytologically confirmed NSCLC and newly diagnosed multiple BM documented by MRI or contrast CT scan, but did not require immediate chemotherapy for symptom control; aged 18–76 years; no previous cranial radiotherapy; at least 28 days since any chemotherapy; Glasgow Coma Score of 14 and greater; Karnofsky performance status of 70 and greater; 3 or fewer sites of extra-cranial metastases; adequate renal and liver function; negative pregnancy test; and age-modified (age cut-off 76 years instead of 66 years) Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA) class I and II (class I is KPS ≥ 70, controlled primary tumor,</td><td>Interventions
WBRT+ placebo versus WBRT+erlotinib
Details
WBRT = standard WBRT administered in 20 Gy in 5 daily fractions, starting within 4 weeks of the baseline CT or MR brain scan. Treatment was delivered by linear accelerator of energy ranging from 4–8 MV photons.

Erlotinib or matched placebo = tablets were taken once daily starting on day 1 of WBRT (continuing through weekends). During WBRT the erlotinib dose was 100 mg/day (this dose was chosen because of</td><td>Results<table><tr><td></td><td>WBRT+Placebo (n=40)</td><td>WBRT+erlotinib (n=40)</td><td>Notes/p value</td></tr><tr><td>Median nuerological PFS</td><td>1.6 months</td><td>1.6 months</td><td>none</td></tr><tr><td>Alive and without neurological progression</td><td>38.5% (23.2 to 53.7)</td><td>38.9% (23.6 to 54.2)</td><td>Unadjusted HR neurological PFS 0.99 (0.62 to 1.58) p=0.97</td></tr><tr><td>Median overall survival</td><td>2.9 months</td><td>3.4 months</td><td>Unadjusted HR OR 0.94 (0.58 to 1.54) p = 0.81</td></tr><tr><td>Mortality</td><td>31</td><td>35</td><td></td></tr><tr><td>Any Grade 3-4</td><td>28</td><td>28</td><td></td></tr><tr><td>Infection</td><td>2</td><td>5</td><td></td></tr><tr><td>Quality of life (EuroQoL EQ-5D) 2 months, median (p25, p75)</td><td>0.60 (0.25 to 0.72)</td><td>0.65 (0.19 to 0.76)</td><td>p>0.40</td></tr></table></td><td>Limitations
Randomisation: Yes. Unclear sequence generation. Patients were randomly assigned to receive erlotinib or placebo after telephoning the trials center. Randomization was stratified using: presence/absence of extra-cranial metastases, number of sites of brain metastases, age-modified</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
Country/ies where the study was carried out UK Study type Two-stage randomized, multicenter, phase II double- blind, placebo controlled trial Source of funding Cancer Research UK (C1438/A6406 and C1438/A10010) and an educational grant from Roche for the translational studies were awarded to SML. Aim of the study	metastases to brain only, and class II is uncontrolled primary tumor, or primary controlled, Exclusion criteria Patients with other previous or current malignant disease, solitary brain metastasis suitable for stereotactic radiosurgery or surgical resection, previously treated with any EGFR anti-cancer therapy or currently being treated with Cox II inhibitor were excluded.	concerns over possible neurotoxicity when the trial was designed). After completing WBRT the erlotinib dose was increased to the standard 150mg/day, until disease progression with symptomatic deterioration. The dose could be reduced or stopped following grade 3 or 4 adverse events that were not controlled by optimal supportive care. Steroids were limited to dexamethasone; at least 4 mg were prescribed during WBRT and for one week after. If medically feasible, the dose was then reduced according to local policy.		RTOG RPA score, and center. Allocation concealment: Yes, telephoning the trials center Patient blinding: yes, double blind Assessor blinding: unclear Investigator blinding: yes, double blind Reporting bias: no SE or p values for some outcomes. Drop out: none dropped out, n=1 ineligible due to protocol. Compliance: Tablet compliance: ≥75%

Study details	Participants	Interventions	Outcomes and results	Comments
Median survival of non-small cell lung cancer (NSCLC) patients with brain metastases is poor. We examined concurrent erlotinib and whole brain radiotherapy (WBRT) followed by maintenance erlotinib in patients with untreated brain metastases, given the potential radiosensitizing properties of erlotinib and its direct effect on brain metastases and systemic activity. Study dates				31/40 Placebo (77.5%): 31/40 Erlotinib 77 .5% (1 patient died before treatment and 1 progressed before treatment in placebo; 3 died before treatment in erlotinib)/ WBRT + Erlotinib n=1 did not receive WBRT; WBRT+Placebo n=5 did not receive 5 consecutive days ITT: yes Single metastases: unclear ≤3 vs.>3

Study details	Participants	Interventions	Outcomes and results	Comments
June 2009 to June 2010				Prior treatments: no previous cranial radiotherapy; at least 28 days since any chemotherapy Mean treatment duration: 12.6 months Time points for measurement: A clinical examination, the mini mental state examination (MMSE), and assessment of motor strength, visual acuity and gait (MVG) were completed before random

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>assignment, two weekly for the first 8 weeks, then monthly until 12 months, and then two-monthly until death.
Other information</td></tr>
<tr><td>Full citation
Mahajan, A., Ahmed, S., McAleer, M. F., Weinberg, J. S., Li, J., Brown, P., Settle, S., Prabhu, S. S., Lang, F. F., Levine, N., McGovern, S., Sulman, E., McCutcheon, I. E., Azeem, S., Cahill, D., Tatsui, C., Heimberger,</td><td>Sample size
N=128 (stereotactic radiosurgery group n=63; observation group n=65)
Characteristics
<table><tr><td></td><td>SRS</td><td>Observation</td></tr><tr><td>% Male</td><td>37 (59%)</td><td>31 (48%)</td></tr><tr><td>Median age (range)</td><td>58 (20-80)</td><td>57 (29-79)</td></tr><tr><td>Primary cancer melanoma</td><td>14(22%)</td><td>13 (20%)</td></tr><tr><td>Primary cancer lung</td><td>13 (21%)</td><td>13 (20%)</td></tr><tr><td>Primary cancer breast</td><td>9(14%)</td><td>14 (22%)</td></tr><tr><td>Primary cancer other</td><td>27 (43%)</td><td>25 (38%)</td></tr><tr><td>Number of mets 1</td><td>38 (60%)</td><td>41 (63%)</td></tr><tr><td>Number of mets 2</td><td>18 (29%)</td><td>14 (22%)</td></tr><tr><td>Number of mets 3</td><td>7 (11%)</td><td>10(15%)</td></tr></table>Inclusion criteria</td><td>Interventions
SRS versus observation
Details
All participants had undergone resection of the metastases at trial at trial entry.
SRS group: patients were treated within 30 days after surgery and underwent a single session of treatment.
Prescription doses were subject to the surgical cavity and were as follows: 16-</td><td>Results
Treatment at local recurrence.
Observation group: 31/65 (48%) of the participants developed local recurrence. Of these, 13 subsequently had SRS alone, 9 had WBRT, 3 had surgery followed by WBRT, 2 had WBRT and SRS, 1 had surgery followed by SRS, 1 had surgery followed by fractionated external beam radiation, 1 had surgery alone, 1 had no treatment.
SRS group: 15/63 (24%) of the participants developed local recurrence. Of these, 7 subsequently had WBRT, 3 had additional SRS, 3 had surgery,1 had laser interstitial thermal therapy 1 had no treatment.

12-month freedom from local recurrence (SRS vs observation group)
Observation group: 43% (95% CI 31-59)
SRS group: 72% (95% CI 60-87)
HR 0.46 (0.24-0.88)</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: Low risk (block randomisation)</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
A. B., Ferguson, S., Ghia, A., Demonte, F., Raza, S., Guha-Thakurta, N., Yang, J., Sawaya, R., Hess, K. R., Rao, G., Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial, Lancet OncologyLancet Oncol, 18, 1040-1048, 2017 Ref Id 676236 Country/ies where the	≥3 y/o; KPS > 70; able to have an MRI scan; had presented with between 1 and 3 resected brain metastases Exclusion criteria Previous RT administered to the brain; previous resection of any brain metastases done before the study; evidence of leptomeningeal disease; small-cell lung cancer or haematological malignancies, pregnancy; postoperative cavity longer than 4 cms.	Gy (≤10 cc); 14-Gy (for 10. 1-15 cc) and 12-Gy (for >15 cc). Dose constraints were less than 12-Gy for brainstem and less than 9-Gy for the optic nerve and tract Both groups had surveillance brain MRI and clinical assessment within 5 to 8 weeks after the craniotomy, and then brain MRI every 9-12 weeks. Local recurrences (in either group) were treated at the discretion of the physician. Patients with new distant brain mets remained in the study. Unresected lesion were treated with SRS as clinically indicated.	Median time to local recurrence Observation group: 7.6 months (95% CI 5.3 to not reached) SRS group: median not reached (95% CI 15.6 months to not reached) HR 0.41 (0.21-0.80) Median overall survival Observation group (39/65 deaths): 18 months (95% CI 13 to not reached) SRS group (46/63 deaths): 17 months (95% CI 13 - 22) HR 1.29 (0.84-1.98) 12-month freedom from distant brain recurrence Observation group: 22/65 [33%] (95% CI 22-49) SRS group: 35/63 [42%] (95% CI 30-58) HR 0.81 (0.51-1.27) Freedom from local recurrence (tumour size) 2.5 to 3.5cm vs ≤2.5 HR 8.3 (2.5-27.5) 3.5cm vs ≤2.5 HR 7.1 (2.1-24.1) Freedom from local recurrence other vs melanoma: HR 0.7 (0.3-1.6) 1 met vs 2 or 3 mets:HR 0.8 (0.4 to 1.4)	Allocation concealment: Low risk (records were pre-allocated to each stratum) Blinding of participants and personnel: High risk for median time to local recurrence (open-label); low risk for overall survival Blinding of outcome assessment: High risk for median time to local recurrence (open-label); low risk for overall survival

Study details	Participants	Interventions	Outcomes and results	Comments
study was carried out USA Study type RCT Source of funding National Institutes of Health Aim of the study To compare post-operative stereotactic radiosurgery to surgical resection alone and assess if it improved time to local recurrence in individuals who had previously undergone complete resection of 1-3 metastases. Study dates 13th August 2009 to 16th				Blinding (performance bias and detection bias): High risk for median time to local recurrence (open-label); low risk for overall survival Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all prespecified outcomes were reported) Other information Median follow-up was 11.1

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>February 2016</td><td></td><td></td><td></td><td>months (IQR4.8-20.4)</td></tr>
<tr><td>Full citation
Lim, S. H., Lee, J. Y., Lee, M. Y., Kim, H. S., Lee, J., Sun, J. M., Ahn, J. S., Um, S. W., Kim, H., Kim, B. S., Kim, S. T., Na, D. L., Sun, J. Y., Jung, S. H., Park, K., Kwon, O. J., Lee, J. I., Ahn, M. J., A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-</td><td>Sample size
n=98 (n=49 SRS and chemotherapy; n=49 chemotherapy)
Characteristics<table><tr><td></td><td>Stereotactic radiosurgery plus chemotherapy(n=49)</td><td>Chemotherapy (n=49)</td></tr><tr><td>Age, mean</td><td>58 (33-77)</td><td>57 (29-85)</td></tr><tr><td>Number of brain metastases</td><td></td><td></td></tr><tr><td>1</td><td>18 (37%)</td><td>28 (57%)</td></tr><tr><td>2-4</td><td>31 (63%)</td><td>21 (43%)</td></tr><tr><td>NSCLC</td><td>100%</td><td>100%</td></tr></table>Inclusion criteria
Inclusion Criteria: patients aged 18 years or older with histological confirmed NSCLC with synchronous brain metastases. All patients had one to four parenchymal brain metastases by contrast-enhanced MRI, each with a maximum diameter of no more than 3 cm with brain edema grade 0–1. None of patients had prior surgical treatment or radiotherapy for brain metastases and leptomeningeal metastases by MRI or cerebrospinal fluid evaluation. Eligible patients had ECOG performance status of 0 or 1 and no symptoms or signs from brain metastases.

