National Institute for Health and Care Excellence

Final

Melanoma: assessment and management

[G] Evidence review for the follow-up of people with melanoma

NICE guideline NG14

Evidence reviews underpinning recommendations 1.9.1 to 1.9.15 and research recommendations in the NICE guideline

July 2022

Final

These evidence reviews were developed by Guideline Updates Team

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1 Surveillance of people with melanoma

1.1 Review questions

RQ 6.1 What is the optimal method, frequency, setting and duration of follow-up for stage I-III melanoma?

RQ 6.2 What is the diagnostic accuracy of body imaging for re-staging during the follow-up of people melanoma?

RQ 6.3 Should brain imaging be included for people with melanoma who are undergoing body imaging as part of follow-up, and who have no neurological signs or symptoms?

RQ 6.4 What is the effectiveness of body imaging for the follow-up of people with stage 4 (and unresectable stage 3) melanoma after concluding treatment, including the optimal frequency and duration?

1.1.1 Introduction

There has been longstanding uncertainty surrounding the optimal surveillance strategies for people with melanoma after completion of treatment. In 2015, NICE recommended that imaging only be considered in stage III disease and higher (or stage IIC disease if the person has not had a sentinel lymph node biopsy [SLNB]). However, the exact role imaging should play in these stages was unclear, particularly for people with high-risk stage II disease (IIB-C) for which evidence shows poor long-term survival.

NICE also recommended a stage-stratified follow-up for clinic visits for stages I-III. However, these recommendations were made on very little evidence and needed to be re-evaluated following the introduction of adjuvant therapies to the treatment of stage III disease and recent changes to how melanoma is staged in the AJCC 8th edition. There was little guidance for the follow-up of stage IV (and unresectable stage III) disease.

The role of ultrasound during follow-up also needed clarifying. Ultrasound is better than alternative modalities at detecting lymph node recurrence but there has been uncertainty as to whether its use leads to improved outcomes such as mortality and distant disease progression.

The 2015 update also recommended that the brain be included as part of imaging for the staging of people with suspected stage IV melanoma and to consider imaging the brain as part of follow-up for all people with melanoma. These recommended were made on very limited evidence and needed to be updated to consider whether a wider range of people (particularly people with stage III melanoma) deemed to be at sufficiently high risk for brain metastases (BM) would benefit from a brain scan. Additionally, clinical practice would benefit from more prescriptive recommendations around how and when imaging of the brain should be conducted during follow-up. Finally, the diagnostic accuracy of different brain imaging modalities for detecting brain metastases is unclear. NICE recommended the use of CT for brain imaging in adults and MRI in children. MRI is thought to be more accurate but is also more costly.

Review questions 6.1 and 6.4 attempted to establish whether different follow-up strategies (less intensive compared to more intensive) identify more recurrences, identify recurrences earlier/later or impact differentially on quality of life. It also looked at the risk of recurrence over time for difference stages and how this is affected by the presence of risk factors (such as ulceration and a high mitotic rate). This review question focused on the follow-up of stages I-III following surgery and/or conclusion of treatment.

Review question 6.2 assessed the diagnostic accuracy of imaging strategies for detecting recurrence or spreading of melanoma in stage IIB-III melanoma in the following scenarios:

- during surveillance in asymptomatic patients
- in those people suspected of recurrence
- for re-staging after completing treatment/surgery

Review question 6.3 assessed the diagnostic accuracy of different imaging modalities in detecting brain metastases. Additionally, it aimed to identify those people at greater risk of brain metastases, who would therefore benefit most from additional investigations of the brain.

Review question 6.4 focused on stage IV (and unresectable III) disease and incorporated all elements covered in questions 6.1 and 6.2.

For the purposes of this review, questions 6.1 and 6.4 were combined into a single search looking at risk factors and patterns of recurrence and/or survival across all stages of melanoma. Review question 6.2 focused specifically on diagnostic accuracy of different imaging modalities and strategies during follow-up and 6.3 looked specifically at the development of brain metastases (and included analyses of both risk factors and diagnostic accuracy for detecting brain metastases). See the PICO below for further information.

1.1.2 Summary of the protocol

Table 1 PICO table for body imaging for follow-up of melanoma

	6.1	6.2	6.3	6.4
Population	Resected I-III	IIB-III	III-IV	IV; or unresectable III
Intervention/ risk factors/ Index tests	Interventions assessed in RCTs: • Intensive follow-up (as defined by study) Predictors: • Age • Gender • Location of primary tumour • Lymph node status • Number of positive lymph nodes • Ulceration • Breslow thickness • ECOG performance status • Lymphovascular invasion • Externally validated nomograms using at least one of the above risk factors	• Computed tomography (CT) • Positron emission tomography-computed tomograph (PET-CT) • Whole body magnetic resonance imaging (MRI) • Ultrasound (US)	Imaging modalities: • Body imaging with brain imaging • Body imaging without brain imaging • Brain CT scan • Brain MRI scan Predictors: • Disease stage • Primary tumour location • Age • Gender • Ulceration • Mitotic rate • Breslow thickness	*See 6.1 and 6.2*
Comparator/ Reference standard	RCTs: • Less intensive follow-up (as defined by study) Prognostic studies:	• Fine needle aspiration cytology (FNAC) • Clinical observation,	Diagnostic accuracy studies: • As defined by study	• See 6.1 and 6.2

	• none	clinical examination (healthcare practitioner and patient examination) or patient reported follow-up • Combination of one or more reference standards	Prognostic accuracy studies: • none	
Outcomes	RCTs: • Quality of life • All-cause mortality • Melanoma-specific mortality • Adverse events • All recurrences • Distant recurrences Prognostic studies: • All recurrences • Distant recurrences • All-cause mortality • Cancer specific mortality • Melanoma-specific mortality	• Sensitivity • Specificity • Likelihood ratios	Diagnostic accuracy studies: • Sensitivity • Specificity • Likelihood ratios Prognostic accuracy studies: • All recurrences • Distant recurrences • All-cause mortality • Cancer specific mortality • Melanoma-specific mortality	• See 6.1 and 6.2

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Sensitivity analyses sequentially removing studies based on whether they received adjuvant therapy following surgical resection demonstrated that overall, the use of adjuvant therapy did not have a major impact on the relative risk of recurrence for each of the predictive factors.

Where studies provided data separately for those receiving and those not receiving adjuvant therapy – such as those RCTs comparing an adjuvant therapy to placebo – these data were entered on separate lines in the analysis.

The outcome of recurrence could be broken down into site of recurrence (local, in-transit, regional or distant), time of recurrence after relapse, symptomatic recurrence, and asymptomatic recurrence.

Prognostic data for each variable were reported in a variety of different formats. For the purposes of this review, the following forms of data were included but not combined with each other in meta-analysis:

- Event data: this will be used for risk ratios.

- Unadjusted hazard ratios.
- Adjusted hazard ratios: adjusted hazard ratios were not entered into meta-analysis as all studies adjusted for different characteristics.

Protocol deviation

For review question 6.2 concerning the diagnostic accuracy of imaging to detect recurrences, the protocol did not specify that the review look at data specific to lymph node recurrences. Additionally, the search was limited to the time of the previous update of this NICE guideline (2015) up to the present day (2021). However, the committee identified that decisions surrounding whether ultrasound surveillance (USS) should be recommended during follow-up relied on evidence that it is more sensitive at detecting lymph node recurrences than other modalities (particularly CT scans). The committee agreed that this needed to be established by a systematic search for evidence, and that the exact difference in sensitivity between modalities also needed to be established to aid decision making.

The committee identified the need for two further deviations. Firstly, there were the two studies contained within evidence review D, which assessed the use of CLND in people with a positive SLNB. These were important to discussions surrounding follow-up as they provided data on lymph node recurrences in people undergoing USS, and when these recurrences occurred. Secondly, case series were included if they reported data on recurrence rates following resection specifically in people with stage IIB-C melanoma. The committee needed to know the relative severity of disease in these stages compared to stage III disease (which is more clearly understood due to there being several large clinical trials in this stage). Additionally, this data helped to identify how frequently recurrences were asymptomatic in these stages, and could therefore benefit from routine imaging surveillance.

A separate search (see appendix B) was conducted looking specifically for meta-analyses of imaging to detect lymph node recurrences during the follow-up of people with melanoma.

1.1.4 Clinical evidence

1.1.4.1 Included studies

A systematic literature search was conducted for this review on optimal surveillance strategy during follow-up. This returned 12,300 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocols, 12,139 references were excluded, and 161 references were ordered for screening based on their full texts.

Of the 161 references screened as full texts, 82 references reporting on 73 unique studies were included:

- 39 references were included in the review for 6.1
- 15 references were included in the review for 6.2
- 13 references were included in 6.3
- 6 references were included in 6.4

Additionally, 8 references were included in this review which did not meet the review protocol for inclusion. These references were highlighted by the committee to help inform discussion as they report data on the frequency and timing of recurrences in key groups of people, such as those with specific stages of disease and rates of specifically lymph node recurrence.

Re-run searches identified an additional 14 references for inclusion (12 pertained to risk factors during follow-up and 2 assessed diagnostic accuracy of imaging for detecting recurrences).

The clinical evidence study selection is presented as a diagram in appendix C.

1.1.4.2 Excluded studies

See Appendix J for a list of references for excluded studies, with reasons for exclusion.

1.1.5 Summary of studies in clinical evidence review

1.1.5.1 RQ 6.1 Risk factors after I-III disease

1.1.5.2 Nomograms

Table 2 Summary of studies included in the analysis of prognostic nomograms

Nomogram	Relevant risk factors	Validation population	Study names (sample size)	Outcomes
EORTC	• Ulceration • Location • Breslow thickness	Sentinel lymph node (SLN) negative (stage I-II)	El-Sharouni 2021 (8,795) Ipenburg 2019 (4,235)	• Recurrences • Overall survival
EORTC-DeCOG	• Ulceration • Age • Tumour burden • Breslow thickness	SLN positive (stage III)	Verver 2020 (692)	• Recurrences (all and distant-only) • Overall survival

Risk factors after stage I-II disease

Table 3 Summary of studies included in the analysis of risk factors for lower risk (stage I-II) resected disease

Study	Stage	Follow-up (average)	Design	Sample	Imaging surveillance	Risk of bias	Notes
Berger 2017	II	5 years	retrospective	581	Unclear, at physician's discretion	Moderate	Limited data reporting, no adjustment
Bertolli 2019	II SLN negative	5 years	retrospective	1,213	Unclear	Moderate	Unclear follow-up, inadequate adjustment
Bleicher 2020	II	5 years	retrospective	580	Physician's discretion	Moderate	Inadequate adjustment
Brecht 2015	I-IV	5 years	retrospective	443	unclear	High	84.2% stage I-II
Echaniq ue 2021	SLN negative	1 year	retrospective	154	unclear	Moderate	-
Egger 2016	II SLN negative	6 years	RCT data	1,998	unclear	Moderate	Unclear surveillance
Garbe 2003	I-IV	2 years	retrospective	2,008	I-II: annual Ab sonography + chest x-ray III: Bi-annually	High	All stages No adjustment

Study	Stage	Follow-up (average)	Design	Sample	Imaging surveillance	Risk of bias	Notes
Hofmann 2002	I-III	4 years (variance between stages)	retrospective	630	I-II: annual Abdomen X-ray / sonography + bi-annual sonography of lymph nodes III: unclear	High	Follow-up variance. No adjustment
Kim 2020	HNM I-IV	unclear	retrospective	191	unclear	High	Disease stage not captured. Unclear follow-up. Inadequate adjustment.
Kim 2021	SLN- <1mm BT	5 years	retrospective	209	unclear	Low	-
Laks 2017	II SLN negative	4 years	retrospective	265	unclear	Moderate	Limited adjustment. Unclear follow-up
Meyers 2009	II-III SLN negative	4 years	retrospective	118	Recommended annual body/brain imaging for III	Moderate	No adjustment
Mooney 1998	I-II	Up to 15 years (large variance)	retrospective	1,004	Unclear	High	No adjustment unclear follow-up
Namin 2019	I-II head/neck	7 years	retrospective	168	unclear	Moderate	Adjusted but unclear follow-up
Oh 2020	I-II	3-4 years	retrospective	340	unclear	Moderate	No adjustment
Poo-Whu 1999	I-II	5 years	retrospective	419	I-II: annual chest X-rays III: Bi-annual + baseline CT (with a second CT at 6-12 m if abnormal)	Moderate	No adjustment
Tas 2019	I-III	5 years	retrospective	1,087	Unclear, NCCN were recommended	Moderate	No adjustment
Verver 2018	SLN-	6 years	retrospective	3,220	Unclear	Moderate	Unclear surveillance
Yang 2019	I-IV	5 years	retrospective	77,509	Unclear	Moderate	Unclear surveillance and

Study	Stage	Follow-up (average)	Design	Sample	Imaging surveillance	Risk of bias	Notes
							missing data
Yang 2020	15-40 years old resected disease I-IV	5 years	retrospective	19,887	Unclear	Moderate	Unclear surveillance and missing data

Risk factors after stage III disease

Table 4 Summary of studies included in the analysis of risk factors for higher risk (stage IIB and above) resected disease

Study	Stage	Adjuvant therapy use	Follow-up	Design	Sample	Imaging surveillance	Bias (Notes)
Barbour 2015	IIIB/C Macro head/ neck	No	5 years	Retro-spective	173	Freq. clinic visits but imaging only if symptomatic	Moderate (No adjustment)
Baum 2017	SLN positiv e	Unclear	Median 53 months	Retro-spective	96	Unclear	Moderate (Unclear bias, no adjustment)
Bloemen dal 2019	IIIB/C	Took place between surgery and starting adj tx.	12 weeks followin g surgery	Retro-spective	120	Imaging done before starting adjuvant therapy	Moderate (No adjustment)
BRIM-8	IIC-IIIC BRAF +	vemu or none	3 years	RCT	498	CE-CT/MRI of chest, ab, and pelvis every 13 weeks for 2y then every 26 w	Low (Arms entered separately)
CHECK MATE 238	IIIB-IV	ipi/nivo	4 years	RCT	906	CT of neck, chest, ab, pelvis + limb, MRI/CT of brain every 12w for first 2y then every 6 m	Low (Both arms combined)
COMBI-AD	IIIA (>1mm)-C BRAF +	dab+tram or placebo	3 years	RCT	870	Imaging every 3m for 1y then every 6m	Low (Arms entered separately)
EORTC 18071	IIIA (>1mm)-C BRAF +	ipi or placebo	3 years	RCT	951	When clinically indicated	Low (Both arms combined)
Grotz 2014	III	GMCSF or placebo	4 years (high	Retro-spective	317	Physician's discretion	Moderate (inadequate adjustment

Study	Stage	Adjuvant therapy use	Follow-up	Design	Sample	Imaging surveillance	Bias (Notes)
			variance)				or standard FU)
Huang 2020	IB-IIC	SLN+	2 years	Retro-spective	530	unclear	Moderate Limited adjustment. Unclear follow-up
Ibrahim 2020	IIB-III	75% no	5 years	Retro-spective	353	Recommended every 6-12m for IIB-C and 6m for III	Moderate (No adjustment)
IMMUNED	IV	ipi+nivo or placebo	2 years	RCT	167	CT or MRI every 12 weeks for 3 years	Low (Placebo entered separately to adj)
Jang 2020	IIB-IIIA	Unclear	5 years	Retro-spective	1,316	Unclear	Moderate (Adjusted but unclear FU)
KEYNOTE-054	IIIA (>1mm)-C BRAF +	pembro or placebo	3 years	RTC	1,019	CT+MRI full chest, ab, Pelvis. Neck CT and/or MRI head + neck every 12w for first 2y then every 6m	
Lee 2017	II	Unclear	Up to 18 years	Retro-spective	738	CT/chest x-rays performed in asymptomatic patients at physician's discretion	Moderate (No adjustment)
Lim 2018	IIB-IIIC	Unclear	Median 23.3 months	Retro-spective	173	Imaging done at 6 monthly intervals for 3 years then annually to 5 years	Moderate (No adjustment)
Madu 2016/2017	IIIB/C	No	Up to 10y (large variance)	Retro-spective		MRI brain and whole-body PET/CT or CT if symptomatic or elevated tumour markers	Low (Multivariate model)
Najjar 2019	IIB-IV	vaccine	17/12 years	2 RCTs	1,916	Unclear	Low (Uses ECOG database for long term FU)
Podlipnik 2016	IIB-III	Unclear	Median 2.5 years	Pro-spective	290	Unclear	Moderate (No adjustment)
Tan 2019	IIC-IIIA	47% IIC/ 69% IIIA	6 years	Retro-spective	128	Unclear	Moderate (Adjusted

Study	Stage	Adjuvant therapy use	Follow-up	Design	Sample	Imaging surveillance	Bias (Notes)
							analyses but unclear reporting and unclear follow-up)
Turner 2020	III	No	5 years	Retro-spective	332	6- or 12-monthly PET/CT	Moderate (No adjustment)

1.1.5.2 RQ 6.2 Diagnostic accuracy of imaging for routine follow-up of high-risk melanoma

Study	Follow-up	Stage	design	Reason for scan	Surveillance strategy	Scans	Recur-rences / TP (%)	#scans asymp atic recurr
Vensby 2017	3 years	Unclear	Retro-spective	Routine follow-up (some scans may have been due to suspected recurrence)	Unclear; Recommended every 3-12m	352	49 (13.9%)	7.2
Lee 2018	Unclear	IIB-IV	Retro-spective	Routine follow-up (some scans may have been due to suspected recurrence)	Unclear; Recommended every 3-12m	29	6 (20.7%)	4.8
Stahlie 2020	3 years	IIIB-C	Pro-spective	Routine follow-up	Every 6m for 2yr, then at 3yr	105	12 (11.4%)	8.8
Helvind 2021	1.5 years median	IIB-III	Pro-spective	Routine follow-up	Every 6m for 2yr, then at 3yr	243	54 (17.7%)	5.7
Leon-ferre 2017	5 years	III-IV	Retro-spective	Routine follow-up (some scans may have been due to suspected recurrence) Unclear if asymptomatic at time of scan	Routine PET/CT in intervals at physician's discretion	1,687	93 (5.5%)	18.1

1.1.5.3 RQ 6.3 Brain imaging

Diagnostic accuracy

Table 5 Summary of included diagnostic accuracy studies characteristics

Author (year)	Stage	Sample size	Aim	Prevalence of BM	Risk of bias
Abdel-Rahman (2019)	I-III	109,971	SEER database containing data on people with melanoma and whether or not they had brain metastases at diagnosis. Study aimed to assess how many people with brain metastases would be captured if using a strategy of only considering imaging for stages IIIC or higher	I-IIIB: 0.2% IIIC: 1.7%	High *Limitations with index test and reference standard*
Lewin (2018)	III	156	Assessed the accuracy of the below surveillance strategy for detecting relapse in stage III patients: IIIA: PET scans at 6 and 18 months; IIIB/C: 6 monthly PET scans for first 2 years + scan at 36 months. IIIC: MRI brain recommended at 6 and 12 months.	3% (only 1/5 was asymptomatic)	High *Limitations with index test and reference standard*
Aukema (2010)	IIIB-C	70	Assessed the diagnostic accuracy of total body PET/CT and brain MRI imaging in the staging of palpable, lymph node metastatic patients.	7.1%	Moderate *Insufficient reference standard*

Risk factors for the development of brain metastases

Table 6 Summary of included prognostic accuracy studies characteristics

Author (year)	Stage	Population	Location	Follow-up	Prevalence of BM	Risk of bias (applicability)
Daryanani (2005)	I-III	324 Head/neck melanoma	Single centre in The Netherlands	Median 2 years	8.0%	Moderate *Unclear when brain imaging would have been conducted.* (Partially applicable: stage I-III)
Haydu (2020)	III	1,918	MD Anderson / MIA databases (1998-2014)	10 years	16.7% 5.7% had CNS involvement in their first distant presentation (42.2% of which were asymptomatic)	Low (directly applicable)
Huismans (2018)	I-II	1,686	MIA database (1980-2000)	10 years or development of brain	7.4%	Moderate *Unclear follow-up protocol, limited reporting*

Author (year)	Stage	Population	Location	Follow-up	Prevalence of BM	Risk of bias (applicability)
				metastases		(partially applicable: patients were stage I-II)
Frankel (2014)	I-III who developed IV during follow-up	607	2 USA centres	10 years (average not reported)	20.0%	Moderate *confounders not adequately adjusted for* (Partially applicable: patients were stage I-III)
Qian (2013)	I-IV	2,341	USA MCG/IMCG databases	10 years (median 98 months)	9.5%	Moderate *Confounders not adequately adjusted for; unclear follow-up protocol* (Partially applicable: patients were stage I-III)
Peuvrel (2014)	III-IV	86	BRAF-positive and treated with vemurafenib	Median 9 months (1-26 months)	19.8%	Moderate *no adjustment or confounders* (Directly applicable)
Samlowski (2017)	IIIAN2a-IIIC	402	Participants in RCT comparing biochemotherapy to HDI;	10 years; Suggested patient imaging included a brain CT or MRI every 3 months	14.7%	Low (Directly applicable)
Wang (2014)	Unresectable, chemotherapy naïve IV	685	Clinical trials of systemic therapies between 1986 and 2004	60 weeks	46.0%	Moderate *No adjustment for treatments received in difference trials* (Directly applicable)
Zhang (2019)	IV	4,369	SEER 2010 - 2015	N/A	35.4%	High *key factors not captured by database. Not all participants underwent scan*

Author (year)	Stage	Population	Location	Follow-up	Prevalence of BM	Risk of bias (applicability)
						Directly applicable
Zukauskaite (2013)	IV asymptomatic for brain metastases	763	Patients entering IL-2 trial and received baseline brain scan	N/A	11.5%	Low Directly applicable

1.1.5.4 RQ 6.4 Risk factors for IV disease (or unresectable III)

Table 7 Summary of studies included in the analysis of risk factors for follow-up of stage IV (and unresectable stage III) disease

Study	Stage	Arms extracted for this review	Design	Sample	Risk of Bias (Notes)
CHECKMATE 37	Unresectable IIIC; or IV	Following arms were combined: -nivo	RCT	271	Low
CHECKMATE 64	Unresectable III; or IV	Following arms were combined: -nivo then ipi -ipi then nivo	RCT	138	Low
CHECKMATE 67	Unresectable III; or IV	Following arms were combined: -nivo+ipi -nivo -ipi	RCT	945	Low
COLUMBUS	Unresectable IIIB, IIIC; or IV	Following arms were combined: -enco+bini -vemu	RCT	380	Low
Faries 2017	Resected IV	Data comes from 4 adjuvant vaccine trials	RCT	496	Low
KEYNOTE-002	Unresectable III; or IV	Following arms were combined: -investigators choice of chemo -pembro 2mg	RCT	359	Moderate (Potential for confounders due to treatment effects)

1.1.6 Summary of the evidence

The below tables represent brief summaries of the GRADE tables found in appendix F. The interpretations of risk ratio evidence are as follows:

- Could not differentiate: 95% confidence intervals cross 1 and contain 0.8 and/or 1.25.
- Effect (more of outcome in one arm than the other): 95% confidence intervals.
- No difference: 90% confidence intervals are contained between 0.8 and 1.25.

The interpretation of hazard ratio evidence are as follows:

- Could not differentiate: 95% confidence intervals cross 1.
- Effect (more of outcome in one arm than the other): 95% confidence intervals do not cross 1.

Risk-stratified follow-up of IB-IIC melanoma

Table 8 Summary of GRADE tables for MelFo studies assessing efficacy of risk stratified follow-up of IB-IIC disease

Overview	Trial	Outcome	Risk ratio	Interpretation (quality of evidence)
Both studies followed patients for 3 years and randomised to follow-up in accordance with either: 1. National guidelines 2. Risk stratified follow-up (at a reduced frequency compared to both national guidelines, particularly for earlier stages) **Risk-stratified protocol** *Stage* / **Year 1** / **Year 2** / **Year 3** / **Year 4** / **Year 5** IB: 1 / 1 / 1 / 1 / 1 IIA: 2 / 2 / 1 / 1 / 1 IIB: 3 / 3 / 2 / 1 / 1 IIC: 3 / 3 / 2 / 1 / 1	UK	Recurrence	RR 1.05 (0.56, 1.97)	Could not differentiate *(low)*
		All-cause mortality	RR 0.81 (0.35, 1.87)	Could not differentiate *(low)*
		Missed visits (year 1)	RR 0.23 (0.09, 0.57)	Fewer missed visits if risk-stratified *(high)*
		Missed visits (years 2-3)	RR 1.10 (0.47, 2.60)	Could not differentiate *(low)*
		Extra visits (year 1)	RR 2.34 (1.22, 4.48)	More unplanned visits if risk-stratified *(high)*
		Extra visits (years 2-3)	RR 1.52 (0.84, 2.74)	Could not differentiate *(moderate)*
		Quality of life measures: Could not differentiate between arms on any scale.		
	Dutch	Recurrence	RR 1.60 (0.76, 3.38)	Could not differentiate *(low)*
		All-cause mortality	RR 1.07 (0.42, 2.72)	Could not differentiate *(low)*
		Missed visits	RR 0.59 (0.18, 1.91)	Could not differentiate *(low)*
		Extra visits	RR 2.67 (1.21, 5.87)	More unplanned visits if risk-stratified *(high)*
		Quality of life measures: lower stress response symptoms but could not differentiate state-trait anxiety, cancer-worry or RAND-36 scales.		

Risk factors during follow-up of stage I-III disease (resected)

Nomograms

Table 9 Summary of studies included in the analysis of prognostic nomograms

Nomogram	Population (for validation)	Outcome	C-statistic	Quality of evidence
EORTC	SLN negative	All recurrences	0.70 (0.68, 0.71)	Low
			0.69 (0.67, 0.71)	Low
		Overall survival	0.69 (0.66, 0.72)	Low
EORTC-DeCOG	SLN positive	All recurrences	0.70 (0.67, 0.74)	Low
		Distant progression	0.72 (0.68, 0.75)	Low
		Overall survival	0.74 (0.71, 0.78)	Moderate

- *Male gender*

Table 10 Male gender as prognostic factor during follow-up

Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation (quality of evidence)
Unadjusted meta-analyses						
14	4,237	IIB-III	RR 1.14 (1.06, 1.22)	-	-	No difference *(high)*
6	Up to 2,589	I-II	RR 1.40 (1.25, 1.57)	-	-	Increased risk *(moderate)*
Analyses with adjustment for confounders						
Jang 2020	1,174	IIB-C	OR 0.88 (0.68, 1.15)	-	-	Could not differentiate *(low)*
Jang 2020	142	IIIA	OR 0.46 (0.21, 0.99)	-	-	Females at higher risk. *(low)*
Grotz 2014	317	III	HR 2.38 (1.56,3.64)	HR 2.38 (1.56,3.64)	-	Males at higher risk *(low)*
Egger 2016	1,998	SLN negative	HR 1.03 (0.80, 1.33)	HR 1.09 (0.80, 1.50)	HR 1.22 (0.97, 1.55)	Could not differentiate *(low)*
Analyses without adjustment for confounders						
Turner 2021	332	III	-	RR 0.95 (0.69, 1.31)	-	Could not differentiate *(very low)*
Tan 2019	129	IIC-IIIA	-	HR 0.89 (0.46–1.73)	HR 0.65 (0.36–1.23)	Could not differentiate *(low)*
Berger 2017	581	II	-	-	RR 1.45 (1.14, 1.84)	Increased risk *(low)*

Age

Table 11 Age as prognostic factor during follow-up

Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation
Unadjusted meta-analyses						
12	3,567	IIB-III	RR 0.87 (0.80, 0.94)	-	-	No difference *(high)*
2	924	I-II	RR 0.87 (0.77, 0.99)	-	-	No difference *(low)*
Analyses with adjustment for confounders						
Madu 2016	183	IIIB	HR 0.63 (0.43, 0.93)	-	HR 0.59 (0.35–0.99)	Increased risk if older age *(high)*
Egger 2016	1,998	SLN negative	HR 0.67 (0.50, 0.89)	HR 1.51 (1.07, 2.18)	HR 0.71 (0.54, 0.92)	Increased risk if older age *(moderate)*
Laks 2017	273	SLN negative	-	HR 1.04 (1.02,1.05) Per year	-	Increased risk if older age *(moderate)*
Analyses without adjustment for confounders						
Tan 2019	128	IIC-IIIA	-	HR 0.51 (0.26–1.00)	HR 0.19 (0.09, 0.40)	Increased risk if older age *(moderate)*
Ibrahim 2020	353	IIB-III	-	-	HR 0.99 (0.98, 1.01) *Post recurrence survival (per year)*	Could not differentiate *(low)*
Madu 2017	205	IIIC	HR 1.00 (0.99–1.01) Per year	-	HR 0.99 (0.98-1.01) per year	Could not differentiate *(low)*
Barbour 2015	107	IIIB/C	RR 0.48 (0.31, 0.76)	-	-	Increased risk if older age *(moderate)*

Breslow thickness

Table 12 Breslow thickness as prognostic factor during follow-up

Studies	Sample	Stage	Comparison	Recurrence	Distant recurrence	Mortality	Interpretation
Unadjusted meta-analyses							
5	1,583	I-II	≥4 vs <4mm:	RR 2.17 (1.57, 2.98)	-	-	Increased risk if ≥4mm *(very low)*
Analyses with adjustment for confounders							
Jang 2020	1,174	IIB-IIC	T4 v T3	OR 1.92 (1.44, 2.54)	-	-	Increased risk if T4 *(moderate)*
Jang 2020	142	IIIA	T4 v T3	OR 1.31 (0.58, 2.99)	-	-	Increased risk if T4 *(moderate)*

Studies	Sample	Stage	Comparison	Recurrence	Distant recurrence	Mortality	Interpretation
Grotz 2014	317	III	Per mm	-	-	HR: 1.1 (1.02,1.18)	Increased risk with each mm *(moderate)*
Egger 2016	1,998	SLN negative	≥2 v <2mm	HR: 1.84 (1.42, 2.38)	HR: 1.92 (1.41, 2.62)	HR: 1.90 (1.50, 2.40)	Increased risk if ≥2 *(moderate)*
Laks 2017	273	SLN negative	Per mm	-	-	HR: 1.02 (0.93,1.13)	Could not differentiate *(low)*
Analyses without adjustment for confounders							
Turner 2021	332	III	>4mm v 0-4mm	-	RR 1.34 [0.95, 1.88]	-	Could not differentiate *(low)*
Madu 2016	183	IIIB	≥2 vs <2mm	HR 1.30 (0.87–1.93)	-	HR 2.04 (1.25–3.35)	Could not differentiate recurrence *(moderate)* Increased mortality *(high)*
Madu 2017	205	IIIC	Per mm	-	HR 1.00 (0.97-1.04)	HR 1.01 (0.98-1.05)	Could not differentiate *(low)*

Ulceration

Table 13 Ulceration as prognostic factor during follow-up

Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation
Unadjusted meta-analyses						
9	3,308	IIB-III	RR 1.28 (1.19, 1.37)	-	-	Increased risk *(moderate)*
2	393	IIIB/C	HR 0.83 (0.63, 1.09)	-	HR 1.01 (0.74, 1.38)	Could not differentiate *(moderate)*
3	916	I-II	RR 1.94 (1.64, 2.30)	-	-	Increased risk *(moderate)*
5	3,592	I-II	HR 1.84 (1.56, 2.15)	-	-	Increased risk *(Very low)*
Analyses with adjustment for confounders						
Najjar 2019	928	III	Adjusted HR 1.34 (1.10–1.65)	-	-	Increased risk *(moderate)*
Jang 2020	1,174	IIB/C	IIB/C: Adjusted OR 1.77 (1.29, 2.43)	-	-	Increased risk *(moderate)*
Egger 2016	1,998	SLN Negative	HR 2.04 (1.58, 2.61)	HR: 2.80 (2.11, 3.70)	HR 2.41 (1.94, 3.00)	Increased risk *(moderate)*
Analyses without adjustment for confounders						

Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation
Turner 2020	332	III	-	RR 1.45 (1.05, 2.01)	-	Increased risk *(low)*
Berger 2017	581	II	-	-	HR 1.46 (0.75, 2.50) Ulceration and ≥4mm Breslow thickness: HR 3.00 (1.50, 6.01)	Could not differentiate when assessing ulceration on its own *(low)* but increased risk if present along with ≥4mm Breslow thickness *(moderate)*

Level of lymph node metastasis

Table 14 lymph node metastasis as prognostic factor during follow-up

Risk factor	Studies	Sample	Stage	Recurrence	Melanoma-specific Mortality	Interpretation
Adjusted meta-analyses						
N-stage 2	2	388	IIIB/C	-	Adjusted HR 1.76 (1.20, 2.58)	Significant increased risk if N-stage 2. *(high)* When separate, only IIIB (and not IIIC) analysis is significant.
Unadjusted meta-analyses						
≥2 positive lymph nodes	6	2,783	IIB-III	RR 1.39 (1.28, 1.51)	-	Increased risk if 2 or more *(high)*
Macro-metastases	9	3,577	IIB-III	RR 1.30 (1.20, 1.40)	-	Increased risk if macroscopic *(moderate)*
N-stage 2	2	388	IIIB/C	Unadjusted HR 1.40 (0.85, 2.30)	-	Significant increase in recurrence and mortality in IIIB but not IIIC *(low)*
Analyses with adjustment for confounders						
N-stage 3	Madu 2017	205	IIIC	Adjusted HR 2.34 (1.47, 3.71)	Adjusted HR 2.51 (1.54, 4.08)	Increased if 3 *(high)*
Analyses without adjustment for confounders						
≥2 positive lymph nodes	Barbour 2015	107	IIIB/C	2-3 vs 1: RR 1.68 (1.13, 2.48)	-	Increased risk if 2-3 *(low)*

Risk factor	Studies	Sample	Stage	Recurrence	Melanoma-specific Mortality	Interpretation
N-stage 2-3	Tas 2021	389	Positive SLN III	-	HR 1.40 (1.01, 1.94)	Increased risk if stage 2-3 *(moderate)*

Other

Table 15 Other clinical factors as prognostic factors during follow-up

Risk factor	Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation
Analyses without adjustment for confounders							
ECOG 1	BRIM-8	495	IIC-III	RR 1.05 (0.80, 1.39)	-	-	Could not differentiate *(moderate)*
	Grotz 2014	317	III	HR 1.50 (0.94, 2.38)	-	Unadjusted HR 1.88 (1.06, 3.34)	Could not differentiate *(low)*
LVI	2	719	I-II	RR 1.40 (1.14, 1.72)	-	-	Increased risk *(low)*
	Egger 2016	1,998	SLN Negative	HR 1.10 (0.65, 1.73)	HR 1.02 (0.52, 1.78)	HR 2.15 (1.60, 2.93)	Could not differentiate *(low)*
Mitotic rate >5	Tan 2019	138	IIC-IIIA >5 vs 0-5	-	HR 2.59 (1.21–5.53)	Unadjusted HR 3.47 (1.62–7.42)	Increased risk *(moderate)*
Mitotic rate in I-II	All studies differed in cut offs but generally found more mitosis to be predictive of recurrence.						
Axial location	3	1,462	I-II	RR 1.27 (1.02, 1.59)	-	-	Increased risk *(low)*
	2	389	I-II	Trunk: HR 1.27 (0.96, 1.68) Head/neck: HR 1.06 (0.67, 1.66)	-	Trunk: HR 1.34 (0.98, 1.84) Head/neck: HR 1.18 (0.81, 1.70)	Could not differentiate *(very low)*
	Egger 2016	1,998	SLN negative	HR 1.46 (1.13, 1.88)	-	HR 1.65 (1.31, 2.09	Could not differentiate *(moderate)*
	Laks 2017	270	SLN negative	Trunk: HR 1.25 (0.79,1.98) Head/neck: HR 1.47 (0.98,2.21)	-	Trunk: HR 1.39 (0.83,2.33) Head/neck: HR 1.41 (0.89,2.25)	Could not differentiate *(low)*
	Bleicher 2017	580	II	Trunk: HR 0.89 (0.59–1.35)	-	-	Could not differentiate *(low)*

Risk factor	Studies	Sample	Stage	Recurrence	Distant recurrence	Mortality	Interpretation
				Head/neck: HR 1.04 (0.66, 1.64)			
Scalp location	Namin 2019	168	I-II head/neck melanomas	HR 2.33 (1.11, 5.00)	-	-	Increased risk if head or neck melanoma *(moderate)*
Tumour location in higher risk (IIB-III) populations	All studies in higher risk (stage IIB-III) populations could not differentiate						

Risk factors during follow-up of children with melanoma

Table 16 Prognostic factors during follow-up of children with melanoma

Risk factor	Studies	Sample	Overall survival	Interpretation *(quality)*
Male	Brecht 2017	443	RR 0.74 (0.25, 2.19)	Could not differentiate *(very low)*
<2mm	Brecht 2017	443	RR 6.24 (2.07, 18.78)	Increased risk *(low)*
Ulceration	Brecht 2017	443	RR 64.24 (8.20, 502.89)	Increased risk *(low)*
Axial location	Brecht 2017	443	RR 0.64 (0.21, 1.97)	Could not differentiate *(low)*

Diagnostic accuracy of imaging strategies during follow-up

Table 17 Summary of GRADE for imaging used in routine follow-up of people with melanoma

All studies below used a composite reference standard that incorporated a period of follow-up, repeat scans and/or physical examination. For more information on this, see appendix D.