Exclusion criteria</td><td>Interventions
Stereotactic surgery (SRS) plus systemic chemotherapy versus upfront chemotherapy alone
Details
SRS: a single high dose of stereotactically focused radiation. Gamma knife radiosurgery (GKS) is SRS using γ-rays from radioactive cobalt-60 installed in Gamma Knife (Elekta Instruments, Stockholm, Sweden).
Chemotherapy: eligible patients received 3 week cycles of the following intravenous chemotherapy; 60 mg/m2 cisplatin on day 1 plus 1000</td><td>Results<table><tr><td></td><td>SRS+ Chemo</td><td>Chemo</td><td>p value/ notes</td></tr><tr><td>Median overall survival months</td><td>14.6 (9.2 to 20)</td><td>15.3 (7.2 to 23.4)</td><td>HR 1.2 (0.77 to 1.89) p=0.418</td></tr><tr><td>Median PFS months</td><td>9.4 (4.2 to 14.6)</td><td>6.6 (2.9 to 10.3)</td><td>HR 1.44 (0.87 to 2.35) p=0.248</td></tr><tr><td>New lesion PFS, months</td><td>11.9</td><td>8.7</td><td>p=0.247</td></tr><tr><td>Overall response rates of cranial disease</td><td>57%</td><td>37%</td><td>p=0.011</td></tr><tr><td>Overall response rates of extra-cranial disease</td><td>43%</td><td>40%</td><td></td></tr><tr><td>PFS of extracranial disease months</td><td>5.4</td><td>5.4</td><td>p=0.824</td></tr><tr><td>Progressed with symptomatic brain metastases</td><td>9 (18.4 %)</td><td>13 (26.5 %)</td><td></td></tr><tr><td>Activity of daily living (Barthel Activities of Daily living, BADL index), 12 months</td><td></td><td></td><td>p=0.9657</td></tr></table></td><td>Limitations
Randomisation: yes, unclear methods
Allocation concealment: unclear
Patient blinding: unclear
Assessor blinding: unclear
Investigator blinding: unclear
Reporting bias: unclear, some outcomes with no raw data only graphs
Lost to follow up: Compliance: 92% SRS excluded n=4/53;</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results				Comments
cell lung cancer, Annals of OncologyAnn Oncol, 26, 762-8, 2015 Ref Id 498451 Country/ies where the study was carried out Korea Study type Single center, randomized phase III trial Source of funding This work was supported in part by Samsung Biomedical Research Institute Grant (SMX1132531) and by Elekta Korea research funds.	Exclusion criteria: Patients with uncontrolled extra-cranial disease, severe co-morbid illnesses and/or active infections were excluded.	mg/m2 gemcitabine on days 1 and 8 or 70mg/m2 cisplatin plus pemetrexed 500 mg/m2 or docetaxel 75 mg/m2 on day 1 or 60 mg/m2 cisplatin plus paclitaxel 175 mg/m2 on day 1 or cisplatin 60 mg/m2 on day 1 plus etoposide 100 mg/m2 on days 1–3. Patients who were ineligible for cisplatin treatment received carboplatin instead.	Activity of daily living (Instrumental ADL - K-IADL) 12 months			p=0.4252	94% Chemotherapy n=3/52 ITT: no, excluded those who were non-compliant Single metastases: 47% Prior treatments: None of patients had prior surgical treatment or radiotherapy for brain metastases and leptomeningeal metastases by MRI or cerebrospinal fluid evaluation Mean treatment duration: unclear 3 weeks?
			Cognitive function MoC-K (Korean version of Montreal Cognitive Assessment) 12 months			p=0.9932	
			Cognitive Assessment (Korean version of Mini-Mental State Examination, K-MMSE) 12 months			p=0.3798	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Aim of the study
It is unclear whether treating brain metastasis before starting systemic chemotherapy can improve survival compared with upfront chemotherapy in non-small-cell lung cancer (NSCLC) with asymptomatic cerebral oligo-metastases

Study dates
2008 and 2013</td><td></td><td></td><td></td><td>Time points for measurement: Median follow up duration 43 months (0.8 to 56.2)
Other information</td></tr>
<tr><td>Full citation
Mulvenna, P., Nankivell, M., Barton, R., Faivre-</td><td>Sample size
538 patients (269 to WBRT and OSC; 269 to OSC alone)
Characteristics</td><td>Interventions
OSC (Optimal Supportive Care) + WBRT vs. WBRT
Details</td><td>Results<table><tr><th></th><th>WBRT+ OSC (n=269)</th><th>OSC (N=269)</th><th>p value/notes</th></tr></table></td><td>Limitations
Randomisation: yes, unclear methods.</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Finn, C., Wilson, P., McColl, E., Moore, B., Brisbane, I., Ardron, D., Holt, T., Morgan, S., Lee, C., Waite, K., Bayman, N., Pugh, C., Sydes, B., Stephens, R., Parmar, M. K., Langley, R. E., Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy</td>
<td>
<table>
<tr><td></td><td>WBRt+OSC (n=269)</td><td>OSC (N=269)</td></tr>
<tr><td>Age (years) median</td><td>66 (38-84)</td><td>67 (45-85)</td></tr>
<tr><td>Brain metastases status</td><td></td><td></td></tr>
<tr><td>Newly diagnosed</td><td>83%</td><td>82%</td></tr>
<tr><td>Progressive disease</td><td>17%</td><td>18%</td></tr>
<tr><td>N brain mets</td><td></td><td></td></tr>
<tr><td>1</td><td>80</td><td>82</td></tr>
<tr><td>2</td><td>56</td><td>56</td></tr>
<tr><td>3</td><td>28</td><td>22</td></tr>
<tr><td>4</td><td>15</td><td>20</td></tr>
<tr><td>5+</td><td>85</td><td>89</td></tr>
<tr><td>NSCLC</td><td>100%</td><td>100%</td></tr>
</table>
Inclusion criteria
Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted (with predefi ned washout periods of 4 weeks for chemotherapy and 1 week for TKIs). Participants were aged 18 years or older. Patients with histologically proven NSCLC and brain metastases (confirmed by CT or MRI).
Exclusion criteria
Exclusion criteria included previous radio therapy to the brain, or previous or current illness thought likely to interfere with protocol treatment.
</td>
<td>Optimal Supportive Care: OSC included oral dexamethasone given with a proton pump inhibitor with the dose of steroid determined by the patients' symptoms and titrated downwards if symptoms improved, as well as support from a named specialist nurse and immediate access to specialised clinicians and palliative care teams.
WBRT was defined as 20 Gy in five daily fractions ideally given over 5–8 days with a 4–8 MV linear accelerator with two parallel opposed fields, commenced as soon as was practical after randomisation.</td>
<td>
<table>
<tr><td>Any serious adverse event</td><td>89 (33%)</td><td>82 (30%)</td><td></td></tr>
<tr><td>Cardiac</td><td>2</td><td>1</td><td></td></tr>
<tr><td>Infection</td><td>17</td><td>16</td><td></td></tr>
<tr><td>Quality of life (EQ-5D) 12 weeks</td><td></td><td></td><td></td></tr>
<tr><td>Maintained or improved quality of life</td><td>24/54</td><td>21/43</td><td></td></tr>
<tr><td>KPS changes at 12 weeks</td><td></td><td></td><td>p=0.0724</td></tr>
<tr><td>Mean (SD)</td><td>18 (15.53)</td><td>13.4 (13.66)</td><td></td></tr>
<tr><td>Overall survival HR 1 met</td><td>79/80</td><td>82/82</td><td>HR 1.00 (0.73 to 1.36)</td></tr>
<tr><td>2</td><td>56/56</td><td>56/56</td><td>HR 1.11 (0.76 to 1.62)</td></tr>
<tr><td>3</td><td>29/28</td><td>22/22</td><td>HR 1.11 (0.63 to 1.95)</td></tr>
<tr><td>4</td><td>15/15</td><td>20/20</td><td>HR 0.70 (0.35 to 1.40)</td></tr>
<tr><td>>5</td><td>84/85</td><td>89/89</td><td>HR 1.37 (1.01 to 1.86)</td></tr>
<tr><td>All patients</td><td>267/269</td><td>269/269</td><td>HR 1.10 (0.93 to 1.31)</td></tr>
</table>
</td>
<td>Allocation concealment: unclear. Allocation to treatment group was done by a phone call from the hospital to the Medical Research Council Clinical Trials Unit Patient blinding: No Assessor blinding: Unclear Investigator blinding: No Reporting bias: unclear Lost to follow up: None appeared to withdraw. ITT was used.</td>
</tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
(QUARTZ): results from a phase 3, non-inferiority, randomised trial, LancetLancet, 2, 2, 2016 Ref Id 498722 Country/ies where the study was carried out UK, Australia Study type Non-inferiority, phase 3 randomised trial Source of funding Funding was provided by Cancer Research UK (C17956/A6414). The trial sponsor was the Medical Research Council in the UK, and the Trans			Median survival weeks: 8.5 (7.1 to 9.9); 9.2 (7.2 to 11.1) Use of dexamethasone 4 weeks: 16/245; 11/233 8 weeks: 30/245; 24/233	Compliance: WBRT+OSC= 30 did not receive WBRT (10 died before starting treatment); 19 received <20 Gy 88% compliance; OSC = 100% ITT: yes, ITT Single metastases: 30% Prior treatments: Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted (with

Study details	Participants	Interventions	Outcomes and results	Comments
Tasman Radiation Oncology Group in Australia. Funding for Australia sites was provided by the National Health and Medical Research Council Australia (NHMRC 441402). Aim of the study We aimed to establish whether WBRT could be omitted without a signifi cant eff ect on survival or quality of life. Study dates March 2, 2007, and Aug 29, 2014,				predefined washout periods of 4 weeks for chemother apy and 1 week for TKIs) Mean treatment duration: mean survival up to 11·1 weeks Time points for measurem ent: 4, 8 or 12 weeks Other information
Full citation	Sample size	Interventions	Results	Limitations

Study details	Participants	Interventions	Outcomes and results	Comments
Soffietti, R., Kocher, M., Abacioglu, U. M., Villa, S., Fauchon, F., Baumert, B. G., Fariselli, L., Tzuk-Shina, T., Kortmann, R. D., Carrie, C., Ben Hassel, M., Kouri, M., Valeinis, E., van den Berge, D., Mueller, R. P., Tridello, G., Collette, L., Bottomley, A., A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation	See Kocher 2011 Inclusion criteria See Kocher 2011 Exclusion criteria See Kocher 2011	See Kocher 2011 Details See Kocher 2011	See Kocher 2011	See Kocher 2011

Study details	Participants	Interventions	Outcomes and results	Comments
in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results, Journal of Clinical OncologyJ Clin Oncol, 31, 65-72, 2013 Ref Id 499368 Country/ies where the study was carried out See Kocher 2011 Study type See Kocher 2011				

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Source of funding

See Kocher 2011

Aim of the study
See Kocher 2011

Study dates
See Kocher 2011</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Sperduto, P. W., Wang, M., Robins, H. I., Schell, M. C., Werner-Wasik, M., Komaki, R., Souhami, L., Buyyounouski, M. K., Khuntia, D., Demas, W., Shah, S. A.,</td><td>Sample size
n=125 (Arm 1 WBRT/SRS n=44; Arm 2 WBRT/SRS/TMZ n=40; Arm 3 WBRT/SRS/ETN n=41)

Characteristics
<table><tr><td></td><td>Arm 1</td><td>Arm 2</td><td>Arm 3</td></tr><tr><td>Median age</td><td>64</td><td>63</td><td>61</td></tr><tr><td>Number of brain mets 1</td><td>45%</td><td>45%</td><td>37%</td></tr><tr><td>2</td><td>30%</td><td>33%</td><td>44%</td></tr><tr><td>3</td><td>25%</td><td>22%</td><td>19%</td></tr></table>
Inclusion criteria</td><td>Interventions
Arm 1 WBRT + SRS stereotactic radiosurgery
Arm 2 WBRT + SRS + TMZ temozolomide
Arm 3: WBRT + SRS + ETN erlotinib