Modality	Outcome	Analysis	Studies	Sample	Sensitivity	Specificity
CT or PET-CT	Any recurrence	People with stage IIB-IIIB melanoma received 6-12 monthly imaging. The schedule was assessed as a whole (ability of imaging to detect recurrence prior to symptoms or detection by other means at any point during follow-up)	Turner 2020	172	0.86 (0.57, 0.96)	0.88 (0.82, 0.92)
CT	Lymph node recurrence	Meta-analysis of studies assessing imaging used during follow-up. Disease stage, type	Xing 2010 (analysis of 3 studies)	439	0.61 (0.15, 0.93)	0.97 (0.70, 1.00)

Modality	Outcome	Analysis	Studies	Sample	Sensitivity	Specificity
CT	Distant recurrence/ Progression	of treatment/surgery received and reason for scanning is not documented.	Xing 2010 (analysis of 3 studies)	439	0.63 (0.46, 0.77)	0.78 (0.58, 0.90)
PET-CT	Any recurrence	Per-scan analysis of routine imaging given during follow-up after resection (primarily stages III-IV)	5	2,416	0.90 (0.85, 0.93)	0.93 (0.90, 0.96)
PET-CT	Any recurrence	People with stage IIB-IIIB. Efficacy of the first scan, given shortly after resection (3-12 months) to pick up recurrences, assessed at different time points following scan	Koskivuo 2016	110	0.79 (0.51, 0.93) 6 months after scan, dropping to 0.26 (0.15, 0.41) 60 months after scan	0.84 (0.76, 0.90) 6 months after scan, dropping to 0.78 (0.67, 0.86) 60 months after scan
PET-CT	Lymph node recurrence	Meta-analysis of studies assessing imaging used during follow-up. Disease stage, type of treatment/surgery received and reason for scanning is not documented.	Xing 2010 (analysis of 5 studies)	571	0.65 (0.20, 0.93)	0.99 (0.92, 1.00)
PET-CT	Distant recurrence/ progression		Xing 2010 (analysis of 2 studies)	324	0.86 (0.76, 0.93)	0.91 (0.79, 0.97)
PET alone	Any recurrence	PET scans given at vary frequency depending on stage	Lewin 2018	156	0.69 (0.57, 0.79)	0.89 (0.81, 0.93)
PET alone	Lymph node recurrence	Meta-analysis of studies assessing imaging used during follow-up. Disease stage, type of treatment/surgery received and reason for scanning is not documented.	Xing 2010 (analysis of 22 studies)	1,531	0.87 (0.67, 0.96)	0.98 (0.93, 1.00)
PET alone	Distant recurrence/ progression		Xing 2010 (analysis of 4 studies)	454	0.82 (0.72, 0.88)	0.83 (0.70, 0.91)
US	Any recurrence	Follow-up after surgery	Rubaltelli 2011	460	0.98 (0.82, 0.99)	0.92 (0.89, 0.94)
US (contrast enhanced)	Any recurrence	Follow-up after surgery	Rubaltelli 2011	460	0.98 (0.82, 0.99)	0.99 (0.98, 0.99)
US	Lymph node recurrence	Meta-analysis of studies assessing imaging used during follow-up. Disease stage, type of treatment/surgery received and	Xing 2010 (analysis of 22 studies)	7,087	0.96 (0.85, 0.99)	0.99 (0.95, 1.00)

Modality	Outcome	Analysis	Studies	Sample	Sensitivity	Specificity
		reason for scanning is not documented.				

Table 18 Summary of GRADE tables for diagnostic accuracy of brain imaging in stage III melanoma

Author	Study design	Sample size	Diagnostic accuracy			Quality
			Sensitivity	Specificity	Likelihood ratios	
Using stage IIIC as a threshold for offering brain imaging						
Abdel-Rahman 2019	Retrospective cohort study	109,971	0.32 (0.26, 0.38)	0.96 (0.96, 0.96)	LR+ 8.33 (6.89, 10.07)	Low
					LR- 0.71 (0.65, 0.78)	Low
Surveillance strategy - Detection of any suspected recurrence: IIIA: PET scans at 6 and 18 months; IIIB/C: 6 monthly PET scans for first 2 years + scan at 36 months. IIIC: MRI brain recommended at 6 and 12 months.						
Lewin 2018	Retrospective cohort study	156	0.69 (0.57, 0.79)	0.89 (0.81, 0.93)	LR+ 6.06 (3.47, 10.57)	Very low
					LR- 0.35 (0.24, 0.50)	Very low
Staging strategy - Detection of in-transit or distant metastases: palpable + lymph node metastatic patients referred for total body PET/CT and brain MRI imaging						
Aukema 2010	Prospective cohort study	70	0.87 (0.70, 0.95)	0.97 (0.84, 1.00)	LR+ 33.97 (4.88, 236.23)	Low
					LR- 0.13 (0.05, 0.33)	Low

Risk factors for brain metastases

Table 19 Summary of GRADE tables for factors predictive of the presence of brain metastases in stage IV melanoma at baseline

Population	No. studies	Sample size	Effect size	Prevalence (if reported)	Interpretation (quality of evidence)
Gender (male vs female)					
IV	2	5,066	RR 1.15 (1.05, 1.25)	33.8% vs 29.4%	No difference *(low)*
Age (<60 vs ≥60)					
IV	Zhang (2019)	4,369	RR 1.25 (1.15, 1.35)	40.7% vs 32.6%	Increased risk if younger age *(low)*
Head/neck location (HNM vs trunk/limbs)					
IV	2	2,163	RR 0.85 [0.70, 1.02]	21.3% vs 22.2%	Could not differentiate *(low)*
Trunk location (trunk vs limbs)					
IV	2	1,599	RR 1.31 [1.05, 1.64]	24.5% vs 17.0%	Increased risk if trunk *(low)*

Population	No. studies	Sample size	Effect size	Prevalence (if reported)	Interpretation (quality of evidence)
Ulceration					
IV	Zhang 2019	1,003	RR 1.01 [0.80, 1.28]	23.1% vs 22.8%	Could not differentiate *(low)*
Breslow thickness (>4mm vs 0-4mm)					
IV	Zhang (2019)	5,066	RR 0.97 [0.78, 1.21]	22.6% vs 23.3%	Could not differentiate *(low)*

Table 20 Summary of GRADE tables for factors predictive of the development of brain metastases in stage III-IV melanoma during follow-up

Analysis	No. studies	Sample size	Effect size	Prevalence (if reported)	Interpretation *(quality of evidence)*
Stage III subgroups (A-D)					
IIIB vs. IIIA	Haydu (2020)	949	HR 2.07 (1.35, 3.17)	-	Increased risk if higher stage *(high)*
IIIC vs. IIIA	Haydu (2020)	1,239	HR 2.46 (1.65, 3.67)	-	Increased risk if higher stage *(high)*
IIID vs. IIIA	Haydu (2020)	489	HR 3.17 (1.75, 5.74)	-	Increased risk if higher stage *(high)*
IIIC vs IIIA-B	Samlowski 2017	402	RR 1.36 (0.82, 2.25)	15.8% vs. 11.6%	Could not differentiate *(moderate)*
Gender (male vs female)					
III	Haydu (2020)	1,918	HR 1.53 (1.18, 1.99)	-	Higher risk if male *(high)*
IV (unresectable)	Wang (2014)	665	HR 1.25 (0.95, 1.65)	-	Could not differentiate *(low)*
III-IV combined	3	665	RR 1.20 [1.01, 1.42]	35.1% vs 30.4%	Higher risk if male *(low)*
Age					
III	Haydu (2020)	1,918	Per 10 years HR 0.90 (0.83, 0.97)* *indicates decline in risk with age	-	Reduced risk with each 10 years of age *(high)*
IV (unresectable)	Wang (2014)	665	HR 1.00 (0.99, 1.00)	-	Could not differentiate *(low)*
Scalp location					

Analysis	No. studies	Sample size	Effect size	Prevalence (if reported)	Interpretation *(quality of evidence)*
III	Haydu (2020)	1,918	Ranging from: HR 1.59 (1.07, 2.32) compared to trunk; to HR 2.56 (1.54, 4.35) Compared to upper extremity	-	Increased risk if located on scalp *(high)*
Head/neck location					
IV only	Wang (2014)	568	HR 1.16 [0.77, 1.76]	-	Could not differentiate *(low)*
Trunk location					
IV only	Wang (2014)	450	HR 1.37 (0.98, 1.91)	-	Could not differentiate *(low)*
Ulceration					
III	Samlowski 2017	301	RR 0.90 [0.49, 1.66]		Could not differentiate *(very low)*
III-IV combined	Peuvrel 2014	70	RR 0.88 [0.33, 2.34]		Could not differentiate *(very low)*
Breslow thickness (>4mm vs 0-4mm)					
IV only	Wang (2014)	463	RR 1.09 [0.89, 1.34]		Could not differentiate *(low)*
Mitotic rate					
III	Haydu (2020)	1,918	5-9 vs 0-4 mitoses: HR 1.77 (1.30, 2.41)	-	Increased risk if higher mitotic rate *(high)*
			>9 vs 0-4 mitoses: HR 2.18 (1.60, 2.98)	-	Increased risk if higher mitotic rate *(high)*

Risk factors during follow-up of stage IV (and unresectable stage III) disease

Table 21 Prognostic factors during follow-up of stage IV

Risk factor	Studies	Sample	Recurrence	Mortality	Interpretation *(quality of evidence)*
Male	3	1,014	RR 1.03 (0.94, 1.12)	RR 1.05 (0.91, 1.20)	No difference *(high)*
Old age	4	1,959	RR 1.02 (0.96, 1.08)	RR 0.98 (0.90, 1.07)	No difference *(high)*

Risk factor	Studies	Sample	Recurrence	Mortality	Interpretation *(quality of evidence)*
ECOG ≥1	4	2,137	RR 1.17 (1.11, 1.24)	RR 1.35 (1.17, 1.55)	Increased mortality *(moderate)* but no difference in recurrence *(high)*
Elevated LDH	4	2,119	RR 1.40 (1.19, 1.65)	RR 1.62 (1.36, 1.94)	Increased risk *(moderate – high)*

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see 0). This search retrieved 7,545 studies and one further studies were included from NG14. Based on title and abstract screening, 7,515 of the studies could confidently be excluded for this question. Twenty nine studies were excluded following the full-text review. Thus, the review for question 6.2 includes 2 studies from the existing literature. The reviews for questions 6.1, 6.3 and 6.4 contained no studies from the existing literature.

1.1.7.2 Excluded studies

See Appendix J for a list of references for excluded studies, with reasons for exclusion.

1.1.8 Summary of included economic evidence

Table 22 Economic Evidence Profile

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost[1] (£)	Effects[2]	ICER[1] (£/Effect[2])	
NG14 model (2014) Standard follow-up (consisting of clinical reviews – 3 monthly years 1-3, 6 monthly years 4-5, annually years 6-10) Standard follow up with the addition of Imaging (MRI head, CT chest, abdomen and pelvis) every 6 months during the first 3 years	Partly applicable[3]	Minor limitations	£2027	0.1206	£16,815	**Deterministic:** Lowering the probability of moving from loco-regional disease to distant disease makes imaging less cost effective. **Probabilistic:** At £20,000/QALY threshold standard follow-up was preferred in 61.75% of iterations. The addition of imaging was preferred over 50% of the time only when the threshold was £25,000/QALY
Krug et al. (2010) Follow-up with suspected pulmonary metastases being examined with whole body computed tomography (CT) Follow-up with suspected pulmonary metastases being	Partly applicable[4]	Potentially serious limitations[5]	£937	0.1929 LMG[6]	PET-CT Dominates	**Deterministic:** Specificity of PET-CT has the greatest impact on the ICER, but changes in this parameter only varies the value of the ICER by less than 1% **Probabilistic:** 71% of the simulations showed that PET-CT was dominant, 22.6% of the simulations showed that PET-CT was dominated and in 6.4% of the simulations PET-CT was cost effective.

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost[1] (£)	Effects[2]	ICER[1] (£/Effect[2])	
examined with fluorine - 18 fluoro - 2 - deoxyglucose (FDG) positron emission tomography (PET) with X - Ray computed tomography (CT)						

1 Costs were adjusted for purchase price parities and inflated to 2020 British Pounds Sterling using Eppi-Centre Cost Converter. https://eppi.ioe.ac.uk/costconversion/default.aspx
2 QALYs unless otherwise stated
3 Model population had not received adjuvant therapy prior to follow-up and therefore the population is not completely indicative patients in current UK clinical practice
4 Belgium healthcare system, life months gained used not QALYs, costs discounted at 3%, life months gained discounted at 1.5%, model population had not received adjuvant therapy prior to follow-up and therefore the population is not completely indicative patients in current UK clinical practice
5 Lack of transparency around the clinical inputs
6 Life months gained (LMG)

1.1.9 Economic model

The committee prioritised 6.2 for original modelling. Table 23 provides a brief summary of the results.

Table 23: Economic evidence profile

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost (£)	Effects	ICER (£/Effect)	
De novo model (2021) (*BRAF* mutant) Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed	Directly applicable	Potentially serious limitations	CT (reduced): £126,338 CT: £126,366	CT (reduced): 8.88965 CT: 8.89157 PET-CT (reduced): 8.93438	Fully incremental analysis: CT vs. CT (reduced): £14,548	**Deterministic:** For CT vs CT (reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT (reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results were congruent to the deterministic results. At

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost (£)	Effects	ICER (£/Effect)	
tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (2 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5) Reduced follow-up (2 years) with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5)			PET-CT (reduced): £128,538 PET-CT: £128,698	PET-CT: 8.93695	PET-CT (reduced) vs. CT: £50,744 PET-CT vs. PET-CT (reduced): £62,167	£20,000 threshold CT was 50% likely to be cost effective.
De novo model (2021) *(BRAF* mutant) Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (0 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, annual years 2-5)	Directly applicable	Potentially serious limitations	CT (reduced): £126,099 CT: £126,366 PET-CT (reduced): £128,115 PET-CT: £128,698	CT (reduced): 8.82752 CT: 8.89157 PET-CT (reduced): 8.87313 PET-CT: 8.93695	Fully incremental analysis: CT vs CT (reduced): £4,169 PET-CT (reduced) vs. CT: CT dominates PET-CT vs. PET-CT (reduced): £51,391	**Deterministic:** For CT vs CT (reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT (reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results were congruent to the deterministic results. At £20,000 threshold CT was 80% likely to be cost effective.

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost (£)	Effects	ICER (£/Effect)	
Reduced follow-up (0 years) with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, annual years 2-5)						
De novo model (2021) (*BRAF* wild type) Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (2 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5) Reduced follow-up (2 years) with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5)	Directly applicable	Potentially serious limitations	CT (reduced): £113,360 CT: £113,386 PET-CT (reduced): £115,299 PET-CT: £115,457	CT (reduced): 9.35189 CT: 9.35241 PET-CT (reduced): 9.39861 PET-CT: 9.40066	Fully incremental analysis: CT vs CT (reduced): £16,785 PET-CT (reduced) vs. CT: £42,332 PET-CT vs. PET-CT (reduced): £76,900	**Deterministic:** For CT vs CT (reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT (reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results were congruent to the deterministic results. At £20,000 threshold CT was 45% likely to be cost effective.

Study	Applicability	Limitations	Incremental			Uncertainty
			Cost (£)	Effects	ICER (£/Effect)	
De novo model (2021) (*BRAF* Wild Type) Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (0 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, annual years 2-5) Reduced follow-up (0 years) with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, annual years 2-5)	Directly applicable	Potentially serious limitations	CT (reduced): £113,031 CT: £113,386 PET-CT (reduced): £114,796 PET-CT: £115,457	CT (reduced): 9.29820 CT: 9.35341 PET-CT (reduced): 9.34600 PET-CT: 9.40066	Fully incremental analysis: CT vs CT (reduced): £6,432 PET-CT (reduced) vs. CT: CT dominates PET-CT vs. PET-CT (reduced): £43,830	**Deterministic:** For CT vs CT (reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT (reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results were congruent to the deterministic results. At £20,000 threshold CT was 70% likely to be cost effective.

1.1.10 Unit costs

Item	Cost	Source
CT Scan	£97.15	NHS National cost collection 2018/19
MRI Scan	£142.76	NHS National cost collection 2018/19
PET-CT Scan	£520.37	NHS National cost collection 2018/19
Follow-up appointment	£128.17	NHS National cost collection 2018/19
Ultrasound scan	£55.33	NHS National cost collection 2018/19

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee agreed that there are numerous, often conflicting, outcomes relevant during the follow-up of people who have had melanoma.

Recurrence is an important outcome due to the impact this has on mortality, morbidity and quality of life. Recurrence in a distant site is of particular importance due to this having a greater impact on these other outcomes.

Regarding the use of imaging, the potential for ionising radiation is also important and must be considered in relation to the imaging modality being considered.

The diagnostic accuracy of imaging to detect specific recurrences is important. As the diagnostic accuracy differs depending on location of metastases, there is a need to establish which imaging modality is best at detecting specific recurrences/progression; in particular, all recurrences, lymph node metastases and spread to distant sites. False negative results are particularly important in this context as missing disease can impact upon mortality.

A false positive (FP) result on a scan during follow-up has the potential to interrupt a person's treatment until a subsequent scan disproves the recurrence. It may also lead to a person being upstaged and potentially receiving incorrect treatment depending on the location of the detected metastases.

A true positive (TP) result correctly identifies disease recurrence or disease progression. This may lead to a person's treatment being interrupted and will lead to them being correctly stage.

A false negative (FN) result will result in a person's recurrence or progression being missed. This can have particularly harmful effects and may result in a person's disease going untreated, spreading and ultimately resulting in death.

A true negative (TN) result will correctly classify the person as being without disease.

Rates of asymptomatic recurrence among people undergoing an imaging strategy would help to infer the benefit of imaging surveillance by identifying the proportion of recurrences found in an early stage (before it becomes symptomatic).

Quality of life and patient preference are important in the context of follow-up as any follow-up routine has the potential to impact on quality of life. For some people more frequent follow-ups have the potential to cause anxiety and worry. Conversely, for other people, less frequent follow-up can also have this effect, particularly in the early stages following diagnosis where many people have uncertainty surrounding the future and desire guidance on what to do and expect.

Brain metastases are indicative of poor prognosis and pose significant risk of mortality, and it is thought that this risk is particularly pronounced if the metastases are not detected until

they become symptomatic. Detecting risk factors for brain metastases will allow for a more thorough imaging schedule for those people at high risk of developing brain metastases and will identify their development early, allowing treatment plans to be modified.

1.1.11.2 The quality of the evidence

Randomised controlled trials

Two parallel-design trials were conducted in the UK and The Netherlands in which participants with stage IB-IIC disease were randomized to follow-up in-line with national guidelines or an experimental risk-stratified follow-up which involved reduced follow-up particularly in the early years following surgery and for the lower stages of disease. No participants received routine imaging. These trials were of low risk of bias but were not likely to have been powered to detect differences in recurrence/mortality rates and did not report data separated by stage.

Prognostic studies for resected stage I-III disease

There are many studies assessing risk factors for recurrence (including data specific to recurrence in a distant site) and mortality. Most of these studies involved retrospective cohorts and some used data taken from subgroup analyses of RCTs.

Data were reported in a variety of different ways which limited meta-analysis. Some studies reported event data, some reported unadjusted hazard ratios and some adjusted hazard ratios. These different forms of analyses were not combined in meta-analysis. Adjusted hazard ratios were not combined with each other (except with a very small number of exceptions) as each study adjusted for different characteristics. This often led to contradictions between studies that could not be reconciled.

The introduction of adjuvant therapies has changed the management of people with resected stage III disease and significantly improved survival and recurrence outcomes. Studies varied in whether their participants received adjuvant therapies, with some studies including a mix and others not reporting adjuvant therapy use. Speculative analyses were conducted which assessed whether the risk associated with prognostic factors varied alongside adjuvant therapy use however these analyses suggested that the use of adjuvant therapy did not have a large impact on whether a clinical characteristic increases risk of recurrence or death. Therefore, studies were combined regardless of whether participants received adjuvant therapy.

Cohort studies were at risk of bias as there is the potential for risk factors to be comorbid. It is therefore possible that a clinical characteristic is associated with recurrence yet does not represent a risk factor in and of itself. Some studies attempted to correct for this bias by controlling analyses for confounding variables however most studies either do not conduct multivariate analyses or only adjusted for a limited number of important clinical characteristics (for example, several studies only adjusted for characteristics that were significant in the univariate analyses rather than adjusting for a prespecified list of potentially relevant characteristics).

Another source of bias for these studies relates to the method of follow-up and detection of recurrence. Studies often did not describe the surveillance strategy used for the included population at the study centre(s). Other studies described their recommended surveillance strategy but did not report (or their data did not specify) how often or accurately this strategy was adhered to. This was less of an issue for predicting the outcome of mortality as this is generally captured by the databases.

Risk factor analyses using data from RCTs did not suffer from this issue as typically follow-up was well detailed, standardised and involved routine imaging as the population had later stages of disease. These studies used data from subgroup analyses and were therefore not

adjusted for confounders. However, drug regiments were standardised and could be mostly accounted for in the present analyses.

Prognostic studies for stage IV (and unresectable (III) disease

Analyses of risk factors for stage IV or unresectable stage III disease typically relied on subgroup data from RCTs assessing systemic therapies or immunotherapies and suffered from bias in the ways outlined above.

One study (Faries, 2017) also used data from RCTs in resected stage IV disease but adjusted for certain confounders. However, this study only reported data on predictors of mortality.

Imaging surveillance to detect any recurrence

A common area of concern in this evidence base is the use of composite reference standards. The index test included a scan done either at baseline or during follow-up and the results of this test were evaluated based on whether the recurrence was confirmed or excluded during a period of time (usually within 6 months) by subsequent imaging, histological examination or based on symptoms/physical examination. This allows for the potential for participants to have undergone different tests as part of their reference standard. Additionally, it is possible that a recurrence was actually there during the first scan but resolved itself within 6 months. Conversely, a recurrence may only have developed during that 6-month period. No studies had a standardised gold standard test.

Analyses were split into per-patient and per-scan analyses. In per-patient analyses the accuracy of 1 scan per patient was entered into the analysis. There are benefits to this approach for analysis of patients suspected of recurrence or those patients undergoing routine re-staging but are less appropriate for assessing the accuracy of surveillance strategies which stipulate that each participant undergo numerous scans. Per-scan analyses were preferred when assessing the accuracy of overall surveillance strategies but are also subject to risk of bias, particularly in retrospective studies where participants may vary in the number of scans received.

Studies assessing the diagnostic accuracy of routine follow-up after surgery were usually retrospective and as such follow-up was typically recommended only, without data on how often this was adhered to. Additionally, as these studies often relied on database records it is unclear whether participants were truly asymptomatic at the time of the index test being conducted. Additionally, it is unclear how accurately the authors could differentiate routine follow-ups from scans being conducted due to suspected recurrence.

The committee noted that one study (Stahlie, 2020) was prospectively conducted and in which routine imaging was given and all participants were asymptomatic at the time of scanning.

Imaging surveillance to detect lymph node recurrences

There were several issues surrounding the available evidence for the use of ultrasound surveillance in people with melanoma.

A search was conducted to identify meta-analyses of the diagnostic accuracy of imaging to detect lymph node recurrences. 1 meta-analysis was included, containing a total of 74 studies and assessed the accuracy of imaging to detect lymph node and distant recurrences at staging and during follow-up. For the purposes of this review, only the latter analyses were extracted.

This meta-analysis had several flaws in the context of this review and was judged to be of moderate-high risk of bias. The analysis included studies spanning all stages of disease and all reasons for scanning during follow-up (due to suspected recurrence, re-staging after a key

event, or routine follow-up). Additionally, there was no attempt to account for differences in surveillance protocols between studies (and study centres). Finally, most studies were quite old leaving possibility that advances in the technologies and diagnostic techniques may not be translatable to the present day. Nonetheless, the analyses combined a large number of different studies and provided precise estimates of diagnostic accuracy.

Several studies from other reviews were identified as being relevant to this review (MSLT-II and DeCOG trials) as they report on lymph node recurrence rates over time in participants followed up with routine ultrasound. These trials were of high-quality but have limitations when applied to this review. The committee were concerned with how frequently recurrences occurred in people with a positive SLN that were limited to the lymph nodes, when these occurred in the 5 years following a positive SLNB and how frequently these were detected using ultrasound alone. The key limitation of these trials is that they did not randomize patients to ultrasound surveillance or no surveillance, as the arm not receiving US surveillance all underwent CLND but the US surveillance arm did not. As such, the two arms differed in their risk of lymph node recurrence.

Brain metastases

The quality of evidence varied considerably, with many of the studies suffering from methodological issues. Most studies were retrospective cohort studies in which databases were searched for patients with a diagnosis of melanoma and with known status for brain metastases. These studies had variable levels of missing data for key predictors and often the level of missing data is not reported. Missing data represents a risk of bias as it is possible that those patients with recorded data are not representative of all patients.

There is the potential that risk factors are comorbid. If brain metastasis is more prevalent in a group of patients with a certain clinical characteristic, it is unclear whether that characteristic is a risk factor in and of itself, or whether other risk factors are more prevalent in people with that specific characteristic. It is possible to account for this issue by conducting multivariate analyses, which assess whether risk factors are independent of each other. Most studies did not conduct multivariate analyses.

A small number of studies were of low risk of bias. In particular, Haydu (2020) combined data from two prospective databases. There was a low level of missing data, analyses were reported as hazard ratios and two multivariate models were conducted which adjusted for various important clinical characteristics. High quality evidence from this paper identified several risk factors for the development of brain metastases.

There was no data pertaining to the interaction of risk factors and of the cumulative risk associated with multiple risk factors being present. The committee advised that this would be important for making recommendations. In particular, the committee agreed that a nomogram would be ideal as it would allow individualised characteristics to be entered into a calculator to identify that person’s relative risk of brain metastases, this would allow recommendations to be made for more frequent imaging (or screening) for patients of sufficiently high risk.

There was limited data on the risk of brain metastases being present at the point of diagnosis. Evidence from two studies reported on risk in people with stage IV melanoma but there were no studies for stage III melanoma.

There was no data on the diagnostic accuracy of CT compared to MRI of the head for people with melanoma. The committee advised that it is generally assumed that MRI is more sensitive for the detection of brain metastases due to the greater spatial resolution of MRI and evidence from other disease areas.

1.1.11.3 Discussions about benefits and harms

Stage I-IIC resected disease

The committee noted that low-high quality evidence from an RCT comparing standard follow-up to reduced frequency, risk-stratified follow-up found that reduced follow-up did not adversely impact quality of life across any of the domains studied after 3 years of follow-up, including several indices assessing anxiety and worry.

The committee discussed their experiences of follow-up in clinical practice. Some members of the committee expressed that a reduced number of follow-up visits has the potential to reduce anxiety in certain people by limiting the perceiving seriousness and urgency of the state of their illness. However, other members expressed that such a reduction may impact negatively on some people as frequent follow-ups allow for the person with melanoma to ask questions regarding their condition; this is particularly relevant during the early stages after treatment where anxiety is high and there are uncertainties surrounding the future of their condition. Frequent follow-up visits allow for opportunities to address these issues.

Additionally, these trials did not find any indication that reduced follow-up would lead to an increase in the number of recurrences, mortality or late detection of recurrence. The committee advised that for stages IA-IIA, the mortality and recurrence risk at 5-10 years following treatment is relatively low and agreed the intensity of the follow-up strategy recommended bin 2015 NICE guidance is not necessary. The committee agreed to recommend a reduced-frequency follow-up in line with that trialled in the MelFo (2019 and 2020) studies but amended the frequency of visits for stage IB disease to 2 visits instead of 1 as they agreed that 1 visit was too few and would not satisfy patient needs and the need to offer comprehensive patient education. Additionally, they recommended 4 follow-up visits per year in years 1-2 for stage IIB-IIC due to the high risk of recurrence associated with these stages and to coincide with ultrasound imaging requirements (see below).

The committee were concerned with the risk of long-term mortality associated with high-risk stage II disease (IIB-C), with evidence suggesting a greater risk of recurrence and mortality than stage IIIA disease. There was a lack of evidence regarding the diagnostic accuracy of imaging surveillance strategies specifically in stage IIB-C disease however evidence from studies in which all participants received routine imaging demonstrated that IIB-C disease has similar or worse recurrence rates than IIIA disease and that around 45-48% of these recurrences presented asymptomatically (Ibrahim 2020; Lee 2017). The committee agreed that the poor prognosis associated with IIB-C disease warranted imaging follow-up alongside clinic visits and recommended imaging at the same frequency as IIIA-C disease (see below). However, due to the lack of cost-effectiveness evidence, the committee agreed to make a weaker recommendation, that CT imaging be considered for people with stage IIB disease, due to its better prognosis than IIC, for which CT imaging should be offered.

Stage III-IV resected disease

Numerous studies reported risk factors associated with stage III melanoma. These studies identified a number of risk factors associated with poor prognosis.

The committee noted that most risk factors for recurrence were also risk factors for distant disease and mortality.

Evidence showed a strong effect of disease stage on prognosis, particularly among people with stages IIB-IV disease. The committee agreed that this risk warranted the use of imaging during follow-up and made recommendations for imaging to be used as part of follow-up for this population of people.

Evidence from cohort studies demonstrated that the recurrence risk up to 5 years in people with stage IIIA melanoma is somewhat lower than those with stage IIB-C disease. Many of the RCTs assessing the use of adjuvant therapies following resection of stage III disease

(CHECKMATE-238, COMBI-AD and KEYNOTE-054) only included participants with IIIA disease if they had nodal involvement >1mm in diameter, demonstrating 3-year recurrence free survival rates of around 80% if receiving adjuvant therapy and 60-65% if not (if receiving placebo). Analyses assessing the relationship between extent of nodal involvement and outcomes of recurrence and survival also found poorer prognosis associated with greater nodal involvement. The committee discussed these data and whether it would be suitable to recommend reduced frequency follow-up for people with stage IIIA disease and <1mm nodal involvement. They concluded that such a follow-up schedule would cause confusion, due to being less rigorous than lower stages and may adversely impact upon patient quality of life, due to having infrequent clinic visits and scans despite having a high stage disease diagnosis.

Similar to stages IIB-C disease, evidence from studies employing routine imaging in people with stage III melanoma suggests that roughly 50% of recurrences detected are asymptomatic.

Diagnostic accuracy studies demonstrated that PET/CT has a high sensitivity and specificity when used during routine follow-up. Overall, analyses showed that PET/CT has a sensitivity of 89% and a specificity of 93%. Stahlie (2020) investigated the accuracy of a PET/CT strategy specifically in stage IIIB-C patients who are asymptomatic at the time of their scans, which are given every 6 months for 2 years and then once more at 3 years. This study found a comparable sensitivity and specificity, and that 8.8 scans were needed to detect 1 asymptomatic recurrence.

One study (Turner, 2020) assessed the use of both CT and PET/CT given either 6- or 12-monthly intervals. They found PET/CT to be more sensitive and CT to be more specific. Additionally, this study found the sensitivity and specificity of imaging to be constant over time, meaning that the ability of these imaging modalities to detect asymptomatic recurrences is the same throughout follow-up. Turner also demonstrated that the number of scans needed to detect a recurrence decreases alongside disease substage, ranging from 24 scans in stage IIIA to 8.4 scans in stage IIIC/D. A similar pattern of results was found in a paper by Stahlie (2020).

The committee agreed that based on this evidence and the evidence from adjuvant therapy trials showing a substantial risk of recurrence in this population, the use of imaging during surveillance was necessary for this population.

The committee noted that there was limited evidence on the diagnostic accuracy of CT during follow-up of stage III melanoma. The little evidence there was suggested a slightly decreased sensitivity compared to MRI. The committee noted that evidence from the economic model (see below) found that follow-up including PET/CT imaging was not cost-effective compared to a strategy involving CT, due primarily to the higher cost of PET/CT.

The committee advised on some practical implications surrounding the use of PET/CT, namely that not all centres have PET/CT facilities and people with melanoma may be required to travel to undergo imaging. Additionally, the noted that there is variation in the use of PET/CT across the UK currently and recommendations specifying which imaging modality to use may help to reduce this variation.

The committee made recommendations for people with stage IIIA-C melanoma undergo CT imaging 6-monthly in years 1-3, then annually for years 4-5, also noting that if the person with melanoma is receiving adjuvant therapy, imaging should be done in accordance with treatment requirements whilst on treatment.

A study by Bloemendal (2019) identified that people with stage IIIB/C melanoma having previously undergone surgery for melanoma (lymph node dissection or SLNB) are at particularly high risk of recurrence in the interim period between surgery and starting adjuvant therapy (imaging was done a median of 7.4 weeks after surgery (range 4.3-10.7

weeks)). 18% of 120 patients had evidence on imaging of early recurrence. Based on this study, the committee recommended that a repeat imaging scan be done prior to starting adjuvant therapy. They discussed how recent this scan should be but agreed they could not specify this in the recommendation due to limited evidence. However, they envisioned that the last scan would definitely be no longer than 12 weeks old as this is the standard in current practice for the period between imaging and starting adjuvant therapy. Ideally, the scan would be no longer than 7-8 weeks old due to evidence from the above trial demonstrating high rates of recurrence within this timeframe.

The committee noted the lack of evidence pertaining to stage IIID melanoma and the limited evidence for resected stage IV melanoma. However, the committee noted that survival curves provided in the AJCC 8th edition and survival curves from the IMMUNED adjuvant therapy trial suggest that stages IIID and IV are of somewhat comparable severity and both represent a greater risk of recurrence and mortality than stages IIIA-C. Based on this, the committee recommended more frequent imaging in these populations: 3-monthly in years 1-3, then 6-monthly in years 4-5.

Ultrasound for surveillance of lymph node basin

The committee discussed in length the issue of whether ultrasound should be done during the follow-up of people with melanoma. The committee agreed that people with a positive SLNB are at high risk for recurrences involving the lymph nodes (23%; 8% with nodal-only recurrences, using data from the observation arm of MSLT-II). They agreed that data from the MSLT-II trial suggests that rates of lymph node recurrence are highest in the first 3 years.

Evidence from a meta-analysis by Xing (2010) found that for the detection of lymph node metastases during follow-up ultrasound was more sensitive (96%) than alternative imaging modalities, particularly compared to CT (61%), which has been recommended as the imaging modality to be used for cross-sectional surveillance. The committee agreed that his meant that lymph node recurrences would be missed (or detected later) if undergoing surveillance with CT alone. The committee discussed the potential consequences of this.

There was limited evidence regarding the benefits of US surveillance. The committee discussed in length the plausibility that US surveillance would improve outcomes, particularly those such as mortality and distant progression. The committee agreed that there was no evidence that US would improve mortality. Additionally, it is unlikely that US detected lymph node recurrence would significantly change the choice of surgical management, except in unique cases of very large metastases in the groin or axilla regions (although the committee noted that such metastases should be detectable clinically). The committee were aware of a paper (Broman, 2020) which found that during the period following publication of the MSLT-II trial 6% of patients undergoing surveillance presented with an isolated nodal recurrence however all recurrences were surgically salvageable (resectable). The committee also noted that this trial (along with data from another paper: Mitra, 2021) identified that rates of nodal recurrence were comparable regardless of whether the person with receiving adjuvant therapy or not.

Diagnostic accuracy evidence suggests that US is much more sensitive than CT for the detection of lymph node metastases, however the reference standard used in these trials typically involves the development of metastases during the 3-6 months following the index scan (and could be detected by repeat scan, alternative imaging methodology or clinical exam). As such it is unclear whether lymph node recurrences missed by CT would be detected just a few months later, either clinically or on a subsequent scan. Additionally, it is unclear whether US in the context of modern surveillance strategies for people with a positive SLN, which involves frequent cross-sectional imaging, would lead to lymph node recurrences being detected significantly earlier. The committee were aware of a paper by Garland-Kledzik (2020) which analysed the data from the surveillance arm of the MSLT-II trial and identified that roughly half (48%) of nodal recurrences were detected by US alone, increasing to 65% in people with obesity. However, there was not a significant reduction in

melanoma specific survival or time to nodal recurrence between those recurrences detected by US-only and those detected by other methods.

Due to these uncertainties, the committee could not agree on the extent of the utility of ultrasound if it were to be used routinely in clinical practice. The committee also identified several negative consequences of using ultrasound, including exposing people with melanoma to anxiety which is often caused by the process of undergoing scans and adding to an already busy imaging (and clinic visit) schedule.

However, other members of the committee identified benefits of ultrasound scanning. The higher sensitivity of US will allow for earlier, more precise staging. It would allow for lymph node recurrences to be detected sooner and although this is unlikely to affect outcomes such as mortality, it is beneficial for local control and limiting morbidity (which will help improve quality of life). Finally, recurrence in the lymph nodes in patients receiving adjuvant therapy would result in the adjuvant therapy being suspended. Better detection of lymph node recurrences would therefore allow for updating therapy regimens to be more precise.

The committee agreed that although US-detected recurrences would not change the type of surgery considered, it would likely lead to the surgical approach being considered earlier. Additionally, some patients who recur and stop receiving adjuvant therapy may be considered for lymph node dissection. The committee also advised that in their experience, there is potential for better detection of local recurrences in the axilla region, neck, pelvis and groin when using US compared specifically to CT.

The committee also noted that MSLT-II data suggests that people with a positive SLN are at greatest risk of lymph node recurrence in the first 2-3 years following biopsy. The committee made recommendations to reflect this, recommending that ultrasound is considered 2 times per year in years 1-3 for people with a positive SLN, intending that these be interspersed with cross-sectional imaging so as to coincide with clinic visits.

The committee also agreed that people who are eligible for SLNB but do not undergo one due to personal choice, comorbidities or pregnancy should undergo US surveillance as their lymph node status is unknown and, if positive, will not have benefited from the removal of their SLNs and may be incorrectly staged (and thus, may not by receiving the correct treatment). The committee agreed that this population of people would be small and made recommendations that US be considered for 3 years.

Brain metastases

The committee agreed that recommendations surrounding what type of imaging be done depends upon how prevalent brain metastases are in a given population.

The committee agreed that the evidence suggests a relatively high rate of disease in resected stages III-IV disease, with evidence suggesting around 16% of people with stage III melanoma developing brain metastases by 5 years. Evidence suggests that this rate increases alongside the substages of disease, at around 6.5% in stage IIIA, increasing to just under 30% in stage IIID.

There was a sparsity of evidence for the diagnostic accuracy of MRI compared to CT however the committee agreed that MRI is better suited to imaging the brain due to its greater spatial resolution. There is also lower exposure to ionising radiation associated with MRI compared to CT. The committee advised that although there is a risk of cataracts if the CT scan is aimed at the lens, scans should not involve aiming at the lens and would require multiple such scans before the risk becomes significant. MRI is therefore likely to lead to the detection of brain metastases earlier than if CT is used.

However, the committee also advised that there were major inconveniences associated with undergoing brain imaging with a modality different to that which is being used for body imaging as patients would have to have to separate scans on different appointments (and

perhaps at different centres depending on availability). Additionally, the cost of MRI is considerably higher than the cost of CT and there is no evidence regarding the survival benefit of identifying brain metastases early, although an RCT attempting to assess this is currently being conducted.

Based on these considerations, the committee recommended that the head be included for those patients undergoing contrast enhanced CT during follow-up (see section 1.1.12). For most people, a head scan using CT would be suitable. However, for specific groups of people, MRI of the brain may be a better option.

The committee noted that numerous clinical variables were associated with increased risk of developing brain metastases during follow-up. These include male gender, younger age, tumour location (scalp, trunk and head and neck) and a high mitotic index. In particular, the committee agreed that based on evidence from Haydu (2020), people with stage IIIC-IV disease are at high risk of developing brain metastases, and that this risk is particularly pronounced if the person's primary tumour is located on the scalp and/or they have a mitotic index of 5 or greater.

The committee agreed that risk factors for the development of brain metastases during follow-up should be the same as being a risk for brain metastases being present at staging. Based on this, the committee recommended that MRI should be considered in the staging of people with stage IIIC-IV disease if one or both of these risk factors are present. They agreed that this would not be necessary during follow-up as these groups of people will receive frequent surveillance imaging with CE-CT of the brain.

Imaging of children and young people, and pregnant women

The committee agreed that recommendations for imaging during staging and follow-up also apply to children and young people (up to 24 years old) and pregnant women. However, due to the risk of ionising radiation associated with CT scans, whole body and brain MRI should be offered to these groups of people instead.

Imaging during staging

The committee agreed that imaging done during the staging of people with melanoma should be consistent with the imaging that the person would receive during follow-up and made recommendations to reflect this.

1.1.11.4 Cost effectiveness and resource use

The committee had limited cost-effectiveness evidence to support their decision making for review questions 6.1, 6.3 and 6.4, as no existing cost-effectiveness studies were identified in the literature review. However, two existing cost-effectiveness studies were identified for review question 6.2, including a model created for the previous iteration of the guideline. Both existing studies assessed different approaches to imaging during follow-up (CT imaging versus no imaging and CT imaging versus PET-CT imaging) for patients with stage IIC/III melanoma. De novo economic modelling was also completed to assist the committee in developing recommendations for review question 6.2 and compared different imaging techniques (CT and PET-CT) and frequencies of imaging in patients with stage III melanoma. In the model, patients had the same frequency of clinical follow-up visits (i.e., appointments with a clinician including a skin check) and depending on the assigned intervention, imaging follow-up with either CT or PET-CT, the frequency of which could be varied by substage (i.e., patients with stage IIIA melanoma could receive imaging follow-up at a reduced frequency compared to patients with stage IIIB or IIIC melanoma). Overall, the committee noted that some of the recommendations are likely to be cost saving given a reduced number of clinical

follow-up visits or imaging frequencies have been recommended compared to current practice. The committee noted that these cost savings could potentially offset any increase in costs associated with other follow-up recommendations where imaging (or an increased frequency of imaging) is now indicated. In addition, the results of the de novo economic model highlighted that the frequency of imaging currently used in clinical practice for stage IIIA-IIIC melanoma was cost-effective when imaging was conducted using CT scans and therefore the committee recommended the use of CT scans for follow-up when imaging was indicated.

The committee felt that introducing ultrasound of the nodal basin would improve the detection of lymph node metastasis. The committee felt that there is a variation in practice across the country, some larger specialist cancer centres will use ultrasound whereas smaller district centres will not. The committee felt that recommendations for ultrasound would reduce this variation in practice. There was no economic evidence on ultrasound in follow-up but the committee used unit cost data to assess the resource impact. The committee acknowledged that the limited evidence does not appear to show that ultrasound affects mortality however, they believed that ultrasound would be beneficial in certain circumstances for example reduced mobility or obesity.

The committee decided to create recommendations for follow-up schedules based on the substage of melanoma, therefore the resource impact for each recommendation was discussed by the committee and is summarised below.

For adults with stage 0 melanoma, the committee did not make any changes to the existing follow-up recommendations as the evidence for this population was not included in the clinical review. The recommendation for follow-up in stage 0 melanoma is, therefore, not expected to be associated with a resource impact.

For adults with stage IA melanoma, the committee made a recommendation to reduce the number of clinical follow-up appointments from a range of 2-4 during the first year after completion of treatment to only 2 follow-up appointments, based on the very high rates of melanoma-specific survival (99% at 5 years and 98% at 10 years) observed in this population in the data used to define the AJCC 8th edition stages (Gershenwald 2017). This is likely to lead to a reduction in resource use and potentially cost savings for follow-up in this population.

For adults with stage IB and IIA melanoma, the committee made recommendations to reduce the number of clinical follow-up appointments over the five years after completion of treatment, based on the results of the MelFo RCT. This RCT investigated risk-adjusted follow-up (based on substage of melanoma) in stage IB-IIC melanoma and in the UK population of the trial indicated no differences in quality of life, recurrence, or all-cause mortality at three years between the risk-adjusted follow-up and conventional follow-up arms. However, there was significantly more extra follow-up appointments in the risk-adjusted arm, but significantly fewer missed appointments and still fewer total follow-up appointments compared to the conventional follow-up arm. Based on this evidence, the committee believed that the use of risk-adjusted follow-up in adults with stage IB and IIA would be unlikely to be associated with a resource impact and would potentially be cost saving. The committee felt that to mitigate the reduced follow up, patients who did not have a sentinel lymph node biopsy (SLNB) could receive ultrasound and therefore there would be an increased examination into the lymph nodes. The committee also only recommended ultrasound for the

first three years of follow up rather than the full five years of clinical follow-up as the recurrence data appeared to show that the first three years of follow-up are where there is the higher risk of recurrence. The committee felt that ultrasound should be used in between the CT scans, they felt that doing this would increase the surveillance of the patient and optimise the use of ultrasound. Ultrasound was not included in the economic model due to the areas of the body being imaged being different; CT and PET-CT examine the whole body and ultrasound examines just the nodal basin, and subsequently they were not considered to be directly comparable. The committee felt that the introduction of ultrasound to a to the small number of patients who did not receive a SLNB is unlikely to have a large budget impact and the additional costs of scans would potentially be mitigated by the saving in the reduction of clinical visits.

For adults with stage IIB and IIC melanoma, the committee made recommendations to reduce the number of clinical follow-up appointments, from 16 over 5 years to 10 over 5 years, based on the results of the MelFo RCT. However, they were concerned about the low rates of melanoma-specific survival observed in these populations based the data used to define the AJCC 8th edition stages (Amin 2017), which were noted to be lower than patients with stage IIIA melanoma and similar to patients with stage IIIB melanoma (when these patients do not receive adjuvant therapy). 5- and 10-year melanoma-specific survival for stage IIIA is 93% and 88% respectively, whereas stage IIB is 87% and 82% respectively and stage IIIB is 83% and 77% respectively (Gershenwald 2017). Given CT imaging has been recommended in most patients with stage III melanoma (see below discussion for details), the committee agreed that patients with stage IIB or IIC melanoma should also receive CT imaging at a similar frequency (total of eight scans over five years) during their follow-up. The committee recognised that reducing the number of clinical follow-up appointments would be cost saving however, considering routine CT imaging in these populations would lead to increased costs. The committee noted that the results of the existing economic model from the previous iteration of the guideline could provide generalisable economic evidence to support this recommendation. The existing economic model compared follow-up with routine imaging to follow-up with no routine imaging in patients with stage IIIA-IIIC melanoma. The patients included in the model, however, did not receive adjuvant therapy and only received surgery and therefore the rates of recurrence were much higher than those used in the de novo economic model developed for this update. As noted above melanoma-specific survival for stage IIB and IIC are similar to those with stage IIIB (when such patients do not receive adjuvant therapy). However, there was large uncertainty around the results of this existing model but overall, there was an indication that routine imaging would be cost-effective compared to no routine imaging for follow-up, especially when a survival benefit as a result of early detection with imaging was considered in the model. The committee noted that currently available treatments for distant disease are more effective than the treatments considered in the existing model and therefore thought that stage IIB or IIC patients with a distant recurrence identified with imaging would actually have greater benefits in current clinical practice than estimated by the existing model. Therefore, providing further support that routine imaging would likely be cost-effective in patients (i.e., stage IIB and IIC) with similar rates of recurrence that were considered in the existing model. The committee also used the findings from the de novo economic model developed for this update for stage IIIA-IIIC melanoma to infer that imaging during follow-up for stage IIB and IIC patients using CT rather than PET-CT would be more likely to be cost-effective and therefore recommended that imaging be conducted using CT scans. The committee felt that patients with stage IIB and IIC who did not receive a SLNB should receive ultrasound similar to stages IB and IIA.

This would be an increase in resource impact but is likely to small as the number of patients with stage IIB and IIC without a SLNB is likely to be small. For the same reason as stage IB and IIA, higher chance of recurrence in the first three years, the committee recommended ultrasound follow up for three years rather than five years. Therefore, it is likely that there will be a resource impact for follow up in stage IIB and IIC.

For adults with stage IIIA, IIIB and IIIC melanoma who do not receive adjuvant therapy, the committee made a recommendation for clinical review and routine imaging using CT based on the most cost-effective follow-up strategy identified in the de novo economic model. However, the one difference being a lower frequency of follow-up in the first year given these patients do not receive adjuvant therapy. The committee agreed that this would not be a substantial change from current practice and therefore believed the recommendation would not be associated with a significant resource impact. The committee also used the findings from the de novo economic model developed for this update that was based on patients with stage IIIA-IIIC melanoma who received adjuvant therapy. The results of the model were used to infer that imaging during follow-up for high-risk stage IIIA and stage IIIB and IIIC patients who do not receive adjuvant therapy using CT rather than PET-CT would be more likely to be cost-effective and therefore recommended that imaging be conducted using CT. The committee felt that patients who had a positive SLNB but did not receive a lymph node dissection should receive ultrasound. The committee felt that it was important to increase the surveillance in these patients as their risk of recurrence is higher than other stage IIIA patients. The number of patients who had a positive SLNB, but no lymph node dissection is likely to be small, so the resource impact of introducing ultrasound is likely to be small.

For adults with stage IIIA, IIIB and IIIC melanoma and are likely to have received adjuvant therapy, the committee based their recommended clinical review and imaging follow-up from the results of the de novo economic model developed for this update. The committee felt that the most cost-effective timing of follow-up was already commonly used in clinical practice and therefore the associated resource impact was likely to be minimal. However, given the results of the de novo economic model showed that routine imaging with CT was cost-effective compared to using PET-CT the committee indicated that the recommendation would likely reduce the variation in the type of imaging used for follow-up across the country, potentially resulting in a reduction of resource use in hospitals that employ PET-CT for routine imaging follow-up. The committee felt that the patients who have had a positive SLNB but have not received a lymph node dissection should receive ultrasound for years 2 and 3 of follow up, after they have finished adjuvant therapy. The committee felt that it was important to increase the surveillance in these patients as their risk of recurrence is higher than other stage IIIA patients. If a recurrence is found in the lymph node, then they may be taken off adjuvant therapy earlier which would result in a cost saving. The number of patients who had a positive SLNB, but no lymph node dissection is likely to be small, so the resource impact of introducing ultrasound in combination of reducing adjuvant therapy when necessary is likely to be small.

For adults with stage IIID and resected stage IV melanoma, the committee made recommendations for an increased frequency of CT imaging compared to stage IIIA, IIIB and IIIC patients who receive or do not receive adjuvant therapy. Stage IIID melanoma is a newly defined substage and only a small number of patients have resectable stage IV melanoma and therefore were not considered in the previous iteration of the guideline. The committee noted that stage IIID (5 years melanoma-specific survival is 32%, 10 years melanoma-

specific survival is 24%) patients are almost twice as likely to die of melanoma as stage IIIC (5 years melanoma-specific survival is 69%, 10 years melanoma-specific survival is 60%) based on data used to define the AJCC 8th edition stages (Amin 2017, Gershenwald 2017) and those with resectable stage IV melanoma are also at an increased risk of recurrence/death from melanoma. The committee therefore agreed that these patient populations should receive an increased frequency of CT imaging during follow-up. The committee noted that this increased frequency would be associated with costs due to an increase in the number of CT scans used. However, indicated that these patients only make up a small proportion of the total melanoma population and therefore expected the resource impact of these recommendations would not be significant.

For adults with unresectable stage IV melanoma the committee did not make any changes to the recommendations from the previous iteration of the guideline. The committee felt that around 10% of melanoma patients have unresectable stage IV melanoma and that the majority of these will be on systemic treatment, which according to the committee requires a personalised follow-up schedule. Since there will be no change in practice from this recommendation, there will not be a significant resource impact.

Given that a number of recommendations made by the committee across several substages indicate that CT should be used for imaging during the follow-up, the committee believed it was also important to acknowledge that using CT would have further benefits than those assessed in the de novo economic analysis. The committee indicated that if imaging of the brain was needed for a particular patient, this could be safely done by conducting both a CT head and body scan in one patient visit. In contrast, if imaging of the brain was required for a patient undergoing imaging with PET-CT, a separate appointment would need to be arranged for the patient to have an MRI of their brain. The latter would therefore be associated with not only the increased cost of an additional outpatient appointment, but also the much larger unit cost associated with an MRI (£142.76) compared to adding another contrast to a CT scan (£97.15). The committee were also aware that there are limited radiologists and scanners and, therefore, extending a CT scan to the head would likely happen earlier than waiting for an MRI scan at another appointment, and so any brain metastases could be identified earlier, potentially resulting in faster referral and more opportunities for treatment.

Finally, the committee did not change the existing recommendation for using MRI imaging in children with melanoma, as it was felt that the number of children who would need a scan was very small, and the risk of a CT scan outweighed any potential benefit. Given, the recommendation has remained unchanged there is unlikely to be any change in current practice and therefore unlikely for this recommendation to have an impact on resources.

1.1.11.5 Other factors the committee took into account

The committee discussed the need for people with melanoma to have direct contact details for specialist services upon discharge. The committee agreed that it important that all patients received such details to be used whenever the person has the need or if symptoms develop. The committee made recommendations to reflect this. The committee also agreed on the need to offer robust and comprehensive patient education.

The committee discussed whether follow-up strategies should be stratified according to certain risk factors. Evidence suggests that certain characteristics are indicative of poorer

prognosis. In particular, there is some evidence to suggest that male sex, age (younger age being associated with the development of brain metastases and older age with recurrence and mortality), Breslow thickness, mitotic rate and greater lymph node involvement to be indicative of poorer prognosis. However, the committee agreed that there is much of this evidence is inconclusive with findings varying between studies. Additionally, they agreed that stratifying follow-up in accordance with risk factors would be too complex and impractical, without evidence that such an approach would improve outcomes.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.9.1 to 1.9.13 and also helped to inform recommendations 1.4.6 to 1.4.11. This evidence review supported the research recommendations on the follow-up of people who have had melanoma and survivorship.

1.1.13 References – included studies

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Appendices

A.1.1 – Review protocols

A.1.1.1 Review protocol for optimal frequency, setting and duration of follow-up for stage I-III (RQ 6.1)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Intensity and frequency of follow-up for stage 1-3 melanoma
2.	Review question	RQ 6.1 What is the optimal method, frequency, setting and duration of follow-up for stage I-III melanoma?
3.	Objective	To determine the optimal method, frequency, setting and duration of follow-up
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date (of last update, 2015) The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Melanoma

6.	Population	• People with a diagnosis of stage I-IIA melanoma who have undergone treatment with curative intent • People with a diagnosis of stage IIB-IIC melanoma • People with a resected stage III melanoma
7.	Intervention (RCTs) / risk factors (prognostic studies)	Interventions assessed in RCTs: • Intensive follow-up (as defined by study) The following risk factors will be assessed in prognostic studies: • Age • Gender • Location of primary tumour • Lymph node status • Number of positive lymph nodes • Ulceration • Breslow thickness • ECOG performance status • Lymphovascular invasion
8.	Comparator	RCTs: • Less-intensive follow-up (as defined by study)
9.	Types of study to be included	• Cohort studies • RCTs
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update this question in response to uncertainty surrounding the most effective form of follow-up

		following treatment for curative intent. In particular, there is uncertainty surrounding the intensity of follow-up for stage I and low risk stage II after surgical resection, and whether imaging has utility in high risk stage II and resected stage III (and if so, which imaging modality is optimal)
12.	Primary outcomes (critical outcomes)	• Mortality (all cause and melanoma related) • Stage at recurrence • Rate of recurrence and time to recurrence • Patient preference • Health-related quality of life • Adverse events including radiation • Performance status at recurrence
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with

		reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	**Subgroups (to be investigated irrespective of presence of statistical heterogeneity):** • Pregnant women. • People with a compromised immune system. • Melanoma stage
18.	Type and method of review	☒Intervention
		☒Prognostic accuracy
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	TBC
22.	Anticipated completion date	TBC
23.	Stage of review at time of this submission	Review stage
		Preliminary searches

		Piloting of the study selection process
		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	a. Named contact Guideline updates team b Named contact e-mail skincancer@nice.nhs.uk c. Organisational affiliation of the review **National Institute for Health and Care Excellence (NICE)**
25.	Review team members	From the Guideline Updates Team • Caroline Mulvihill • Thomas Jarratt • Brett Doble • Steph Armstrong • Jeremy Dietz • Jemma Deane
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	• Melanoma • Skin cancer • Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 7.1 in NICE Guideline NG14 Melanoma: assessment and management
34.	Current review status	☒Completed
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.1.1.2 Review protocol for accuracy of body imaging during follow-up of stage IIB-III (RQ 6.2)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Body imaging for follow-up of stage 2B - 3 melanoma

2.	Review question	RQ 6.2 What is the diagnostic accuracy of body imaging for re-staging during the follow-up of people with stage 2C (with no sentinel lymph node biopsy) and stage 3 melanoma?
3.	Objective	To determine the accuracy of body imaging for re-staging during the follow-up of stage IIB-III melanoma
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date (of last update, 2015) The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion.
5.	Condition or domain being studied	Melanoma
6.	Population	• People with a diagnosis of stage IIB or IIC melanoma (with no SLNB) or; • People with a diagnosis of stage 3 melanoma
7.	Intervention/Test	• CT • PET-CT • Whole body MRI • US
8.	Comparator/Reference standard	• FNAC • Clinical observation, clinical examination (healthcare practitioner and patient examination) or patient reported follow-up • Combination of one or more reference standards

9.	Types of study to be included	• Diagnostic accuracy studies
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update this question in response to uncertainty surrounding the role of imaging during follow-up.
12.	Primary outcomes (critical outcomes)	• Likelihood ratios • Sensitivity/specificity
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.

16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	**Subgroups (to be investigated irrespective of presence of statistical heterogeneity):** • Duration of follow-up • Frequency of follow-up • Pregnant women. • People with a compromised immune system. • Melanoma stage • Patients with recurring brain metastases
18.	Type and method of review	☒Diagnostic accurcy
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	TBC
22.	Anticipated completion date	TBC

The follow up of people with melanoma

23.	Stage of review at time of this submission	Review stage
		Preliminary searches
		Piloting of the study selection process
		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	a. Named contact Guideline updates team b Named contact e-mail skincancer@nice.nhs.uk c Organisational affiliation of the review **National Institute for Health and Care Excellence (NICE)**
25.	Review team members	From the Guideline Updates Team • Caroline Mulvihill • Thomas Jarratt • Brett Doble • Steph Armstrong • Jeremy Dietz • Jemma Deane
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	• Melanoma • Skin cancer • Skin tumour • Follow up • CT • PET-CT • Total body MRI • US
33.	Details of existing review of same topic by same authors	This is a new review question for this update
34.	Current review status	☒Diagnostic accuracy
35..	Additional information	

36.	Details of final publication	www.nice.org.uk

A.1.1.3 Review protocol for brain imaging at staging and follow-up (RQ 6.3)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Brain imaging during follow-up
2.	Review question	RQ 6.3 Should brain imaging be included for people with melanoma who are undergoing body imaging as part of follow-up, and who have no neurological signs or symptoms?
3.	Objective	To determine the role of brain imaging in addition to body imaging as part of follow-up for people who have no neurological signs or symptoms
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date (of last update, 2015) The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Melanoma

6.	Population	People with a diagnosis of stage IIC-IV melanoma at time of diagnosis
7.	Test (diagnostic accuracy studies)/ prognostic factors	Diagnosis accuracy studies • Routine brain imaging given at baseline or during follow-up • Care as usual (without inclusion of brain in field of view) Prognostic studies • Age • Gender • Tumour stage • Ulceration • Mitotic rate • Tumour location
8.	Reference standard	Diagnostic accuracy studies: • Symptomatic development of brain metastases during follow-up
9.	Types of study to be included	• RCTs • Non-randomized controlled trials • Cohort studies (prospective and retrospective)
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need

		to update this question in response to uncertainty surrounding the role of brain imaging during follow-up
12.	Primary outcomes (critical outcomes)	Diagnostic accuracy studies • Sensitivity/specificity • Likelihood ratios Prognostic studies • Brain metastasis presence at baseline or development during follow-up
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

		Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	**Subgroups (to be investigated irrespective of presence of statistical heterogeneity):** • Imaging modality • Pregnant women. • People with a compromised immune system. • Type (MRI vs. CT) and intensity of brain imaging • Melanoma stage
18.	Type and method of review	☒Prognostic accuracy
		☒Diagnostic accuracy
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	TBC
22.	Anticipated completion date	TBC
23.	Stage of review at time of this submission	Review stage
		Preliminary searches
		Piloting of the study selection process

		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	5a. Named contact Guideline updates team 5b Named contact e-mail skincancer@nice.nhs.uk 5e Organisational affiliation of the review **National Institute for Health and Care Excellence (NICE)**
25.	Review team members	From the Guideline Updates Team • Caroline Mulvihill • Thomas Jarratt • Brett Doble • Steph Armstrong • Jeremy Dietz • Jemma Deane
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155

29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	• Brain imaging • Melanoma • Follow up • Skin cancer • Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 2.5 in NICE Guideline NG14 Melanoma: assessment and management
34.	Current review status	☒Completed
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

A.1.1.4 Review protocol for follow-up of stage IV (and unresectable III) disease (RQ 6.4)

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Follow-up body imaging for stage 4 (and unresectable stage 3) melanoma

2.	Review question	RQ 6.4 What is the effectiveness of body imaging for the follow-up of people with stage 4 (and unresectable stage 3) melanoma after concluding treatment, including the optimal frequency and duration?
3.	Objective	To determine the efficacy of body imaging for follow-up of stage 4 (and unresectable stage 3) melanoma
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date (of last update, 2015) The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Melanoma
6.	Population	• People with a diagnosis of stage 4 melanoma or; • People with a diagnosis of unresectable stage 3 melanoma
7.	Test (diagnostic accuracy studies)/risk factors (prognostic studies)	The following index tests will be assessed in diagnostic accuracy studies*: • CT • PET-CT • Whole body MRI • US
8.	Reference standard (diagnostic accuracy studies)	• Imaging methods compared to each other *Analysis will be stratified by intensity, frequency and duration of imaging during follow-up

		The following risk factors will be assessed in prognostic studies: • Age • Gender • Location of primary tumour • Lymph node status • Number of positive lymph nodes • Ulceration • Breslow thickness • ECOG performance status • Lymphovascular invasion
9.	Types of study to be included	• RCTs • Non-randomized controlled studies • Prospective cohort studies
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update this question in response to uncertainty surrounding the role of imaging during follow-up.
12.	Primary outcomes (critical outcomes)	• Mortality (all cause and melanoma related) • Stage at recurrence • Rate of recurrence and time to recurrence • Patient preference • Health-related quality of life • Adverse events including radiation
13.	Secondary outcomes (important outcomes)	None

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow. Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

		Meta-analyses will be performed in Cochrane Review Manager V5.3
17.	Analysis of sub-groups	**Subgroups (to be investigated irrespective of presence of statistical heterogeneity):** • Duration of follow-up • Frequency of follow-up • Pregnant women. • People with a compromised immune system. • Melanoma stage
18.	Type and method of review	☒Diagnostic accuracy
		☒Prognostic accuracy
		☒Intervention
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	TBC
22.	Anticipated completion date	TBC
23.	Stage of review at time of this submission	Review stage
		Preliminary searches
		Piloting of the study selection process
		Formal screening of search results against eligibility criteria
		Data extraction
		Risk of bias (quality) assessment
		Data analysis
24.	Named contact	5a. Named contact Guideline updates team 5b Named contact e-mail skincancer@nice.nhs.uk 5e Organisational affiliation of the review

		National Institute for Health and Care Excellence (NICE)
25.	Review team members	From the Guideline Updates Team • Caroline Mulvihill • Thomas Jarratt • Brett Doble • Steph Armstrong • Jeremy Dietz • Jemma Deane
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10155
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

32.	Keywords	• Melanoma • Follow-up • Skin cancer • Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 2.5 in NICE Guideline NG14 Melanoma: assessment and management
34.	Current review status	☒Completed
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Searches were run on 9th December 2020 in Medline, Medline in Process, Medline epub, the Cochrane Database of Systematic Reviews (CRD/CENTRAL) and DARE (Wiley platform). These searches are presented below.

Table 5 Search strategy for Medline

Database: Medline
1 exp Melanoma/ (96197)
2 Skin Neoplasms/ (122179)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (104932)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (62202)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (25240)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (69)
7 dubreuilh*.tw. (74)
8 (maligna* adj2 lentigo*).tw. (1077)
9 LMM.tw. (896)
10 or/1-9 (253749)
11 diagnostic imaging/ (41253)
12 (diagnos* adj imag*).tw. (14491)
13 exp Ultrasonography/ (442717)
14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (358379)
15 exp Tomography, X-Ray Computed/ (439691)
16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (113134)
17 cine-ct.tw. (154)
18 ((comput* or electron beam) adj3 tomogra*).tw. (259726)
19 tomodensitometr*.tw. (945)
20 exp Tomography, Emission-Computed/ (114564)
21 (PET adj (CT or examination* or imag* or scan*)).tw. (39193)
22 (positron adj2 tomograph*).tw. (49323)
23 spect.tw. (25116)
24 exp Magnetic Resonance Imaging/ (461319)
25 magnet* resonance.tw. (290200)
26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (1006485)
27 ((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (83271)
28 ((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (16480)
29 Whole Body Imaging/ (5062)
30 (whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (4543)
31 wbmr*.tw. (93)
32 or/11-31 (2288055)
33 Follow-Up Studies/ (651891)
34 (follow-up or followup).tw. (877661)
35 (checkup*1 or check-up*1).tw. (13118)
36 surveillance.tw. (156194)
37 (re-examin* or reexamin*).tw. (24666)
38 ((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (2652)
39 or/33-38 (1407445)

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Database: Medline
40 32 or 39 (3469441)
41 Neoplasm Staging/ (176383)
42 Neoplasm Recurrence, Local/ (119904)
43 exp Neoplasm Metastasis/ (206033)
44 (disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (2246242)
45 ((AJCC or UICC) adj4 (classification* or system*)).tw. (2111)
46 (sensitiv: or predictive value:).mp. or accurac:.tw. (1913345)
47 prognosis.sh. (518913)
48 prognos:.tw. (527238)
49 or/41-48 (4479075)
50 10 and 40 and 49 (29926)
51 limit 50 to english language (26589)
52 animals/ not humans/ (4728824)
53 51 not 52 (25661)
54 limit 53 to (letter or historical article or comment or editorial or news or case reports) (5688)
55 53 not 54 (19973)
56 limit 55 to ed=20141001-20201209 (6216)

Table 24 Search strategy for Medline in progress

Database: Medline in Process
1 exp Melanoma/ (0)
2 Skin Neoplasms/ (0)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (12680)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (6978)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (3242)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (1)
7 dubreuilh*.tw. (0)
8 (maligna* adj2 lentigo*).tw. (82)
9 LMM.tw. (183)
10 or/1-9 (20702)
11 diagnostic imaging/ (0)
12 (diagnos* adj imag*).tw. (2205)
13 exp Ultrasonography/ (0)
14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (57478)
15 exp Tomography, X-Ray Computed/ (0)
16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (18604)
17 cine-ct.tw. (9)
18 ((comput* or electron beam) adj3 tomogra*).tw. (47254)
19 tomodensitometr*.tw. (60)
20 exp Tomography, Emission-Computed/ (0)
21 (PET adj (CT or examination* or imag* or scan*)).tw. (8826)
22 (positron adj2 tomograph*).tw. (9026)
23 spect.tw. (2686)
24 exp Magnetic Resonance Imaging/ (0)
25 magnet* resonance.tw. (51557)
26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (145300)

Database: Medline in Process	
27	((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (9632)
28	((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (2184)
29	Whole Body Imaging/ (0)
30	(whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (570)
31	wbmr*.tw. (11)
32	or/11-31 (270170)
33	Follow-Up Studies/ (0)
34	(follow-up or followup).tw. (116085)
35	(checkup*1 or check-up*1).tw. (2076)
36	surveillance.tw. (23133)
37	(re-examin* or reexamin*).tw. (2969)
38	((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (556)
39	or/33-38 (141982)
40	32 or 39 (390678)
41	Neoplasm Staging/ (0)
42	Neoplasm Recurrence, Local/ (0)
43	exp Neoplasm Metastasis/ (0)
44	(disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (361984)
45	((AJCC or UICC) adj4 (classification* or system*)).tw. (351)
46	(sensitiv: or predictive value:).mp. or accurac:.tw. (257466)
47	prognosis.sh. (0)
48	prognos:.tw. (87482)
49	or/41-48 (634304)
50	10 and 40 and 49 (2835)
51	limit 50 to english language (2810)
52	animals/ not humans/ (1)
53	51 not 52 (2810)
54	limit 53 to (letter or historical article or comment or editorial or news or case reports) (460)
55	53 not 54 (2350)
56	limit 55 to dt=20141001-20201209 (1861)

Table 25 Search strategy for Medline Epub

Database: Medline Epub	
1	exp Melanoma/ (0)
2	Skin Neoplasms/ (0)
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (1795)
4	((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (975)
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (401)
6	(hutchinson* adj2 (freckle* or melano*)).tw. (1)
7	dubreuilh*.tw. (0)
8	(maligna* adj2 lentigo*).tw. (25)
9	LMM.tw. (32)
1	exp Melanoma/ (0)
2	Skin Neoplasms/ (0)

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Database: Medline Epub
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (1685)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (951)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (429)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (1)
7 dubreuilh*.tw. (0)
8 (maligna* adj2 lentigo*).tw. (26)
9 LMM.tw. (30)
10 or/1-9 (2744)
11 diagnostic imaging/ (0)
12 (diagnos* adj imag*).tw. (326)
13 exp Ultrasonography/ (0)
14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (7031)
15 exp Tomography, X-Ray Computed/ (0)
16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (2600)
17 cine-ct.tw. (2)
18 ((comput* or electron beam) adj3 tomogra*).tw. (5847)
19 tomodensitometr*.tw. (1)
20 exp Tomography, Emission-Computed/ (0)
21 (PET adj (CT or examination* or imag* or scan*)).tw. (1640)
22 (positron adj2 tomograph*).tw. (1661)
23 spect.tw. (774)
24 exp Magnetic Resonance Imaging/ (0)
25 magnet* resonance.tw. (5951)
26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (15544)
27 ((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (1527)
28 ((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (308)
29 Whole Body Imaging/ (0)
30 (whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (75)
31 wbmr*.tw. (3)
32 or/11-31 (31724)
33 Follow-Up Studies/ (0)
34 (follow-up or followup).tw. (22005)
35 (checkup*1 or check-up*1).tw. (260)
36 surveillance.tw. (4453)
37 (re-examin* or reexamin*).tw. (282)
38 ((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (83)
39 or/33-38 (26362)
40 32 or 39 (54359)
41 Neoplasm Staging/ (0)
42 Neoplasm Recurrence, Local/ (0)
43 exp Neoplasm Metastasis/ (0)
44 (disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (43106)
45 ((AJCC or UICC) adj4 (classification* or system*)).tw. (39)
46 (sensitiv: or predictive value:).mp. or accurac:.tw. (26578)
47 prognosis.sh. (0)
48 prognos:.tw. (11771)
49 or/41-48 (72277)
50 10 and 40 and 49 (436)

Database: Medline Epub
51 limit 50 to english language (435)
52 animals/ not humans/ (0)
53 51 not 52 (435)
54 limit 53 to (letter or historical article or comment or editorial or news or case reports) (7)
55 53 not 54 (428)

Table 26 Search strategy for Embase

Database: Embase
1 exp melanoma skin cancer/ or melanoma/ or cutaneous melanoma/ or metastatic melanoma/ or superficial spreading melanoma/ or skin carcinoma/ (158548)
2 skin tumor/ or skin cancer/ or epithelium tumor/ (67513)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (164955)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (93967)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (40015)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (80)
7 dubreuilh*.tw. (73)
8 (maligna* adj2 lentigo*).tw. (1692)
9 LMM.tw. (1532)
10 or/1-9 (334417)
11 *diagnostic imaging/ (46635)
12 (diagnos* adj imag*).tw. (23356)
13 exp *echography/ (217556)
14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (614134)
15 *computer assisted tomography/ or *electron beam tomography/ or *x-ray computed tomography/ (132662)
16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (232577)
17 cine-ct.tw. (223)
18 ((comput* or electron beam) adj3 tomogra*).tw. (397090)
19 tomodensitometr*.tw. (1072)
20 exp *computer assisted emission tomography/ (72306)
21 (PET adj (CT or examination* or imag* or scan*)).tw. (101045)
22 (positron adj2 tomograph*).tw. (79490)
23 spect.tw. (48330)
24 exp *nuclear magnetic resonance imaging/ (259626)
25 magnet* resonance.tw. (435776)
26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (1608252)
27 ((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (143563)
28 ((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (28432)
29 exp *whole body imaging/ (4828)
30 (whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (8830)
31 wbmr*.tw. (256)
32 or/11-31 (3020465)
33 *follow up/ or *aftercare/ or *"evaluation and follow up"/ (48101)
34 (follow-up or followup).tw. (1612359)
35 (checkup*1 or check-up*1).tw. (22527)
36 surveillance.tw. (253734)