Details
WBRT -began within 1 week of</td><td>Results
<table><tr><td></td><td>Arm 1</td><td>Arm 2</td><td>Arm 3</td><td>p value notes</td></tr><tr><td>Median survival</td><td>13.4 (6.5 to 20.8)</td><td>6.3 (3.4 to 10.1)</td><td>6.1 (3.6 to 12.1)</td><td>HR:[WBRT/SRS/TMZ vs WBRT/SRS]=1.43, 95% CI: 0.89-2.31, P=0.93 [1-sided]); HR [WBRT/SRS/ETN vs WBRT/SRS]=1.47, 95% CI: 0.92-2.36, P=0.95 (1-sided</td></tr></table></td><td>Limitations
Randomisation: yes, in a permuted block design
Allocation concealment: unclear
Patient blinding: unclear
Assessor blinding: unclear</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results					Comments
Nedzi, L. A., Perry, G., Suh, J. H., Mehta, M. P., A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 85, 1312-8, 2013 Ref Id	Inclusion criteria:age>18years; histologically confirmed NSCLC; 1 to 3 brain metastases confirmed by magnetic resonance imaging (MRI); maximum sizeof any brain metastasis————————————4.0 cm; Zubrod status 0 to 1 (Karnofskyperformance status 70-100); neurologic function status 0, 1, or 2; stable extracranial metastases (defined as no progression in the month before enrollment); adequate bone marrow reserve (definedas hemoglobin ———————————— 8 g/dL, absolute neutrophil count ———————————— 1000/mm3,platelets ———————————— 100,000/mm3); liver function test results<2 times theinstitutional upper limit of normal; bilirubin within normal limits;no liver metastases; negative pregnancy test; no evidence of leptomeningeal disease; no brainstem metastases; no prior cranial irradiation. Prior resection of a brain metastasis was allowed if the patient had a separate brain metastasis that would be treated with SRS. Exclusion criteria Exclusion criteria: Patients who had with brain metastases at the time of initial diagnosis were considered eligible and did not need to demonstrate 1 month of stable scans.	randomization. A dose of 2.5 Gy was delivered with 4 to 10 megavoltage machines, 5 days per week, for 15 fractions for a total of 37.5 Gy. SRS - The SRS was delivered to each of the brain metastases within 14 days of completion of WBRT. the SRS dose was size dependent: lesions <2 cm, 2.1 to 3.0 cm, and 3.1 to 4.0 cm received 24, 18, and 15 Gy, respectively. TMZ -75 mg/m2/day was prescribed for 21 days beginning on day 1 of WBRT. After completion of WBRT and SRS, the TMZ could be discontinued at the investigators' discretion or continued at 150 mg/m2/day for 5	CNS progression rates 6 months	16%	29%	20%	P=0.30 for WBRT/SRS vs WBRT/SRS/TMZ and P=0.48 for WBRT/SRS vs WBRT/SRS/ETN, respectively	Investigator blinding: unclear Reporting bias: none Lost to follow-up: none lost to follow up Discontinued: Arm 1 n=4; Arm 2 n=24; Arm 3 n=26, due to progression of disease, death, refusal, toxicity, other Compliance: Arm 1 = 100%; Arm 2 =97.5%; Arm 3 = 100% ITT: yes, including all of the eligible and randomized patients regardless
			Time to new metastases 6 months rate	9%	21%	15%		
			Performance status at 6 months	52.50%	85.70%	85.70%	P=0.002 for WBRT/SRS vs WBRT/SRS/TMZ and P<.001 for WBRT/SRS vs WBRT/SRS/ETN	
			Steroid use at 6 months	54%	44%	41%		
			Death due to CNS	17%	15%	19%	p=0.78 for WBRT/SRS vs WBRT/SRS/TMZ and	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>499407
Country/ies where the study was carried out
USA
Study type
Phase III RCT
Source of funding
Radiation Therapy Oncology Group (RTOG) and was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI).

Aim of the study
Aim: temozolomide (TMZ) and erlotinib</td>
<td></td>
<td>days/month for as long as 6 months. ETN - 150 mg/day was prescribed beginning on day 1 of WBRT. After WBRT and SRS, the ETN could be discontinued at the investigators' discretion or continued for as long as 6 months.</td>
<td>
<table>
<tr><td></td><td></td><td></td><td></td><td>0.80 for WBRT/SRS vs WBRT/ SRS/ETN), respectively</td></tr>
<tr><td>Median CNS progression free survival, months</td><td>8.1</td><td>4.6</td><td>4.8</td><td></td></tr>
<tr><td>Serious grade 3-5 toxicity</td><td>11%</td><td>41%</td><td>49%</td><td></td></tr>
<tr><td>Brain necrosis grade 4</td><td>0</td><td>0</td><td>1</td><td></td></tr>
<tr><td>Steroid use at 6 months</td><td>54%</td><td>44%</td><td>41%</td><td></td></tr>
</table>
</td>
<td>of treatment
Single metastases: 41%
Prior treatments: Prior resection of a brain metastasis was allowed if the patient had a separate brain metastasis that would be treated with SRS.
Mean treatment duration: median follow-up time was 33.6 months
Time points for measurement: 6 and 12 months
Other information</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>(ETN) cross the bloodbrain barrier and have documented activity in NSCLC, a phase 3 study was designed to test whether these drugs would improve the OS associated with WBRT þ SRS.
Study dates October 2004 and August 2009</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
Verger, E., Gil, M., Yaya, R., Vinolas, N., Villa, S., Pujol, T., Quinto, L., Graus, F., Temozolomide and concomitant whole brain</td><td>Sample size
n=82
Characteristics<table><tr><td></td><td>WBRT (N=41)</td><td>WBRT+TMZ (n=41)</td></tr><tr><td>Age mean (SD)</td><td>58.3 (11.6)</td><td>57.8 (12.2)</td></tr><tr><td>Primary tumor</td><td></td><td></td></tr></table></td><td>Interventions
WBRT versus WBRT+TMZ
Details
WBRT - was delivered five times weekly, in 10 doses of 3 Gy, to a total dose of 30 Gy
TMZ -TMZ was given at 75 mg/m2/d during RT,</td><td>Results<table><tr><td></td><td>WBRT (N=41)</td><td>WBRT + TMZ (n=41)</td><td>Notes</td></tr><tr><td>Complete response 30 days</td><td>2</td><td>2</td><td></td></tr></table></td><td>Limitations
Randomisation: yes unclear
Allocation concealment: unclear
Patient blinding: unclear</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
radiotherapy in patients with brain metastases: A phase II randomized trial, International Journal of Radiation Oncology Biology Physics, 61, 185-191, 2005 Ref Id 499632 Country/ies where the study was carried out Spain Study type Phase II randomised trial Source of funding Grant C03/10, Red Tematica del Cancer, Instituto Carlos III, Spain.	<table><tr><td>Lung</td><td>22</td><td>20</td></tr><tr><td>Breast</td><td>7</td><td>6</td></tr><tr><td>Other</td><td>12</td><td>15</td></tr><tr><td>Previous chemotherapy - yes</td><td>31</td><td>31</td></tr><tr><td>no</td><td>10</td><td>10</td></tr><tr><td>Median brain metastases</td><td>3 (1 to 19)</td><td>2 (1 to 56)</td></tr></table>Inclusion criteria age 18 years, KPS 50, no chemotherapy in the previous 3 weeks, and no prior cranial RT. Laboratory requirements included the following: absolute granulocyte count 1.5 ——————————— 109/L; platelet count 100 ——————————— 109/L; alanine aminotransferase, aspartate aminotransferase, and total bilirubin at or less than twice the normal limit; and creatinine 1.5 times the upper normal limit. Exclusion criteria The exclusion criteria were leptomeningeal involvement or intratumoral hemorrhage and clinical or psychiatric conditions that prevented the study completion or interfere with the required evaluations.	5 d/wk for 2 weeks, followed by two cycles of 200 mg/m2/d for 5 days (150 mg/m2 in heavily pretreated patients) every 28 days. Between the end of concurrent treatment and the 5-day cycles of TMZ, there was a 4-week interval.	<table><tr><td>Partial response 30 days</td><td>11</td><td>11</td><td></td></tr><tr><td>Stable disease 30 days</td><td>12</td><td>17</td><td>* for statistical reasons patients who could not be evaluated were considered to have neurological progression</td></tr><tr><td>Progressive disease 30 days</td><td>6</td><td>5</td><td></td></tr><tr><td>Not evaluated 30 days</td><td>10</td><td>6</td><td></td></tr><tr><td>Complete response 90 days</td><td>0</td><td>1</td><td></td></tr><tr><td>Partial response 90 days</td><td>2</td><td>6</td><td>* for statistical reasons patients who could not be evaluated were considered to have neurological progression</td></tr><tr><td>Stable disease 90 days</td><td>4</td><td>10</td><td></td></tr><tr><td>Progressive disease 90 days</td><td>9</td><td>3</td><td></td></tr><tr><td>Not evaluated 90 days</td><td>26</td><td>21</td><td></td></tr></table>	Assessor blinding: yes Investigator blinding: unclear Reporting bias: none Lost to follow up: 1 withdrew and 2 lost to follow up Compliance: WBRT 76% 31/41 ; WBRT + TMZ 92% 38/41 ITT: yes Single metastases : unclear Prior treatments: no prior cranial RT Mean treatment duration: RT 2 weeks TMZ until patients achieved an absolute

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Schering-Plough provided the study drug, as well as funding for a data manager and statistical analysis

Aim of the study

The aim of our study was to assess the safety and efficacy of WBRT concomitant with TMZ, followed by two additional cycles of TMZ, in patients with BM from different primary malignancies .

Study dates</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>Patients free of brain mets at 90 days</td><td>54 %</td><td>72%</td><td>p=0.03</td></tr>
<tr><td>Median survival months</td><td>3.1</td><td>4.5</td><td></td></tr>
</table>
</td>
<td>neutrophil count 1.5

109/L and platelet count 100

109/L and nonhematologic toxicities had resolved to Grade 1 or less
Time points for measurement: Days 30 and 90 and the 90-day progression-free survival (PFS) of BM confirmed by clinical or radiologic evaluation.</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>October 2000 and closed prematurely in August 2002</td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation
Kepka, L., Tyc-Szczepaniak, D., Osowiecka, K., Sprawka, A., Trabska-Kluch, B., Czeremszynska, B., Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial, Clinical and Translational Oncology, 1-10, 2017</td><td>Sample size
60 participants were randomised; 30 were allocated to stereotactic radiotherapy to the tumour bed; 30 were allocated to whole brain radiotherapy
Characteristics
See entry for Kepka 2016
Inclusion criteria
See entry for Kepka 2016
Exclusion criteria
See entry for Kepka 2016</td><td>Interventions
See entry for Kepka 2016
Details
See entry for Kepka 2016, except:
ITT analysis was not performed for this publication.
Participants who received initial treatment with stereotactic radiotherapy to the tumour bed (n = 24) were compared to those who received whole brain radiotherapy (n = 34).</td><td>Results<table><tr><th></th><th>SRS-TB group n = 24</th><th>WBRT group n = 34</th><th>Notes/p value</th></tr><tr><td>Global quality of life scores at 2 months</td><td>65.9 (±24.6)</td><td>61.4 (±25.7)</td><td>p = 0.60
Mean scores of QLQ-C30 and BN-20 questionnaire measures.</td></tr><tr><td>Global quality of life scores at 5 months</td><td>55.7 (±26.9)</td><td>67.1 (±23.7)</td><td>p =0.19</td></tr></table></td><td>Limitations
Other information</td></tr>
</table>

Study details	Participants	Interventions	Outcomes and results	Comments
Ref Id 676193 Country/ies where the study was carried out Poland Study type RCT Source of funding None reported. Aim of the study To compare the health related quality of life for people who receive stereotactic radiotherapy to the tumour bed, as compared with whole brain radiotherapy, following surgical resection of a single brain metastasis. Study dates				

Study details	Participants	Interventions	Outcomes and results	Comments
December 2011 to September 2015				

Evidence tables for review 5a - Follow-up for glioma

Not applicable - no evidence was identified.

Evidence tables for review 5b - Follow-up for meningioma

Not applicable - no evidence was identified.

Evidence tables for review 5c - Follow-up for brain metastases

Not applicable - no evidence was identified.

Evidence tables for review 5d - Late effects of treatment

Not applicable - no evidence was identified.

Evidence tables for review 5e - Care needs of people with brain tumours

Study details	Participants	Methods/Limitations	Outcomes and results
Full citation: Moore, G., Collins, A., Brand, C., Gold, M., Lethborg, C., Murphy, M., Sundararajan, V., Philip, J., Palliative and	Participants: 21 included studies with a total of 219 patients and 301 carers, that used structured, semi-structured and in-depth	Methods: Narrative synthesis used as methodology to underpin this review. “The steps included (1) theory development which is articulated in the aim, research question, and search strategy	2/21 included studies met criteria for the highest level of evidence as generalisable studies; 8/21 studies met Level II criteria as conceptual studies, and 11/21 studies met Level III criteria as descriptive studies.

Study details	Participants	Methods/Limitations	Outcomes and results
supportive care needs of patients with high-grade glioma and their carers: a systematic review of qualitative literature, Patient Education & Counseling Patient Educ Couns, 91, 141-53, 2013 Ref ID: 553958 Design: Systematic review Country: Authors based in Australia, included studies conducted in Sweden (8), the US (7), Japan (1), Australia (3) or the UK (2) Study aim: “What is the quality of evidence regarding the supportive and palliative care needs of patients with PMG [primary malignant glioma] and their carers, what are the key areas of our current knowledge, and what gaps exist?”	interviews and face-to-face or telephone questionnaires describing the needs and perceptions of care of patients and carers of patients with primary malignant glioma (PMG) Inclusion/exclusion criteria: - Patients with PMG at any stage across the illness trajectory or their carers (current and bereaved). - Qualitative studies which detailed the direct reports of the palliative and supportive care needs (including communication, information, support and service provision outcomes) as expressed by PMG patients or their caregivers. - Published in English - Studies satisfying at least the minimum criteria for rigour: ‘Was there a clear statement of the aims?’ and ‘Is a qualitative methodology appropriate?’ Exclusion criteria: - Reviews and case reviews	undertaken; (2) preliminary synthesis and data extraction through tabulation of findings; (3) exploration of relationships by a thematic analysis; and (4) assessment of the robustness of the synthesis and evaluation of the studies according to previously defined methods of qualitative appraisal including” CASP, and hierarchy of evidence for-practice (p. 142). Limitations assessed with the ROBIS checklist: 1.1 Did the review adhere to pre-defined objectives and eligibility criteria? Yes 1.2 Were the eligibility criteria appropriate for the review question? Yes 1.3 Were eligibility criteria unambiguous? Yes 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? Yes 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? Yes, only English language, published studies of sufficient quality	Four themes based on patient and carer needs presented in the included studies, were extracted: 1. Information needs - need for information for patients and their carers. The kind of information and how it was provided were both important. - dissatisfaction from carers about the lack of consistent advice to support them as carers - patients were generally found to be satisfied with the information provided, but not many of them asked about prognosis, rather they expressed satisfaction by just be informed about their diagnosis and treatment regime. - There were some specific information needs expressed by patients and carers relating to postoperative information that would allow active involvement in care, disease and treatment information, side effects of treatment, effect of diagnosis on quality of life, medication management, prognosis information, proactive and understandable financial resources, information supporting the effective navigation of the health system, and information about resources such as access to support groups. - This systematic review found that the information needs changed over the course of the illness, and that they were emergent and specific and corresponded to the illness trajectory and rapid shifts in status of patients with PMG. -The need for information by patients and carers was for individualised information that should relate to the specific prognosis of the patient, be delivered in a timely manner that pre-empted any crisis events and should be delivered a way, using different media that was acceptable to each patient. 2. Communication needs - Need for timely communication so it is possible for PMG patients to express their desires and coordinate care plans prior to cognitive and communication difficulties.