Database: Embase
37 (re-examin* or reexamin*).tw. (32848)
38 ((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (5812)
39 or/33-38 (1886491)
40 32 or 39 (4618731)
41 *cancer staging/ (34319)
42 *tumor recurrence/ (9839)
43 *metastasis/ or exp *lymphatic system metastasis/ or exp *metastatic melanoma/ or *skin metastasis/ (110706)
44 (disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (3652089)
45 ((AJCC or UICC) adj4 (classification* or system*)).tw. (4091)
46 (sensitiv: or predictive value:).mp. or accurac:.tw. (2669859)
47 prognosis.sh. (596167)
48 prognos:.tw. (948927)
49 or/41-48 (6608083)
50 10 and 40 and 49 (41894)
51 limit 50 to english language (38550)
52 nonhuman/ not human/ (4766142)
53 51 not 52 (37341)
54 (conference abstract or conference paper or conference proceeding or "conference review" or letter or editorial).pt. (6545646)
55 53 not 54 (23501)
56 limit 55 to dc=20141001-20201209 (8944)

Table 27 Search strategy for Cochrane Wiley

Database: Cochrane Wiley (CRD/CENTRAL)
ID Search Hits
#1 MeSH descriptor: [Melanoma] explode all trees 1815
#2 MeSH descriptor: [Skin Neoplasms] this term only 1570
#3 ((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)):ti,ab,kw 5439
#4 (((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))):ti,ab,kw 4014
#5 (((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*))):ti,ab,kw 693
#6 ((hutchinson* NEAR/2 (freckle* or melano*))):ti,ab,kw 9
#7 (dubreuilh*):ti,ab,kw 0
#8 (maligna* NEAR/2 lentigo*) 55
#9 (LMM):ti,ab,kw 120
#10 {or #1-#9} 8568
#11 MeSH descriptor: [Diagnostic Imaging] this term only 124
#12 ((diagnos* NEAR/1 imag*)):ti,ab,kw 28145
#13 MeSH descriptor: [Ultrasonography] explode all trees 13683
#14 ((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)):ti,ab,kw 45042
#15 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees 5027
#16 (((CT or CAT) NEAR/1 (electron beam or examination* or imag* or scan* or x ray*))):ti,ab,kw 8541

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Database: Cochrane Wiley (CRD/CENTRAL)	
#17	(cine-ct):ti,ab,kw 3
#18	(((comput* or electron beam) NEAR/3 tomogra*)):ti,ab,kw 20536
#19	(tomodensitometr*):ti,ab,kw 66
#20	MeSH descriptor: [Tomography, Emission-Computed] explode all trees 2473
#21	((PET NEAR/1 (CT or examination* or imag* or scan*))):ti,ab,kw 3425
#22	((positron NEAR/2 tomograph*)):ti,ab,kw 4252
#23	(spect):ti,ab,kw 1750
#24	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 7784
#25	((magnet* NEAR/1 resonance)):ti,ab,kw 27352
#26	((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*)):ti,ab,kw 24043
#27	(((magnet* or MR*) NEAR/1 (examination* or imag* or scan* or tomograph*))):ti,ab,kw 9811
#28	(((diffusion or planar or echoplanar or echo-planar or functional) NEAR/1 (imag* or scan* or tomogra*))):ti,ab,kw 1126
#29	MeSH descriptor: [Whole Body Imaging] this term only 66
#30	((whole body NEAR/1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*))):ti,ab,kw 417
#31	(wbmr*):ti,ab,kw 29
#32	{or #11-#31} 115702
#33	MeSH descriptor: [Follow-Up Studies] this term only 59090
#34	((follow-up or followup)):ti,ab,kw 242661
#35	((checkup* or check-up*)):ti,ab,kw 1371
#36	(surveillance):ti,ab,kw 8106
#37	((re-examin* or reexamin*)):ti,ab,kw 1459
#38	(((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR/1 (assess* or examin* or evaluat* or monitor* or screen*))):ti,ab,kw 1425
#39	{or #33-#38} 251160
#40	#32 or #39 340601
#41	MeSH descriptor: [Neoplasm Staging] this term only 6395
#42	MeSH descriptor: [Neoplasm Recurrence, Local] this term only 4211
#43	MeSH descriptor: [Neoplasm Metastasis] explode all trees 5169
#44	((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM)):ti,ab,kw 213387
#45	(((AJCC or UICC) NEAR/4 (classification* or system*))):ti,ab,kw 215
#46	(sensitiv*):ti,ab,kw 73157
#47	MeSH descriptor: [Sensitivity and Specificity] this term only 8596
#48	((predictive NEAR/1 value*)):ti,ab,kw 13460
#49	MeSH descriptor: [Predictive Value of Tests] this term only 6985
#50	(accurac*):ti,ab,kw 21630
#51	MeSH descriptor: [Prognosis] this term only 13514
#52	(prognos*):ti,ab,kw 43647
#53	{or #41-#52} 317430
#54	#10 AND #40 AND #53 with Cochrane Library publication date Between Oct 2014 and Dec 2020 1347
#55	#10 AND #40 AND #53 with Publication Year from 2014 to 2020, in Trials 1035
#56	#54 or #55 1363

Table 28 Search strategy for CRD (DARE)

Database: CRD (DARE)		
Search	Hits	
1	MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES	221
2	MeSH DESCRIPTOR skin neoplasms	193
3	((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*))	329
4	(((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)))	386
5	(((maligna* or melano*) NEAR2 (freckle* or lesion* or mole* or nev* or naev*)))	102
6	((hutchinson* NEAR2 (freckle* or melano*)))	0
7	(dubreuilh*)	0
8	((maligna* NEAR2 lentigo*))	0
9	(LMM)	0
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	630
11	MeSH DESCRIPTOR diagnostic imaging	176
12	((diagnos* NEAR1 imag*))	387
13	MeSH DESCRIPTOR Ultrasonography EXPLODE ALL TREES	1154
14	((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*))	2531
15	MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES	1044
16	(((CT or CAT) near1 (electron beam or examination* or imag* or scan* or x ray*)))	342
17	(cine-ct)	0
18	(((comput* or electron beam) NEAR3 tomogra*))	1400
19	(tomodensitometr*)	1
20	MeSH DESCRIPTOR Tomography, Emission-Computed EXPLODE ALL TREES	665
21	((PET NEAR1 (CT or examination* or imag* or scan*)))	309
22	((positron NEAR2 tomograph*))	626
23	(spect)	118
24	MeSH DESCRIPTOR Magnetic Resonance Imaging EXPLODE ALL TREES	840
25	(magnet* resonance)	1248
26	((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*))	620
27	(((magnet* or MR*) NEAR1 (examination* or imag* or scan* or tomograph*)))	1121
28	(((diffusion or planar or echoplanar or echo-planar or functional) NEAR1 (imag* or scan* or tomogra*)))	60
29	MeSH DESCRIPTOR Whole Body Imaging	18
30	((whole body NEAR1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*)))	46
31	(wbmr*)	0
32	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	5213
33	MeSH DESCRIPTOR Follow-Up Studies	2032
34	((follow-up or followup))	15587
35	((checkup* or check-up*))	61
36	(surveillance)	1119
37	((re-examin* or reexamin*))	66
38	(((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR1 (assess* or examin* or evaluat* or monitor* or screen*)))	70
39	#33 OR #34 OR #35 OR #36 OR #37 OR #38	16403
40	#32 OR #39	20088
41	MeSH DESCRIPTOR Neoplasm Staging	826
42	MeSH DESCRIPTOR Neoplasm Recurrence, Local	660

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Database: CRD (DARE)		
43	MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES	705
44	((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM))	12588
45	(((AJCC or UICC) NEAR4 (classification* or system*)))	3
46	(sensitiv*)	16009
47	MeSH DESCRIPTOR sensitivity and specificity	3305
48	((predictive NEAR1 value*))	1692
49	MeSH DESCRIPTOR predictive value of tests	1168
50	(accurac*)	3291
51	MeSH DESCRIPTOR prognosis	1656
52	(prognos*)	4385
53	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	28086
54	#10 AND #40 AND #53	218
55	* IN DARE FROM 2014 TO 2020	9540
56	#54 AND #55	9

RQ 6.3 Should brain imaging be included for people with melanoma who are undergoing body imaging as part of follow-up, and who have no neurological signs or symptoms?

An additional search was run on 31st March 2021 in Medline, Medline in Process, Medline epub, the Cochrane Database of Systematic Reviews (CRD/CENTRAL) and DARE (Wiley platform). These searches are presented below.

An additional search was requested in March 2021 to capture references from 2000 as the clinical experts discovered that some elements of the review will be new and not simply an update of the evidence from 2015, so therefore we needed to search back further to capture earlier papers. The previous search that was ran in December 2020 covered the time period between 2014-2020.

**Additional brain imaging terms have also been added to the strategy (lines 58-60).

Table 10 Search strategy for Medline

Database: Medline, Medline in Process, ePubs ahead of print		
Ovid MEDLINE(R) <1996 to March 30, 2021>		
1	exp Melanoma/	65642
2	Skin Neoplasms/	80667
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw.	78606
4	((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw.	46433
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.	19849
6	(hutchinson* adj2 (freckle* or melano*)).tw.	14
7	dubreuilh*.tw.	12
8	(maligna* adj2 lentigo*).tw.	754
9	LMM.tw.	742
10	or/1-9	175057
11	diagnostic imaging/	36732
12	(diagnos* adj imag*).tw.	12740
13	exp Ultrasonography/	341860
14	(ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw.	281359

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Database: Medline, Medline in Process, ePubs ahead of print		
15	exp Tomography, X-Ray Computed/	362903
16	((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw.	93575
17	cine-ct.tw.	80
18	((comput* or electron beam) adj3 tomogra*).tw.	215708
19	tomodensitometr*.tw.	454
20	exp Tomography, Emission-Computed/	102933
21	(PET adj (CT or examination* or imag* or scan*)).tw.	39276
22	(positron adj2 tomograph*).tw.	45413
23	spect.tw.	20971
24	exp Magnetic Resonance Imaging/	430826
25	magnet* resonance.tw.	257823
26	(fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw.	866952
27	((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw.	73263
28	((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw.	15280
29	Whole Body Imaging/	5187
30	(whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw.	3994
31	wbmr*.tw.	96
32	or/11-31	1921555
33	Follow-Up Studies/	491626
34	(follow-up or followup).tw.	759793
35	(checkup*1 or check-up*1).tw.	10851
36	surveillance.tw.	143180
37	(re-examin* or reexamin*).tw.	16566
38	((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw.	2280
39	or/33-38	1167540
40	32 or 39	2881991
41	Neoplasm Staging/	151308
42	Neoplasm Recurrence, Local/	93087
43	exp Neoplasm Metastasis/	136282
44	(disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw.	1815237
45	((AJCC or UICC) adj4 (classification* or system*)).tw.	1860
46	(sensitiv: or predictive value:).mp. or accurac:.tw.	1565719
47	prognosis.sh.	396664
48	prognos:.tw.	442891
49	or/41-48	3566220
50	10 and 40 and 49	25628
51	limit 50 to english language	23240
52	animals/ not humans/	2587558
53	51 not 52	22493
54	limit 53 to (letter or historical article or comment or editorial or news or case reports)	5054
55	53 not 54	17439
56	limit 55 to ed=20141001-20201209	6238
57	limit 55 to ed=20000101-20141001	9368
58	exp Neuroimaging/	128214
59	((Brain* or neur* or head or cereb* or crani* or intracrani* or skull*) adj (imag* or mr* or radiograph* or scan* or screen* or tomograph* or exam* or CT or CAT or PET or x-ray or diagnos*)).tw.	55362

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Database: Medline, Medline in Process, ePubs ahead of print		
60	Neuroimag*.tw.	40792
61	or/58-60	198828
62	10 and 49 and 61	266
63	limit 62 to english language	231
64	animals/ not humans/	2587558
65	63 not 64	224
66	limit 65 to (letter or historical article or comment or editorial or news or case reports)	105
67	65 not 66	172
68	limit 66 to ed=20000101-20210331	101

Table 11 Search strategy for Embase

Database: Embase		
1	exp melanoma skin cancer/ or melanoma/ or cutaneous melanoma/ or metastatic melanoma/ or superficial spreading melanoma/ or skin carcinoma/	162062
2	skin tumor/ or skin cancer/ or epithelium tumor/	68561
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw.	168674
4	((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw.	96084
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.	40922
6	(hutchinson* adj2 (freckle* or melano*)).tw.	82
7	dubreuilh*.tw.	75
8	(maligna* adj2 lentigo*).tw.	1738
9	LMM.tw.	1604
10	or/1-9	341428
11	*diagnostic imaging/	48271
12	(diagnos* adj imag*).tw.	23842
13	exp *echography/	221332
14	(ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw.	627935
15	*computer assisted tomography/ or *electron beam tomography/ or *x-ray computed tomography/	133714
16	((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw.	238390
17	cine-ct.tw.	219
18	((comput* or electron beam) adj3 tomogra*).tw.	406758
19	tomodensitometr*.tw.	1082
20	exp *computer assisted emission tomography/	74127
21	(PET adj (CT or examination* or imag* or scan*)).tw.	104135
22	(positron adj2 tomograph*).tw.	81064
23	spect.tw.	48864
24	exp *nuclear magnetic resonance imaging/	259416
25	magnet* resonance.tw.	442359
26	(fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw.	1633780
27	((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw.	144572
28	((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw.	28144
29	exp *whole body imaging/	4916
30	(whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw.	8868
31	wbmr*.tw.	268
32	or/11-31	3074858

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Database: Embase		
33	*follow up/ or *aftercare/ or *"evaluation and follow up"/	50070
34	(follow-up or followup).tw.	1658054
35	(checkup*1 or check-up*1).tw.	23163
36	surveillance.tw.	261535
37	(re-examin* or reexamin*).tw.	33321
38	((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw.	5973
39	or/33-38	1939842
40	32 or 39	4717481
41	*cancer staging/	35913
42	*tumor recurrence/	9960
43	*metastasis/ or exp *lymphatic system metastasis/ or exp *metastatic melanoma/ or *skin metastasis/	113169
44	(disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw.	3747662
45	((AJCC or UICC) adj4 (classification* or system*)).tw.	4208
46	(sensitiv: or predictive value:).mp. or accurac:.tw.	2720692
47	prognosis.sh.	608797
48	prognos:.tw.	980095
49	or/41-48	6760233
50	10 and 40 and 49	43060
51	limit 50 to english language	39699
52	nonhuman/ not human/	4800682
53	51 not 52	38468
54	(conference abstract or conference paper or conference proceeding or "conference review" or letter or editorial).pt.	6714124
55	53 not 54	24057
56	limit 55 to dc=20141001-20201209	8694
57	limit 55 to dc=20000101-20141001	10716
58	neurologic examination/	69426
59	((Brain* or neur* or head or cereb* or crani* or intracrani* or skull*) adj (imag* or mr* or radiograph* or scan* or screen* or tomograph* or exam* or CT or CAT or PET or x-ray or diagnos*)).tw.	135435
60	Neuroimag*.tw.	74897
61	or/58-60	248620
62	10 and 49 and 61	868
63	limit 62 to english language	821
64	nonhuman/ not human/	4800682
65	63 not 64	808
66	(conference abstract or conference paper or conference proceeding or "conference review" or letter or editorial).pt.	6714124
67	65 not 66	436
68	limit 67 to dc=20000101-20210331	371

Table 29 Search strategy for Cochrane Wiley

Database: Cochrane Wiley (CRD/CENTRAL)		
#1	MeSH descriptor: [Melanoma] explode all trees	1843
#2	MeSH descriptor: [Skin Neoplasms] this term only	1598
#3	((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)):ti,ab,kw	5578

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Database: Cochrane Wiley (CRD/CENTRAL)
#4 (((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))):ti,ab,kw 4117
#5 (((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*))):ti,ab,kw 709
#6 ((hutchinson* NEAR/2 (freckle* or melano*))):ti,ab,kw 9
#7 (dubreuilh*):ti,ab,kw 0
#8 (maligna* NEAR/2 lentigo*) 57
#9 (LMM):ti,ab,kw 129
#10 {or #1-#9} 8772
#11 MeSH descriptor: [Diagnostic Imaging] this term only 126
#12 ((diagnos* NEAR/1 imag*)):ti,ab,kw 28707
#13 MeSH descriptor: [Ultrasonography] explode all trees 13854
#14 ((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)):ti,ab,kw 46442
#15 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees 5099
#16 (((CT or CAT) NEAR/1 (electron beam or examination* or imag* or scan* or x ray*))):ti,ab,kw 8891
#17 (cine-ct):ti,ab,kw 3
#18 (((comput* or electron beam) NEAR/3 tomogra*)):ti,ab,kw 21208
#19 (tomodensitometr*):ti,ab,kw 65
#20 MeSH descriptor: [Tomography, Emission-Computed] explode all trees 2492
#21 ((PET NEAR/1 (CT or examination* or imag* or scan*))):ti,ab,kw 3548
#22 ((positron NEAR/2 tomograph*)):ti,ab,kw 4395
#23 (spect):ti,ab,kw 1776
#24 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 7924
#25 ((magnet* NEAR/1 resonance)):ti,ab,kw 28397
#26 ((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*)):ti,ab,kw 24962
#27 (((magnet* or MR*) NEAR/1 (examination* or imag* or scan* or tomograph*))):ti,ab,kw 10153
#28 (((diffusion or planar or echoplanar or echo-planar or functional) NEAR/1 (imag* or scan* or tomogra*))):ti,ab,kw 1156
#29 MeSH descriptor: [Whole Body Imaging] this term only 67
#30 ((whole body NEAR/1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*))):ti,ab,kw 424
#31 (wbmr*):ti,ab,kw 29
#32 {or #11-#31} 119343
#33 MeSH descriptor: [Follow-Up Studies] this term only 59748
#34 ((follow-up or followup)):ti,ab,kw 249825
#35 ((checkup* or check-up*)):ti,ab,kw 1441
#36 (surveillance):ti,ab,kw 8379
#37 ((re-examin* or reexamin*)):ti,ab,kw 1488
#38 (((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR/1 (assess* or examin* or evaluat* or monitor* or screen*))):ti,ab,kw 1481
#39 {or #33-#38} 258629
#40 #32 or #39 350896
#41 MeSH descriptor: [Neoplasm Staging] this term only 6493
#42 MeSH descriptor: [Neoplasm Recurrence, Local] this term only 4295
#43 MeSH descriptor: [Neoplasm Metastasis] explode all trees 5237
#44 ((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM)):ti,ab,kw 219435
#45 (((AJCC or UICC) NEAR/4 (classification* or system*))):ti,ab,kw 220

Database: Cochrane Wiley (CRD/CENTRAL)		
#46	(sensitiv*):ti,ab,kw	75163
#47	MeSH descriptor: [Sensitivity and Specificity] this term only	8640
#48	((predictive NEAR/1 value*)):ti,ab,kw	13768
#49	MeSH descriptor: [Predictive Value of Tests] this term only	7050
#50	(accurac*):ti,ab,kw	22493
#51	MeSH descriptor: [Prognosis] this term only	13730
#52	(prognos*):ti,ab,kw	44898
#53	{or #41-#52}	326371
#54	#10 AND #40 AND #53 with Cochrane Library publication date Between Oct 2014 and Dec 2020	1359
#55	#10 AND #40 AND #53 with Publication Year from 2014 to 2020, in Trials	1066
#56	#54 or #55	1394
#57	#10 and #40 and #53 with Cochrane Library publication date Between Jan 2000 and Oct 2014	388
#58	#10 and #40 and #53 with Publication Year from 2000 to 2014, in Trials	708
#59	#57 or #58	750
#60	MeSH descriptor: [Neuroimaging] explode all trees	2918
#61	((Brain* or neur* or head or cereb* or crani* or intracrani* or skull*) NEAR (imag* or mr* or radiograph* or scan* or screen* or tomograph* or exam* or CT or CAT or PET or x-ray or diagnos*)):ti,ab,kw	29126
#62	Neuroimag*:ti,ab,kw	3623
#63	#60 or #61 or #62	31964
#64	#10 and #53 and #63 with Cochrane Library publication date Between Jan 2000 and Mar 2021	129
#65	#10 and #53 and #63 with Publication Year from 2000 to 2021, in Trials	124
#66	#64 or #65	129

Table 30 Search strategy for CRD (DARE)

Line	Search	Hits	
1	MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES	221	Delete
2	MeSH DESCRIPTOR Skin Neoplasms EXPLODE ALL TREES	194	Delete
3	(((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)))	329	Delete
4	((((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))))	386	Delete
5	((((maligna* or melano*) NEAR2 (freckle* or lesion* or mole* or nev* or naev*))))	102	Delete
6	(((hutchinson* NEAR2 (freckle* or melano*))))	0	Delete
7	((dubreuilh*))	0	Delete
8	(((maligna* NEAR2 lentigo*)))	0	Delete
9	((LMM))0		Delete
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	631	Delete
11	MeSH DESCRIPTOR Diagnostic Imaging EXPLODE ALL TREES	4336	Delete
12	(((diagnos* NEAR1 imag*)))	387	Delete
13	MeSH DESCRIPTOR Ultrasonography EXPLODE ALL TREES	1154	Delete
14	(((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)))	2531	Delete
15	MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES	1044	Delete

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16	((((CT or CAT) near1 (electron beam or examination* or imag* or scan* or x ray*)))) 342	Delete	
17	((cine-ct))	0	Delete
18	((((comput* or electron beam) NEAR3 tomogra*)))	1400	Delete
19	((tomodensitometr*))	1	Delete
20	MeSH DESCRIPTOR Tomography, Emission-Computed EXPLODE ALL TREES 665	Delete	
21	(((PET NEAR1 (CT or examination* or imag* or scan*))))	309	Delete
22	(((positron NEAR2 tomograph*)))	626	Delete
23	((spect))	118	Delete
24	MeSH DESCRIPTOR Magnetic Resonance Imaging EXPLODE ALL TREES 846	Delete	
25	((magnet* resonance))	1248	Delete
26	(((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*)))	620	Delete
27	((((magnet* or MR*) NEAR1 (examination* or imag* or scan* or tomograph*)))) 1121	Delete	
28	((((diffusion or planar or echoplanar or echo-planar or functional) NEAR1 (imag* or scan* or tomogra*))))	60	Delete
29	MeSH DESCRIPTOR Whole Body Imaging EXPLODE ALL TREES	18	Delete
30	(((whole body NEAR1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*))))	46	Delete
31	((wbmr*))	0	Delete
32	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	6258	Delete
33	MeSH DESCRIPTOR Follow-Up Studies EXPLODE ALL TREES	2032	Delete
34	(((follow-up or followup)))	15587	Delete
35	(((checkup* or check-up*)))	61	Delete
36	((surveillance))	1119	Delete
37	(((re-examin* or reexamin*)))	66	Delete
38	((((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR1 (assess* or examin* or evaluat* or monitor* or screen*)))) 70	Delete	
39	#33 OR #34 OR #35 OR #36 OR #37 OR #38	16403	Delete
40	#32 OR #39	20827	Delete
41	MeSH DESCRIPTOR Neoplasm Staging EXPLODE ALL TREES	826	Delete
42	MeSH DESCRIPTOR Neoplasm Recurrence, Local EXPLODE ALL TREES 660	Delete	
43	MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES	705	Delete
44	(((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM)))	12588	Delete
45	((((AJCC or UICC) NEAR4 (classification* or system*))))	3	Delete
46	((sensitiv*))	16009	Delete
47	MeSH DESCRIPTOR Sensitivity and Specificity EXPLODE ALL TREES	4223	Delete
48	(((predictive NEAR1 value*)))	1692	Delete
49	MeSH DESCRIPTOR Predictive Value of Tests EXPLODE ALL TREES	1168	Delete
50	((accurac*))	3291	Delete
51	MeSH DESCRIPTOR Prognosis EXPLODE ALL TREES	16311	Delete
52	((prognos*))	4385	Delete

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53	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52	37013	Delete		
54	#10 AND #40 AND #53	232	Delete		
55	* IN DARE FROM 2000 TO 2014			42943	Delete
56	#54 AND #55	123	Delete		
57	MeSH DESCRIPTOR Neuroimaging EXPLODE ALL TREES			99	Delete
58	(((Brain* or neur* or head or cereb* or crani* or intracrani* or skull*) NEAR (imag* or mr* or radiograph* or scan* or screen* or tomograph* or exam* or CT or CAT or PET or x-ray or diagnos*)))	824	Delete		
59	(Neuroimag*)	61	Delete		
60	#57 OR #58 OR #59	883	Delete		
61	#10 AND #53 AND #60	9	Delete		
62	* IN DARE FROM 2000 TO 2021			43354	Delete
63	#61 AND #62	3	Delete		

An additional search was run on 1st June 2021 in Medline, Embase, the Cochrane Database of Systematic Reviews (CRD/CENTRAL) and DARE (Wiley platform). These searches are presented below.

An additional search was requested in May 2021 to capture references as clinical experts required an additional search to cover the use of imaging to detect lymph node recurrences in people with melanoma, specifically looking for meta-analyses and with no date limit.

Table 31 Search strategy for Medline

Database: Medline
Database: Ovid MEDLINE(R) ALL <1946 to July 01, 2021>
Search Strategy:
---
1 exp Melanoma/ (99237)
2 Skin Neoplasms/ (125881)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (123104)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (72047)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (29784)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (71)
7 dubreuilh*.tw. (74)
8 (maligna* adj2 lentigo*).tw. (1222)
9 LMM.tw. (1191)
10 or/1-9 (284958)
11 diagnostic imaging/ (42411)

Database: Medline

12 (diagnos* adj imag*).tw. (17706)

13 exp Ultrasonography/ (455069)

14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (437734)

15 exp Tomography, X-Ray Computed/ (455362)

16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (140553)

17 cine-ct.tw. (166)

18 ((comput* or electron beam) adj3 tomogra*).tw. (326656)

19 tomodensitometr*.tw. (1056)

20 exp Tomography, Emission-Computed/ (119248)

21 (PET adj (CT or examination* or imag* or scan*)).tw. (52548)

22 (positron adj2 tomograph*).tw. (62476)

23 spect.tw. (29261)

24 exp Magnetic Resonance Imaging/ (481568)

25 magnet* resonance.tw. (361745)

26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (1206082)

27 ((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (97393)

28 ((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (19532)

29 Whole Body Imaging/ (5293)

30 (whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (5334)

31 wbmr*.tw. (119)

32 or/11-31 (2677913)

33 Follow-Up Studies/ (665970)

34 (follow-up or followup).tw. (1059591)

35 (checkup*1 or check-up*1).tw. (16135)

36 surveillance.tw. (193663)

37 (re-examin* or reexamin*).tw. (28525)

38 ((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (3456)

39 or/33-38 (1635748)

Database: Medline
40 32 or 39 (4052683)
41 Neoplasm Staging/ (181505)
42 Neoplasm Recurrence, Local/ (126570)
43 exp Neoplasm Metastasis/ (210985)
44 (disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (2763550)
45 ((AJCC or UICC) adj4 (classification* or system*)).tw. (2632)
46 (sensitiv: or predictive value:).mp. or accurac:.tw. (2276170)
47 prognosis.sh. (540614)
48 prognos:.tw. (659783)
49 or/41-48 (5386723)
50 10 and 40 and 49 (34368)
51 exp Lymph Nodes/ (92600)
52 (lymph* or germinal*).tw. (974474)
53 51 or 52 (994456)
54 50 and 53 (8143)
55 meta analysis.pt. (136681)
56 ((meta adj3 analy*) or (meta-analy* or metaanaly*)).ti. (134926)
57 55 or 56 (176407)
58 54 and 57 (23)

Table 32 Search strategy for Embase

Database: Embase
1 exp melanoma skin cancer/ or melanoma/ or cutaneous melanoma/ or metastatic melanoma/ or superficial spreading melanoma/ or skin carcinoma/ (164410)
2 skin tumor/ or skin cancer/ or epithelium tumor/ (69061)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (170451)
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (96906)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (41287)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (80)
7 dubreuilh*.tw. (73)

Database: Embase

8 (maligna* adj2 lentigo*).tw. (1767)

9 LMM.tw. (1635)

10 or/1-9 (345149)

11 *diagnostic imaging/ (49118)

12 (diagnos* adj imag*).tw. (24133)

13 exp *echography/ (223220)

14 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (633582)

15 *computer assisted tomography/ or *electron beam tomography/ or *x-ray computed tomography/ (134610)

16 ((CT or CAT) adj (electron beam or examination* or imag* or scan* or x ray*)).tw. (241205)

17 cine-ct.tw. (217)

18 ((comput* or electron beam) adj3 tomogra*).tw. (411419)

19 tomodensitometr*.tw. (1081)

20 exp *computer assisted emission tomography/ (75286)

21 (PET adj (CT or examination* or imag* or scan*)).tw. (105741)

22 (positron adj2 tomograph*).tw. (81925)

23 spect.tw. (49193)

24 exp *nuclear magnetic resonance imaging/ (263000)

25 magnet* resonance.tw. (447906)

26 (fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*).tw. (1650198)

27 ((magnet* or MR*) adj (examination* or imag* or scan* or tomograph*)).tw. (145859)

28 ((diffusion or planar or echoplanar or echo-planar or functional) adj1 (imag* or scan* or tomogra*)).tw. (28388)

29 exp *whole body imaging/ (4970)

30 (whole body adj (imag* or mr* or radiograph* or scan* or screen* or tomograph*)).tw. (8940)

31 wbmr*.tw. (276)

32 or/11-31 (3106116)

33 *follow up/ or *aftercare/ or *"evaluation and follow up"/ (50784)

34 (follow-up or followup).tw. (1680948)

35 (checkup*1 or check-up*1).tw. (23449)

Database: Embase
36 surveillance.tw. (266192)
37 (re-examin* or reexamin*).tw. (33410)
38 ((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) adj1 (assess* or examin* or evaluat* or monitor* or screen*)).tw. (6077)
39 or/33-38 (1967072)
40 32 or 39 (4771361)
41 *cancer staging/ (36905)
42 *tumor recurrence/ (10048)
43 *metastasis/ or exp *lymphatic system metastasis/ or exp *metastatic melanoma/ or *skin metastasis/ (114132)
44 (disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM).tw. (3792595)
45 ((AJCC or UICC) adj4 (classification* or system*)).tw. (4258)
46 (sensitiv: or predictive value:).mp. or accurac:.tw. (2753897)
47 prognosis.sh. (612077)
48 prognos:.tw. (994916)
49 or/41-48 (6839380)
50 10 and 40 and 49 (43613)
51 exp lymph node/ (182143)
52 (lymph* or germinal*).tw. (1304868)
53 51 or 52 (1333683)
54 50 and 53 (11279)
55 meta-analysis/ (219301)
56 ((meta adj3 analy*) or (meta-analy* or metaanaly*)).ti. (168192)
57 55 or 56 (259607)
58 54 and 57 (69)
59 limit 58 to (conference abstract or conference paper or "conference review") (30)
60 58 not 59 (39)

Table 33 Search strategy for Cochrane Wiley

Database: Cochrane Wiley (CDSR/CENTRAL)

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Database: Cochrane Wiley (CDSR/CENTRAL)

ID	Search	Hits
#1	MeSH descriptor: [Melanoma] explode all trees	1876
#2	MeSH descriptor: [Skin Neoplasms] this term only	1632
#3	((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)):ti,ab,kw	5697
#4	(((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))):ti,ab,kw	4217
#5	(((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*))):ti,ab,kw	726
#6	((hutchinson* NEAR/2 (freckle* or melano*))):ti,ab,kw	9
#7	(dubreuilh*):ti,ab,kw	0
#8	(maligna* NEAR/2 lentigo*)	59
#9	(LMM):ti,ab,kw	135
#10	{or #1-#9}	8964
#11	MeSH descriptor: [Diagnostic Imaging] this term only	128
#12	((diagnos* NEAR/1 imag*)):ti,ab,kw	29243
#13	MeSH descriptor: [Ultrasonography] explode all trees	14024
#14	((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)):ti,ab,kw	47334
#15	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	5168
#16	(((CT or CAT) NEAR/1 (electron beam or examination* or imag* or scan* or x ray*))):ti,ab,kw	9091
#17	(cine-ct):ti,ab,kw	4
#18	(((comput* or electron beam) NEAR/3 tomogra*)):ti,ab,kw	21724
#19	(tomodensitometr*):ti,ab,kw	69
#20	MeSH descriptor: [Tomography, Emission-Computed] explode all trees	2512
#21	((PET NEAR/1 (CT or examination* or imag* or scan*))):ti,ab,kw	3646
#22	((positron NEAR/2 tomograph*)):ti,ab,kw	4512
#23	(spect):ti,ab,kw	1800
#24	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	8053
#25	((magnet* NEAR/1 resonance)):ti,ab,kw	29091
#26	((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*)):ti,ab,kw	25581

Database: Cochrane Wiley (CDSR/CENTRAL)

#27 (((magnet* or MR*) NEAR/1 (examination* or imag* or scan* or tomograph*))):ti,ab,kw 10387

#28 (((diffusion or planar or echoplanar or echo-planar or functional) NEAR/1 (imag* or scan* or tomogra*))):ti,ab,kw 1179

#29 MeSH descriptor: [Whole Body Imaging] this term only 68

#30 ((whole body NEAR/1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*))):ti,ab,kw 433

#31 (wbmr*):ti,ab,kw 29

#32 {or #11-#31} 121776

#33 MeSH descriptor: [Follow-Up Studies] this term only 60241

#34 ((follow-up or followup)):ti,ab,kw 254727

#35 ((checkup* or check-up*)):ti,ab,kw 1475

#36 (surveillance):ti,ab,kw 8577

#37 ((re-examin* or reexamin*)):ti,ab,kw 1517

#38 (((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR/1 (assess* or examin* or evaluat* or monitor* or screen*))):ti,ab,kw 1515

#39 {or #33-#38} 263739

#40 #32 or #39 357867

#41 MeSH descriptor: [Neoplasm Staging] this term only 6567

#42 MeSH descriptor: [Neoplasm Recurrence, Local] this term only 4368

#43 MeSH descriptor: [Neoplasm Metastasis] explode all trees 5285

#44 ((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM)):ti,ab,kw 223722

#45 (((AJCC or UICC) NEAR/4 (classification* or system*))):ti,ab,kw 230

#46 (sensitiv*):ti,ab,kw 76504

#47 MeSH descriptor: [Sensitivity and Specificity] this term only 8670

#48 ((predictive NEAR/1 value*)):ti,ab,kw 13958

#49 MeSH descriptor: [Predictive Value of Tests] this term only 7098

#50 (accurac*):ti,ab,kw 23191

#51 MeSH descriptor: [Prognosis] this term only 13879

#52 (prognos*):ti,ab,kw 45870

#53 {or #41-#52} 332613

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Database: Cochrane Wiley (CDSR/CENTRAL)		
#54	#10 AND #40 AND #53	1977
#55	MeSH descriptor: [Lymph Nodes] explode all trees	832
#56	(lymph* or germinal*):ti,ab,kw	53479
#57	#55 or #56	53479
#58	#54 and #57	595 (3 CDSR)

Table 34 Search strategy for CRD (DARE)

Database: CRD (DARE)			
Line	Search	Hits	
1	(MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES)	221	Delete
2	(MeSH DESCRIPTOR skin neoplasms)	193	Delete
3	(((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)))	329	Delete
4	((((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*))))	386	Delete
5	((((maligna* or melano*) NEAR2 (freckle* or lesion* or mole* or nev* or naev*))))	102	Delete
6	(((hutchinson* NEAR2 (freckle* or melano*))))	0	Delete
7	((dubreuilh*))	0	Delete
8	(((maligna* NEAR2 lentigo*)))	0	Delete
9	((LMM))	0	Delete
10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	630	Delete
11	(MeSH DESCRIPTOR diagnostic imaging)	176	Delete
12	(((diagnos* NEAR1 imag*)))	387	Delete
13	(MeSH DESCRIPTOR Ultrasonography EXPLODE ALL TREES)	1154	Delete
14	(((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)))	2531	Delete
15	(MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES)	1044	Delete
16	((((CT or CAT) near1 (electron beam or examination* or imag* or scan* or x ray*))))	342	Delete
17	((cine-ct))	0	Delete
18	((((comput* or electron beam) NEAR3 tomogra*)))	1400	Delete

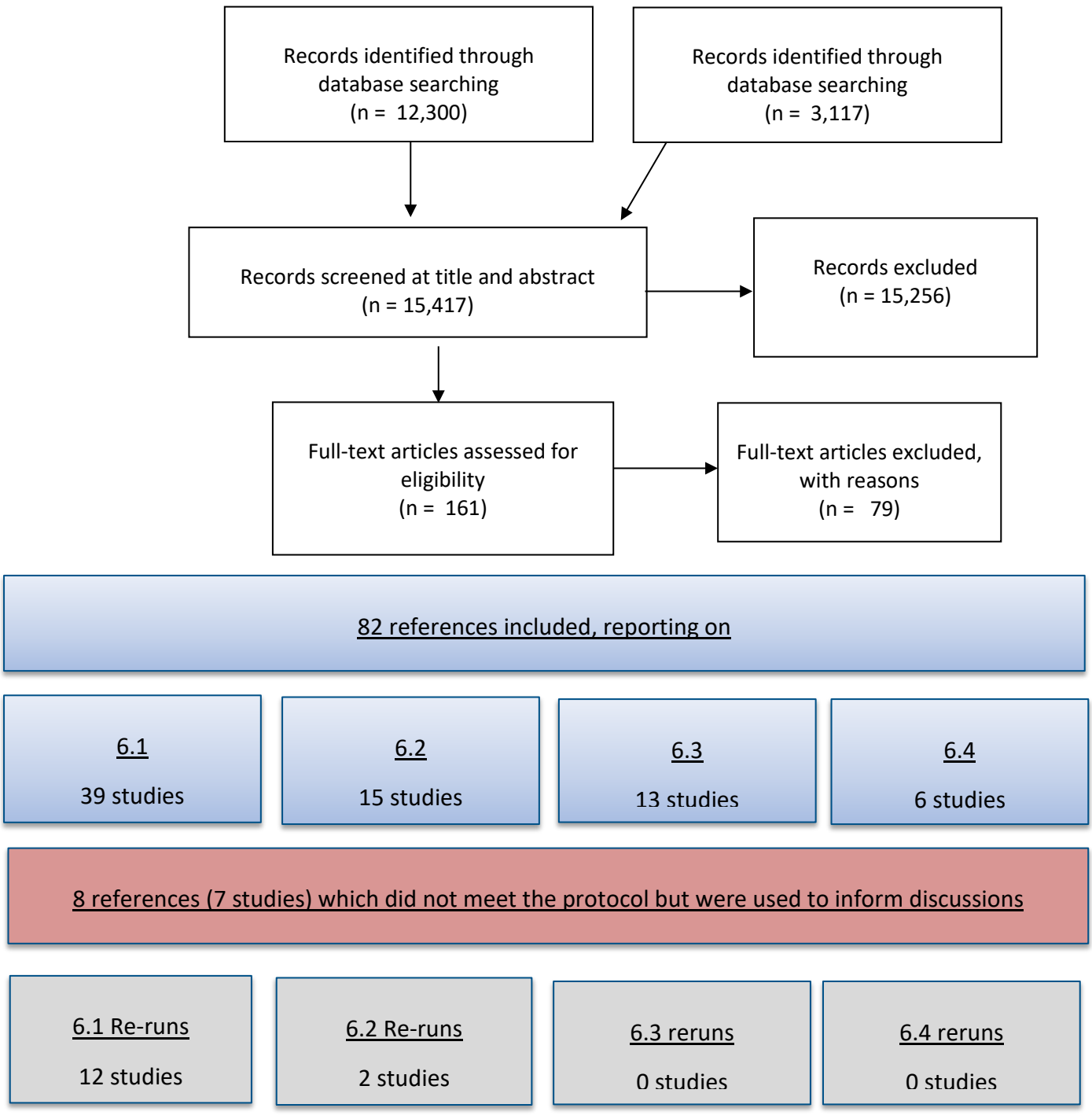
Database: CRD (DARE)

19	((tomodensitometr*))	1	Delete
20	(MeSH DESCRIPTOR Tomography, Emission-Computed EXPLODE ALL TREES)	665	Delete
21	(((PET NEAR1 (CT or examination* or imag* or scan*))))	309	Delete
22	(((positron NEAR2 tomograph*)))	626	Delete
23	((spect))	118	Delete
24	(MeSH DESCRIPTOR Magnetic Resonance Imaging EXPLODE ALL TREES)	846	Delete
25	((magnet* resonance))	1248	Delete
26	(((fMRI or MRI or MR*2 or NMR*1 or MP-MR* or MPMR*)))	620	Delete
27	((((magnet* or MR*) NEAR1 (examination* or imag* or scan* or tomograph*))))	1121	Delete
28	((((diffusion or planar or echoplanar or echo-planar or functional) NEAR1 (imag* or scan* or tomogra*))))	60	Delete
29	(MeSH DESCRIPTOR Whole Body Imaging)	18	Delete
30	(((whole body NEAR1 (imag* or mr* or radiograph* or scan* or screen* or tomograph*))))	46	Delete
31	((wbmr*))	0	Delete
32	(#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)	5213	Delete
33	(MeSH DESCRIPTOR Follow-Up Studies)	2032	Delete
34	(((follow-up or followup)))	15587	Delete
35	(((checkup* or check-up*)))	61	Delete
36	((surveillance))	1119	Delete
37	(((re-examin* or reexamin*)))	66	Delete
38	((((aftercare or after-care or post-care or post-hospital* or post-operat* or post-surg* or post-therap* or post-treat*) NEAR1 (assess* or examin* or evaluat* or monitor* or screen*))))	70	Delete
39	(#33 OR #34 OR #35 OR #36 OR #37 OR #38)	16403	Delete
40	(#32 OR #39)	20088	Delete
41	(MeSH DESCRIPTOR Neoplasm Staging)	826	Delete
42	(MeSH DESCRIPTOR Neoplasm Recurrence, Local)	660	Delete
43	(MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES)	705	Delete

The follow up of people with melanoma

Database: CRD (DARE)				
44	(((disseminat* or metasta* or migration or spread* or stage* or staging or recurr* or relaps* or restag* or re-stag* or upstag* or up-stag* or TNM)))	12588	Delete	
45	((((AJCC or UICC) NEAR4 (classification* or system*))))	3	Delete	
46	((sensitiv*))	16009	Delete	
47	(MeSH DESCRIPTOR sensitivity and specificity)	3305	Delete	
48	(((predictive NEAR1 value*)))	1692	Delete	
49	(MeSH DESCRIPTOR predictive value of tests)	1168	Delete	
50	((accurac*))	3291	Delete	
51	(MeSH DESCRIPTOR prognosis)	1656	Delete	
52	((prognos*))	4385	Delete	
53	(#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)	28086	Delete	
54	(#10 AND #40 AND #53)	218	Delete	
55	MeSH DESCRIPTOR Lymph Nodes EXPLODE ALL TREES	152	Delete	
56	(lymph* or germinal*)	1938	Delete	
57	#55 OR #56	1938	Delete	
58	#54 AND #57	45	Delete	
59	MeSH DESCRIPTOR meta-analysis	87	Delete	
60	(((meta near analy*) or (meta-analy* or metaanaly*))):TI	17790	Delete	
61	#59 OR #60	17817	Delete	
62	#58 AND #61	11	Delete	

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence

- 6.1 Surveillance strategies for resected disease
    - *6.1.1 RCT comparing follow-up schedules*

MelFo: UK study

MelFo study, 2020a

Bibliographic Reference	Moncrieff, M.D.; Underwood, B.; Garioch, J.J.; Heaton, M.; Patel, N.; Bastiaannet, E.; Hoekstra-Weebers, J.E.H.M.; Hoekstra, H.J.; The MelFo Study UK: Effects of a Reduced-Frequency, Stage-Adjusted Follow-Up Schedule for Cutaneous Melanoma 1B to 2C Patients After 3-Years; Annals of Surgical Oncology; 2020; vol. 27 (no. 11); 4109-4119

Study arms

NICE follow-up (N = 103)	Follow-up in accordance with NICE NG14 recommendations: consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging stage 1B at the end of 5 years and stage IIA-C having 1 visit per year. Do not routinely offer imaging investigations.
Reduced frequency, stage adjusted (N = 104)	Follow up visits adjusted by stage and overall reduced frequency: IB: 1 visit per year IIA: 2 visits per year for first 2 years then 1 visit per year IIB-IIC: 3 visits per year for first 2 years; 2 visits in second year then 1 visit per year.

Study details

Other publications associated with this study included in review	Deckers, E.A., Hoekstra-Weebers, J.E.H.M., Damude, S. et al. (2020) The MELFO Study: A Multicenter, Prospective, Randomized Clinical Trial on the Effects of a Reduced Stage-Adjusted Follow-Up Schedule on Cutaneous Melanoma IB-IIC Patients-Results After 3 Years. Annals of Surgical Oncology 27(5): 1407-1417
Study type	Randomised controlled trial (RCT)

Study location	UK
Study setting	Department of Surgical Oncology at the University Medical Center of Groningen
Study dates	2010-2015
Inclusion criteria	Sentinel lymph node negative melanoma Undergone sugery with curative intent 1b-2c
Outcome measures	Quality of life The patients completed questionnaires at study entry shortly after diagnosis (T1), after 1 year (T2), and 3 years later (T3). At T1, the patients answered questions on gender, age, level of education, relationship status, daily activities, and comorbidities. At T1 and T3, they answered questions on schedule satisfaction, frequency of self-inspection, and number of melanoma-related general practitioner/primary care physician (GP) visits. The treating clinicians gave diagnostic information (primary melanoma site, Breslow thickness, ulceration, AJCC classification) and follow-up information (date of every outpatient visit, date and location of recurrence, date and cause of death). The patients completed the following patient-reported outcome measures (PROMs) at T1, T2, and T3: 1. The State-Trait Anxiety Inventory-state version (STAI-s), a 20-item questionnaire measuring the transitory emotional condition of stress or tension perceived by the patient. Items are scored on a 4-point scale ranging from 1 (not at all) to 4 (very much) (range, 20–80).21 2. The 3-item Cancer Worry Scale (CWS) measuring concerns about cancer developing again and the impact on daily activities.22–24 Higher scores mean more worries (range, 3–12). 3. The 15-item Impact-of-Event Scale (IES) evaluating the extent to which patients experience life hazards, in this case having a melanoma, in terms of avoidance and intrusion.25, 26 A higher score (range, 0–75) corresponds to a higher level of stress response symptoms. 4. The RAND-36, a 36-item health-related QoL questionnaire, of which the mental component score (MCS) and the physical component summary scores (PCS) were used. The summary scores are standardized with a mean of 50 and a standard deviation of 10. Extra (unplanned) visits to clinic Recurrence Self-detection as method of recurrence detection

Number of participants	207
Duration of follow-up	3 years

Study-level characteristics

Characteristic		**NICE follow-up (N = 207)**
Female		47.8%
Stage		
	Ib	65.7%
	IIA	15.9%
	IIIC	15.9%
	IV	2.4%
Aged 65 or older		37.2%
Location		
	Extremities	44%
	Head/neck	16.4%
	Trunk	39.6%
Ulceration		19.8
>2mm breslow thickness		27.5

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Moderate *(Limited reporting of randomisation procedure and allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Blinding not possible for this comparison)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate *(More patients in the reduced frequency arm had unplanned extra visits to the clinic. Note that unplanned visits in an outcome of interest to this review and this issue is therefore not relevant for that outcome.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Moderate *(~20% of participants did not complete QoL questionnaires at time 3)*
Overall bias and Directness	Risk of bias judgement	Moderate *(Variance in adherence to intervention. Unclear reporting of randomization process.)*
Overall bias and Directness	Overall Directness	Directly applicable

MelFo: Dutch study

MelFo study, 2020a

Bibliographic Reference	Deckers, E. A., Hoekstra-Weebers, J. E., Damude, S., Francken, A. B., Ter Meulen, S., Bastiaannet, E., & Hoekstra, H. J. (2019). The MELFO Study: A Multicenter, Prospective, Randomized Clinical Trial on the Effects of a Reduced Stage-Adjusted Follow-Up Schedule on Cutaneous Melanoma IB–IIC Patients—Results After 3 Years. *Annals of surgical oncology*, 1-11

Study arms

Dutch melanoma guideline recommended follow-up (N = 103)	Follow-up in accordance with Dutch guideline recommendations: consider follow-up every 3 months for the first year after completion of treatment, every 4 months for second year, then every 6 months for years 3-5. At the end of 5 years, stage IB are discharged, and stage IIA-C are followed once annually for years 6-10. Do not routinely offer screening investigations.
Reduced frequency, stage adjusted (N = 104)	Follow up visits adjusted by stage and overall reduced frequency: IB: 1 visit per year IIA: 2 visits per year for first 2 years then 1 visit per year IIB-IIC: 3 visits per year for first 2 years; 2 visits in second year then 1 visit per year.

Study details

Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Department of Surgical Oncology at the University Medical Center of Groningen
Study dates	2010-2015
Inclusion criteria	Sentinel lymph node negative melanoma 1b-2c
Outcome measures	Quality of life The patients completed questionnaires at study entry shortly after diagnosis (T1), after 1 year (T2), and 3 years later (T3). At T1, the patients answered questions on gender, age, level of education, relationship status, daily activities, and comorbidities. At T1 and T3, they answered questions on schedule satisfaction, frequency of self-inspection, and number of melanoma-related general

	practitioner/primary care physician (GP) visits. The treating clinicians gave diagnostic information (primary melanoma site, Breslow thickness, ulceration, AJCC classification) and follow-up information (date of every outpatient visit, date and location of recurrence, date and cause of death). The patients completed the following patient-reported outcome measures (PROMs) at T1, T2, and T3: 1. The State-Trait Anxiety Inventory-state version (STAI-s), a 20-item questionnaire measuring the transitory emotional condition of stress or tension perceived by the patient. Items are scored on a 4-point scale ranging from 1 (not at all) to 4 (very much) (range, 20–80).21 2. The 3-item Cancer Worry Scale (CWS) measuring concerns about cancer developing again and the impact on daily activities.22–24 Higher scores mean more worries (range, 3–12). 3. The 15-item Impact-of-Event Scale (IES) evaluating the extent to which patients experience life hazards, in this case having a melanoma, in terms of avoidance and intrusion.25, 26 A higher score (range, 0–75) corresponds to a higher level of stress response symptoms. 4. The RAND-36, a 36-item health-related QoL questionnaire, of which the mental component score (MCS) and the physical component summary scores (PCS) were used. The summary scores are standardized with a mean of 50 and a standard deviation of 10. Extra (unplanned) visits to clinic Recurrence Self-detection as method of recurrence detection
Number of participants	180
Duration of follow-up	3 years

Study-level characteristics

Characteristic	**Dutch MelFo study (N = 180)**
Female	50.9 %
Stage	
Ib	59.1 %
IIA	21.8 %
IIIC	13.6 %

Characteristic	Dutch MelFo study (N = 180)
IV	5.5 %
Location	
extremities	48.2 %
Head/neck	10 %
Trunk	41.8 %
Ulceration	22.7 %
>2mm breslow thickness	35.5 %

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Moderate *(Limited reporting of randomisation procedure and allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Blinding not possible for this comparison)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate *(More patients in the reduced frequency arm had unplanned extra visits to the clinic. Note that unplanned visits in an outcome of interest to this review and this issue is therefore not relevant for that outcome.)*

Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Moderate *(~20% of participants did not complete QoL questionnaires at time 3)*
Overall bias and Directness	Risk of bias judgement	Moderate *(Variance in adherence to intervention. Unclear reporting of randomization process.)*
Overall bias and Directness	Overall Directness	Directly applicable

Ravichandran 2020

Ravichandran, 2020

Bibliographic Reference Ravichandran, S.; Nath, N.; Jones, D.C.; Li, G.; Suresh, V.; Brys, A.K.; Hanks, B.A.; Beasley, G.M.; Salama, A.K.S.; Howard, B.A.; Mosca, P.J.; The utility of initial staging PET-CT as a baseline scan for surveillance imaging in stage II and III melanoma; Surgical Oncology; 2020; vol. 35; 533-539

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location • USA Study setting • Single centre Study dates • January 1, 2005 to December 1, 2019 Sources of funding

	none
Inclusion criteria	• Stage II-III • PET/CT scan < 3 months of initial diagnosis • Complete surgical resection
Exclusion criteria	• another malignancy for which they were under-going active treatment or surveillance. • if the melanoma was a cutaneous metastasis with an unknown primary • if the patient had a prior stage IIC or higher stage melanoma. • Patients with IIA or IIB melanoma diagnosed within the prior 10 years were excluded • patients with stage IA and IB diagnosis within the prior 5 years.
Number of participants and recruitment methods	258
Length of follow-up	at least 12 months following diagnosis
Outcome(s) of interest	Use of cross-sectional imaging during follow-up, recurrence and how recurrence was detected: Records were also reviewed to determine whether or not patients received surveillance cross-sectional imaging, whether or not they experienced a melanoma recurrence, and when the recurrence occurred and how it was detected. Clinical data was used to determine which patients received surveillance cross-sectional imaging with PET-CT, CT, or brain MRI, and the duration and frequency for which they received surveillance. Time to recurrence was defined as the time from definitive resection of all gross disease (such as date of wide local excision with or without sentinel lymph node biopsy or lymph node excision/dissection for those with clinically positive nodes) to the date at which melanoma recurrence was documented (most commonly by cross-sectional imaging). Follow-up was defined as time from initial melanoma diagnosis to the date of last documented dermatology, surgical oncology or medical oncology clinic visit or death. Patients were excluded if they were lost to follow-up within 12 months or died within 12 months of initial primary melanoma surgery of unknown causes, or if there was no identifiable disease-free period. Patients lost to follow-up were subcategorized into those lost to followup within 3 months of initial melanoma surgery or after the determination of

	whether or not they would receive surveillance imaging. Patients with no disease-free interval were subcategorized according to whether they had metastatic disease at diagnosis, advanced regional nodal disease at presentation or unresectable/incompletely resected primary tumor at presentation
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Baseline PET/CT scan: Baseline PET-CT was considered positive if there were findings suspicious for distant metastasis that were confirmed to be melanoma within the ensuing 6 months of follow-up. PET-CT was considered equivocal if there were findings possibly consistent with distant metastasis that remained unclear in etiology after 6 months of follow-up. Acceptable means of follow-up included additional cross-sectional imaging and/or histological sampling. PET-CT was considered negative if there was no suspicion for distant metastasis
Covariates adjusted for in the multivariable regression modelling	none

Participant characteristics

	Study (N = 258)
Female	31.4%
Mean age (SD)	60 (±15.8) years
Tumour location	
Head/neck	22.5%
Trunk	31.4%
Extremities	46.1%
Stage	
IIA	10.1%

	Study (N = 258)
IIB	20.5%
IIC	13.2%
IIIA	13.6%
IIIB	22.9%
IIIC	19.8%
Ulceration	59.3%
Surgical procedure	
Wide local excision	89.5%
SLNB	76.0%
Lymph node dissection	34.1%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Study was non-randomized. Decision to use imaging during follow-up was likely influenced by factors other than the results of the baseline scan. Different rates in recurrences between those who did or did not receive surveillance imaging may be the result of differences in clinical characteristics: those not receiving imaging during follow-up were slightly younger, more likely to be lower stage disease and had thinner melanomas)*

Selection of participants	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(comparison of outcomes between patients receiving imaging during follow-up and those not receiving imaging is limited as there is no standard follow-up strategy for when/how frequent imaging should be done in the surveillance group)*
Predictors or their assessment	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
Outcome or its determination	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	High
Overall Risk of bias and Applicability	Concerns for applicability	Low

- *6.1.2 Prognostic risk factor studies*

Barbour 2015

Barbour, 2015

Bibliographic Reference	Barbour, Samantha; Mark Smithers, B; Allan, Chris; Bayley, Gerard; Thomas, Janine; Foote, Matthew; Burmeister, Bryan; Barbour, Andrew P; Patterns of Recurrence in Patients with Stage IIIB/C Cutaneous Melanoma of the Head and Neck Following Surgery With and Without Adjuvant Radiation Therapy: Is Isolated Regional Recurrence Salvageable?.; Annals of surgical oncology; 2015; vol. 22 (no. 12); 4052-9

Study Characteristics

Study design	Retrospective cohort study Review of prospectively collected database

Study details	• Study location
	  ○ Australia
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ 1997-2012

Inclusion criteria	• TLND ○ neck dissection with curative intent. With or without adjuvant radiotherapy • Stage IIIB-C • macroscopic disease • Head/neck melanoma
Exclusion criteria	• Treated with preoperative therapy • Mucosal primary • Positive SLNB
Number of participants and recruitment methods	173
Length of follow-up	Up to 10 years with main analysis conducted at 5 years

Surveillance strategy	Following surgery, patients were followed every 3 months for the first 2 years, then every 6 months for the next 3 years, and then annually up to 10 years. At follow up, investigations including imaging were directed at symptoms. Follow-up was complete on all patients at the time of analysis. Recurrence was defined as histological proof or unequivocal radiological evidence of the event as follows: regional nodal (within the boundaries of the previous lymphadenectomy); in-transit (between the primary site and draining lymphatic basins); and distant (all other sites). Recurrence was considered synchronous if detected in two anatomical sites within 30 days of each other. For the purpose of analysis, the site or sites of first recurrence were used
Outcome(s) of interest	Recurrence up to 5 years Recurrence was defined as histological proof or unequivocal radiological evidence of the event as follows: regional nodal (within the boundaries of the previous lymphadenectomy); in-transit (between the primary site and draining lymphatic basins); and distant (all other sites). Recurrence was considered synchronous if detected in two anatomical sites within 30 days of each other. For the purpose of analysis, the site or sites of first recurrence were used
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Age • Location • Ulceration • Stage

Participant characteristics

	Study (N = 173)
Female	18%
Median age (range)	61 (15-92)
Tumour location	

	Study (N = 173)
Head/neck	61%
Trunk	17%
Extremities	2%
Stage	
IIIB	64%
IIIC	36%
Extracapsular invasion	37%
Ulceration	20%
Lymph node stage	
2	25%
3	12%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(follow-up protocol and definition of recurrence was clearly detailed)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(only significant univariate predicters were entered into multivariate model and reported)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Inadequate adjustment for confounders)*
	Concerns for applicability	Low

Baum 2017

Baum, 2017

Bibliographic Reference	Baum, C., Weiss, C., Gebhardt, C., Utikal, J., Marx, A., Koenen, W., & Géraud, C. (2017). Sentinel node metastasis mitotic rate (SN-MMR) as a prognostic indicator of rapidly progressing disease in patients with sentinel node-positive melanomas. *International journal of cancer*, *140*(8), 1907-1917

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ Germany
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ All patients diagnosed with a positive SNB between September 1, 2002 and January 31, 2012

Inclusion criteria	• Positive SLNB
Number of participants and recruitment methods	96
Length of follow-up	Median follow-up was 53 months (range 1-146) months
Surveillance strategy	Unclear surveillance strategy
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness • Tumour penetrative depth • Maximum tumour diameter

	• No. positive sentinel nodes

Participant characteristics

	Study (N = 173)
Female	42.7%
Median age	59.0 years
Number of positive SLNs	
1	76.0%
2	21.9%
3+	2.0%
SN mitotic rate <1 per mm2	71.9%
Median (range) Breslow thickness	2.20 mm (0.70 – 9.00)

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(unclear follow-up protocol and large variation between participants in duration of follow-up)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(limited number of factors adjusted for)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Inadequate adjustment for confounders, unclear surveillance strategy with large variance in follow-up time)*
	Concerns for applicability	Low

Berger 2017

Berger, 2017

Bibliographic Reference	Berger, Adam C; Ollila, David W; Christopher, Adrienne; Kairys, John C; Mastrangelo, Michael J; Feeney, Kendra; Dabbish, Nooreen; Leiby, Benjamin; Frank, Jill A; Stitzenberg, Karyn B; Meyers, Michael O; Patient Symptoms Are the Most Frequent Indicators of Recurrence in Patients with American Joint Committee on Cancer Stage II Melanoma.; Journal of the American College of Surgeons; 2017; vol. 224 (no. 4); 652-659

Study Characteristics

Study design	Retrospective cohort study
Study details	• Study location: USA • Study setting: Databases of Thomas Jefferson University and University of North Carolina • Study dates: January 2009 - December 2012 • Sources of funding: nr
Inclusion criteria	SLNB II
Number of participants and recruitment methods	581
Length of follow-up	5 years; At University of North Carolina, patients were generally followed every 3 months the first 2 years and every 6 months thereafter in alternating fashion between their primary dermatologist and the surgical oncology care team, although determination of follow-up plans for individual patients at both institutions was left to the discretion of the treating physicians (surgeons, medical oncologists, and dermatologists) with regard to examinations and imaging. At Thomas Jefferson University, patients were seen every 3 to 6 months for examination and often had a chest x-ray performed at least every 6 months. Cross-sectional imaging was at the discretion of the treating physicians.
Outcome(s) of interest	Overall survival
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration • T stage/Breslow (categorical) • Stage

	• Age • Thickness (continuous)
Covariates adjusted for in the multivariable regression modelling	• Stage • Regression • Ulceration • Age

Participant characteristics

	Study (N = 581)
Female	38%
Tumour location	
Head/neck	25%
Trunk	31%
Extremities	44%
Stage	
IIA	50%
IIB	35%
IIC	15%
Ulceration	52%

	Study (N = 581)
T stage 4a	14%
T stage 4b	15%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	High *(Study included all patients with stage II melanoma who underwent SLNB. It is unclear whether the study included both patients with negative SLNB and those with positive SLNB . Unclear what proportion of patients underwent definitive treatment)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Univariate analyses only reported for significant predictors and only these predictors were entered into the multivariate model. Event data not reported)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(limited reporting for certain predictors and inadequate adjustment for confounders.)*
	Concerns for applicability	Moderate *(Unclear if patients had definitive treatment)*

Bertolli 2019

Bertolli, 2019

Bibliographic Reference	Bertolli, E., de Macedo, M. P., Calsavara, V. F., Pinto, C. A. L., & Neto, J. P. D. (2019). A nomogram to identify high-risk melanoma patients with a negative sentinel lymph node biopsy. *Journal of the American Academy of Dermatology*, *80*(3), 722-726

Study Characteristics

Study design	Retrospective cohort study
Study details	• Study location: Brazil • Study setting: Single centre • Study dates: 2000-2015

	• Sources of funding: nr
Inclusion criteria	Negative SLNB
Number of participants and recruitment methods	1,213
Length of follow-up	Median 5 years
Outcome(s) of interest	All recurrences at 5 years
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (continuous) • Breslow thickness • Mitotic rate • Ulceration
Covariates adjusted for in the multivariable regression modelling	Cox regression models were used to evaluate which features were related to melanoma recurrence in follow-up with the stepwise forward method for the purposes of creating a nomogram. Age, topography, histology, Breslow thickness, mitotic index.

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study. No reporting of baseline characteristics of cohort. Potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(unclear follow-up protocol at study centre)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(multivariate analysis conducted but hazard ratios only reported for those predictors which made up the final model)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(potential for confounders not adequately adjusted for.)*
	Concerns for applicability	Moderate *(Unclear if patients had definitive treatment)*

Bleicher 2020

Bleicher, 2020

Bibliographic Reference	Bleicher, J.; Swords, D.S.; Mali, M.E.; McGuire, L.; Pahlkotter, M.K.; Asare, E.A.; Bowles, T.L.; Hyngstrom, J.R.; Recurrence patterns in patients with Stage II melanoma: The evolving role of routine imaging for surveillance; Journal of Surgical Oncology; 2020

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ between 01 January 2000 and 31 December 2017
	• Sources of funding
	  ○ nr

Inclusion criteria	• Stage II
Exclusion criteria	• <1 month follow-up data
Number of participants and recruitment methods	580 (590 identified, 10 did not have sufficient follow-up data)
Length of follow-up	Median age was 62 (interquartile range [IQR], 48–74) and most patients were male.

Surveillance strategy	"There was no uniform institutional protocol for surveillance of patients with Stage II melanoma during this study period. Surveillance was performed by a small group of surgeons, oncologists, and dermatologists, each with unique practice patterns and preferences. In general, clinical surveillance was performed every 3–6 months in accordance with NCCN guidelines. Routine imaging surveillance was performed at the discretion of the physician based on individual patient and tumour characteristics. When routine imaging surveillance was performed, our institution used computed tomography (CT) of the chest, abdomen, and pelvis in conjunction with a brain magnetic resonance imaging for screening. Other radiographic surveillance (including positron emission tomography [PET-CT]) was performed very rarely for patients with melanoma"

Outcome(s) of interest	• Recurrence
	  ○ Recurrences were classified as local/in-transit, regional nodal, and distant. Throughout, classification of recurrent disease was based on patient's first episode and location of recurrence.
	  ○ Recurrences were classified as having been detected by the patient, routine imaging, or physician exam. If patient symptoms prompted an imaging study, this was recorded as a patient-detected recurrence. Similarly, if imaging was obtained following a concerning finding on physician history or physical exam, this was recorded as physician exam-detected recurrence. Only recurrences detected by routine surveillance imaging were recorded as imaging-detected recurrences.

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Location • Stage • Breslow thickness • Ulceration • Mitoses per mm2 • Histologic type
Covariates adjusted for in the multivariable regression modelling	adjusted for age and stage

Participant characteristics

	Study (N = 580)
Female	39.3%
Median age (range)	62 (48-74) years
Tumour location	
Head/neck	37.6%
Trunk	22.0%
Extremities	25.4%
Ulceration	61.7%
Breslow thickness	
<1mm	0.3%
1-2mm	20.2%
2.01-4.00mm	50.3%
>4mm	29.1%
Mitotic rate >1	80.2%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Unclear *(Unclear if patients had definitive treatment and whether this differed between patients)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Author outlines that there was no standard surveillance for stage II patients during study period)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Only univariate predictors with a p <.20 were entered into multivariate model, only significant (p <.05) adjusted predictors were reported from multivariate model.)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No standard follow-up for study cohort. Potential for confounders not adequately adjusted for.)*
	Concerns for applicability	Low

Bloemendal 2019

Bloemendal, 2019

Bibliographic Reference Bloemendal, Martine; van Willigen, Wouter W; Bol, Kalijn F; Boers-Sonderen, Marye J; Bonenkamp, Johannes J; Werner, J E M; Aarntzen, Erik H J G; Koornstra, Rutger H T; de Groot, Jan Willem B; de Vries, I Jolanda M; van der Hoeven, Jacobus J M; Gerritsen, Winald R; de Wilt, Johannes H W; Early Recurrence in Completely Resected IIIB and IIIC Melanoma Warrants Restaging Prior to Adjuvant Therapy.; Annals of surgical oncology; 2019; vol. 26 (no. 12); 3945-3952

Study Characteristics

Study design	Retrospective cohort study • retrospective review of participants screened for an RCT. The RCT investigated an adjuvant dendritic cell vaccination and all participants were screened within 6 weeks of the trial beginning to exclude relapse.

Study details	• Study location
	  ○ The Netherlands
	• Study setting
	  ○ 5 sites
	• Study dates
	  ○ Between November 2016 and July 2018
	• Sources of funding

	○ supported by NWO Grant 837004014. I.J.M. de V. received NWO Vici Grant 91814655.
Inclusion criteria	• Complete radical lymph node disection • IIIB/C
Exclusion criteria	• Autoimmune disease ○ except for skin disease, hypothyroidism after autoimmune thyroiditis, and type 1 diabetes mellitus • second malignancy in last 5 years ○ except for adequately treated carcinoma in situ and basal or squamous cell carcinoma of the skin) • concomitant use of oral or intravenous immunosuppressive drugs, and uncontrolled infectious disease
Number of participants and recruitment methods	120
Length of follow-up	None; participants screening within 6 weeks of starting study
Outcome(s) of interest	Recurrence occurring <12 weeks following complete radical LND. Recurrence was considered symptomatic if suspected by symptoms and/or abnormalities during physical examination. Otherwise, recurrence was considered asymptomatic.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Stage • Breslow • Ulceration • Histological type • Location • Extracapsular extension • In-transit/micro-metastatic disease • BRAF mutation status
Covariates adjusted for in the	none

multivariable regression modelling	

Participant characteristics

	Study (N = 120)
Female	37%
Median age (range)	54 (27-79) years
Tumour location	
Head/neck	14%
Trunk	38%
Extremities	39%
Stage	
IIIB	58%
IIIC	43%
Extracapsular invasion	25%
Ulceration	32%
Breslow thickness 4mm or greater	32%
Macroscopic lymph node involvement	83%

	Study (N = 120)
BRAF mutation	65%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? - Development studies	No
	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No Adjustment for confounders)*
	Concerns for applicability	Low

Brecht 2015

Brecht, 2015

Bibliographic Reference	Brecht, Ines B; Garbe, Claus; Gefeller, Olaf; Pfahlberg, Annette; Bauer, Jurgen; Eigentler, Thomas K; Offenmueller, Sonja; Schneider, Dominik T; Leiter, Ulrike; 443 paediatric cases of malignant melanoma registered with the German Central Malignant Melanoma Registry between 1983 and 2011.; European journal of cancer (Oxford, England : 1990); 2015; vol. 51 (no. 7); 861-8

Study Characteristics

Study design	• Retrospective cohort study ○ Review of prospective database

Study details	• Study location
	  ○ Germany
	• Study setting
	  ○ The German Central Malignant Melanoma Registry (CMMR) between 1983 and 2011, which registers approximately 35-50% of all melanoma patients in Germany.
	• Study dates
	  ○ Registered with the German Central Malignant Melanoma Registry (CMMR) between 1983 and 2011

Inclusion criteria	• <19 years old • Cutaneous or ocular melanoma ○ only 1 patient had ocular melanoma

	• I-IV ○ 84.2% stage I-II
Number of participants and recruitment methods	443
Length of follow-up	median follow-up: 113 months
Loss to follow up	3 patients
Outcome(s) of interest	Overall survival at 5 years
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• age • Gender • location • ulceration • histological type
Covariates adjusted for in the multivariable regression modelling	none

Participant characteristics

	Study (N = 443)
Female	54.3%
Aged 1-9 years	8.6%

	Study (N = 443)
Aged 10-18 years	90.7%
Tumour location	
Head/neck	9.1%
Trunk	44.1%
Extremities	46.0%
Ulceration	5.2%
Breslow thickness ≤1 mm	60.3%
Disease stage	
I	70.0%
II	14.2%
III	6.1%
IV	0.7%

Risk of bias

Section	Question	Answer
Selection of participants	Concerns for applicability for selection of participants domain	Low *(Risk factors are likely comorbid. Study includes a wide range of patients (I-IV) and information on treatments is unclear.)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High
Overall Risk of bias and Applicability	Risk of bias	High *(high potential for confounders and analysis was unadjusted.)*
	Concerns for applicability	Low

BRIM-8

BRIM-8 trial

Bibliographic Reference	Maio, M., Lewis, K., Demidov, L., Mandalà, M., Bondarenko, I., Ascierto, P. A., ... & Whitman, E. (2018). Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *The Lancet Oncology*, *19*(4), 510-520

Study Characteristics

Study design	RCTs

Study details	• Study location
	  ○ 23 countries
	• Study setting
	  ○ 124 centres
	• Study dates
	  ○ enrolment between Sept 10, 2012, and Aug 10, 2015
	• Sources of funding
	  ○ trial was designed and funded by the sponsor (F Hoffmann–La Roche Ltd)

Inclusion criteria	• Stage IIC-IIIC: Stage IIIA stage IIIA melanoma were required to have one or more nodal metastases greater than 1 mm in diameter and patients with lymph node involvement at initial presentation or a first metachronous nodal recurrence. • at least 18 years old • Completely resected • BRAF positive • ECOG 0-1 • adequate haematological, liver, and renal function • a full recovery from the effects of any major surgery or any previous substantial traumatic injury • life expectancy of at least 5 years.
Exclusion criteria	• history of, or current, clinical, radiographic, or pathological evidence of in-transit metastases, satellite, or microsatellite lesions • history of any systemic, local, or radiotherapy for cancer. • major surgical procedures within 4 weeks of study entry • active or chronic infection • autoimmune disease • history of malabsorption

	• unwillingness or inability to comply with study and follow-up procedures
Number of participants and recruitment methods	498
Length of follow-up	median study follow-up was 33·5 months (IQR 25·9–41·6) in cohort 2 (IIIC) and 30·8 months (25·5–40·7) in cohort 1 (IIC-IIIB)
Surveillance schedule	Surveillance for tumour recurrence, including contrast-enhanced CT or MRI of the chest, abdomen, and pelvis (every 13 weeks for the first 2 years and then every 26 weeks for years 3–5), and physical examination were done
Outcome(s) of interest	• Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Type of lymph node metastases at baseline • Ulceration OR mitosis at baseline
Covariates adjusted for in the multivariable regression modelling	None
Additional comments	Patients were randomly assigned to receive placebo or vemurafenib.