Study details	Participants	Methods/Limitations	Outcomes and results
Study dates: The search covered January 2010 – December 2010 Source of funding: Victorian Cancer Agency [EO109_29], Australia	- Studies focussing on medical/clinical treatment, biochemistry or cell-biology, or prognostification.	Concerns regarding specification of study eligibility criteria LOW 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? No, no search for unpublished studies 2.2 Were methods additional to database searching used to identify relevant reports? No 2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Probably yes 2.4 Were restrictions based on date, publication format, or language appropriate? No, no search for unpublished, non-English language studies 2.5 Were efforts made to minimise error in selection of studies? No information Concerns regarding methods used to identify and/or select studies HIGH 3.1 Were efforts made to minimise error in data collection? Yes, duplicate, independent assessment of eligibility of full-text articles 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? Yes	- Need for specific communication, such as opportunities for communication with health care professionals (HCPs) and assistance with decisions about treatment and care, facilitated discussion around reduced life expectancy and independence, and conversations about their illness - Need for opportunities for patients and carers to discuss their expectations of the patients' impending death, in order to enable families to adjust their social support, strengthen coping skills, understand information, and reconcile hope and emotional pain - Need for supportive communication between patients and HCPs, which was used as tool to maintain hope, particularly during key crisis points, such as diagnosis, discussion of prognosis, anticipation of scan results, point of recurrence and preparation of end-of-life discussion - A need for separate patient and family consultation to discuss the dying process - A need for bereaved families to have the opportunity to communicate after the patient's death 3. Service provision needs - A need for a specialist nurse to act as a contact that can assist carers in managing the multiple care needs of the patients with PMG, including medication management, how to combine caring and working, how to find support groups, financial issues and expectations after neurosurgery. - A need for each patient to have a dedicated case manager or primary nurse to assist with uncertainty, social isolation and facilitate discussion around end-of-life issues - A need for investigation into the role of rehabilitation for PMG patients, including specific interventions involving: family education and counselling, speech and occupational therapy and employment assistance.

Study details	Participants	Methods/Limitations	Outcomes and results
		3.3 Were all relevant study results collected for use in the synthesis? Yes 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria? Yes (CASP) 3.5 Were efforts made to minimise error in risk of bias assessment? Yes, duplicate, independent study appraisal Concerns regarding methods used to collect data and appraise studies LOW 4.1 Did the synthesis include all studies that it should? Yes 4.2 Were all pre-defined analyses reported or departures explained? Yes 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? Yes 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis? Yes 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? NA 4.6 Were biases in primary studies minimal or addressed in the synthesis? No Concerns regarding the synthesis and findings LOW	- A need for addressing financial and psychological distress through the identification of rehabilitation and support, and provision of that to patients and families in a proactive and understandable format - A need for neuropsychological assessment to support coping strategies with a particular focus on managing difficult patient behaviours - A need for an improved measure of cognitive change and psychological evaluation in order to enable increased responsiveness of services and appropriate counselling - A need for respite in order to reduce the burden of care, with the respite service providing additional support that includes competent seizure first aid, either in the home or inpatient setting. 4. Psychological and social needs - Psychosocial needs for: maintaining hope, methods of coping, the importance of relationships, information, supportive counselling, quality of survival, cognitive changes and associated sense of loss, emotional pain, dependency and isolation

Study details	Participants	Methods/Limitations	Outcomes and results
		A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4? No B. Was the relevance of identified studies to the review's research question appropriately considered? Yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance? NA Risk of bias in the review RISK: LOW	
Full citation: Arber A, Hutson N, de Vries K, Guerrero D. Finding the right kind of support: a study of carers of those with a primary brain tumour. Eur J Oncol Nurs 17(10: 52-58; 2013 Design: Qualitative study Country: United Kingdom Study aim: "to explore the experience of family caregivers when caring for a person with a primary malignant brain tumour."	Participants: 22 carers; 12 female partners, 5 male partners, 2 daughters,1 son,1 mother and 1 father. N = 17 were aged < 60 years and 15 were female. N = 14 had been caring for < 1 year with N = 8 caring for 2-5 years. Inclusion criteria: Age > 18 years, currently caring for a person with a primary malignant brain tumour (glioblastoma multiforme, ependymoma, oligodendroglioma, astrocytoma), and identified by the patient as their primary caregiver.	Methods: Interviews taking an open-ended approach asking few questions instead of many to allow the participants to tell their story without preconceptions of the researcher regarding the content or direction of the interview. Study conducted with a constructivist grounded theory approach. The raw data were analysed by using the steps of open coding using line-by-line analysis and codes attached to words and sentences. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes	- Need for someone to help with benefits. Quote from the paper: "And they got ( ) carers in touch with us, which was Mary Wilson and she's been fantastic and she has given me all the help that I need. She's contacted other people for me, she's explained things, she's helped us with our benefits, as we weren't getting loads of stuff and she helped us and she gave us all the information and she's got me into days like relaxation days. .But before then we had nothing and we were told nothing. We just plodded along coping on our own." (p. 54) - Time out from caring / professionals to rely on (e.g., the Marie Curie nurse) - Importance of having a relationship with the person providing care, and the need for those providing care to be both acceptable to the carer and to the person needing the care. "The quality of the care that can be provided in the home is of utmost importance and building a relationship with someone who can be trusted to provide good care is crucial." (p. 55). - Safe places and comfort zones Need for connecting to support available in the local community, hospital and hospice support groups. Quote from paper: "The other source of help has been the Apple Tree in

Study details	Participants	Methods/Limitations	Outcomes and results
Study dates: 2006-2007 Source of funding: The Surrey, West Sussex and Hampshire Cancer Network.	Exclusion criteria: None reported	4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC Recruitment until theoretical saturation	Stockley. They are a centre, which support anyone with cancer and they have been absolutely fantastic. He has been going there for a year and a half now. He's had counselling there. He's had treatments like Reiki, massages and a couple of days ago he had a session up there where they were making necklaces. So it is all really therapeutic stuff and I know he can go there once a week and feel safe. It is a set time say, two hours and that's really great for him" (p. 55). - Need for safe place to express feelings about being a carer, e.g,, carers meeting at the local hospice. - Need for practical advice and signposting to services and respite from the caring role for carers. - Need for locating the right type and quality of support
Full citation: Cavers, D., Hacking, B., Erridge, S. C., Morris, P. G., Kendall, M., Murray, S. A., Adjustment and support needs of glioma patients and their relatives: Serial interviews, Psycho-Oncology, 22, 1299-1305, 2013 Ref ID: 575808	Participants: Eighty interviews conducted with 26 patients (14 men; mean age (SD, range) 50.7 (13.8, 21–76) years) with 15 glioma multiforme, 2 astrocytoma grade 2, 1 brainstem glioma, 2 anaplastic astrocytoma grade 3, 1 oligodendro-glioma, 5 'others', and 23 relatives. Serial interviews over roughly 1 year at Time 1	Methods: "Participant-guided in-depth qualitative interviews, explored the multi-dimensional illness experience including psychological distress" The raw data "were analysed using a constructionist grounded theory approach to integrate, interpret and explain the data using within and cross-case analysis". Limitations assessed with the CASP checklist:	Three themes (only results relevant to the current question reported): 1. Distress, anxiety and worry from before diagnosis onwards No relevant results to the current question reported in the article 2. Variations and timing of information preferences: - Participants strategic in handling of information, seeking only positive information to create a sense of hope. Quotes from paper: "(If) I knew it was good news I'd want more information, (if) you knew it's bad news you do not want the information. So what do you do? (p. 1302) "I don't think you'd want it to be too doom and gloom in case it frightened you too

Study details	Participants	Methods/Limitations	Outcomes and results
Design: Qualitative study Country: United Kingdom Study aim: "To understand factors influencing the process of adjustment to a diagnosis of glioma." Study dates: May 2006-app May 2007 Source of funding: "This study was funded by a donation from a bereaved relative to the University of Edinburgh."	(immediately preceding or in the week following surgery but before confirmed pathological diagnosis); Time 2: (approximately 3–4 weeks since time 1; after confirmation of diagnosis immediately preceding the start of radiation +/- chemo-therapy or within the first week of treatment); Time 3: (approximately 8–10 weeks after time 2; after initial treatment ends); and Time 4: 6-month follow-up after time 3. Bereavement interviews: ≥ 3 months after patient's death. Inclusion criteria: Recruitment at a UK regional neuro-surgical Centre, tailored to represent a range of ages, genders, tumour types (including high and low grade gliomas), symptom profiles and backgrounds. Recruitment of relatives via patients (most were the patient's spouse).	1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC Recruitment until data saturation	much. I think they need to give you something positive to hold on to, something that's going to lift your spirits a wee bit." (p. 1302) -There were differences between patients' and their relatives' information preferences, such as about prognosis, and this was a source of tension and distress. Quote from paper: "Is she gonna be here in 3 years time? Is she gonna be here in 5 years time? [..] But every time I've been with [patient], you're not wanting to ask any questions in front of her." (p 1302) 3. The importance of reassurance, support and hope: - Need for professional reassurance and support by having a caring manner, being available, listening and providing information. Quote from paper: "She just says the right thing at the right time. And she is just supportive. And just easy to get to and use. [..] And she has time for everybody." (p. 1302) - Need for hope, regardless of adverse circumstances (e.g, for a positive outcome and good quality care along the way), which changed over time and gave the participants a focus to help move them forward. Quote from paper: "And even in the hardest times we'll be comforted, there'll be something. It's not all negative." (p. 1302). - Need for professionals' manner when delivering information to allow the participants to create and maintain hope. It was distressing for patients and relatives when they perceived a lack of reassurance and emotional support, with the focus instead being on physical care, and this impaired their capacity for adjustment as time went on. Quote from paper: "OK, the medical profession can cope with the, you know, dispensing drugs and all the rest of it, but I needed to understand what the hell was going on. [. . .] And obviously I figured it out for myself. But a few, 2 or 3 months down the line, by that time I was exhausted." (p. 1303).