Participant characteristics

	Stage IIIC vemurafenib (n= 93)	Stage IIIC placebo (n= 93)	Stage IIC, IIIA [>1 mm], and IIIB vemurafenib (n=157)	Stage IIC, IIIA [>1 mm], and IIIB placebo (n=157)
Female	44%	35%	46%	44%

	Stage IIIC vemurafenib (n= 93)	Stage IIIC placebo (n= 93)	Stage IIC, IIIA [>1 mm], and IIIB vemurafenib (n=157)	Stage IIC, IIIA [>1 mm], and IIIB placebo (n=157)
Median age (IQR)	55 (40-61)	50 (38-58)	51 (43-60)	49 (40-59)
Stage				
IIC	-	-	10%	8%
IIIA	-	-	23%	25%
IIIB	-	-	68%	68%
IIIC	100%	100%		
Non-white ethnicity	10%	11%	4%	4%
ECOG 1				

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving adjuvant therapy and those given placebo.*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

CHECKMATE 238

CHECKMATE 238 trial

Bibliographic Reference	Ascierto, P. A., Del Vecchio, M., Mandalá, M., Gogas, H., Arance, A. M., Dalle, S., ... & Weber, J. (2020). Adjuvant nivolumab versus ipilimumab in resected stage IIIB–C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *The Lancet Oncology*, *21*(11), 1465-1477

Study Characteristics

Study design	RCTs

Study details	• Study location
	  ○ 25 countries
	• Study setting
	  ○ 130 centres
	• Study dates
	  ○ enrolment between March 30 and Nov 30, 2015
	• Sources of funding
	  ○ Funding for the study was provided by Bristol Myers Squibb and Ono Pharmaceutica

Inclusion criteria	• Stage IIIB-IV • Completely resected within 12 weeks before randomisation • ECOG 0-1 •
Exclusion criteria	• ocular melanoma • history of autoimmune disease • previous non-melanoma cancer without complete remission for more than 3 years • systemic use of glucocorticoids • previous systemic therapy for melanoma • except adjuvant interferon if completed at least 6 months before randomisation
Number of participants and recruitment methods	906
Length of follow-up	minimum of 4 years (median 51·1 months [IQR 41·6–52·7] in the nivolumab group and 50·9 months [36·2–52·3] in the ipilimumab group)

Surveillance schedule	Disease recurrence was assessed by the investigator every 12 weeks for the first 2 years and every 6 months thereafter until 5 years had passed. Each assessment included a physical examination; a CT scan of the neck, chest, abdomen, and pelvis, as well as involved limb, if appropriate; and MRI or CT of the brain. Baseline tumour PD-L1 membrane expression was assessed at a central laboratory with the Dako PD-L1 IHC 28-8 pharmDx Kit (Dako, an Agilent Technologies company, Santa Clara, CA, USA). A
Outcome(s) of interest	• Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Type of lymph node metastases at baseline • Ulceration
Covariates adjusted for in the multivariable regression modelling	None
Additional comments	Patients were randomly assigned to receive ipilimumab or nivolumab

Participant characteristics

	Nivolumab (n= 453)	**Ipilimumab (n= 453)**
Female	43%	41%
Median age (IQR)	56 (45-65)	54 (43-65)
Stage		
IIIB	36%	32%

	Nivolumab (n= 453)	Ipilimumab (n= 453)
IIIC	45%	48%
IV	18%	19%
Macroscopic lymph node involvement	48%	47%
BRAF mutated	41%	43%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving each adjuvant therapy)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

COMBI-AD

COMBI-AD

Bibliographic Reference	Long, Georgina V; Hauschild, Axel; Santinami, Mario; Atkinson, Victoria; Mandala, Mario; Chiarion-Sileni, Vanna; Larkin, James; Nyakas, Marta; Dutriaux, Caroline; Haydon, Andrew; Robert, Caroline; Mortier, Laurent; Schachter, Jacob; Schadendorf, Dirk; Lesimple, Thierry; Plummer, Ruth; Ji, Ran; Zhang, Pingkuan; Mookerjee, Bijoyesh; Legos, Jeff; Kefford, Richard; Dummer, Reinhard; Kirkwood, John M; Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma.; The New England journal of medicine; 2017; vol. 377 (no. 19); 1813-1823

Study Characteristics

Study design	• RCTs

	○ RCT comparing Dabrafenib plus Trametinib to placebo
Study details	• Study location ○ 26 countries • Study setting ○ 169 sites • Study dates ○ From January 2013 through December 2014 • Sources of funding ○ Supported by GlaxoSmithKline and Novartis.
Inclusion criteria	• BRAF-mutated, resected high-risk melanoma • undergone complete resection of histologically confirmed stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma • recovered from definitive surgery
Exclusion criteria	previous systemic anticancer treatment or radiotherapy for melanoma
Number of participants and recruitment methods	870
Length of follow-up	minimum follow-up time was 2.5 years (median, 2.8 years)
Surveillance strategy	Imaging was performed every 3 months during the first 24 months, then every 6 months until disease recurrence or the completion of the trial
Outcome(s) of interest	Recurrence-free survival
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Age • Lymph node involvement (micrometastases vs macrometastases)

	• Ulceration
Covariates adjusted for in the multivariable regression modelling	None however there is analysis of interaction between lymph node involvement and ulceration
Additional comments	Dabrafenib+trametinib: Participants in this arm were assigned to receive oral dabrafenib at a dose of 150 mg twice daily plus trametinib at a dose of 2 mg once daily (combination therapy). Placebo arm received two matched placebo tablets.

Participant characteristics

	Dab+tram (n=438)	**Placebo (n=432)**
Female	55%	55%
Median age (IQR)	50 (18-89)	51 (20-85)
Stage		
IIIA	19%	16%
IIIB	39%	43%
IIIC	41%	38%
Node involvement		
Microscopic	35%	36%

	Dab+tram (n=438)	Placebo (n=432)
Macroscopic	36%	37%
2 or more positive lymph nodes	36%	35%
BRAF mutated	100%	100%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving adjuvant therapy and those given placebo.*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Echanique 2021

Echanique, 2021

Bibliographic Reference	Echanique, K. A., Ghazizadeh, S., Moon, A., Kwan, K., Pellionisz, P. A., Rünger, D., ... & St. John, M. Head & neck melanoma: A 22-year experience of recurrence following sentinel lymph node biopsy. *Laryngoscope Investigative Otolaryngology*

Study Characteristics

Study design	• Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ unclear
	• Study dates
	  ○ January 1997 to July 2019

	• Sources of funding ○ supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI (Clinical and Translational Science Institute) Grant Numbers UL1TR001881 and UL1TR000124UCLA
Inclusion criteria	• Negative SLNB • Head or neck melanoma
Number of participants and recruitment methods	154
Length of follow-up	Median follow up for all patients was 68.6 weeks and the average time to recurrence was 109.9 weeks
Surveillance strategy	Unclear; All patients underwent SLNB using lymphoscintography with a technetium labeled colloid injected at the primary site.
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness • Age • Gender • Stage • Ulceration • Mitotic rate • Location • LVI • Number of positive nodes
Covariates adjusted for in the	significant univariate predictors ($p<0.1$) entered into each multivariate model:

multivariable regression modelling	• Stage • Ulceration • Mitotic rate • Location

Participant characteristics

	Study (N = 154)
Female	17.5%
Mean (SD) age, years	61.3 (14.9)
Ulceration	36.2%
Mean (SD) breslow thickness	1.9 (1.6)
>1 positive lymph node	45.5%
LVI	7.4%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid. Study was a post-hoc analysis with included participants being from slightly different treatment pathways.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear follow-up procedure)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low *(all univariate predictors with a P<0.1 were entered into the multivariate model.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Unclear follow-up procedure. Multivariate model conducted on all significant predictors [p<0.1])*
	Concerns for applicability	Low

Egger 2016

Egger, 2016

Bibliographic Reference	Egger, Michael E; Bhutiani, Neal; Farmer, Russell W; Stromberg, Arnold J; Martin, Robert C G 2nd; Quillo, Amy R; McMasters, Kelly M; Scoggins, Charles R; Prognostic factors in melanoma patients with tumor-negative sentinel lymph nodes.; Surgery; 2016; vol. 159 (no. 5); 1412-21

Study Characteristics

Study design	• RCTs ○ Post-hoc analysis of data from an RCT

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ 79 centres
	• Sources of funding
	  ○ no funding

Inclusion criteria	• Negative SLNB ○ As part of the study from which this sample is derived, a cohort of patients underwent SLNB, WLE + lymphatic mapping. Those with a negative SLNB were contained in this review. These patients underwent PCR testing with positive tests subsequently randomised to LN dissection with observation (300 patients) or observation only (150 patients). Those with a negative PCR underwent observation (450 patients) • Aged 18-70 years • Primary cutaneous melanoma of 1mm thickness or more
Exclusion criteria	Clinical evidence of regional or distant metastasis
Number of participants and recruitment methods	1998

Length of follow-up	median follow-up of 70 months
Surveillance strategy	Distant recurrence was defined as recurrent disease at systemic sites, outside of local or nodal recurrences. LITRFS event was defined as recurrence in the skin or subcutaneous tissue within 5 cm of the primary tumor site or between the excision site and the mapped nodal basin. In patients with multiple sites of recurrence, the site of first recurrence was used to categorize their recurrence type for this study. Most distant site of recurrence also was evaluated for each patient; the proportion of patients with metastases at each given site was not substantially different than that based on the site of first recurrence. Mitotic rate was not included in this analysis, because it was not a required data element in the Sunbelt Melanoma Trial.
Outcome(s) of interest	Recurrence (segmented into local, regional, previously mapped negative regional lymph node basin, previously unmapped nodal basin, regional lymph node basin after CLDN and distant) and OS
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness • Age • Gender • Ulceration • Location • Histological type
Covariates adjusted for in the multivariable regression modelling	significant univariate predictors entered into each multivariate model

Participant characteristics

	Study (N = 900)
Female	43.3%

	Study (N = 900)
Aged <45 years	31.1%
Ulceration	23.8%
Breslow thickness >4mm	7.1%
LVI	6.3%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear follow-up procedure)*
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	Low *(only significant univariate predictors were entered into the multivariate model.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Unclear follow-up procedure. Potential for confounders not adequately adjusted for.)*
	Concerns for applicability	Low

EORTC 18071

EORTC 18071 trial

Bibliographic Reference Eggermont, Alexander M M; Chiarion-Sileni, Vanna; Grob, Jean-Jacques; Dummer, Reinhard; Wolchok, Jedd D; Schmidt, Henrik; Hamid, Omid; Robert, Caroline; Ascierto, Paolo A; Richards, Jon M; Lebbe, Celeste; Ferraresi, Virginia; Smylie, Michael; Weber, Jeffrey S; Maio, Michele; Konto, Cyril; Hoos, Axel; de Pril, Veerle; Gurunath, Ravichandra Karra; de Schaetzen, Gaetan; Suciu, Stefan; Testori, Alessandro; Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial.; The Lancet. Oncology; 2015; vol. 16 (no. 5); 522-30

Study Characteristics

Study design	RCT

Study details	• Study location
	  ○ 19 countries
	• Study setting
	  ○ 91 hospitals
	• Study dates
	  ○ enrolment Between July 10, 2008, and Aug 1, 2011

Inclusion criteria	• ECOG 0-1 • Completely excised stage III ○ histologically confirmed melanoma metastatic to lymph nodes only. According to the AJCC 2009 (for stage III identical to AJCC 2002) classification, patients had to have either stage IIIA melanoma (if N1a, at least 1 metastasis >1 mm), stage IIIB or stage IIIC, with no in-transit metastasis. The primary cutaneous melanoma must have been completely excised with adequate surgical margins. Complete regional lymphadenectomy was required within the 12 weeks before randomisation
Exclusion criteria	• Uveal or mucosal melanoma • autoimmune disease • use of systemic corticosteroids • previous systemic therapy for melanoma • uncontrolled infections • cardiovascular disease • abnormal blood tests ○ white blood cell count lower than 2·5 × 10^9 cells per L, absolute neutrophil count lower than 1·0 × 109 cells per L, platelets lower than 75 × 10^9 cells per L, haemoglobin con centration less than 9 g/dL, creatinine higher than 2·5 times the upper normal limit, hepatic enzymes or lactate dehydrogenase higher than two times the upper normal limit
Number of participants and recruitment methods	951
Length of follow-up	The overall median follow-up was 2·74 years (IQR 2·28–3·22), 2·60 years (2·10–3·07) in the ipilimumab group and 2·76 years (2·29–3·26) in the placebo group.
Surveillance strategy	Patients in both study groups were planned to be assessed for recurrence and distant metastases every 3 months during the first 3 years and every 6 months thereafter. Physical examination, chest radiography, CT, or other imaging techniques were used as clinically indicated. Patients were assessed at baseline during the screening phase, within maximum 6 weeks before randomisation.

Outcome(s) of interest	Recurrence o Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed irrespective of the method of assessment.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	o Ulceration o Type of lymph node involvement
Covariates adjusted for in the multivariable regression modelling	None however data were available for the interaction between ulceration and lymph node involvement
Additional comments	Patients were randomly assigned (1:1) to receive either ipilimumab or placebo. Patients received either intravenous infusions of 10 mg/kg or placebo every 3 weeks for four doses, then every 3 months for up to a maximum of 3 years, or until disease recurrence, unacceptable toxicity, major protocol violation,

Participant characteristics

	Ipilimumab (n=475)	**Placebo (n=476)**
Female	38%	38%
Aged <50 years	45%	44%
Stage		
IIIA	21%	21%
IIIB	38%	38%

	Ipilimumab (n=475)	Placebo (n=476)
IIIC	41%	41%
Lymph node involvement		
Microscopic	44%	41%
macroscopic	56%	59%
Ulceration	41%	43%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT however note that imaging was not routinely employed).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving each of the adjuvant therapies).*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Garbe 2003

Garbe, 2003

Bibliographic Reference	Garbe C; Paul A; Kohler-Späth H; Ellwanger U; Stroebel W; Schwarz M; Schlagenhauff B; Meier F; Schittek B; Blaheta HJ; Blum A; Rassner G; Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2003; vol. 21 (no. 3)

Study Characteristics

Study design	Prospective cohort study
Study details	• Study location ○ Germany

	• Study setting
	  ○ All patients referred to the Department of Dermatology of the University of Tuebingen
	• Study dates
	  ○ from August 1996 to August 1998
	• Sources of funding
	  ○ Supported by grant no. M3/95/Ga I from the Deutsche Krebshilfe, Bonn, Germany

Inclusion criteria	• I-IV
	  ○ All patients underwent excision of a primary melanoma. The majority of these patients were free of any sign of metastasis at the time of study inclusion, with metastases first occurring during the study period.
	  ○ Attend regular follow-up examinations at the university hospital

Exclusion criteria	• Suspected metastasis • Patients who had not previously undergone observation of their disease and who were referred with a suspected metastasis • discontinued previous follow-up ○ and then returned with a possible metastasis
Number of participants and recruitment methods	2,008
Length of follow-up	25 months
Surveillance strategy	Guidelines recommend follow-up examinations every 3 months in the first 5 years after resection of the primary tumor, continued every 6 months until the 10th postoperative year. During the initial consultations, patients were extensively educated regarding the clinical characteristics of melanoma and its metastases, with particular emphasis on self-examination and the recognition of the signs and symptoms of recurrence. Each examination consisted of a complete history, inspection of the entire skin and the adjacent mucosae, and clinical examination of the scar of primary resection, the lymphatic drainage area(s), and all lymphatic regions.

	Abdominal sonography and x-ray of the chest were performed every 12 months in stage I to II disease and every 6 months in stage III disease. Similarly, annual blood testing for patients in stages I to II and biannual testing for stage III patients was performed to examine the following parameters: full blood count and differential, erythrocyte sedimentation rate, renal function (urea and creatinine), liver enzymes ALT, AST, alkaline phosphatase (AP), gamma-glutamyltransferase, and lactate dehydrogenase (LDH) as potential markers of metastasis. In patients with a high risk of metastasis, protein S100 levels also were measured during the second half of the study period. Furthermore, within the first 5 years, sonographic examination of the resected tumour scar, lymphatic drainage area(s), and regional node region(s) was performed once a year in patients with stage I melanoma, every 6 months in patients with stage II melanoma, and every 3 to 6 months in patients with stage III melanoma. The examinations were alternated between the university Department of Dermatology and dermatology practices, with imaging procedures performed only at the university hospital. All examinations were prospectively documented and evaluated within the frame of this study.
Outcome(s) of interest	breakdown of how recurrence was detected
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	how recurrence was detected

Participant characteristics

	Study (N = 2,008)
Breslow thickness	
<0.76mm	50.3%
0.76-1.5mm	24.6%
1.51-4mm	16.6%

	Study (N = 2,008)
>4mm	3.0%

Risk of bias

Section	Question	Answer
Selection of participants	Concerns for applicability for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Variety in different imaging methods employed. Ideally, all patients would have undergone the same routine imaging method)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High *(Potential for confounders not adjusted for, particularly stage as all stages were included in analysis. Variance in imaging modalities used. Unclear degree of variance in surveillance strategies employed.)*
	Concerns for applicability	Low

Groen 2019

Groen, 2019	
Bibliographic Reference	Groen, L. C., Lazarenko, S. V., Schreurs, H. W., & Richir, M. C. (2019). Evaluation of PET/CT in patients with stage III malignant cutaneous melanoma. *American journal of nuclear medicine and molecular imaging*, *9*(2), 168

Study Characteristics

Study design	• Retrospective cohort study

Study details	• Study location
	  ○ The Netherlands
	• Study setting
	  ○ Multiple centres
	• Study dates
	  ○ January 2012 to January 2016
	• Sources of funding
	  ○ supported by NIH/NCRR/NCATS CTSA Grant Number UL1 TR000135. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Inclusion criteria	• Stage III melanoma

Number of participants and recruitment methods	73
Length of follow-up	Staging only
Predictor factors	• Location • Breslow thickness • Ulceration
Outcome(s) of interest	Result of PET/CT scan assessing distant metastases

Participant characteristics

	Study (N = 317)
Female	50.7%%
Mean age (range)	66.5 (48-88) years among PET/CT positive, 64.3 (26-89) among PET/CT negative.
Tumour location	
Head/neck	5.5%
Trunk	45.2%
Extremities	47.9%
Ulceration	32.9%

	Study (N = 317)
T-stage	
X	4.1%
1	9.6%
2	34.2%
3	35.6%
4	16.4%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(study was retrospective and it is therefore likely that those patients staged with PET/CT are not representative of all stage III patients. It is noted that all patients underwent PET/CT due to presence of positive lymph nodes or satellite/in-transit lesions however it is unclear whether PET/CT was routinely given in these patients. Additionally, data is not presented separately for these two cohorts..)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders))*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No adjustment for confounders. Lack of clarity as to when PET/CT was used at study centres.)*
	Concerns for applicability	Low

Grotz 2014

Grotz, 2014

Bibliographic Reference	Grotz, Travis E; Kottschade, Lisa; Pavey, Emily S; Markovic, Svetomir N; Jakub, James W; Adjuvant GM-CSF improves survival in high-risk stage iiic melanoma: a single-center Study.; American journal of clinical oncology; 2014; vol. 37 (no. 5); 467-72

Study Characteristics

Study design	• Retrospective cohort study

	○ main purpose of the study was to compare the use of GM-CSF to clinical observation in people with resected III.
Study details	• Study location ○ USA • Study setting ○ Single institution • Study dates ○ 2001-2010 • Sources of funding ○ supported by NIH/NCRR/NCATS CTSA Grant Number UL1 TR000135. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.
Inclusion criteria	• Stage III melanoma • Surgically resected disease • Received no adjuvant therapy or received GM-CSF
Number of participants and recruitment methods	317
Length of follow-up	up to 10 years; median of 44 months.
Surveillance strategy	There were 165 (52%) patients observed expectantly with history and physical exam every 3–6 months, imaging as per physician discretion and at minimum annual dermatological examinations including the skin and lymph node basins. There were 152 (48%) patients treated with adjuvant GM-CSF in addition to routine surveillance
Outcome(s) of interest	recurrence; melanoma-specific mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Age • Stage

	• ECOG • Use of GM-CSF adjuvant therapy
Covariates adjusted for in the multivariable regression modelling	multivariate model adjusted for Gender, age, stage, ECOG and breslow thickness

Participant characteristics

	Study (N = 317)
Female	64%
Median age (IQR)	55 (44-66) years
Tumour location	
Head/neck	24%
Trunk	23%
Extremities	37%
Stage	
IIIA	32%
IIIB	40%
IIIC	28%

	Study (N = 317)
ECOG 0	89%
Ulceration	26%
Breslow thickness, median (IQR)	2.3 (1.3-4.0)mm

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(clear protocol for follow-up however use of imaging was at physician's discretion only and it is unclear how much variation in use there was.)*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(multivariate analysis was conducted but did not adjust for adjuvant therapy (radiotherapy or GM-CSF))*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(inadequate adjustment for confounders. Unclear variation in use of imaging.)*
	Concerns for applicability	Low

Hofmann 2002

Hofmann, 2002

Bibliographic Reference	Hofmann U; Szedlak M; Rittgen W; Jung EG; Schadendorf D; Primary staging and follow-up in melanoma patients--monocenter evaluation of methods, costs and patient survival.; British journal of cancer; 2002; vol. 87 (no. 2)

Study Characteristics

Study design	• Retrospective cohort study ○ review of hospital database

Study details	• Study location
	  ○ Germany
	• Study setting
	  ○ Single centre

	• Study dates ○ between January 1983 and November 1999
Inclusion criteria	• I-III • Excision of primary melanoma ○ at least one documented staging result at time of primary excision.
Exclusion criteria	<6 months follow-up
Number of participants and recruitment methods	630
Length of follow-up	up to 10 years; median follow-up time of 4.1 and 1.5 years, for stages I/II and III, respectively
Surveillance strategy	For stage I-II, Chest X-ray and sonography of the abdomen were annually done on each patient. Lymph node sonography of peripheral nodes was routinely performed every 6 months during the years 1986 – 1997 at follow-up of patients in stage I/II. The postsurgical follow-up of patients with loco-regional recurrence were usually extended by increasing the frequency of diagnostic imaging (Chest X-ray+sonography of abdomen twice a year, sonography of lymph nodes four times a year)
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness • How recurrence was detected: clinical follow-up (history and physical examination) or imaging
Covariates adjusted for in the multivariable regression modelling	None

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Imaging modalities used during follow-up varied and may have influenced the ability to detect recurrence. Large differences in follow-up length between stages.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders.)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High *(Confounders were not adjusted for. Large difference in follow-up length between stages. Differences between participants in imaging modality used during follow-up)*
	Concerns for applicability	Low

Huang 2020

Huang 2020

Bibliographic Reference	Huang, K., Misra, S., Lemini, R., Chen, Y., Speicher, L. L., Dawson, N. L., ... & Gabriel, E. M. (2020). Completion lymph node dissection in patients with sentinel lymph node positive cutaneous head and neck melanoma. *Journal of Surgical Oncology*, *122*(6), 1057-1065

Study Characteristics

Study design	• Retrospective cohort study ○ Retrospective review of National Cancer Database

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Multiple centres across USA
	• Study dates
	  ○ From 1st January 2012 to 31st December 2014

Inclusion criteria	• Clinical stage 1b-2c • Cutaneous head or neck melanoma • Positive SLNB

Exclusion criteria	• Missing stage or survival data • Second primary cancer
Number of participants and recruitment methods	530
Length of follow-up	28.2 months (same for SLNB only and SLNB + CLND groups)
Surveillance strategy	Unclear
Outcome(s) of interest	Overall survival
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Scalp vs other face locations • Ulceration • Breslow thickness • Mitosis • LVI • >1 positive LN
Covariates adjusted for in the multivariable regression modelling	Unclear how factors were selected for multivariate analysis. The following factors were adjusted for in multivariate model: • Age • Location • Ulceration • Positive lymph nodes

Participant characteristics

	Study (N = 530)
Female	24.9%
Median (IQR) age	60 (46-69) years
Tumour location	
Scalp/neck	44.3%
Face	55.7%
Stage (AJCC 7th ed.)	
IIIA	42.6%
IIIB/IIIC	50.4%
Ulceration	38.3%
LVI	15.5%
≥2 positive lymph nodes	36.2%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Unclear surveillance protocol.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(limited number of factors were adjusted for an it is unclear how these factors were selected.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Confounders not adequately adjusted for. Limited reporting on methods for multivariate analysis and for surveillance.)*
	Concerns for applicability	Low

IMMUNED

IMMUNED trial

Bibliographic Reference	Zimmer, Lisa; Livingstone, Elisabeth; Hassel, Jessica C; Fluck, Michael; Eigentler, Thomas; Loquai, Carmen; Haferkamp, Sebastian; Gutzmer, Ralf; Meier, Friedegund; Mohr, Peter; Hauschild, Axel; Schilling, Bastian; Menzer, Christian; Kieker, Felix; Dippel, Edgar; Rosch, Alexander; Simon, Jan-Christoph; Conrad, Beate; Korner, Silvia; Windemuth-Kieselbach, Christine; Schwarz, Leonora; Garbe, Claus; Becker, Jurgen C; Schadendorf, Dirk; Dermatologic Cooperative Oncology, Group; Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial.; Lancet (London, England); 2020; vol. 395 (no. 10236); 1558-1568

Study Characteristics

Study design	RCTs

Study details	• Study location
	  ○ Germany
	• Study setting
	  ○ 20 academic medical centres
	• Study dates
	  ○ Between Sept 2, 2015, and Nov 20, 2018
	• Sources of funding
	  ○ funded by Bristol-Myers Squibb

Inclusion criteria	• ECOG 0-1 • aged 18–80 years • no evidence of disease after surgery or radiotherapy • known BRAF status • tumour tissue from the resected site available for immunohistochemical assessment of programmed cell death ligand 1 (PD-L1) expression and biomarker analyses • IV
Exclusion criteria	• Uveal or mucosal melanoma • previous therapy with checkpoint inhibitors • any previous immunosuppressive therapy within the past 30 days before study drug administration

Number of participants and recruitment methods	167
Length of follow-up	median follow-up of 28·4 months (IQR 17·7–36·8).
Outcome(s) of interest	recurrence-free survival; • Assessments for tumour recurrence were done every 12 weeks for the first 3 years after randomisation and every 6 months in year 4. Assessments included CT or MRI, or both. In years 5 and 6, patients are to undergo lymph node ultrasonography every 6 months. Physical examinations are done quarterly for the first 6 years after randomisation.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Presence of brain metastases • BRAF status
Covariates adjusted for in the multivariable regression modelling	none
Additional comments	Patients were randomized to either ipilimumab + nivolumab, nivolumab only or placebo

Participant characteristics

	Study (N = 187)
Female	43%
Age <65 years	74%

	Study (N = 187)
ECOG 1	7%
Previous systemic therapy in metastatic setting	2%
Previous adjuvant systemic therapy	32%
BRAF mutation	45%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving adjuvant therapy and those given placebo.*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Jang 2020

Jang, 2020

Bibliographic Reference	Jang, S.; Poretta, T.; Bhagnani, T.; Harshaw, Q.; Burke, M.; Rao, S.; Real-World Recurrence Rates and Economic Burden in Patients with Resected Early-Stage Melanoma; Dermatology and Therapy; 2020; vol. 10 (no. 5); 985-999

Study Characteristics

Study design	• Retrospective cohort study ○ retrospective review of prospectively collected database

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ SEER database
	• Study dates
	  ○ January 2010 - December 2013

	• Sources of funding ○ funded by Bristol Myers Squibb
Inclusion criteria	• Resection of primary lesion ○ within 4 months of diagnosis • IIB-IIIA
Exclusion criteria	• < 12 months of enrollment in Medicare part A or part B before and after the index date • an age of <18 years at the index date • evidence of resection in the preindex period • ocular/uveal melanoma or any other nonmelanoma malignancies • a record of enrollment in a health maintenance organization after the index date
Number of participants and recruitment methods	1316
Length of follow-up	5-years
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Type of melanoma • T-status • Ulceration • Use of adjuvant therapy

Covariates adjusted for in the multivariable regression modelling	unadjusted

Study-level characteristics

	Stage IIB-C (N = 1,174)	**Stage IIIA (N = 142)**
% Female	36%	44%
Mean age (SD)	79.1 (9.3)	71.9 (11.0)
Ulceration	73%	N/A
N stage 0	100%	
N stage 1-2		87%
		13%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Concerns for applicability for selection of participants domain	High *(Patients recruited from SEER database. Risk factors are likely to be comorbid. No information on how often use of adjuvant therapy was captured by database..)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low.

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(unclear follow-up procedure(s) and the extent to which these differed between study centres. Unclear when and how often imaging was employed. Study used a proxy measure of recurrence which included hospitalisation following initial melanoma, secondary melanoma, presence of metastasis at subsequent point in time.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Unclear *(Adjusted for a variety of important clinical characteristics including whether or not the patient receiving adjuvant therapy. However, it is unclear how often this variable is captured by the database.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Adjustment for confounders however information on how this was conducted is limited, including the level of missing data for key confounders (including use of adjuvant therapy). Unclear follow-up procedure.)*
	Concerns for applicability	Low

KEYNOTE-054

KEYNOTE-054

Bibliographic Reference	Eggermont, A.M.M.; Blank, C.U.; Mandala, M.; Long, G.V.; Atkinson, V.G.; Dalle, S.; Haydon, A.M.; Meshcheryakov, A.; Khattak, A.; Carlino, M.S.; Sandhu, S.; Larkin, J.; Puig, S.; Ascierto, P.A.; Rutkowski, P.; Schadendorf, D.; Koornstra, R.; Hernandez-Aya, L.; Di Giacomo, A.M.; van den Eertwegh, A.J.M.; Grob, J.-J.; Gutzmer, R.; Jamal, R.; Lorigan, P.C.; van Akkooi, A.C.J.; Krepler, C.; Ibrahim, N.; Marreaud, S.; Kicinski, M.; Suciu, S.; Robert, C.; Longer Follow-Up Confirms Recurrence-Free Survival Benefit of Adjuvant Pembrolizumab in High-Risk Stage III Melanoma: Updated Results From the EORTC 1325-MG/KEYNOTE-054 Trial; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2020; vol. 38 (no. 33); 3925-3936

Study Characteristics

Study design	RCTs

Study details	• Study location
	  ○ 22 countries
	• Study dates
	  ○ enrolment from August 2015 through November 2016
	• Sources of funding
	  ○ Supported by Merck & Co.

Inclusion criteria	• Stage III melanoma
	  ○ Patients had either stage IIIA melanoma (patients with N1a or N2a had to have at least one micrometastasis measuring > 1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases.
	• at least 18 years old
	• Complete regional lymphadenectomy
	  ○ complete regional lymphadenectomy performed within 13 weeks before the start of treatment.

Exclusion criteria	• use of systemic corticosteroids • previous systemic therapy for melanoma • uncontrolled infections • use of systemic corticosteroids
Number of participants and recruitment methods	1019

Length of follow-up	The median follow-up was 36.6 months (interquartile range [IQR], 35.0-40.2 months) overall, 36.6 months (IQR, 34.9-39.8 months) in the pembrolizumab group, and 36.5 months (IQR, 35.0-40.5 months) in the placebo group
Surveillance schedule	Computed tomography (CT) scans and magnetic resonance imaging (MRI; full chest, abdomen, and pelvis CT and/or MRI, neck CT and/or MRI for head and neck primaries, CT and/or MRI for other localizations [eg, brain, deep soft tissue], only if clinically indicated) were performed every 12 weeks for the first 2 years and every 6 months through year 5.
Outcome(s) of interest	Recurrence • Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed was taken into account. RFS was defined as the time from random assignment until the date of first recurrence (local, regional, or distant metastasis) or death as a result of any cause. For patients without any event, the follow-up was censored at the latest disease evaluation performed according to the protocol.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• BRAF mutation status • High risk stage IIIA vs all IIIB • Gender • Breslow thickness
Covariates adjusted for in the multivariable regression modelling	None
Additional comments	Patients were randomly assigned (1:1) to receive either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses for approximately 1 year or until disease recurrence, unacceptable toxicity, major protocol violation, or withdrawal of consent

Participant characteristics

	Pembrolizumab (n=514)	Placebp (n=505)
Female	37%	39.8%
<50 years old	37.5%	36.8%
Stage		
IIIA	15.6%	15.8%
IIIB	46.1%	45.5%
IIIC	38.3%	38.6%
Lymph node involvement		
Macroscopic	36.4%	31.9%
Microscopic	63.6%	68.1%
>1 positive lymph node	55.8%	53.1%
Ulceration	40.5%	39.0%
BRAF mutation	54.7%	57.6%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data is provided for those receiving adjuvant therapy and those given placebo.*
Overall Risk of bias and Applicability	Risk of bias	Low

Section	Question	Answer
	Concerns for applicability	Low

Kim 2020

Kim, 2020

Bibliographic Reference	Kim, E., Obermeyer, I., Rubin, N., & Khariwala, S. S. (2021). Prognostic significance of regression and mitotic rate in head and neck cutaneous melanoma. *Laryngoscope Investigative Otolaryngology*, *6*(1), 109-115

Study Characteristics

Study design	• Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ SEER database
	• Study dates
	  ○ May 2002 and March 2019
	• Sources of funding
	  ○ funded by Bristol Myers Squibb

Inclusion criteria	• Head and neck melanoma • underwent wide local excision
Exclusion criteria	• ocular or choroidal melanoma • mucosal melanoma • metastatic melanoma to the head or neck with no known primary tumor • melanoma of the head or neck with no surgical intervention • multiple head or neck melanomas on initial presentation • nonmelanoma skin cancers of the head and neck

Number of participants and recruitment methods	191
Length of follow-up	Unclear
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Breslow thickness • Ulceration • Mitoses
Covariates adjusted for in the multivariable regression modelling	Only data from multivariate modelling was reported. The following factors were adjusted for: • Regression • Breslow thickness • Mitoses • Nodular melanoma • Age • Ulceration

Study-level characteristics

	Study population (N = 191)
% Female	30.9%
Mean age (range), years	62.6 (20-97)
Ulceration	16.3%
Mean mitotic rate (range), per mm2	2.8 (0.-20)
Underwent SLNB	60.5%
Positive SLNB	25.2%
Mean breslow thickness (range), mm	1.9 (range 0.1-15.0)

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Concerns for applicability for selection of participants domain	High *(Patients were identified using healthcare database codes. Disease stage not captured. Risk factors are likely comorbid.)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low.
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(unclear follow-up protocol and unclear average length of (and variation in) follow-up.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Unclear *(Univariate analyses for outcomes of relevance to this review were not reported. Multivariate modelling for constructed to identify the relationships of specifically regression with recurrence and is therefore not optimised for other variables of interested to this review.)*
Overall Risk of bias and Applicability	Risk of bias	High *(confounders were not adequately adjusted for. Unclear follow-up protocol and length. Disease stage not captured).*
	Concerns for applicability	Low

Kim 2021

Kim, 2021

Bibliographic Reference	Kim, D., Chu, S., Khan, A. U., Compres, E. V., Zhang, H., Gerami, P., & Wayne, J. D. (2021). Risk factors and patterns of recurrence after sentinel lymph node biopsy for thin melanoma. *Archives of dermatological research*, 1-8

Study Characteristics

Study design	• Retrospective cohort study ○ Review of Northwestern Medicine Enterprise Data Warehouse database
Study details	• Study location ○ Germany

	• Study setting
	  ○ Single centre
	• Study dates
	  ○ 1999 to 2018
	• Sources of funding
	  ○ partially supported by the IDP Foundation and the Melanoma Research Foundation (SP0043559)

Inclusion criteria	• SLNB negative • <1mm Breslow thickness
Number of participants and recruitment methods	209
Length of follow-up	Median (IQR) follow up time after initial SLNB for the entire cohort was 62 (29–106) months
Outcome(s) of interest	• All recurrences • Distant recurrences
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Location • Ulceration
Covariates adjusted for in the multivariable regression modelling	Significant univariate predictors were entered into multivariate modelling. All recurrences analysis adjusted for: • Location • Ulceration

	• Mitosis Distant recurrences analysis adjusted for: • Location • Ulceration • Mitosis

Study-level characteristics

	Study population (N = 209)
% Female	44.5%
Mean age (range), years	55.0 (39–65)
Ulceration	6.2%
Breslow thickness 0-8mm	35.8%
Tumour location	
Head/neck	22%
Trunk	36%
Extremities	42%

Risk of bias

Section	Question	Answer
Selection of participants	Concerns for applicability for selection of participants domain	Low *(Risk factors are likely comorbid. However, population is very specific and likely contains patients with a similar level of disease severity)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low.
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear (Unclear follow-up protocol for included participants at study centre)
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Multivariate modelling however only significant univariate predictors were controlled for. However, inclusion criteria limited variation in several other important clinical characteristics.)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Kurtz 2017

Kurtz, 2017	
Bibliographic Reference	Kurtz, James; Beasley, Georgia M; Agnese, Doreen; Kendra, Kari; Olencki, Thomas E; Terando, Alicia; Howard, J Harrison; Surveillance strategies in the follow-up of melanoma patients: too much or not enough?.; The Journal of surgical research; 2017; vol. 214; 32-37

Study Characteristics

Study design	• Retrospective cohort study ○ Retrospective review of prospective database

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single institution
	• Study dates
	  ○ 2009-2015
	• Sources of funding
	  ○ Authors had support from Bristol-Myers Squibb, Karyopharm, Pfizer and Tracon.