Study details	Participants	Methods/Limitations	Outcomes and results
	Exclusion criteria: None reported		No gender differences found that were central to the themes.
Full citation: Coolbrandt, A., Sterckx, W., Clement, P., Borgenon, S., Decruyenaere, M., De Vleeschouwer, S., Mees, A., Dierckx De Casterle, B., Family Caregivers of Patients with a High-Grade Glioma: A Qualitative Study of Their Lived Experience and Needs Related to Professional Care, Cancer Nursing, 38, 406-413, 2015 Ref ID: 575850 Design: Qualitative study Country: Belgium Study aim: "to explore the experience of family caregivers of patients with HGG and their needs related to professional care."	Participants: N = 16 family carer givers; mean (range) age = 54.2 (31-68) years; 6 males/10 females; Relation with patient: Partner (13) Parents (2) Friend (1); Living with the patient yes (15), no (1); Phase in the illness trajectory: First-line treatment (6), Second-line treatment (7), After patient's death (3). Four family caregivers participated in a follow-up interview in order to grasp their experience after a relevant change in their situation: Death of the patient (n = 2), progressive disease and end of treatment (n = 1), and progressive disease and start of second-line chemotherapy (n = 1). Inclusion criteria: Family caregivers recruited at the oncology wards of the	Methods: Semistructured interviews analysed using a Grounded Theory approach. "The interview questions were constantly revised and supplemented with concepts emerging during the interim analyses. Topics included, diagnosis, symptoms, relationships, support, caregiving tasks, future, communication, and information. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes	Only results relevant to the current question reported: - Need for information to help deal with complex high grade glioma-related symptoms and problems (eg, epilepsy, medication schedules), to help them feel prepared, and to know what to expect and how to deal with issues such as treatment adverse effects and neurological symptoms. Quote from paper: "Nobody wants or dares to tell you what is going to happen, because indeed, it depends on the patient, but somehow you really need to know. (…) Luckily, I had read on that Web site about what can happen; I was prepared to so many things, because those last months were really hard. He stood up in the middle of the night, and he was convinced that it was the day. Luckily, I knew from that Web site that this could happen." (p. 410) - Need for access to and availability of professionals for the reassurance of knowing that they could get help dealing with questions, problems, and insecurities." Quote from paper "That was the most important thing for me: that I would know whom to turn to with questions and not to stand there like…, ''And now I'm still alone here and what do I need to do now? Whom can I call?'' (p. 411) - Need for accessible professional caregivers for consideration and support, to be able to share concerns and difficulties, even just in short conversations, or as evidenced by the professional caregiver showing interest or creating an opportunity to address the family caregiver's viewpoint and needs. This need for consideration and support sometimes continued after the patient's death. - Need for professionals to share their goal to provide the patient with the best possible care, including the acknowledgement by professionals that high grade glioma is particularly severe and the reflection of this in the way

Study details	Participants	Methods/Limitations	Outcomes and results
Study dates: February-July 2011 and April-November 2012. Source of funding: Funded by Kom op tegen Kanker, the campaign of the Flemish League against Cancer/Vlaamse Liga tegen Kanker VZW	University Hospitals Leuven, Belgium, chosen by the patient and/or the professional team as the main informal (family or nonfamily) caregiver of any high grade glioma patient treated with chemotherapy and/or radiotherapy or in the follow-up phase after such treatment, able to speak Dutch. Exclusion criteria: Family caregivers physically, mentally, or emotionally unable to participate not invited for participation, or invited at a later stage.”	8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC Recruitment continued until data saturation.	professionals cared for the patient. Quote from the paper: ‘‘Cancer patients need to be cared for 300% friendly.” (p. 411).
Full citation: Cornwell, P., Dicks, B., Fleming, J., Haines, T. P., Olson, S., Care and support needs of patients and carers early post-discharge following treatment for non-malignant brain tumour: establishing a new reality, Supportive Care in Cancer, 20, 2595-2610, 2012 Ref ID: 575855	Participants: Brain tumour participant: N = 9; 3 males/6 females; mean age (range) = 55.9 (36-70) years. Family carer participants: N = 5; 2 males/3 females; all were spouses/partners. The brain tumour participants had undergone neurosurgical excision of their tumour prior to inclusion in the study, and none were receiving radiotherapy or	Methods: In-depth Semi-structured interviews conducted at two time points: 2 weeks post-discharge from hospital and 3 months post-discharge with participants encouraged to tell their stories of ‘life since discharge’ and answering questions about experiences and feelings of life at home since discharge, ongoing therapy and support services, perceived needs, and barriers and facilitators to goal achievement.	Three categories: Coping with available supports, adjusting to routines and relationships and, emotional responses; with an overarching theme of ‘establishing a new reality’ (only results relevant to the current question reported): 1. Coping with available support Comprised of the following sub-categories: Reliance on informal care, unmet information and support needs, sufficiency of support, and support for carers themselves. Unmet information and support needs: - need for further information and organisation of support services.

Study details	Participants	Methods/Limitations	Outcomes and results
Design: Qualitative study Country: Australia Study aim: "to understand how patients diagnosed with a non-malignant brain tumour and their carers experience the early discharge period after diagnosis and neurosurgical intervention, thereby provide insights into their perceived care and support needs [" Study dates: January-August 2008 Source of funding: South Area Health Services Cancer Clinical Network Training and Developmental Programme	chemotherapy during the study period. Inclusion criteria: Patients diagnosed with a primary non-malignant brain tumour and undergoing neurosurgical intervention with curative treatment, aged ≥ 18 years, providing written informed consent and able to communicate sufficiently in English for participation in a semi- structured interview. Exclusion criteria: Documented evidence of preexisting neurological conditions, intellectual impairment or mental illness impeding the ability to provide informed consent and communicate adequately	Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC Recruitment until data saturation for brain tumour patients	- Quote from paper: "I think that right now if I needed help from somewhere I wouldn't have a clue where to go" (Table 3) Sufficiency of support: - The responses about the general adequacy of support ranged from sufficient to insufficient: Particularly carers, were more likely to consider that services were insufficient when there was lack of information, miscommunication between service providers or delays in the system, whereas participants with brain tumour were more inclined to report adequate levels of support for their daily needs if carers/friends were available and able to provide continued assistance. Patients with carers tended to report more satisfactory levels of support overall, compared to those with no carer support. - 5/9 participants reported an unmet need of home help/domestic cleaning Support for carers themselves: - Unmet need for support for the carers themselves (identified by both carers and patients). Quote from paper: "If I had needed assistance I wouldn't have known where to go. I would have had to go back to [the GP] and sort of say that I'm losing a bit here but then again if you don't know that you're like that until you're over it or you've gone right under" (p. 2602)
Full citation: Edvardsson, T., Ahlstrom, G., Being the	Participants: 28 adult next of kin of 27 patients. 25/27 patients had a low grade	Methods: Semi-structured qualitative interviews conducted with next of kin of persons with a predominantly low	Four themes (only results relevant to the current question reported): 1. Extremely stressful emotions:

Study details	Participants	Methods/Limitations	Outcomes and results
next of kin of a person with a low-grade glioma, Psycho-Oncology, 17, 584-591, 2008 Ref ID: 575948 Design: Qualitative study Country: Sweden Study aim: “to explore the experience of being the next of kin of an adult person diagnosed with a low-grade glioma” Study dates: Not reported Source of funding: The study was supported by grants from the Centre for Rehabilitation Research.	glioma, and 2/27 patients had a grade III glioma with a clinical picture corresponding to having low-grade glioma. 15 next of kin were spouses or co-habitants and 13 lived separate from their relative (3 live-apart partners, 8 parents, 1 sibling, 1 adult child). Of the 28 next of kin 8 were men and 20 women, with a mean (range) age = 52.5 (25-77) years; mean (range) time since diagnosis = 12 (< 1 year-46) years. Inclusion criteria: Recruitment through personal contact with patients from a previous study Exclusion criteria: None reported	grade glioma, during which the next of kin were encouraged to talk about their own situation and more specifically their experiences with regard to their relatives. The following thematic areas were explored: Life before illness, Onset of illness, Current life situation, Experiences of encounters with professionals in care, and Thoughts about the future.” The study used a mixed-method, descriptive qualitative and quantitative data analysis. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Can’t tell 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can’t tell 7. Have ethical issues been taken into consideration? Yes	No relevant results to the current question reported in the article 2. Being invisible and neglected: - ‘Unsatisfied needs and feelings of powerlessness’ [subtheme] referred to wishes or requests in care. - Need for emotional support. - Unmet need for information particularly in relation to consequences post-surgery and for life together, rehabilitation and continuous support. - Quote from paper: ‘‘I felt so awful I felt I needed help from a psychologist. But it was a very long-drawn-out business, because I didn’t get a referral. Getting a referral to a proper psychologist was just impossible, hopeless! It was though private contacts I did get a referral.’ (p. 587) 3. Changed relations and roles: No relevant results 4. Enabling strength in everyday life: - Sub-theme of “Opportunity to suggest improvement in care”: - Unmet need for emotional and psychological support, - Unmet need for information, also regarding the next of kin’s contribution of information about the patient, which should not be overlooked by health-care staff. - Need for answers given with honesty and in a manner that preserves hope. - Request for broader professional teams in care, extended support after discharge and health-care staff with special responsibility to be easily accessible to the patients and families.

Study details	Participants	Methods/Limitations	Outcomes and results
		8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC No mention of data saturation	
Full citation: Nixon, A., Narayanasamy, A., The spiritual needs of neuro-oncology patients from patients' perspective, Journal of Clinical Nursing, 19, 2259-2270, 2010 Ref ID: 576519 Design: Qualitative study Country: United Kingdom Study aim: “to gain insights into the spiritual needs of neuro-oncology patients and determine their implications for practice.”	Participants: 21/43 invited patients (due to attend a neuro-oncology outpatients appointment during a two -month period) took part in the study. All had been admitted to a neurosurgical unit for a biopsy and/or a craniotomy and debulking of their tumour since the onset of their illness; diagnoses were grade III or IV glioma (19), anaplastic meningioma (1), grade II glioma (1); age range = 18–69 years; time since diagnosis ranged from 3-5 months to ≥ 1 year; 2 high grade gliomas had initially presented as a low grade glioma; all patients had also received radiotherapy and/or chemotherapy for their brain tumours.	Methods: Data collected through a Critical Incident Technique questionnaire and analysed using thematic content analysis.” The questionnaire was used to obtain critical incidents related to the following: 1 You feel you had spiritual needs. 2 Were you helped by nursing staff to meet your spiritual needs? If so how? 3 If you weren’t assisted with your spiritual needs by nursing staff was there opportunity for them to do so? 4 What were the effects on you of the support/lack of support you received from nursing staff regarding your spiritual needs? The questionnaires were completed by the patient alone or with the researcher or family members. Spirituality was defined for all participants as:	Subcategories of patient spiritual needs (only results relevant to the current question reported): - reassurance, - family support, - need to talk about issues and fears related to death - solitude - emotional support, - need for connection/loneliness/depression, - plans for the future/sense of normality, - no spiritual needs for some patients during their hospital stay - religious needs mostly concerned with talking to the hospital chaplain/ someone religious, and with access to the chapel. - thoughts about meaning of life - ‘other strategies to meet neuro-oncology patients’ spiritual needs’ (identified with five sub headings: Support of family/friends, Religious/chaplaincy support, Faith/belief, Denial and Maintaining positive attitude/laughter) Strategies, identified by patients, that nurses could use to support patients with their spiritual needs: - flexibility with hospital policies, - communication, - link to family, - providing privacy,

Study details	Participants	Methods/Limitations	Outcomes and results
Study dates: Not reported Source of funding: Supported by Cancer Research UK (CUK) grant number C19648/A6216.	Inclusion/exclusion criteria: Patients diagnosed with a brain tumour who had previously been hospital inpatients on a neurosurgical unit and who were cognitively and emotionally able to participate in the study.	"Spirituality is the non-physical part of our life which is considered to be the essence of our being. It gives meaning and purpose to our existence. Some associate it with religion, while others do not. Healthcare professionals are responsible for providing holistic care, which requires attention to the body, mind and spirit." (p. 2261) Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Can't tell 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes	- religious support, - emotional support, - company/reassurance, - explanations and practical support, - sensitivity, -providing a positive caring environment - the data shows that some patients with brain tumours have spiritual needs during their hospital stay on neurosurgical units which in some cases are not met by nurses

Study details	Participants	Methods/Limitations	Outcomes and results
		9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC No mention of data saturation	
Full citation: Ownsworth, T., Goadby, E., Chambers, S. K., Support after brain tumor means different things: Family caregivers' experiences of support and relationship changes, Frontiers in Oncology, 5 (FEB) (no pagination), 2015 Ref ID: 576550 Design: Qualitative study Country: Australia Study aim: "1. How do caregivers perceive their support needs in the context of brain tumor? In addressing this question, emphasis was placed on their perceptions of (a) the support needs of the	Participants: N = 11 caregivers; 6 males/5 females; mean (SD, range) age 57.91 (12.62, 33–79) years; relationship to the person with brain tumour: Married/de facto partner/parents 6/2/3 (2 mothers, 1 father); tumour type: benign or low grade /malignant: 6/5; mean (SD, range) time post diagnosis mean 5.88 (6.3, 9 months – 22 years) years. All patients had undergone treatment involving surgery and either radiation, chemotherapy or both. Inclusion criteria: Participants recruited from a broader study, looking at how people with brain tumours make sense of and adjust to their illness. These patients were recruited from a brain	Methods: In-depth semi-structured interviews, with a format and topics designed to support caregivers to reflect back on the time of diagnosis of their family member and to facilitate open dialog about their experiences of support, the impact on their relationship, and what they have learnt from their experience. Interview data analysed using thematic analysis on the open, axial, and selective coding approach. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes probably 5. Was the data collected in a way that addressed the research issue? Yes	Only results relevant to the current question reported: - Need for psychological support for caregivers themselves: Quote from paper: "I've actually started to admit to myself he's not the person he used to be… you've lost that person you've married and you've got to deal with that." (p. 7; Wife of a person who had significant changes in personality) - Caregivers expressed a need for easy to understand information on what to expect when caring for someone with a brain tumor, including different types of brain tumor, treatment, and side effects." Quote from paper: "I wasn't really seeking support, most of the support that I was looking for was knowledge." (p. 7) – Adjustment to caregiver role would have been helped by access to information. Quote from paper: "Even if we had been aware of the support group and all the information available… that could have made our lives so much easier." (p. 7) - Emotional support from health-care professionals, particularly in their manner of interaction, was also considered very important by caregivers. Quote from paper: "His [neurosurgeon] manner's been very encouraging and very supportive and I would classify him as being a source of support. (p. 8) - Even when giving bad news, doctors who had a kind and caring manner were seen as providing emotional support. Quote from paper: She(neuro - surgeon) had to give us some bad news some of the time… and you couldn't ask for a better manner in her delivery of that bad news, or her support in what we were going through." (p. 8)

Study details	Participants	Methods/Limitations	Outcomes and results
person with brain tumor; and (b) the caregiver's own support needs. 2. How does brain tumor impact on the relationship between the caregiver and person with brain tumor? Additionally, the influence of social support on relationship changes was explored." Study dates: Not reported Source of funding: Cancer Council Queensland	tumour support group or a neurosurgical practice. The caregiver participants for the current study were a selected subgroup of caregivers from the broader sample. They were selected using purposive sampling to identify 12 caregivers with diverse characteristics likely to impact on perceptions of support. "The primary selection criterion was that participants should be caring for an adult with a benign/ malignant tumor, followed by selection on the basis of caregiver gender,age (<50, 50–60, >60 years) and relationship to the individual with braintumor (married/de facto or parent)." Exclusion criteria: None reported	6. Has the relationship between researcher and participants been adequately considered? Yes probably 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC No mention of data saturation	– Two caregivers had had negative experiences with other medical professionals who they saw as cold and clinical or offering little hope or reassurance." Quote from paper: "We asked do you think she will live? And he very tersely told us well, you want to be grateful that we're not dead now…from our point of view all we really wanted was a little bit of reassurance." (p. 8) – Caregivers did not agree on whether support should be offered to, or sought by them - Several caregivers would have liked to receive more information about brain tumours once the initial shock had subsided. Quote from paper: "I guess we just wish that someone would have said to us right at the beginning here's a very good guide, because when you have a brain tumor situation, oh you're lost." "I think that's the time when some sort of support would be very helpful perhaps to a lot of families." (p. 8) - Caregivers considered information about the range of support services available, and what to expect as a caregiver important and helpful for caregivers to receive soon after diagnosis. Quote from paper: "I think that's one of the biggest problems with the services, it's hard when you don't know where to even begin…I did not know where to go really and I suppose that was half the problem of not getting help." (p. 8) - In summary, the Meanings of Support theme identified differences in caregivers' own support needs, however they agreed on the need for caregiver-specific information."
Full citation: Sherwood, P, Hricik, A, Donovan, H, Bradley, Se, Given, Ba, Bender, Cm, Newberry, A, Hamilton, R, Given, Cw, Changes in caregiver perceptions over time in response to	Participants: N = 10 caregivers (2 males/8 females), all Caucasian, mean age (range) = 48 (21-63) years [mean (range) patient age = 50.3 (26-75) years]; 5 spouses, 2 parents, 3	Methods: Interview data collected at baseline and four months following diagnosis. The interviews consisted of 11 open-ended questions asked at both time points and analysed using thematic content analysis.	Only results relevant to the current question reported: - At 4 month follow-up: Caregivers more interested in support from others, who were not necessarily a close friend/relative, but who had been in similar situations." Quote from paper: "Just talking to other people who are going through the same things that I am. Just being able to talk to them and knowing that I'm not going crazy, and that they're going through it too,

Study details	Participants	Methods/Limitations	Outcomes and results
providing care for a loved one with a primary malignant brain tumor, Oncology Nursing ForumOncol Nurs Forum, 38, 149-55., 2011 Ref ID: 576769 Design: Qualitative study Country: USA Study aim: “ To examine how family members of patients with a primary malignant brain tumor transition into the caregiver role and how their perceptions of this transition change over time.” Study dates: Not reported Source of funding: Not reported	others (child, nephew, or friend); 6 glioblastoma multiforme, 4 astrocytoma (grade I-III). Inclusion criteria: Caregivers recruited within one month of the patient’s diagnosis from the neurosurgery and neuro-oncology clinics of a regional medical center.” Caregivers aged ≥ 21 years, caring for someone with pathologically verified primary malignant brain tumour, able to read and speak English. Exclusion criteria: Caregivers currently providing care for anyone other than children.	Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Can’t tell 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can’t tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC No mention of data saturation (only theme saturation in the available data).	and how they cope. It has really helped a lot, just having people that know what you’re going through.” (p. 153)

Study details	Participants	Methods/Limitations	Outcomes and results
Full citation: Sterckx, W., Coolbrandt, A., Clement, P., Borgenon, S., Decruyenaere, M., De Vleeschouwer, S., Mees, A., Dierckx de Casterle, B., Living with a high-grade glioma: A qualitative study of patients' experiences and care needs, European Journal of Oncology Nursing, 19, 383-90, 2015 Ref ID: 576814 Design: Qualitative study Country: Belgium Study aim: “to better understand how patients with HGG experience life with a brain tumor, and to explore their professional care needs.” Study dates: February-July 2011 and April-November 2012.	Participants: N = 17 patients; mean (range) age = 50.5 (28-73) years; 10 males/7 females; Surgical procedure: Tumour resection (15), biopsy alone (2); Phase in the illness trajectory: First-line treatment (8), Second-line treatment/progressive disease (8). 2 patients participated in a follow-up interview due to unclear data from the first interview (1) or disease progression and end of treatment shortly after the first interview (1). Inclusion criteria: Recruitment at the oncology wards of the University Hospitals Leuven, Belgium. Patients diagnosed with a HGG treated with chemotherapy and/or radiotherapy or in the follow-up phase after such treatment, able to be interviewed, give informed consent and speak Dutch. Exclusion criteria: Patients physically, mentally or	Methods: Semi-structured interviews were conducted and analysed using a Grounded Theory approach. The topic list was constantly revised and supplemented with concepts that emerged during the interim analyses. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Yes 5. Was the data collected in a way that addressed the research issue? Yes 6. Has the relationship between researcher and participants been adequately considered? Can’t tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC	Only results relevant to the current question reported): - Hope, rarely, if ever for a cure, but rather to live as long as possible without relapse, for no complications, for stable symptoms, and/or to regain the ability to participate in certain activities. Patients needed hope and it helped them to keep going. - The importance of hearing positive, hopeful, encouraging words from their professional caregivers when they received their diagnosis, their relapse, or their prognosis. - Particularly, in terms of the consequences of their disease and about what to expect, the patients expressed a need for information. - The need for honest, correct, thoroughly, spontaneous, clear, direct information. - The need to feel that they can share their emotions and concerns. If the patients thought they were being denied this opportunity during their hospital appointments, then it was truly disappointing and some patients as a consequence felt that there was no attention given to them as a person. - Patients felt supported and acknowledged when professional caregivers took time to listen and/or talk with them - It was very important for patients to have access to available professional caregivers so they could get information when they had questions or concerns, and so they could share thoughts and emotions with their professional caregivers. It was very stressful for patients if they did not know how to get to a professional or if they felt unable to connect with them. - If patients saw the same professional every time, they found it easier to reach out to a professional.

Study details	Participants	Methods/Limitations	Outcomes and results
Source of funding: Funded by Kom op tegen Kanker, the campaign of the Flemish League against Cancer/Vlaamse Liga tegen Kanker VZW	emotionally unable to participate (according to physician or head nurse).	Recruitment continued until data saturation.	
Full citation: Wong, J., Mendelsohn, D., Nyhof-Young, J., Bernstein, M., A qualitative assessment of the supportive care and resource needs of patients undergoing craniotomy for benign brain tumours, Supportive Care in Cancer, 19, 1841-1848, 2011 Ref ID: 576969 Design: Qualitative study Country: Canada Study aim: "to evaluate the supportive care and resource needs of patients undergoing	Participants: N = 29, 9 males/20 females, mean age 60.4 (20-88) years; tumour histology (WHO grade I): meningioma (25, 3 with recurrence), other (4); married / common law (22), single/ separated (7). Inclusion criteria: Convenience sample of one of the senior author's patients, who were eligible if diagnosed with a benign brain tumour, underwent craniotomy for the tumour within the past 2 years, able to communicate adequately in English (or with translator) and (4) was sufficiently cognitively intact. Exclusion criteria: None reported.	Methods: Semi-structured, face-to-face interviews focussing on patients' concerns, changes in daily activities, access to supports, and satisfaction with supports throughout their experience with disease, surgery and recovery, and analysed using thematic analysis with themes inductively generated as per grounded theory. Limitations assessed with the CASP checklist: 1. Was there a clear statement of the aims of the research? Yes 2. Is a qualitative methodology appropriate? Yes 3. Was the research design appropriate to address the aims of the research? Yes 4. Was the recruitment strategy appropriate to the aims of the research? Can't tell 5. Was the data collected in a way that addressed the research issue? Yes	5 overarching themes emerged (only results relevant to the current question reported): 1. Need for formal support from diagnosis onwards - The majority of the participants said that they had no access to formal support systems, such as support groups or counselling services. Even though they were aware of the much better prognoses of benign brain tumours compared to cancer, the participants would still have liked to access such supports. Quote from paper: "I still think there needs to be just more support in general, you know, for people who have this type of surgery.…It's not like cancer, where you get the follow-up and you get the ongoing care.…It would be nice to have more supports available, at least to access if people choose to access them." (p 1842) - Respondents were interested in formal support systems from the moment of their diagnosis. 2. Complexity of supportive needs during postoperative recovery - Honest explanations by neurosurgeon about the symptoms and what they meant as well as about what activities could be undertake post-operatively were reported to be important to patients - A preference expressed by many patients to have been able to speak to others about what to expect postoperatively. Quote from paper: "There were a few concerns that nobody ever told me that I would know or face.…" (p. 1843)

Study details	Participants	Methods/Limitations	Outcomes and results
craniotomy for benign brain tumours." Study dates: Not reported Source of funding: Not funded .		6. Has the relationship between researcher and participants been adequately considered? Can't tell 7. Have ethical issues been taken into consideration? Yes 8. Was the data analysis sufficiently rigorous? Yes 9. Is there a clear statement of findings? Yes 10. How valuable is the research? TBC Recruitment until data saturation	- Respondents believed that support groups could have enhanced their physical and mental recovery during the recovery period. - Quote from paper: "But I'll tell you one thing that would have been helpful—would be that if after the surgery, they had some kind of therapy, maybe a group therapy, to tell you what to expect from this brain surgery and to give you maybe exercises to build up your strength, to build up your morale…" (p. 1843) - Many of the respondents had difficulty performing activities of daily living, and they therefore expressed a need for practical help post-operation. 3. Importance of regular long-term monitoring by physicians - Regular, long-term monitoring by physicians, including their neurosurgeon and family physician, was also a need expressed by the participants. - Apart from regular monitoring, most respondents thought there would be few future needs or focused on the present. Quote from paper: "I'm thinking that I'm going to be fantastic in 2 more weeks and that's as far as I see" (p. 1844) 4. Influence of psychosocial factors on supportive needs and 5. Existence of barriers to equal access to available supports No relevant results

Evidence tables for review 6a – Neurorehabilitation assessment needs of people with brain tumours

Not applicable - no evidence was identified.

Health economic global evidence

Literature search for global economic evidence

Date of initial search: 14/04/2016

Database: 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: 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/
2	(glioma* or glioblastoma* or gliosarcoma* or astrocytoma* or astroblastoma* or oligodendroglioma* or oligodendrocytoma* or oligoastrocytoma* or GBM).tw.
3	ependymoma*.tw.
4	(glial adj3 (neoplas* or cancer* or tumo* or carcin* or malign* or metasta*)).tw.
5	or/1-4
6	Meningioma/
7	Meningeal Neoplasms/
8	meningioma*.tw.
9	(mening* adj3 (neoplas* or cancer* or carcin* or tumo* or malign* or metasta*)).tw.
10	or/6-9
11	exp Neoplasm Metastasis/
12	exp Brain Neoplasms/
13	exp Brain/
14	12 or 13
15	11 and 14
16	((brain or cereb* or intracranial or mening*) adj3 (metasta* or micrometasta* or spread* or involvement or carcinosis or secondar* or disseminat* or migrat*)).tw.
17	15 or 16
18	or/5,10,17
19	Economics/
20	Value of life/
21	exp "Costs and Cost Analysis"/
22	exp Economics, Hospital/

#	Searches
23	exp Economics, Medical/
24	Economics, Nursing/
25	Economics, Pharmaceutical/
26	exp "Fees and Charges"/
27	exp Budgets/
28	budget*.ti,ab.
29	cost*.ti.
30	(economic* or pharmaco?economic*).ti.
31	(price* or pricing*).ti,ab.
32	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
33	(financ* or fee or fees).ti,ab.
34	(value adj2 (money or monetary)).ti,ab.
35	or/19-34
36	18 and 35
37	limit 36 to yr="2014 -Current"

1 Date of initial search: 14/04/2016

2 Database: Embase 1974 to 2017 April 13 2016

3 Date of re-run: 12/09/2017

4 Database: Embase 1980 to 2017 Week 36

5

#	Searches
1	exp glioma/
2	(glioma* or glioblastoma* or gliosarcoma* or astrocytoma* or astroblastoma* or oligodendroglioma* or oligodendrocytoma* or oligoastrocytoma* or GBM).tw.
3	ependymoma*.tw.
4	(glial adj3 (neoplas* or cancer* or tumo* or carcin* or malign* or metasta*)).tw.
5	or/1-4
6	exp meningioma/
7	meningioma*.tw.
8	(mening* adj3 (neoplas* or cancer* or carcin* or tumo* or malign* or metasta*)).tw.
9	or/6-8
10	exp metastasis/
11	exp brain tumor/
12	exp brain/
13	11 or 12
14	10 and 13
15	exp brain metastasis/