Inclusion criteria	• Stage II-III • Surgery as initial therapy ○ with surgically rendered no evidence of disease. Surgical therapy at the time of diagnosis consisted of the following: (1) wide local excision (WLE) only in 2% (6/247), (2) WLE plus sentinel lymph node biopsy (SLNB) in 66% (162/247), and (3) WLE, SLNB, plus completion node dissection in 32% (79/ 247).
Exclusion criteria	<6 months follow-up
Number of participants and recruitment methods	369

Length of follow-up	5 years
Surveillance strategy	It total 27% underwent clinical examination follow-up without routine imaging; 73% underwent routine clinical and radiological follow-up. Almost all IIIB/C patients underwent both clinical and radiological follow-up (see figure 1 in paper for rough illusions of strategy breakdown by stage) Imaging involved "some combination of chest x-rays, CT scans (including chest, abdomen, pelvis, and neck for head and neck primary), magnetic resonance imaging (MRIs), whole body PET/CTs, or other directed imaging (ultrasound)."
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	N/A
Covariates adjusted for in the multivariable regression modelling	N/A

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Choice of strategy will have been influenced by patient characteristics.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(No detail on the frequency/intensity of strategies employed and how much this differed between and within disease stages)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(variance in type of imaging used will have influenced ability to detect recurrence)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	High *(no adjustment for confounders. limited detail on surveillance strategies.)*
	Concerns for applicability	Low

Laks 2017

Laks, 2017

Bibliographic Reference	Laks, Shachar; Meyers, Michael O; Deal, Allison M; Frank, Jill S; Stitzenberg, Karyn B; Yeh, Jen Jen; Thomas, Nancy E; Ollila, David W; Tumor Mitotic Rate and Association with Recurrence in Sentinel Lymph Node Negative Stage II Melanoma Patients.; The American surgeon; 2017; vol. 83 (no. 9); 972-978

Study Characteristics

Study design	Retrospective cohort study review of prospective melanoma database

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single institution
	• Study dates
	  ○ from September 1997 to July 2015

Inclusion criteria	• Stage II • Negative SLNB • T2-4
Number of participants and recruitment methods	265
Length of follow-up	All patients had at least 6 months follow-up data Median follow-up among survivors was 4 years (6m-7y range)
Surveillance strategy	Unclear follow-up/surveillance procedure.
Outcome(s) of interest	Recurrence-free survival; Recurrence was categorized as local, regional (in transit or regional lymph node basin), or distant. For a patient with multiple simultaneous recurrences, the most advanced recurrence was selected. Lymphatic metastases were considered regional disease if they occurred in a potentially draining basin and considered distant recurrence if occurred in an unlikely draining basin. Overall survival

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (continuous) • Breslow (continuous) • T stage (continuous) • Ulceration • Mitosis (continuous or dichotomous) • TIL • Location
Covariates adjusted for in the multivariable regression modelling	• Age (continuous) • Breslow (continuous) • T stage (continuous) • Ulceration • Mitosis (continuous)

Participant characteristics

	Study (N = 265)
Female	37.7%
Mean age (range)	67 (21-91)
Tumour location	
Head/neck	30.9%
Trunk	23.4%
Extremities	45.7%

	Study (N = 265)
Breslow thickness, mean (range) mm	2.80 (1.03-24.0)
Ulceration	57.6%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear surveillance procedure during study period)*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Only significant univariate predictors were entered into multivariate model.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Inadequate adjustment for confounders and no information on surgical procedures. Unclear surveillance protocol.)*
	Concerns for applicability	Low

Liang 2020

Liang, 2020

Bibliographic Reference	Liang, C., Hu, W., Li, J., Zhang, X., Zhou, Z., & Liang, Y. (2021). Early time to recurrence predicts worse survival in patients with localized or regionally advanced cutaneous melanoma. *Dermatologic Therapy*, e14981.

Study Characteristics

Study design	• Retrospective cohort study ○ review of prospective melanoma database

Study details	• Study location
	  ○ China
	• Study setting
	  ○ Single institution
	• Study dates

	○ Resected from January 1995 – December 2016 (final follow-up October 2019)
Inclusion criteria	• Stage I-III (AJCC 8th) • Underwent primary lesion excision with or without LND
Number of participants and recruitment methods	731
Length of follow-up	During a median follow-up time of 55.6 months (IQR: 33.9 - 94.2 months)
Surveillance strategy	Unclear
Outcome(s) of interest	All recurrences
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Tumour size • Location (trunk vs lower extremity)
Covariates adjusted for in the multivariable regression modelling	• Gender • Tumour size • Location (trunk vs lower extremity) • Topography • Tumour stage • Physical stimulation • Extended resection • Surgical margin • Adjuvant therapy

Participant characteristics

	Study (N = 265)
Female	48.7%
Median age (IQR), years	53 (42-63)
Tumour location	
Trunk	13.5%
Lower extremity	72%
Upper extremity	14.5%
Positive SLNB	9.4%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Large variance in disease stages included.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear surveillance protocol for follow-up at study centre.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low *(multivariate model adjusted for most important clinical characteristics.)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Madu 2016 and 2017

Madu, 2016 and 2017

Bibliographic Reference	A) Madu, M. F., Wouters, M. W., Klop, W. M. C., van der Hiel, B., van de Wiel, B. A., Jóźwiak, K., ... & van Akkooi, A. C. (2016). Clinical prognostic markers in stage IIIB melanoma. *Annals of surgical oncology*, *23*(13), 4195-4202.

B) Madu, Max F; Schopman, Jaap H H; Berger, Danique M S; Klop, Willem M C; Jozwiak, Katarzyna; Wouters, Michel W J M; van der Hage, Jos A; van Akkooi, Alexander C J; Clinical prognostic markers in stage IIIC melanoma.; Journal of surgical oncology; 2017; vol. 116 (no. 2); 244-251

Study Characteristics

Study type	Retrospective cohort study

Study details	• Study location
	  ○ The Netherlands
	• Setting
	  ○ Single centre
	• Study dates
	  ○ 2000-2016

Inclusion criteria	• IIIB • IIIC • Lymph node dissection
Exclusion criteria	• mucosal melanoma • multiple primary melanomas • distant metastases before or during LND • unresectable regional lymph node metastases • no formal lymph node dissection after IIIB/C diagnosis • Other (exclusion criteria for stage IIIC only) ○ neo-adjuvant or adjuvant therapy trials with recently developed (from 2010) targeted therapies or immunotherapies, and repeat LND in the same regional nodal basin. Since we only included patients who underwent LND, patients with an ulcerated primary tumor with in-transit metastasis and no nodal involvement (T1-4bN2cM0) were excluded from the study

Number of participants	IIIC: 205 IIIB: 250
Surveillance strategy	Follow-up took place at 6 and 12 weeks after discharge from the hospital, every 3 months in the first year, every 4 months in the second year, every 6 months in year 3-5, and yearly thereafter. At each visit, physical examination and laboratory examination with S100B took place. When patients presented with symptoms or elevated tumor markers, they were restaged with imaging (MRI brain and whole body PET/CT or CT). Recurrences were scored as locoregional recurrence (LRR), regional nodal recurrence, or distant recurrence. LRR recurrence was defined as local recurrence, satellite metastasis, or an in-transit metastasis. Regional recurrence was defined as regional nodal recurrence in the draining lymph nodal basin. Distant recurrence was defined as subcutaneous or nodal recurrence beyond the regional nodal basin, or visceral recurrence
Length of follow-up	IIIC: Up to 10 years: Median follow-up was 20 months (interquartile range 11-43 months); IIIB: Up to 10 years: Median follow-up was 52 months (interquartile range 29– 108 months); unclear follow-up protocol
Loss to follow-up	• Predicted outcome: recurrence • Predictors: • Gender • Age • Location • Breslow • Ulceration • Extracapsular extension

Participant characteristics

	IIIB, clinically detectable (N = 205)	**IIIC (N=250)**
Female	65%	41%

	IIIB, clinically detectable (N = 205)	IIIC (N=250)
Median age (IQR)	nr	60 (51-68)
>50 years old	67%	Nr
Tumour location		
Head/neck	28.4%	19%
Trunk	25.1%	30.2%
Extremities	28.4%	44.4%
N-Stage		
1	64.5%	53%
2	35.5%	47%
3	-	105%
T4	Nr	30.2%
Ulceration	0%	54.1%
Breslow thickness, median (IQR)	nr	3.0 (1.9-4.7)

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low *(Multivariate model adjusted for all risk factors assessed in the study. No participants received adjuvant therapy)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Meyers 2009

Meyers, 2009

Bibliographic Reference	Meyers MO; Yeh JJ; Frank J; Long P; Deal AM; Amos KD; Ollila DW; Method of detection of initial recurrence of stage II/III cutaneous melanoma: analysis of the utility of follow-up staging.; Annals of surgical oncology; 2009; vol. 16 (no. 4)

Study Characteristics

Study design	Retrospective cohort study
Inclusion criteria	• Negative SLNB (if stage II) ○ Indications for SLN biopsy at our institution included any melanoma with Breslow depth of C.75 mm and any melanoma\.75 mm with ulceration, regression, or extension to the deep margin of the biopsy specimen • Stage II-III • underwent surgical treatment
Number of participants and recruitment methods	118
Length of follow-up	up to 9 years; The median follow-up of survivors was 44 months (range, 8–115 months).
Surveillance strategy	This schedule suggests routine follow-up examinations with a health care provider (surgical oncologist, dermatologist, surgical nurse practitioner) every 3 months for the first 3 years, followed by every 6 months in years 3 to 5 and then at least annually to year 10. It is recommended that during routine examination, the patient undergo full-body examination of the skin and lymph node basins. In addition to routine physical examination, our recommendations suggest annual routine blood work, including LDH, and annual CXR in patients with stage II melanoma. For patients with stage III melanoma, we have also recommended annual routine body and brain imaging in years 1 to 3 of follow-up, although some patients have had routine imaging for 3 years. Before January 2003, we routinely used CT of the chest/abdomen/pelvis to follow patients. Since then, whole-body PET/CT scan became available at our institution and has been the test of choice. In addition to whole-body imaging, we have suggested routine imaging of the brain as well. This has been carried out primarily with contrast MRI. Although a number of patients have undergone routine brain MRI, our most recent paradigm has been to omit this.

Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• How recurrence was detected (Patient, symptomatic, physician or imaging detected) • Location • Gender • Ulceration • Stage
Covariates adjusted for in the multivariable regression modelling	None

Participant characteristics

	Study (N = 118)
Female	35%
Non-white ethnicity	9%
Tumour location	
Head/neck	32%
Trunk	23%
Extremities	45%
Stage	

	Study (N = 118)
IIA	25%
IIB	26%
IIC	12%
III	30%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Standardized protocol however it is unclear how much variance in imaging use there was in practice)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No adjustment for confounders. Unclear how much variance there was in imaging done during follow-up)*
	Concerns for applicability	Low

Mitra, 2021

Mitra, 2021

Bibliographic Reference	Mitra, D., Ologun, G., Keung, E. Z., Goepfert, R. P., Amaria, R. N., Ross, M. I., ... & Guadagnolo, B. A. (2021). Nodal Recurrence is a Primary Driver of Early Relapse for Patients with Sentinel Lymph Node-Positive Melanoma in the Modern Therapeutic Era. *Annals of surgical oncology*, *28*(7), 3480-3489

Study Characteristics

Study design	Retrospective cohort study
Study dates	March 2016 – December 2019

Source of funding	Supported by Cancer Center Support grant CA016672
Inclusion criteria	• Positive SLNB during study dates • Did not undergo CLND
Number of participants and recruitment methods	215
Length of follow-up	median follow-up of 20 months (IQR 12–28.5 months)
Surveillance strategy	"institutional practice is to follow SLN NEGATIVEpositive patients who do not have CLND every 3–4 months for 2 years, followed by every 6 months for years 3–5. Follow-up includes patient history, patient physical, ultrasound of the draining nodal basin, and cross-sectional imaging of the chest, abdomen, and pelvis, similar to the monitoring performed for MSLT-2. For patients with nodal disease of the head and neck, cross sectional imaging of the neck and involved nodal basin are included. Dedicated CNS imaging is also performed annually for surveillance"
Outcome(s) of interest	• Any disease recurrence • Nodal control (nodal recurrence in same basin as SLNB)
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Location • Breslow thickness • Microsatellites • LVI • >1mm nodal deposit • ≥2 positive lymph nodes • Ulceration • Stage

Covariates adjusted for in the multivariable regression modelling	

Participant characteristics

	Study (N = 215)
Female	37%
Non-white ethnicity	12%
Tumour location	
Head/neck	16%
Trunk	35%
Extremities	49%
LVI	35%
BRAF positive	37%
Ulceration	40%
>1 mitosis/mm2	81%
Adjuvant therapy	
Immunotherapy	44%

	Study (N = 215)
Dabrafenib + trametinib	3%
Radiation therapy	8%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low *(Adjustment for confounders: all univariate predictors with an association of p<0.10 with outcome.)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Mooney 1998

Mooney, 1998

Bibliographic Reference	Mooney MM; Kulas M; McKinley B; Michalek AM; Kraybill WG; Impact on survival by method of recurrence detection in stage I and II cutaneous melanoma.; Annals of surgical oncology; 1998; vol. 5 (no. 1)

Study Characteristics

Study design	• Retrospective cohort study ○ retrospective analysis of medical records and the tumor registry database at singe institute

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ between 1971 and 1995

	• Sources of funding ○ supported by T-32 training grant CA 09581-08, awarded to the Division of Surgical Oncology, Roswell Park Cancer Institute by the National Institutes of Health.
Inclusion criteria	Stage I-II
Number of participants and recruitment methods	1004
Length of follow-up	Up to 15 years; Median follow-up for patients who were alive and free of disease at the time of this study was 7.1 years. Approximately 98% of the cohort had had complete follow-up within 2 years of the end of this study (1995), and 81% had had complete follow-up within 12 months of the end of the study
Outcome(s) of interest	Recurrence (or progression) - separated into asymptomatic and symptomatic recurrences. Only first recurrences were recorded to avoid double counting. The total number of first recurrences is 170 however data on predictors is only given for 154. Overall sample sizes are not reported meaning that a small number of non-recurrence participants will actually have had a recurrence.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Gender location
Covariates adjusted for in the multivariable regression modelling	none

Participant characteristics

	Study (N = 1,004)
Non-white ethnicity	0.5%
Mean age	51 years
Tumour location	
Head/neck	16%
Trunk	33%
Extremities	51%
Female	52%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	High *(Unclear if patients underwent excision of primary tumour)*

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(Total number of participants used in analysis is not given. 16 patients had recurrences that were not included in analysis. For this review, these will be captured in the 'no recurrences' group. However, this is a small number compared to the total sample size.)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(However note variance in follow-up time)*
	Concerns for applicability for outcome or its determination domain	Low
nalysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders.)*
Overall Risk of bias and Applicability	Risk of bias	High *(No adjustment for confounders. Long study period with large variance in follow-up time. Unclear follow-up protocol and how this changed over study period. Poor reporting of sample sizes.)*
	Concerns for applicability	Moderate *(unclear if patients had surgical excision.)*

Najjar 2019

Najjar, 2019

Bibliographic Reference	Najjar, Yana G; Puligandla, Maneka; Lee, Sandra J; Kirkwood, John M; An updated analysis of 4 randomized ECOG trials of high-dose interferon in the adjuvant treatment of melanoma.; Cancer; 2019; vol. 125 (no. 17); 3013-3024

Study Characteristics

Study design	• RCTs ○ Uses data from 4 RCTs

Study details	• Study location
	  ○ International (unclear)
	• Study setting
	  ○ Multicentre (unclear)
	• Study dates
	  ○ enrolled between 1985 and 2000 and continue to be actively followed. Current outcomes data including relapse and survival are as of September 2016, and were extracted from the ECOG database.
	• Sources of funding
	  ○ Developmental Funds from P30CA047904. MP, SJL: ECOG Funding

Inclusion criteria	• ECOG 0-1 • IIB - IV ○ in 3 of the included studies, patients were required to have AJCC 6th edition stage IIB (deep primary tumor in the absence of regional lymph node involvement) or stage III melanoma (regional lymph node involvement either at presentation or recurrence. In the 4th study, patients could have had in-transit or subcutaneous metastases, or extracapsular extension (AJCC stage IIIC or IV). • adequate hematological and end organ function • Underwent complete wide excision with adequate margins • One of the four studies also required complete regional lymphadenectomy
Exclusion criteria	prior chemotherapy, radiation or immunotherapy

Number of participants and recruitment methods	1916
Length of follow-up	Median follow-up times were 17.9 years for E1684, 12.2 years for E1690, 16.0 years for E1694, and 16.5 years for E2696.
Surveillance strategy	each study had a standardised follow-up procedure however this study utilises data from the ECOG databases, which includes outcome data long after the end of the official study periods and it is therefore unclear what level of surveillance participants would have undergone for the majority of the study.
Outcome(s) of interest	recurrence and overall survival
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • ECOG • ulceration • recurrent disease vs primary disease • location • breslow thickness • age
Covariates adjusted for in the multivariable regression modelling	only significant predicotrs of univariate analysis ($p<0.2$) were entered into the multivariate models Models controlled for High dose interferon use (recurrence model only), age, white blood cell count, recurrence disease and ulceration
Additional comments	studies randomised patients to high dose interferon adjuvant therapy or no adjuvant therapy

Participant characteristics

	Cohort 1 (N = 286)	Cohort 2 (N = 642)
Female	40%	35%
Median age (range)	48 (17-79)	47 (17-78)
Tumour location		
Head/neck	10%	12%
Trunk	45%	46%
Extremities	34%	38%
ECOG 1	22%	13%
Ulceration	16%	36%
Micrometastases	2%	3%
Extranodal extension	5%	12%
Breslow thickness >4mm	31%	43%
Abnormal LDH	14%	7%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled. Although the sample came from 4 different RCTs, inclusion criteria was relatively homogenous. However, there is still potential that risk factors were comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Unclear *(Unclear level of missing data for predictors that were not entered into the multivariate model (multivariate predictors all had <30% missing data))*
	Concerns for applicability for predictors or their assessment domain	
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Outcome data relies on use of ECOG databases, this is particularly an issue for the analysis for predicting recurrence as it is unclear what surveillance strategies participants would have undergone beyond the main study periods. It is also likely that this differed between trials.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(In developing multivariate Cox models variables with p-values less than 0.2 in univariate models were considered for inclusion. Variables with more than 30% missing data were excluded. Patients with non-missing values for all candidate variables were included in the model-selection process. The final models were then re-fit using patients with complete data for the selected covariates.)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High *(High risk: Univariate predictors of recurrence (unclear missing data, unclear surveillance strategy meaning that outcome data may not have been accurately captured, no adjustment for confounders). Moderate risk: univariate predictors of overall survival and multivariate predictors of recurrence. There are still issues with these analyses as follow-up is unclear and only significant univariate predictors were adjusted for in the multivariate analyses. Low risk: multivariate predictors of overall survival.)*
	Concerns for applicability	Low

Namin 2019

Namin, 2019

Bibliographic Reference	Namin, Arya W; Cornell, Georgeanne E; Thombs, Lori A; Zitsch, Robert P 3rd; Patterns of recurrence and retreatment outcomes among clinical stage I and II head and neck melanoma patients.; Head & neck; 2019; vol. 41 (no. 5); 1304-1311

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ January 1, 2000 to December 31, 2015

Inclusion criteria	• Stage I-II • Received definitive treatment for primary melanoma

	○ Patients undergoing excision of melanoma in this study had the excision margins chosen generally based on lesion thickness. For melanomas with thickness of 1.00 mm or less, the recommended margin of excision was 1 cm. For melanomas with thickness greater than 2.00 mm, the recommended maragin of excision was 2 cm. For melanomas with thickness between 1.01 and 2.00 mm, the recommended margin of excision was 1-2 cm
Number of participants and recruitment methods	168
Loss to follow up	unclear; scatterplot axis extends to 6.8 years
Outcome(s) of interest	Recurrence; unclear follow-up procedure.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	○ Gender ○ Histological type ○ Location ○ Excision margin ○ Ulceration ○ SLNB status ○ Breslow thickness
Covariates adjusted for in the multivariable regression modelling	Location, ulceration, SLNB status, Breslow thickness were entered into a multivariate analysis

Participant characteristics

	Study (N = 168)
Female	25%

	Study (N = 168)
Mean age	62 years
Tumour location	
Scalp	32.1%
Other head/neck location	67.9%
Ulceration	29.2%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear protocol / average length of follow-up)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Unclear *(Multivariate analysis was conducted with adjusted for various important clinical factors. However, it is unclear how these factors were selected and whether they were selected prior to the study)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Unclear follow-up and lack of clarity regarding follow-up protocol and average length)*
	Concerns for applicability	Low

Oh 2020

Oh, 2020

Bibliographic Reference	Oh, Y.; Choi, S.; Cho, M.Y.; Nam, K.A.; Shin, S.J.; Chang, J.S.; Oh, B.H.; Roh, M.R.; Chung, K.Y.; Male Gender and Breslow thickness are important risk factors for recurrence of localized melanoma in Korean populations; Journal of the American Academy of Dermatology; 2020; vol. 83 (no. 4); 1071-1079

Study Characteristics

Study design	Retrospective cohort study
Study details	○ Study location ○ South Korea

	○ Study setting ○ Single centre ○ Study dates ○ 2000-2017 ○ Sources of funding ○ Supported by a National Research Foundation of Korea grant funded by the Korea Government (MSIT) (No. 2017R1C1B2005574)
Inclusion criteria	○ Stage I-II ○ >6 months follow-up ○ Only patients who visited the clinic for more than 6 months after removal of the primary melanoma were included.
Number of participants and recruitment methods	340
Length of follow-up	at least 6 months of documented clinical visits; mean follow-up period for patients was 46.2 months, and the median follow-up period was 36.5 months.
Outcome(s) of interest	Recurrence; any kind of recurrence after removal; Clinical types of recurrence were subclassified as local recurrence (LR), in-transit metastasis, nodal metastasis, and DM
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	○ age ○ Gender ○ SLNB status ○ BRAF mutation status ○ LVI ○ TIL ○ Breslow thickness ○ Ulceration ○ Mitotic rate

	○ Stage ○ Tumour location
Covariates adjusted for in the multivariable regression modelling	No multivariate analysis. Although data is presented for the interaction of the Gender with Breslow thickness predictor variables.

Participant characteristics

	Study (N = 340)
Female	57.4%
<60 years old	52.4%
Tumour location	
Head/neck	10%
Trunk	8.2%
Extremities	81.8%
Stage	
IA	18.5%
IB	16.8%
IIA	16.2%

	Study (N = 340)
IIB	14.7%
IIC	11.2%
Ulceration	37.1%
Breslow thickness >4mm	18.5%
LVI	5.7%
BRAF mutation	29.6%
Mitotic rate <1.69/mm2	67.4%
SLNB	56.5%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(Low level of missing data).*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(All patients had a minimum follow-up of 6 months of clinical visits. However, due to study design, variation in follow-up type and frequency is likely to have differed between patients.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders risk factors.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No adjustment for confounders and potential for variation in follow-up)*
	Concerns for applicability	Low

Park 2017

Park, 2017

Bibliographic Reference	Park, Tristen S; Phan, Giao Q; Yang, James C; Kammula, Udai; Hughes, Marybeth S; Trebska-McGowan, Kasia; Morton, Kathleen E; White, Donald E; Rosenberg, Steven A; Sherry, Richard M; Routine Computer Tomography Imaging for the Detection of Recurrences in High-Risk Melanoma Patients.; Annals of surgical oncology; 2017; vol. 24 (no. 4); 947-951

Study Characteristics

Study design	• Retrospective cohort study ○ retrospective analysis was performed using patients enrolled in one of four different institutional review boardaapproved adjuvant immunotherapy trials conducted in the Surgery Branch, National Cancer Institute between 1998 and 2009.

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ between 1998 and 2009.

Inclusion criteria	• II-IV ○ included patients with stage II, stage III, and resected stage IV cutaneous melanoma. Patients with ulcerated or C1.5-mm primary melanomas, completely resected local regional nodal disease, or completely resected metastatic disease were eligible if HLA appropriate and enrolled within 6 months of surgery.
Exclusion criteria	• Uveal or mucosal melanoma • required steroids
Number of participants and recruitment methods	466
Surveillance strategy	Eligible patients were screened with physical exam, lab tests, brain MRI, and CT scan of chest, abdomen, and pelvis. Following adjuvant immunotherapy, patients were monitored closely for recurrence by physical examination, labs, and imaging as required by protocol for 5 years. All protocols required CT imaging of chest, abdomen, and pelvis and MRI brain imaging within 4 weeks of protocol enrollment. Subsequent brain imaging was obtained if neurologic symptoms were detected or as part of a metastatic survey following disease progression at other sites. Because each protocol had a different vaccination schema, there were minor variations in surveillance schedules during year 1. However, all patients had complete

	clinical evaluations and CT imaging within 4 weeks of protocol enrollment and at least two more times during the first year of the study. Subsequently, all clinical trials included a clinic visit + CT every 6 months in year 2 and annually in years 3-5 (with the exception of one trial which had a visit+ CT every 6 months up to year 5).
Length of follow-up	5 years
Outcome(s) of interest	recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	How recurrence was detected (patient, physician or imaging).
Covariates adjusted for in the multivariable regression modelling	none

Participant characteristics

	Study (N = 466)
Female	37%
Median age (IQR)	49 (17-79)
Tumour location	
Head/neck	15%
Trunk	36%
Extremities	41%
Stage	

	Study (N = 466)
II	255
III	70%
IV	5%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Original studies prospectively enrolled participants to the trial. Although confounders are likely to be present, these are unlikely to specifically influence the relationship of predictor variables (of interest to this review) to the outcome.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(All patients underwent standardized follow-up. Only slight variation in surveillance strategy between the four included studies)*
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Poo-Hwu 1999

Poo-Hwu, 1999

Bibliographic Reference	Poo-Hwu WJ; Ariyan S; Lamb L; Papac R; Zelterman D; Hu GL; Brown J; Fischer D; Bolognia J; Buzaid AC; Follow-up recommendations for patients with American Joint Committee on Cancer Stages I-III malignant melanoma.; Cancer; 1999; vol. 86 (no. 11)

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single institution
	• Study dates
	  ○ from January 1988 to December 1994
	• Sources of funding
	  ○ Supported by National Institutes of Health research grant CA-16359 from the National Cancer Institute

Inclusion criteria	• Stage I-II • Surgically resected disease

Number of participants and recruitment methods	419
Length of follow-up	5 years
Surveillance strategy	In September 1987, a uniform follow-up protocol was adopted that combined frequent, comprehensive examinations with extensive patient education: Stage I: examinations every 6 months for 3 years then annually. Stage II: exam every 4 monthd for 3 years then every 6 months or 2 years then annually. Stage III: exam every 3 months for 3 years then every 6 months for 2 years then annually. At each visit, a history, physical examination, complete blood count, and liver function tests (serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and lactate dehydrogenase [LDH]) were performed. Chest X-rays were obtained annually for all Stage I and II patients and every 6 months for Stage III patients during the first 5 years of follow-up. All patients with Stage III disease had a baseline computed tomography (CT) scan for complete staging examination. Follow-up CT scans were obtained in 6 –12 months only if there were abnormal findings initially that were not clearly indicative of metastatic disease. Patients who developed multiple primary melanomas were continued on the follow-up schedule according to the highest stage of the invasive melanoma. The patient education was provided by the physicians and by clinical nurse specialists with direct discussion of clinical characteristics of melanoma, in-transit metastases, and lymph node drainage. During the first and/or second clinic visit, all patients received instructions in performing self-examination of the skin and a list of signs and symptoms of recurrence (i.e., pain, progressive fatigue, weight loss, nausea and emesis, headache, shortness of breath) that should alert them to contact their physicians. Pamphlets and videotape were used to educate patients and family members for photoprotection and melanoma prevention.
Outcome(s) of interest	Recurrence

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Stage • How recurrence was detected (patient or physician)
Covariates adjusted for in the multivariable regression modelling	raw data on how recurrence was detected is broken down by stage and Gender

Participant characteristics

	Study (N = 419)
Female	43.7%
Mean age (range)	49.8 (12-81) years
Tumour location	
Head/neck	14.7%
Trunk	41.8%
Extremities	42.1%
Stage	
I	51.7%
II	31.9%
III	16.4%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(inadequate adjustment for confounders)*

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Potential for confounders not adequately adjusted for)*
	Concerns for applicability	Low

Romano 2010

Romano, 2010

Bibliographic Reference	Romano E; Scordo M; Dusza SW; Coit DG; Chapman PB; Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2010; vol. 28 (no. 18)

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ Between December 1998 and January 2002 (due to underrepresentation, patients were included up to 2004 if they have stage IIIA disease)

Inclusion criteria	• Stage III melanoma • Rendered disease free but later relapsed
Number of participants and recruitment methods	280

Length of follow-up	Up to 10.5 years; Median follow-up for patients without relapse was 77 months (range, 5 to 148 months).
Surveillance strategy	Our standard approach in medical oncology was a physical examination every 3 months for the first 2 years, then every 6 months. In addition to medical oncology visits, patients underwent surgical and dermatologic visits. CT scans were typically obtained before these follow-up visits as were CBCs, comprehensive panels, and lactate dehydrogenase (LDH).We extracted demographic information, characteristics of the primary melanoma such as site, stage III substage, and adjuvant treatments.
Outcome(s) of interest	Recurrence; • Descriptive information relative to first recurrence was captured such as site, sign of first recurrence, person/method of its detection (ie, symptoms, physical examination by a physician or family/ friends, radiographic examinations, or blood tests), number of clinical evaluations before recurrence, treatment administered for the recurrence and outcome, current disease, and survival status. Patients who first relapsed at several sites concomitantly were scored on the basis of the site that was most advanced (eg, systemic sites outranked nodal sites which outranked local/ in-transit sites).
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	How recurrence was detected (patient reported; physician exam; imaging)
Covariates adjusted for in the multivariable regression modelling	None

Participant characteristics

	Study (N = 280)
Female	36%

	Study (N = 280)
Median age (range)	57 (11-95) years
Tumour location	
Head/neck	15%
Trunk	26%
Extremities	51%
Stage	
IIIA	28%
IIIB	46%
IIIC	26%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(predictors variables of interest [how recurrence was detected] will have impacted on the likelihood of receiving diagnostic imaging)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(study was retrospective without information on when routine imaging is conducted. Those participants suspected of recurrence are therefore more likely to have undergone more rigorous diagnostic testing)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	High *(retrospective study without routine imaging being conducted)*
	Concerns for applicability	Low

Tan 2019

Tan, 2019

Bibliographic Reference	Tan, Sally Y; Najita, Julie; Li, Xiaoxue; Strazzulla, Lauren C; Dunbar, Haili; Lee, Mee-Young; Seery, Virginia J; Buchbinder, Elizabeth I; Tawa, Nicholas E; McDermott, David F; Lee, Sandra J; Atkins, Michael B; Kim, Caroline C; Clinicopathologic features correlated with paradoxical outcomes in stage IIC versus IIIA melanoma patients.; Melanoma research; 2019; vol. 29 (no. 1); 70-76

Study Characteristics

Study design	• Retrospective cohort study • retrospective chart review

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Beth Israel Deaconess Medical Center Cutaneous Oncology Program
	• Study dates
	  ○ between 1995 and 2011 with clinical follow-up through 2015
	• Sources of funding
	  ○ supported in part by grants from the National Cancer Institute of the National Institutes of Health (R21CA182241) (Li, Najita, Kim, and Lee) and Research Scientist (Najita) developmental funds from the Department of Biostatistics and Computational Biology at Dana-Farber Cancer Institute.

Inclusion criteria	IIC-IIIA
Number of participants and recruitment methods	128
Length of follow-up	Median follow-up time was 5.7 years (range: 0.1–15.5 years)

Outcome(s) of interest	Time to death and time to distant metastases
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Breslow thickness • Stage • Mitotic rate • TIL • LVI
Covariates adjusted for in the multivariable regression modelling	HR reported were not adjusted in multivariate analyses. However it is noted that after stage was no longer a significant predictor or DM (after adjusting for mitotic rate) or OS (still significant after adjusting for nodular subtype (P= 0.010), Breslow depth (P < 0.001), and age (P =0.032) but became not significant after adjusting for mitotic rate.

Participant characteristics

	IIC (N = 45)	**IIIA (N = 83)**
Female	68.9%	53.0%
Median age (range)	63 (28-86)	50 (16-82)
Tumour location		
Scalp	15.6%	6.0%
Rest of head/neck	26.7%	9.6%
Trunk	24.4%	35.0%

	IIC (N = 45)	IIIA (N = 83)
Extremities	28.9%	48.2%
LVI	22.2%	8.4%
Breslow thickness, median mm (range)	5.2 (4.0 - 55.0)	1.9 (0.6 – 11.0)
Mitotic rate, median per mm2 (range)	10.0 (1.0-50.0)	2.0 (0.0 – 25.0)

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear protocol for surveillance of distant metastases)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Multivariate models were conducted but only selective reporting of p values and no reporting of adjusted hazard ratios.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Poor reporting of multivariate analyses. Unclear protocol for follow-up)*
	Concerns for applicability	Low

Tas 2019

Tas, 2019

Bibliographic Reference	Tas, Faruk; Erturk, Kayhan; Early and late relapses of cutaneous melanoma patients.; Postgraduate medicine; 2019; vol. 131 (no. 3); 207-211

Study Characteristics

Study design	Retrospective cohort study
Study details	• Study location ○ Turkey

	• Study setting
	  ○ Single centre
	• Study dates
	  ○ 1993-2017
	• Sources of funding
	  ○ no funding

Inclusion criteria	• I-III • Surgery • Definitive surgical excision: The lesions with intermediate-thickness underwent pathological nodal staging by sentinel lymph node biopsy (SLNB) or elective lymph node dissection. Patients with pathologically positive SLNB underwent a completion lymphadenectomy. After lymph node status was determined by radical lymph node dissection (RLND)
Number of participants and recruitment methods	1,087
Length of follow-up	at least 5 years
Outcome(s) of interest	Relapse up to 5 years relapses were separated into early (first 18 months from definitive surgical excision) and later (>18 months) relapses
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Site of lesion • Ulceration • Breslow thickness • TIL • Mitotic rate • LVI

	• BRAF status • Stage
Covariates adjusted for in the multivariable regression modelling	multivariate models for early and later relapse controlled for the following factors: • Age • Gender • Ulceration • Mitotic rate • Stage • LVI

Participant characteristics

	Among those who did not relapse (N=219)	**Among those who did relapse (N=365)**
Female	59.4%	37.5%
<50 years old	53.9%	45.8%
Tumour location		
Axial	55.6%	57.1%
Extremities	44.4%	42.9%
Ulceration	38%	71.4%
Breslow thickness <4mm	18%	44.2%

	Among those who did not relapse (N=219)	Among those who did relapse (N=365)
LVI	7.1%	15.3%
BRAF mutation	0%	42.5%
Stage I-II	79.0%	53.6%
Stage III	21.0%	46.4%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Contained a wide range of disease stages (I-III). Clinical presentations likely very varied and risk factors may be comorobid. Type of surgical procedure differed between patients and this was not captured in the database/analysis.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Patients were treated and followed-up according to standard international guidelines including National Comprehensive Cancer Network guidelines.)*

Section	Question	Answer
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Multivariate model conducted, which controls for various important clinical factors but was only conducted for subgroup analysis on late/early relapse and not ovreall)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Overall analysis will be marked down once as only the early and late relapse analyses were multivariate.)*
	Concerns for applicability	Low

Tas 2021

Tas, 2021

Bibliographic Reference	Tas, F., & Erturk, K. (2021). Mitotic rate in node-positive stage III melanoma: it might be as important a prognostic factor as node number. *Japanese Journal of Clinical Oncology*, *51*(6), 873-878

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ Turkey
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ unclear

	• Sources of funding ○ no funding
Inclusion criteria	• SLN positive • Stage III • Underwent SLNB or elective LND
Number of participants and recruitment methods	389
Length of follow-up	Up to 10 years
Outcome(s) of interest	Relapse-free survival and overall survival up to 5 years.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender • Location • Breslow thickness • Ulceration • Mitotic rate • LVI
Covariates adjusted for in the multivariable regression modelling	multivariate model for RFS controlled for the following factors: • Mitotic rate • Number of involved lymph nodes Multivariate model for OS did not adjust for predictors of relevance to this review.