#	Searches
16	((brain or cereb* or intracranial or mening*) adj3 (metasta* or micrometasta* or spread* or involvement or carcinosis or secondar* or disseminat* or migrat*)).tw.
17	or/14-16
18	or/5,9,17
19	health economics/
20	exp economic evaluation/
21	exp health care cost/
22	exp fee/
23	budget/
24	funding/
25	budget*.ti,ab.
26	cost*.ti.
27	(economic* or pharmaco?economic*).ti.
28	(price* or pricing*).ti,ab.
29	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
30	(financ* or fee or fees).ti,ab.
31	(value adj2 (money or monetary)).ti,ab.
32	or/19-31
33	18 and 32
34	limit 33 to yr="2014 -Current"

Date of initial search: 14/04/2016

Database: The Cochrane Library, Issue 4 of 12, April 2016 (Health Technology Assessment Database: Issue 2 of 4, April 2016; NHS Economic Evaluation Database: Issue 2 of 4, April 2015)

Date of re-run: 12/09/2017

Database: Cochrane Library, Issue 9 of 12, September 2017 (Health Technology Assessment Database: issue 6 of 12, October 2016; NHS Economic Evaluation Database: Issue 2 of 4, April 2015)

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*))

ID	Search
#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

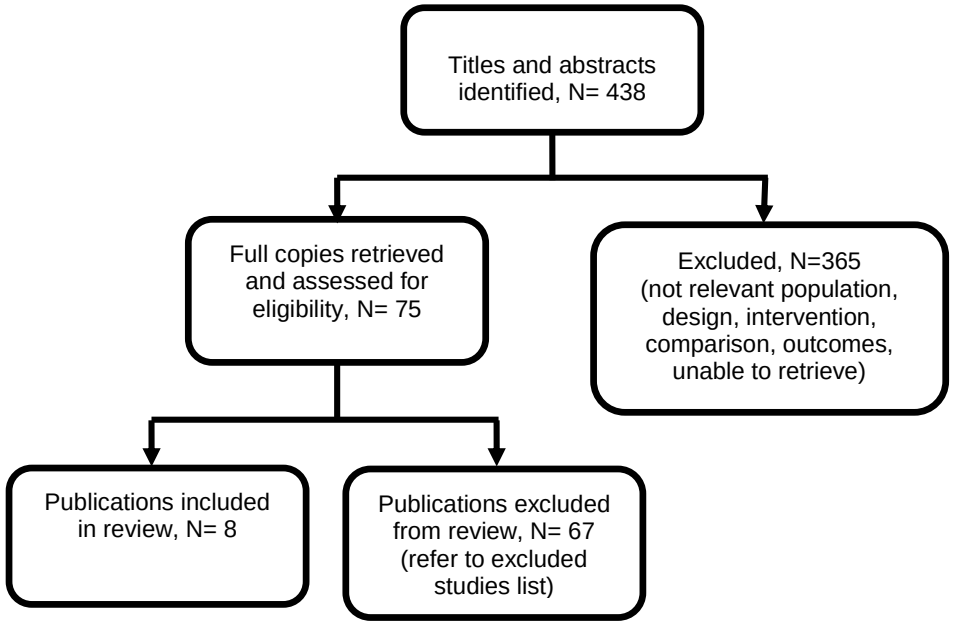
PRISMA flowchart for global economic evidence

A single search was undertaken for all health economic content in the guideline.

Figure 1 below provides an illustration of the process used to select those papers and

presents the number of papers identified according to the area in the guideline. Full details of the search strategies are presented in the section titled ‘Literature search for global economic ’ above.

Figure 1: Flow diagram of selection for economic evaluations



Included studies for global economic evidence

Table 1: Number of included economic studies by clinical area covered in the guideline

Area	Include
Initial management of high-grade glioma	2
Resection of glioma	3
Management of one or more confirmed brain metastases	3
All other topics	0
Total	8

The methods and results for each of those 8 economic evaluations are presented in the relevant sections and health economic evidence tables and health economic evidence profiles are presented in the relevant Evidence Report. Specifically, for information on:

- initial management of high-grade glioma see Evidence Report A, Appendix G (evidence tables) and Appendix H (evidence profiles)
- resection of glioma see Evidence Report A, Appendix G (evidence tables) and Appendix H (evidence profiles)
- management of one or more confirmed brain metastases see Evidence Report C Appendix G (evidence tables) and Appendix H (evidence profiles).

Excluded studies for global economic evidence

Study	Reason For Exclusion
Burkhardt, J. K., B. J. Shin, C. D. Schlaff, H. Riina and J. A. Boockvar (2011) "Cost analysis of intra-arterial versus intra-venous delivery of bevacizumab for the treatment of recurrent glioblastoma multiforme (Provisional abstract)." Journal of Experimental Therapeutics and Oncology 9, 183-186.	Conference abstract
Burton, E., B. Ugiliweneza, S. Woo, S. Skirboll and M. Boaky (2015). "A Surveillance, Epidemiology and End Results-Medicare data analysis of elderly patients with glioblastoma multiforme: Treatment patterns, outcomes and cost." Molecular and Clinical Oncology 3(5): 971-978.	No quality adjusted outcomes reported
Burton, E., B. Ugiliweneza, S. Woo, S. Skirboll and M. Boakye (2014). "A SEER-medicare data analysis of elderly glioblastoma patients: Treatment patterns, outcomes and cost." Neuro-Oncology 16: v66.	No quality adjusted outcomes reported
Colice, G. L., J. D. Birkmeyer, W. C. Black, B. Littenberg and G. Silvestri (1995) "Cost-effectiveness of head CT in patients with lung cancer without clinical evidence of metastases (Structured abstract)." Chest 108, 1264-1271.	Population not relevant to any PICO

Study	Reason For Exclusion
De Paepe, A., N. Vandeneede, D. Strens and P. Specenier (2015). "The Economics of the Treatment and Follow-Up of Patients with Glioblastoma." Value in Health 18(7): A448.	No quality adjusted outcomes reported
Diebold, G., F. Ducray, A. M. Henaine, D. Frappaz, J. Guyotat, S. Cartalat-Carel, V. Breant, A. Fouquet, G. Aulagner, J. Honnorat and X. Armoiry (2014). "Management of glioblastoma: comparison of clinical practices and cost-effectiveness in two cohorts of patients (2008 versus 2004) diagnosed in a French university hospital." Journal of Clinical Pharmacy & Therapeutics 39(6): 642-648.	No quality adjusted outcomes reported
Dinnes, J., C. Cave, S. Huang, K. Major and R. Milne (2001) "The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review (Structured abstract)." Health Technology Assessment Database, 1.	Intervention not covered by the scope of the guideline
Escalona Lopez, S., M. Reza Goyanes, J. A. Blasco Amaro, R. Linertova, L. Garcia Perez and P. Serrano Aguilar (2008) "Surgery guided by imaging assessment: efficacy, safety and economic impact of Intraoperative Magnetic Resonance Imaging (Structured abstract)." Health Technology Assessment Database.	Population not specific to brain tumours
Esteves, S., M. Alves, M. Castel-Branco and W. Stummer (2015). "A pilot cost-effectiveness analysis of treatments in newly diagnosed high-grade gliomas: the example of 5-aminolevulinic Acid compared with white-light surgery." Neurosurgery 76(5): 552-562; discussion 562.	Analysis not performed from an OECD country's perspective
Fathi, A. R., S. Marbacher and A. Lukes (2008) "Cost-effective patient-specific intraoperative molded cranioplasty (Provisional abstract)." Journal of Craniofacial Surgery 19, 777-781.	Conference abstract
Flechi, B., C. Sax, M. Ackerl, J. A. Hainfellner, G. Widhalm, K. Dieckmann, A. Wohrer, M. Preusser and C. Marosi (2014). "The course of QOL and neurocognition in newly diagnosed patients with GBM." Neuro-Oncology 16: v134.	Only reported quality of life. No cost evidence reported
Flechl, B., C. Sax, M. Ackerl, J. Hainfellner, G. Widhalm, K. Dieckmann, A. Woehrer, M. Preusser and C. Marosi (2014). "The course of QOL and neurocognition in newly diagnosed patients with GBM." Neuro-Oncology 16: ii76.	Only reported quality of life. No cost evidence reported
Garcia Lopez, J. L., J. M. Rodriguez Barrios, J. Puig-Junoy and A. Carrato Mena (2014). "Cost-effectiveness analysis of bevacizumab, fotemustine and extended-dose temozolomide in patients with recurrent glioblastoma in Spain." Value in Health 17 (7): A638.	Conference abstract
Garside, R., M. Pitt, R. Anderson, G. Rogers, M. Dyer and S. Mealing (2007) "The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation (Structured abstract)." Health Technology Assessment Database, 1.	Interventions not relevant to the guideline

Study	Reason For Exclusion
Greanya, E. D., S. C. M. Taylor, F. Hu, J. Barnett and B. Thiessen (2004) "Temozolomide for malignant gliomas in British Columbia: a population-based cost-effectiveness analysis (Structured abstract)." Journal of Oncology Pharmacy Practice 10, 201-209.	Interventions not relevant to the guideline
Hall, M. D., J. L. McGee, M. C. McGee, K. A. Hall, D. M. Neils, J. D. Klopfenstein and P. W. Elwood (2014). "Cost-effectiveness of stereotactic radiosurgery with and without whole-brain radiotherapy for the treatment of newly diagnosed brain metastases." Journal of Neurosurgery 121 Suppl: 84-90.	Population included small cell lung cancer and therefore was not relevant to the populations considered in the guideline
Heinzel, A., D. Muller, K. J. Langen, M. Blaum, F. A. Verburg, F. M. Mottaghy and N. Galldiks (2013) "The use of O-(2-18F-fluoroethyl)-L-tyrosine PET for treatment management of bevacizumab and irinotecan in patients with recurrent high-grade glioma: a cost-effectiveness analysis (Provisional abstract)." Journal of Nuclear Medicine 54, 1217-1222.	Outcomes reported a cost per additional correct diagnosis. Not a cost utility study
Heinzel, A., S. Stock, K. J. Langen and D. Muller (2012) "Cost-effectiveness analysis of amino acid PET-guided surgery for supratentorial high-grade gliomas (Provisional abstract)." Journal of Nuclear Medicine 53, 552-558.	No quality adjusted outcomes reported
Heinzel, A., S. Stock, K. J. Langen and D. Muller (2012) "Cost-effectiveness analysis of FET PET-guided target selection for the diagnosis of gliomas (Provisional abstract)." European Journal of Nuclear Medicine and Molecular Imaging 39, 1089-1096.	Outcomes reported a cost per additional correct diagnosis. Not a cost utility study
Hirano, E., H. Fuji, T. Onoe, V. Kumar, H. Shirato and K. Kawabuchi (2014). "Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood." Journal of Radiation Research 55(2): 320-327.	Population not relevant to the guideline
Javier Cerezo, J., J. Espinosa de los Monteros, R. Villegas Portero, A. Llanos Mendez, R. Rodriguez Romero and J. Vivancos Garcia (2008) "Perfusion MR Imaging in differentiating brain gliomas. Meta-analysis and economic assessment (Structured abstract)." Health Technology Assessment Database.	No quality adjusted outcomes reported
Jenkinson, M. D., M. Javadpour, B. J. Haylock, B. Young, H. Gillard, J. Vinten, H. Bulbeck, K. Das, M. Farrell, S. Looby, H. Hickey, M. Preusser, C. L. Mallucci, D. Hughes, C. Gamble and D. C. Weber (2015). "The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: Study protocol for a randomised controlled trial." Trials 16 (1) (no pagination)(519).	Study protocol
Johannesen, T. B., J. Norum, K. Lote, D. Scheie and H. Hirschberg (2002) "A cost-minimising analysis of standard radiotherapy and two experimental therapies in glioblastoma (Structured abstract)." Radiotherapy and Oncology 62, 227-231.	Cost minimisation study
Kimmell, K., D. Sanchez and N. Marko (2014). "Cost effectiveness analysis of glioblastoma multiforme therapies." Neuro-Oncology 16: v181.	Conference abstract
Konski, A., P. Bracy, S. Weiss and P. Grigsby (1997) "Cost-utility analysis of a malignant glioma protocol (Structured abstract)." International Journal of Radiation Oncology, Biology, Physics 39, 575-578.	No quality adjusted outcomes reported

Study	Reason For Exclusion
Kotecha, R., S. Krishnan, J. H. Suh, E. S. Murphy, C. A. Reddy, G. Barnett, M. A. Vogelbaum, L. Angelov, A. Mohammadi, G. H. J. Stevens, D. Peereboom, M. Ahluwalia and S. T. Chao (2015). "Determining the optimal management of patients with limited-brain metastases: A cost analysis approach." International Journal of Radiation Oncology Biology Physics 1): E354.	No quality adjusted outcomes reported
Kwekkeboom, D. J., S. W. Lamberts, J. D. Habbema and E. P. Krenning (1996) "Cost-effectiveness analysis of somatostatin receptor scintigraphy (Structured abstract)." Journal of Nuclear Medicine 37, 886-892.	Interventions not relevant to the guideline
Lachaine, J., I. Benmouhoub and K. Mathurin (2015). "Economic Evaluations Of Glioblastoma." Value in Health 18(7): A461.	Conference abstract
Lam, T. C., A. Sahgal, E. L. Chang and S. S. Lo (2014). "Stereotactic radiosurgery for multiple brain metastases." Expert Review of Anticancer Therapy 14(10): 1153-1172.	Systematic review, included studies identified elsewhere
Lamers, L. M., R. Stupp, M. J. Bent, M. J. Al, T. Gorlia, J. B. Wasserfallen, N. Mittmann, J. S. Soo, R. Crott and C. A. Uyl-de Groot (2008) "Cost-effectiveness of temozolomide for the treatment of newly diagnosed glioblastoma multiforme: a report from the EORTC 26981/22981 NCI-C CE3 intergroup study (Provisional abstract)." Cancer 112, 1337-1344.	Not a cost utility study
Lester, S. C., G. B. Taksler, J. G. Kuremsky, J. T. Lucas, Jr., D. N. Ayala-Peacock, D. M. Randolph, 2nd, J. D. Bourland, A. W. Laxton, S. B. Tatter and M. D. Chan (2014). "Clinical and economic outcomes of patients with brain metastases based on symptoms: an argument for routine brain screening of those treated with upfront radiosurgery." Cancer 120(3): 433-441.	Not a cost utility study
Mabasa, V. H. and S. C. Taylor (2006) "Re-evaluation of the cost effectiveness of temozolomide for malignant gliomas in British Columbia (Provisional abstract)." Journal of Oncology Pharmacy Practice 12, 105-111.	Not a cost utility study
Macalalad, A., M. Sasane, J. Zhang, K. Culver, K. Dea, R. Nitulescu, E. Wu and A. Guerin (2014). "Symptomatic and economic burden of brain metastases in patients with ALK+ NSCLC." Neuro-Oncology 16: v36.	Not a cost utility study
Madden, J. R., M. S. Hemenway, N. K. Foreman and S. Z. Rush (2014). "How to do more with less: Outpatient chemotherapy." Neuro-Oncology 16: i110.	Not a cost utility study
Magnusson, A., A. C. Wallgren, E. Brekkan, M. Lonnemark, A. Karlsson-Parra and A. Laurell (2015). "Long-term survival in unfavorable-risk mRCC patients after intra-tumoral administration of a cell-based allogeneic vaccine adjuvant." Journal of Clinical Oncology. Conference 33(15 SUPPL. 1).	Not a cost utility study
Maher, O., S. Khatua and W. Zaky (2014). "Challenges and opportunities of molecularly targeted therapy in recurrent or refractory pediatric brain tumors." Neuro-Oncology 16: i142.	Patient population not relevant to the guideline

Study	Reason For Exclusion
Mailhot Vega, R., S. C. Formenti and S. MacDonald (2015). "Cost-effective analysis of proton therapy for breast irradiation." International Journal of Radiation Oncology Biology Physics 1): S91.	Patient population not relevant to the guideline
Mailhot Vega, R. B., J. Kim, M. Bussiere, J. Hattangadi, A. Hollander, J. Michalski, N. J. Tarbell, T. Yock and S. M. MacDonald (2013) "Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma (Provisional abstract)." Cancer 119, 4299-4307.	Patient population not relevant to the guideline
Mandilaras, V., N. Bouganim, J. Spayne, R. Dent, A. Arnaout, J. F. Boileau, M. Brackstone, S. Meterissian and M. Clemons (2015). "Concurrent chemoradiotherapy for locally advanced breast cancer-time for a new paradigm?" Current Oncology 22(1): 25-32.	Patient population not relevant to the guideline
Mandonnet, E., P. De Witt Hamer, J. Pallud, L. Bauchet, I. Whittle and H. Duffau (2014). "Silent diffuse low-grade glioma: Toward screening and preventive treatment?" Cancer 120(12): 1758-1762.	Not a cost utility stud.
Mansur, D. B. (2014). "Incorporating a compact proton therapy unit into an existing National Cancer Institute-designated comprehensive cancer center." Expert Review of Anticancer Therapy 14(9): 1001-1005.	Not a cost utility study
Marcus, L. P., B. A. McCutcheon, A. Noorbakhsh, R. P. Parina, D. D. Gonda, C. Chen, D. C. Chang and B. S. Carter (2014). "Incidence and predictors of 30-day readmission for patients discharged home after craniotomy for malignant supratentorial tumors in California (1995-2010)." Journal of Neurosurgery 120(5): 1201-1211.	No costs reported. Not a cost utility study
Markarian, A., M. De Lemos, L. Kovacic, K. Schaff and S. Walisser (2015). "Clinical outcomes of patients with gliomas treated with bevacizumab in British Columbia (BC)." Journal of Clinical Oncology. Conference 33(15 SUPPL. 1).	Not a cost utility study
Marshall, A. L. and J. M. Connors (2014). "Anticoagulation for noncardiac indications in neurologic patients: Comparative use of non-vitamin K oral anticoagulants, low-molecular-weight heparins, and warfarin." Current Treatment Options in Neurology 16 (9) (no pagination)(309).	No costs reported. Not a cost utility study
Marshall, D., L. Marcus, B. McCutcheon, S. Goetsch, J. Alksne, K. Ott, B. Carter, J. Hattangadi, T. Koiso, M. Yamamoto and C. Chen (2015). "Survival patterns of patients with cerebral metastases who underwent multiple rounds of stereotactic radiosurgery (SRS)." Neuro-Oncology 17: v46.	No costs reported. Not a cost utility study
Marshall, D. C., T. Kim, S. Goetsch, J. Alksne, K. Ott, D. Hodgens, B. Carter, J. Hattangadi-Gluth and C. Chen (2015). "Survival patterns of patients with cerebral metastases after multiple rounds of stereotactic radiosurgery (SRS)." Journal of Neurosurgery 123 (2): A539-A540.	No costs reported. Not a cost utility study
Martikainen, J. A., A. Kivioja, T. Hallinen and P. Vihinen (2005) "Economic evaluation of temozolomide in the treatment of recurrent glioblastoma multiforme (Structured abstract)." Pharmacoeconomics 23, 803-815.	Interventions not relevant to the guideline

Study	Reason For Exclusion
Mayr, N. A., W. T. Yuh, M. G. Muhonen, D. J. Fisher, H. D. Nguyen, J. C. Ehrhardt, B. C. Wen, J. F. Doornbos and D. H. Hussey (1994) "Cost-effectiveness of high-dose MR contrast studies in the evaluation of brain metastases (Structured abstract)." American Journal of Neuroradiology 15, 1053-1061.	Not a cost utility study
Medina, L. S., K. M. Kuntz and S. Pomeroy (2001) "Children with headache suspected of having a brain tumor: a cost-effectiveness analysis of diagnostic strategies (Structured abstract)." Pediatrics 108, 255-263.	Patient population not relevant to the guideline
Mehta, M., W. Noyes, B. Craig, J. Lamond, R. Auchter, M. French, M. Johnson, A. Levin, B. Badie, I. Robbins and T. Kinsella (1997) "A cost-effectiveness and cost-utility analysis of radiosurgery vs resection for single-brain metastases (Provisional abstract)." International Journal of Radiation Oncology, Biology, Physics 39, 445-454.	No quality adjusted outcomes reported
Messali, A., J. W. Hay and R. Villacorta (2013) "The cost-effectiveness of temozolomide in the adjuvant treatment of newly diagnosed glioblastoma in the United States (Provisional abstract)." Neuro-Oncology 15, 1532-1542.	Interventions not relevant to the guideline
Messali, A., R. Villacorta and J. W. Hay (2014). "A review of the economic burden of glioblastoma and the cost effectiveness of pharmacologic treatments." Pharmacoeconomics 32(12): 1201-1212.	Not a cost utility study
Mohler, A., D. Ney, L. Gaspar, D. Damek, B. Kavanagh, K. Reddy and C. Chen (2015). "Health-related quality of life (HRQoL) in a phase II trial of hypofractionated intensity-modulated radiation therapy (hypo-IMRT) with temozolomide (TMZ) and bevacizumab (BEV) for patients with newly diagnosed glioblastoma multiforme (GBM)." Neuro-Oncology 17: v191.	Conference abstract
Mueller-Riemenschneider, F., C. Schwarzbach, A. Bockelbrink, I. Ernst, C. Vauth, S. N. Willich and J. M. G. v. d. Schulenburg (2009) "Medical and health economic assessment of radiosurgery for the treatment of brain metastasis (Structured abstract)." Health Technology Assessment Database.	Not a cost utility stud.
Nieder, C., J. Norum, J. G. Stemland and A. Dalhaug (2010) "Resource utilization in patients with brain metastases managed with best supportive care, radiotherapy and/or surgical resection: a Markov analysis (Provisional abstract)." Oncology 78, 348-355.	Only costs reported
Norum, J. (1996) "Radiotherapy costs in glioblastoma: a cost effective analysis (Structured abstract)." Oncology Reports 3, 777-780.	Only costs reported.
Price, S. J. (2014). "A meta-analysis of the diagnostic ability, efficacy, safety and cost effectiveness of 5-aminolevulinic acid guided resection of high grade gliomas." Neuro-Oncology 16: vi13.	Conference abstract
Rogers, G., R. Garside, S. Mealing, M. Pitt, R. Anderson, M. Dyer, K. Stein and M. Somerville (2008) "Carmustine implants for the treatment of newly diagnosed high-grade gliomas: a cost-utility analysis (Structured abstract)." PharmacoEconomics 26, 33-44.	Interventions not relevant to the guideline

Study	Reason For Exclusion
Rupa, V., A. Job, M. George and V. Rajshekhar (2003) "Cost-effective initial screening for vestibular schwannoma: auditory brainstem response or magnetic resonance imaging? (Structured abstract)." Otolaryngology - Head and Neck Surgery 128, 823-828.	Patient population not relevant to the guideline
Rutigliano, M. J., L. D. Lunsford, D. Kondziolka, M. J. Strauss, V. Khanna and M. Green (1995) "The cost effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of solitary metastatic brain tumors (Structured abstract)." Neurosurgery 37, 445-453.	Not a cost utility study
Savitz, S. T., R. C. Chen and D. J. Sher (2015). "Cost-effectiveness analysis of neurocognitive-sparing treatments for brain metastases." Cancer 121(23): 4231-4239.	Not a cost utility study
Voigt, J. D. and G. Barnett (2016). "The value of using a brain laser interstitial thermal therapy (LITT) system in patients presenting with high grade gliomas where maximal safe resection may not be feasible." Cost Effectiveness & Resource Allocation 14: 6.	Interventions not relevant to the guideline
Vuong, D. A., D. Rades, A. T. Eck, G. A. Horstmann and R. Busse (2013) "Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: stereotactic radiosurgery versus surgical resection (Provisional abstract)." Clinical Neurology and Neurosurgery 115, 276-284.	Analysis not performed from an OECD country's perspective
Vuong, D. A., D. Rades, A. N. Le and R. Busse (2012) "The cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of brain metastasis in Vietnam from the perspective of patients and families (Provisional abstract)." World Neurosurgery 77, 321-328.	Analysis not performed from an OECD country's perspective
Weber, D. C. and C. H. Combescure (2014). "How useful and valid are cost effectiveness studies for the treatment of cancer with proton beam therapy?" Radiotherapy and Oncology 111: S131-S132.	Not a cost utility study
Ye, J. C., M. Yondorf, S. C. Pannullo, J. A. Boockvar, P. E. Stieg, T. H. Schwartz, R. J. Scheff, B. Parashar, D. Nori, K. Chao and A. Wernicke (2014). "Cost-effective analysis of hypofractionated versus standard 30-fraction IMRT in patients with poor prognosis glioblastoma multiforme." International Journal of Radiation Oncology Biology Physics 1): S589.	Conference abstract
Yondorf, M., B. Parashar, D. Nori, K. S. C. Chao, J. A. Boockvar, S. Pannullo, P. Stieg, T. H. Schwartz and A. G. Wernicke (2014). "The cost-effectiveness of surgical resection (s) and cesium-131 (CS-131) intra-operative brachytherapy versus s and stereotactic radiosurgery (SRS) versus s and whole brain radiotherapy (WBRT) versus WBRT in the treatment of metastatic brain tumors." Journal of Radiation Oncology 3 (2): 240.	Paper identical to study already included in evidence review

1