Participant characteristics

	Among those who did relapse (N=389)
Female	40.6%
Median (range) age, years	50 (16-86)
Tumour location	
Axial	54.6%
Extremities	45.4%
Mitotic rate, >3/mm2	68.9%
Breslow thickness, ≥2mm	84.0%
Ulcerated	67.4%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(Risk factors are likely to be comorbid. However, study population was specific and likely contained participants of a similar disease severity)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Patients were treated and followed-up according to standard international guidelines including National Comprehensive Cancer Network guidelines.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Multivariate model conducted but only controlled for a limited number of variables.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(inadequate adjustment for confounders.)*
	Concerns for applicability	Low

Turner 2020

Turner 2020

Bibliographic Reference	Turner, R. M., Dieng, M., Khanna, N., Nguyen, M., Zeng, J., Nijhuis, A. A., ... & Morton, R. L. (2021). Performance of long-term CT and PET/CT surveillance for detection of distant recurrence in patients with resected stage IIIA–D melanoma. *Annals of Surgical Oncology*, 1-9

Study Characteristics

Study type	Prospective cohort study
Study details	• Study location

	○ Australia • Setting ○ (MIA) single centre • Study dates ○ 2000 – 2017
Inclusion criteria	no evidence of disease following surgical treatment
Number of participants	332
Length of follow-up	median follow-up 61 months
Index test(s)	PET-CT Patients included in the study cohort underwent iodinebased contrast CT imaging of the chest and abdomen ± pelvis, or whole-body PET/CT imaging. The brain was imaged using MRI or CT. The first index test was defined as follow-up imaging performed 6 or 12 months (± 3- month window) after surgical treatment of stage III melanoma, in a patient without symptoms or clinical suspicion of distant metastatic disease. Subsequent index tests (2, 3, 4, and 5) were performed at regular 6- or 12-month intervals after the first index test. Where two CT imaging tests were performed on the same day as a whole body PET/CT, the whole-body PET/CT scan was considered the index test. A CT scan of three or more areas of the body (e.g. brain, chest, and abdomen ± pelvis) was considered a whole-body CT.
Reference standard (s)	Composite • composite reference standard of any abnormality using histopathology, confirmatory radiological imaging (e.g. repeat CT or PET/CT, MRI, bone scintigraphy, or ultrasound) and/or 6 months of clinical follow-up was applied to assess the test performance of the index CT or PET/CT. Two independent assessors (MD, NK) reviewed each index test and reference standard result from detailed clinical notes for the presence of distant metastatic melanoma. The reference standard always occurred after the index test to verify the results of the test. Where a patient had no additional tests or clinical follow-up before their subsequent index test, the patient was assumed to be free of disease. Further patient files and trial records were reviewed when there were discrepancies between assessors. Discrepant findings were resolved through discussion with co-authors and the MIA database coding manager.

Participant characteristics

	Study (N = 340)
Female	35%
Median age at time of stage III diagnosis	53 years
Tumour location	
Head/neck	16%
Trunk	34%
Extremities	37%
Stage	
IIIA	25%
IIIB	31%
IIIC	42%
IIID	1%
Ulceration	32%
Breslow thickness >4mm	22%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors likely to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low (clear surveillance protocol).
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders risk factors.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(No adjustment for confounders)*
	Concerns for applicability	Low

Verver 2018 – EORTC development cohort

Verver 2018

Bibliographic Reference	Verver, D., van Klaveren, D., Franke, V., van Akkooi, A. C. J., Rutkowski, P., Keilholz, U., ... & Verhoef, C. (2019). Development and validation of a nomogram to predict recurrence and melanoma-specific mortality in patients with negative sentinel lymph nodes. *Journal of British Surgery*, *106*(3), 217-225

Study Characteristics

Study design	• Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ 4 EORTC Melanoma Group centres
	• Study dates
	  ○ 1997-2013
	• Sources of funding
	  ○ Not reported

Inclusion criteria	• Negative SLNB
Exclusion criteria	Clinical evidence of regional or distant metastasis
Number of participants and recruitment methods	3,220
Length of follow-up	median follow-up of 70 months
Surveillance strategy	Distant recurrence was defined as recurrent disease at systemic sites, outside of local or nodal recurrences. LITRFS event was defined as recurrence in the skin or subcutaneous tissue within 5 cm of the primary tumor site or between the excision site and the mapped nodal basin. In patients with multiple sites of recurrence, the site of first recurrence was used to categorize their recurrence type for this study. Most distant site of recurrence also was evaluated for each patient; the proportion of patients with metastases at each given site was not substantially different than that based on the site of first recurrence. Mitotic rate was not included in this analysis, because it was not a required data element in the Sunbelt Melanoma Trial.
Outcome(s) of interest	Recurrence (segmented into local, regional, previously mapped negative regional lymph node basin, previously unmapped nodal basin, regional lymph node basin after CLDN and distant) and OS

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness • Ulceration • Age • Gender • Histology • No. of positive sentinel nodes • Multiple sentinel node fields • Location
Covariates adjusted for in the multivariable regression modelling	All factors were entered into the initial multivariate model.

Participant characteristics

	Study (N = 900)
Female	52.5%
Age, median (IQR) years	55 (44-67)
Ulceration	24.8%
location	
Extremities	48.8%
Trunk	42.8%

	Study (N = 900)
Head/neck	8.1%
Breslow thickness, median (IQR) mm	1.70 (1.10-3.00)
Mitosis present	3.5%
Total no. SNs, median (IQR)	1 (1-2)

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear follow-up procedure, variance in follow-up duration.)*
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	*(All factors were entered into multivariate model)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(unclear surveillance)*
	Concerns for applicability	Low

Xing 2010

Xing, 2010

Bibliographic Reference	Xing, Y., Bronstein, Y., Ross, M. I., Askew, R. L., Lee, J. E., Gershenwald, J. E., ... & Cormier, J. N. (2011). Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. *Journal of the National Cancer Institute*, *103*(2), 129-142

Study Characteristics

Study design	Meta-analysis of retrospective and prospective cohort studies
Databases searched	MEDLINE (from January 1, 1990, through June 30, 2009), EMBASE (from January 1, 2001, through June 30, 2009), Cancerlit (from January 1, 1990, through October 31, 2002), and the Controlled Trials Register from the Cochrane Library (from January 1, 1990, through June 30, 2009)
Study dates	1990-2009
Inclusion criteria	• > 10 patients with melanoma. • Included comparisons of single or multiple imaging modalities (ie, ultrasonography, CT, PET, and/or PET-CT) to a gold standard. • No language restrictions were applied.

Number of studies (participants)	74 (10,528)
Index tests	• PET-CT • CT • US • PET
Reference standard	• Patient-level data were extracted and used to construct two-by-two tables. • For primary staging of regional lymph nodes, sentinel lymph node biopsy with pathological confirmation is the gold standard for clinically lymph node–negative patients. • For surveillance studies, a minimum of 6 months of follow-up was required for clinical confirmation.
Outcome(s) of interest	Sensitivity/specificity

Risk of bias

Section	Question	Answer
Study eligibility criteria	Overall risk of bias for study eligibility	High *(Eligibility criteria were appropriate for the review question but were overly inclusive. Both prospective and retrospective cohort studies were included. No restrictions were made on follow-up schedules (and whether participants received routine imaging).*
Identification and selection of studies	Overall risk of bias for identification and selection of studies	Low

Section	Question	Answer
Data collection and study appraisal	Overall risk of bias for data collection and study appraisal	Low *(risk of bias was conducted using appropriate tools and was reported in detail)*
Synthesis and findings	Overall risk of bias for synthesis and findings	High *(Tests of heterogeneity not reported. Likelihood of analyses suffering from heterogeneity is high as the analyses combined studies with participants of all disease stages and, for those studies assessing imaging during surveillance, combined all participants irrespective of the reason for their scan [routine follow-up, suspected recurrence, or re-staging]. The extent to which study centres offered routine imaging is also not accounted for. The author notes that models assessing accuracy were conducted included as covariates various important clinical characteristics, including study design, reason for imaging and whether the analysis was per-patient or per-lesion. However, it is likely that combining these different studies was inappropriate and the ability of the model to account for these issues is unclear.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate-high

Yang 2019

Yang, 2019

Bibliographic Reference	Yang, J., Pan, Z., Zhou, Q., Liu, Q., Zhao, F., Feng, X., & Lyu, J. (2019). Nomogram for predicting the survival of patients with malignant melanoma: A population analysis. *Oncology letters*, *18*(4), 3591-3598

Study Characteristics

Study design	Retrospective review of prospectively collected SEER database
Study dates	between January 2007 and December 2015

Inclusion criteria	• All patients with melanoma diagnosis
Exclusion criteria	• Cases that were not confirmed by microscopy or only by autopsy • Unknown or incomplete variables. • <18 years old
Number of studies (participants)	77,508
Length of follow-up	• Up to 5 years
Surveillance strategy	• Unclear
Outcome(s) of interest	• All-cause mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Race • Gender • Marital status • Tumour location • AJCC stage • SEER stage • Insurance status • Family income

Covariates adjusted for in the multivariable regression modelling	• All factors were entered into multivariate model

Participant characteristics

	(N=77,508)
Female	40.3%
Median (IQR) age	62 (52-74)
Tumour location	
Head and neck	21.8%
Trunk	31.1%
Extremities	42.9%
Stage I-II	85.3%
Stage III	14.7%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid.)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Unclear *(unclear level of missing data for key prognostic factors)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear follow-up procedures for participants, will have varied between sites)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	*(All factors were entered into multivariate model)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Unclear surveillance* strategy and unclear level of missing data*)*
	Concerns for applicability	Low

Yang 2020

Yang, 2020

Bibliographic Reference	Yang, C., Liao, F., & Cao, L. (2020). Web-based nomograms for predicting the prognosis of adolescent and young adult skin melanoma, a large population-based real-world analysis. *TRANSLATIONAL CANCER RESEARCH*, *9*(11), 7103-7112.

Study Characteristics

Study design	Retrospective review of prospectively collected SEER database
Study dates	between January 2004 and December 2014
Inclusion criteria	• 15-40 years old • Cutaneous melanoma • Diagnosed between 2004 and 2014 • Received surgical resection • Cutaneous melanoma was primary tumour
Exclusion criteria	• Distant metastasis • Unknown information of thickness or lymph node metastasis • All patients staged according to AJCC
Number of studies (participants)	19,887
Length of follow-up	• Up to 5 years
Surveillance strategy	• Unclear
Outcome(s) of interest	• All-cause mortality
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Gender

	• Marital status • Tumour location • AJCC stage • SEER stage • Insurance status • Family income
Covariates adjusted for in the multivariable regression modelling	• All factors were entered into multivariate model

Participant characteristics

	(N=19,887)
Female	62.9%
Aged 15-25 years	17.0%
Aged 26-40 years	83.0%
Tumour location	
Head and neck	9.2%
Trunk	41.5%

	(N=19,887)
Extremities	49.2%
Stage I	85.4%
Stage II	6.9%
Stage III	7.6%
Breslow thickness >4mm	3.2%
N stage	
N0	92.4%
N1	4.7%
N2-3	2.9%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors are likely comorbid. Study involved broad inclusion criteria with a wide range of disease stages. Participants were only included if they had been staged using AJCC. It is unclear how many potential participants would have been excluded for this reason.)*
	Concerns for applicability for selection of participants domain	Low

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(no information on how patients were followed up. Use of SEER database means that there is likely variance in frequency/intensity of follow-up between centres.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	*L*ow *(All factors were entered into multivariate model)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(unclear surveillance* strategy and unclear level of missing data*)*
	Concerns for applicability	Low

- *6.1.3 Nomograms for risk during follow-up (external validation studies only)*

EORTC nomogram – El Sharouni 2021

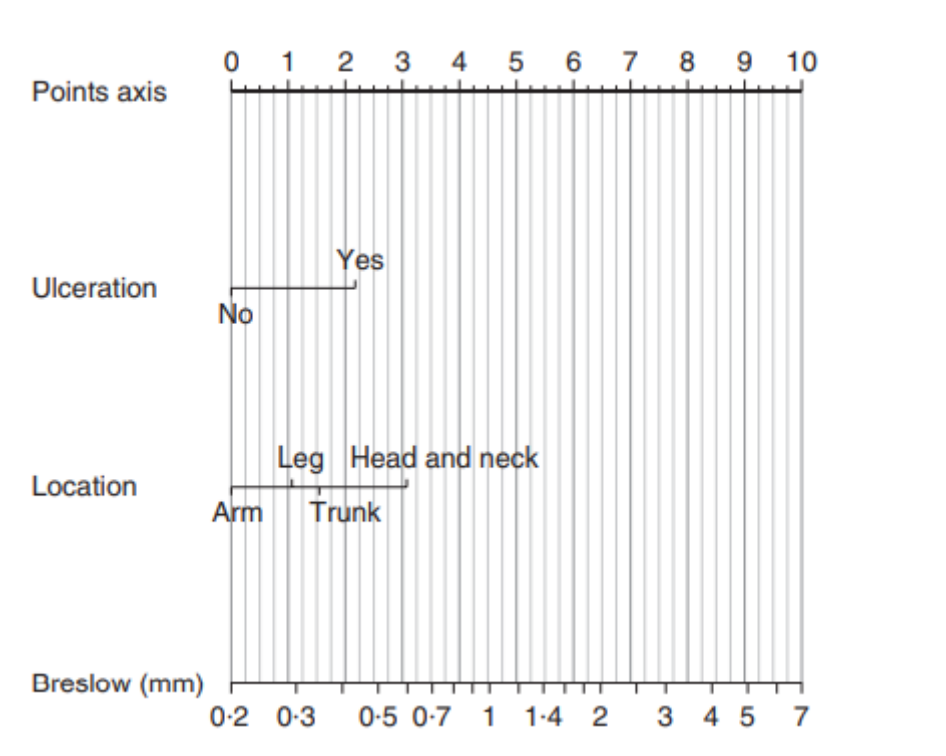
El Sharouni 2021	
Bibliographic Reference	El Sharouni, M. A., Ahmed, T., Witkamp, A. J., Sigurdsson, V., van Gils, C. H., Nieweg, O. E., ... & Lo, S. N. (2021). Predicting recurrence in patients with sentinel node-negative melanoma: validation of the EORTC nomogram using population-based data. *British Journal of Surgery*, *108*(5), 550-553

Study Characteristics

Study design	Retrospective cohort study • Study used data from the Dutch Nationwide Network and Registry of Histopathology and Cytopathology, a prospective database

Study details	• Study location
	  ○ Australia and The Netherlands (all data used to validate model came from The Netherlands)
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ Diagnosed between 1 January 2000 and 31 December 2014

Inclusion criteria	• Negative SLNB
Exclusion criteria	• Locoregional or distant metastases within 6 weeks of diagnosis (stage III and IV) • Aged less than 18 years • Multiple primary melanomas
Number of participants and recruitment methods	8,795
Length of follow-up	Median 6.0 (i.q.r. 3.7–10.2) years

Surveillance strategy	Unclear
Outcome(s) of interest	C-statistic for predicting recurrence-free survival up to 5 years of follow-up
Nomogram	Low risk = 0-6 Medium risk = 7-9 High risk = 10 

Participant characteristics

	Study (N = 8,795)
Female	53.7%
Age, median (IQR) years	55 (44–65)
Tumour location	
Head/neck	6.1%
Trunk	41.8%
Extremities	49.2%
Ulceration	20.2%
Breslow thickness, median (IQR) mm	1.6 (1.2–2.4)
Mitosis present	54.9%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain 1.1 *were appropriate data sources used?* 1.2 *Were inclusion/exclusion criteria appropriate?*	Low (issues with use of retrospective records search are delineated below).
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High

Section	Question	Answer
	2.1 were predictors defined and assessed in a similar way for all participants? *2.2 Were predictor assessments made without knowledge of data?* *2.3 Are all predictors available at the time the model is intended to be used?*	(14% of participants did not have ulceration status on record. Unclear level of missing data for Breslow thickness).
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain *3.1 was the outcome determined appropriately?* *3.2 was a prespecified or standard outcome definition used?* *3.3 were predictors excluded from the outcome definition?* *3.4 was the outcome defined and determined in a similar way for all participants?* *3.5 was the outcome determined without knowledge of predictor information?* *3.6 was the time interval between predictor assessment and outcome determination appropriate?*	High (unclear follow-up schedule at study centre. Retrospective study design means that there is risk that outcome was not captured by database.).
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain *4.1 were there a reasonable number of participants with the outcome?* *4.2 were continuous and categorical predictors handled appropriately?* *4.3 were all enrolled participants included in the analysis?* *4.4 were participants included in the analysis?* *4.5 was selection of predictors based on univariate analysis avoided?*	Low (study was a validation analysis)

Section	Question	Answer
	4.6 were complexities in the data accounted for appropriately? *4.7 were relevant model performance measures evaluated appropriately?* *4.8 were model overfitting, underfitting, and optimism in model performance accounted for?* *4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariate analysis?*	
Overall Risk of bias and Applicability	Risk of bias	Moderate (retrospective study design, issues with missing data for predictors and risk associated with classifying outcome)
	Concerns for applicability	Directly applicable

EORTC nomogram – Ipenburg 2019

Ipenburg 2019

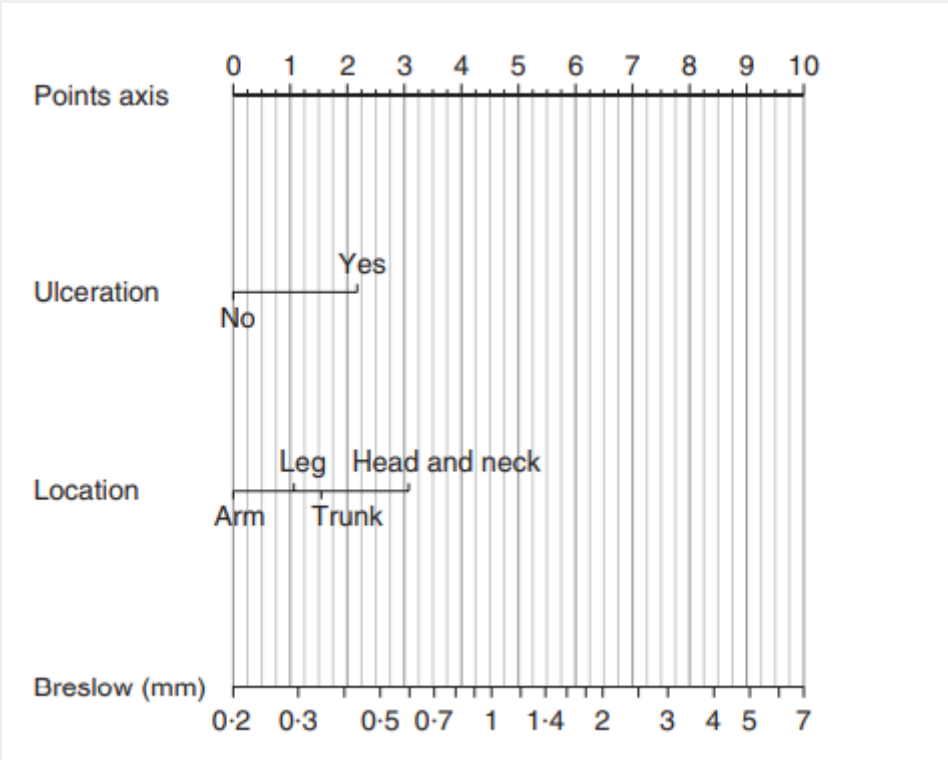
Bibliographic Reference	Ipenburg, N. A., Nieweg, O. E., Ahmed, T., van Doorn, R., Scolyer, R. A., Long, G. V., ... & Lo, S. (2019). External validation of a prognostic model to predict survival of patients with sentinel node-negative melanoma. *Journal of British Surgery*, *106*(10), 1319-1326

Study Characteristics

Study design	Retrospective cohort study • Study used data from the Melanoma Institute Australia database
Study details	• Study location ○ Australia • Study setting

	○ Multiple centres • Study dates ○ Diagnosed between January 1992 and December 2015,
Inclusion criteria	• Negative SLNB
Exclusion criteria	• Patients were excluded if they had melanoma in situ • microsatellites • in-transit metastases • preoperative ultrasound examination had revealed nodal metastasis • participated in the MSLT II, had a negative SN on histological assessment but a positive RT–PCR finding in their SNs.
Number of participants and recruitment methods	4,235
Length of follow-up	median 50 (IQR 18·5–81·5) months
Surveillance strategy	Unclear
Outcome(s) of interest	C-statistic for overall survival
Nomogram	Low risk = 0-6 Medium risk = 7-9 High risk = 10

The follow up of people with melanoma



Participant characteristics

	Study (N = 4,235)
Female	41.8%
Age, median (IQR) years	58 (48–69)
Tumour location	

	Study (N = 4,235)
Head/neck	16.9%
Trunk	38.1%
Extremities	45.0%
Ulceration	23.7%
Breslow thickness, median (IQR) mm	1.8 (1.0–2.6)
Mitosis present	85.7%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain 1.3 *were appropriate data sources used?* 1.4 *Were inclusion/exclusion criteria appropriate?*	Low (issues with use of retrospective records search are delineated below).
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain *2.1 were predictors defined and assessed in a similar way for all participants?* *2.2 Were predictor assessments made without knowledge of data?* *2.3 Are all predictors available at the time the model is intended to be used?*	Unclear (8% of participants did not have ulceration status on record. Unclear level of missing data for Breslow thickness).
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain *3.1 was the outcome determined appropriately?* *3.2 was a prespecified or standard outcome definition used?* *3.3 were predictors excluded from the outcome definition?* *3.4 was the outcome defined and determined in a similar way for all participants?* *3.5 was the outcome determined without knowledge of predictor information?* *3.6 was the time interval between predictor assessment and outcome determination appropriate?*	High (unclear follow-up schedule at study centres. Retrospective study design means that there is risk that outcome was not captured by database.).
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain *4.1 were there a reasonable number of participants with the outcome?* *4.2 were continuous and categorical predictors handled appropriately?* *4.3 were all enrolled participants included in the analysis?* *4.4 were participants included in the analysis?* *4.5 was selection of predictors based on univariate analysis avoided?* *4.6 were complexities in the data accounted for appropriately?* *4.7 were relevant model performance measures evaluated appropriately?* *4.8 were model overfitting, underfitting, and optimism in model performance accounted for?*	Low (study was a validation analysis)

Section	Question	Answer
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariate analysis?	
Overall Risk of bias and Applicability	Risk of bias	Moderate (retrospective study design, issues with missing data for predictors and risk associated with classifying outcome)
	Concerns for applicability	Directly applicable

EORTC-DeCOG nomogram – Verver 2020

Verver 2020

Bibliographic Reference	Verver, D., Rekkas, A., Garbe, C., van Klaveren, D., van Akkooi, A. C., Rutkowski, P., ... & Grünhagen, D. J. (2020). The EORTC-DeCOG nomogram adequately predicts outcomes of patients with sentinel node–positive melanoma without the need for completion lymph node dissection. *European Journal of Cancer*, *134*, 9-18.

Study Characteristics

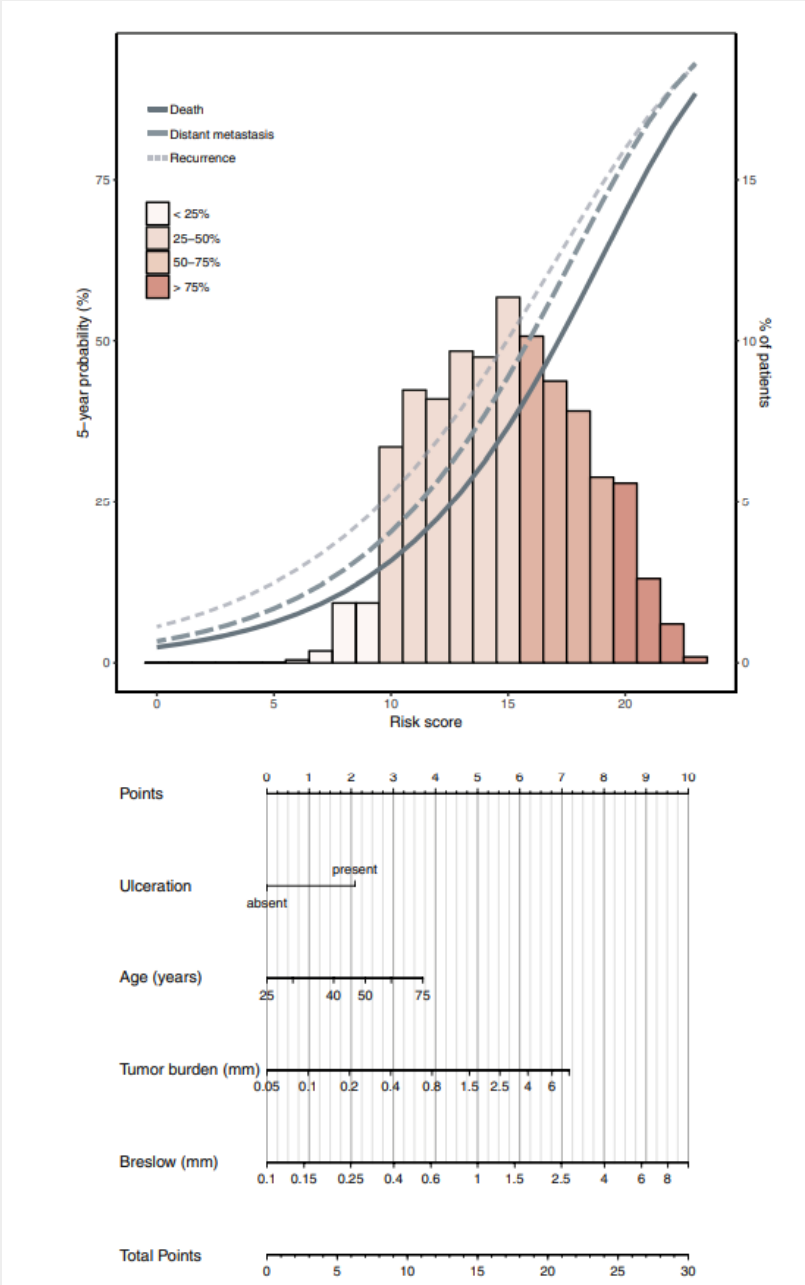
Study design	Retrospective cohort study • Used data taken from an RCT (DeCOG SLT trial) and data from patients screened at a single centre for entry to the DeCOG SLT trial but were ultimately not included.

Study details	• Study location
	  ○ Germany
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ Diagnosed between 1 January 2000 and 31 December 2014

	• Funding ○ none
Inclusion criteria	• Positive SLNB • Participant in DeCOG SLT trial or a patient at University Hospital Tuebingen, screened for inclusion in the DeCOG-SLT trial but ultimately not included. • Tumour thickness of at least 1 mm • Underwent surgery between 2006 and 2014.
Exclusion criteria	• Duplicate cases
Number of participants and recruitment methods	• Derivation cohort: 1,078 • Validation cohort: 692
Length of follow-up	Median 6.0 (i.q.r. 3.7–10.2) years
Surveillance strategy	Patients were followed-up in line with trial protocol if they were contained within the DeCOG cohort. It is unclear how patients from the single centre who were not included in DeCOG trial were followed-up.
Outcome(s) of interest	C-statistic for predicting recurrence at 5 years of follow-up

The follow up of people with melanoma

Nomogram



Nomogram scoring	Low risk (6-9 points): 25% risk of recurrence at 5 years, 4.1% of the population. Intermediate risk (10-15 points): 25-50% risk of recurrence at 5 years, 52.9% of the population High risk (16-19 points): 50-75% risk of recurrence at 5 years, 33.2% of the population Very-high risk (20-23 points): >75% risk of recurrence at 5 years, 10.0% of the population

Participant characteristics

	Study (N = 692)
Female	38.6%
Age, median (IQR) years	47 (46-68)
Positive SNs	
1	90.3%
2	8.7%
>2	1.0%
Tumour location	
Extremities	47.0%
Trunk	51.3%
Head/neck	1.7%

	Study (N = 692)
Ulceration	48.7%
SN tumour burden >1.0mm	27.8%
Breslow thickness, median (IQR) mm	2.4 (1.6-4.0)

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain 1.1 *were appropriate data sources used?* 1.2 *Were inclusion/exclusion criteria appropriate?*	High (Study used a combination of two cohorts, the first being patients excluded from the DeCOG SLT trial and the second being those included in the DeCOG trial. As a result the two cohorts differed in whether they received a CLND, disease severity and likely the intensity of follow-up).
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain *2.1 were predictors defined and assessed in a similar way for all participants?* *2.2 Were predictor assessments made without knowledge of data?* *2.3 Are all predictors available at the time the model is intended to be used?*	High (10% of participants did not have ulceration status on record. 5% had missing data on tumour burden. Unclear level of missing data for Breslow thickness).
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low

Section	Question	Answer
	3.1 was the outcome determined appropriately? *3.2 was a prespecified or standard outcome definition used?* *3.3 were predictors excluded from the outcome definition?* *3.4 was the outcome defined and determined in a similar way for all participants?* *3.5 was the outcome determined without knowledge of predictor information?* *3.6 was the time interval between predictor assessment and outcome determination appropriate?*	(Follow-up schedule at study centre is not clear for those who were rejected from the DeCOG trial however it is suggested that participants were followed up in a similar manner to those included.).
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain *4.1 were there a reasonable number of participants with the outcome?* *4.2 were continuous and categorical predictors handled appropriately?* *4.3 were all enrolled participants included in the analysis?* *4.4 were participants included in the analysis?* *4.5 was selection of predictors based on univariate analysis avoided?* *4.6 were complexities in the data accounted for appropriately?* *4.7 were relevant model performance measures evaluated appropriately?* *4.8 were model overfitting, underfitting, and optimism in model performance accounted for?* *4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariate analysis?*	Low

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Moderate *(issues with missing data for predictor variables and potential for some degree of selection bias.)*
	Concerns for applicability	Directly applicable

- 6.2 Accuracy of imaging for suspected recurrence studies

Albano 2020

Albano, 2020

Bibliographic Reference	Albano, Domenico; Familiari, Demetrio; Fornito, Maria C; Scalisi, Salvatore; Laudicella, Riccardo; Galia, Massimo; Grassedonio, Emanuele; Ruggeri, Antonella; Ganduscio, Gloria; Messina, Marco; Spada, Massimiliano; Midiri, Massimo; Alongi, Pierpaolo; Clinical and Prognostic Value of 18F-FDG-PET/CT in the Restaging Process of Recurrent Cutaneous Melanoma.; Current radiopharmaceuticals; 2020; vol. 13 (no. 1); 42-47

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Italy Setting • Two institutions

	Study dates • January 2008 - December 2016
Inclusion criteria	• Underwent PET/CT for restaging • Underwent conventional imaging to confirm recurrence within 2 months of PET/CT • Suspicion of distant recurrent disease or metastatic progression disease • Surgically resected cutaneous melanoma • Sufficient follow-up data • Availability of clinical-diagnostic follow-up ○ medical records, clinical notes and multidisciplinary team case notes containing diagnostic imaging report (ultrasound, CT, MRI, bone scans) for at least 24 months
Number of participants	74
Length of follow-up	unclear but at least 24 months
Index test(s)	<u>PET-CT</u> Procedure • 18F-FDG-PET/CT examinations were performed using a total-body imaging protocol (from the top of the head till the feet) according to the guidelines of the European Association of Nuclear Medicine. • Before 18F-FDG-PET/CT examination, patients were treated as follows: 48 surgery, 14 surgery+chemotherapy, 8 neoadjuvant chemotherapy+ surgery+radiotherapy, 4 neoadjuvant chemotherapy+ surgery. Interpretation • 18F-FDG-PET/CT scans were qualitatively evaluated by two experienced nuclear medicine physicians with more than 5 years of clinical practice in 18FFDG PET/CT. The two raters were blinded to clinical data. A qualitative assessment of PET images was performed using the target/background method adapted for each region.

Reference standard (s)	Composite • histology (n=21 patients), other diagnostic imaging modalities (Dicom images of CT in 52/74 patients and MRI in 18/74 patients) and clinical follow-up (n=74 patients) with previous reports on conventional imaging, useful for the confirmation of PET findings.

Study-level characteristics

	Study (N = 74)
Female	43%
Mean age (SD)	62 (8) years
cutaneous/subcutaneous	8.4%
lymph nodes	18.9%
liver	12.6%
lung	5.6%
bone	4.2%
brain	1.4

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Strict inclusion criteria. Participants were only included if follow-up data of at least 24 months was available and that confirmatory imaging was done within 2 months*

Section	Question	Answer
		of PET/CT. It is unclear how often these factors were present for people undergoing re-staging.)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear average length of follow-up. Unclear whether subsequent confirmatory imaging was conducted blind to the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for selection bias and a lack of clarity regarding the reference standard.)*
	Directness	Directly applicable

El-Shourbagy 2020

El-Shourbagy, 2020

Bibliographic Reference	El-Shourbagy, K.H.; Mashaly, E.M.; Khodair, S.A.; Houseni, M.M.; Abou Khadrah, R.S.; PET/CT in restaging, prognosis, and recurrence in patients with malignant melanoma; Egyptian Journal of Radiology and Nuclear Medicine; 2020; vol. 51 (no. 1); 167

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Egypt Setting • Single centre Study dates • November 2017 to September 2019 Sources of funding • This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Inclusion criteria	• Melanoma *Histopathologically proven to have malignant melanoma* • Blood glucose <150 mg/dL

	• Underwent PET/CT due to suspected relapse or (if stage IV) during follow-up after 6 months of chemotherapy/radiotherapy (and/or surgical excision of primary tumour).
Exclusion criteria	• Pregnancy • Unable to remain supine for 30 min • Unable to put his or her arms overhead • Uncontrolled hyperglycemia (blood glucose level >250 mg/dL) • Vital sign instability, severe diabetes, severe illness, active infection renal disease who had serum creatinine level >2.0 mg/dL
Number of participants	50 but only 29 included in this review (11 underwent restaging and stage IV underwent detection of metastatic deposits)
Index test(s)	PET-CT Procedure • Multi-slices CT images were performed immediately preceding the acquisition of PET emission data. The patients were asked for quiet breathing to avoid motion artifacts and to match co-registration of CT and PET images in the area of the diaphragm. • The images were displayed in the axial, coronal, and sagittal planes. The images were assessed by both visual inspection and quantitative analysis of the area of abnormal uptake that was done followed by measuring of SUVmax by putting the region of interest (ROI). PET-CT images were evaluated regarding the primary tumor and the presence of lymph nodes and distant metastases. Patients were staged using 7th edition of the TNM staging system. Preparation • The patient was asked to fast for 6 h prior to the scan. All metallic items were removed from the patient, including dentures, pants with zipper, bra, belts, and bracelets. An 18-gauge cannula was inserted in the patient's anti-cubital fossa for administration of 18F-FDG. • Patients were instructed to avoid caffeinated or alcoholic beverages and avoid any kind of strenuous activity; only water was allowed to prior to the examination and following the injection of the radioisotope to avoid physiologic muscle uptake of FDG.

	• For the diabetic patients, good control of blood glucose is essential because the uptake of FDG into cells is competitively inhibited by glucose, as they use a common transport mechanism (glucose transporters [GLUT]) for facilitated transport into both normal and tumor cells. • Serum glucose was routinely measured prior to 18FFDG injection, and it should be below 150 mg/dL. Diabetic patients should not have regular insulin administered subcutaneously within 4 h from FDG administration. • Oral contrast media was used for all patients to distend the bowel wall and help to distinguish between bowl loops and any lymph nodes or masses in the abdomen and pelvic region. • The 18F-FDG was injected into the patient either in a dosage of 0.14 mCu/kg or as prescribed by the physician. The patient waited for 45 to 60min after FDG administration. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and transported into the patient's cells. • Patients were asked to rest in a quiet room, devoid of distractions, and they were also asked to keep their movements, including talking, at an absolute minimum. This minimizes physiologic uptake of FDG into skeletal muscle, which can confound interpretation of the scan.
Reference standard (s)	Clinical examination, histopathology, and imaging CT

Study-level characteristics

	Study (N = 50)
Female	44%
Mean age (SD)	55.9 (13.4) years
Tumour location *(%)*	
head and neck	36%
Trunk	30%
Lower extremity	16%

	Study (N = 50)
Upper extremity	14%
Tumour stage *(%)*	
IIA	4%
IIB	8%
IIC	10%
IIIA	14%
IIIB	8%
IIIC	20%
IV	54%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study is retrospective; characteristic of participants were not disaggregated for patients undergoing restaging)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Characteristic of participants were not disaggregated for patients undergoing restaging)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear blinding)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear blinding)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Limited information on the timing of the index test and reference standard. Additionally, participants likely received different reference standards.)*
Overall risk of bias and directness	Risk of Bias	High *(Characteristics of participants were not disaggregated for patients undergoing restaging; unclear blinding; limited information on the timing of the index test and reference standard; participants likely received different reference standards.)*
	Directness	Directly applicable

Iagaru 2007

Iagaru, 2007

Bibliographic Reference	Iagaru A; Quon A; Johnson D; Gambhir SS; McDougall IR; 2-Deoxy-2-[F-18]fluoro-D-glucose positron emission tomography/computed tomography in the management of melanoma.; Molecular imaging and biology; 2007; vol. 9 (no. 1)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • USA Setting • Single institution Study dates • January 1, 2003 to June 30, 2005. Sources of funding • Nr
Inclusion criteria	• Whole body PET/CT for re-staging after therapy • Melanoma *histopathologically proven diagnosis of melanoma*
Number of participants	106
Index test(s)	PET-CT • A joint Nuclear MedicineYRadiology readout assures the accuracy of the findings on the CT portion of the exams during routine interpretation of the PET/CT exams. Reinterpretation of the studies by board-certified Nuclear Medicine physicians was performed for consistency. The FDG-PET/CT scans were acquired by using a Discovery LS PET/CT unit (GE Medical Systems, Milwaukee, WI). The patients fasted at least 6 hours before imaging and their blood glucose levels were less than 150 mg/dl at the time of the tracer injection. A standard dose of 15 mCi was prescribed for adult patients. Approximately 60 minutes after tracer administration, a CT scan (5 mm contiguous

	axial cuts) was obtained in four integrated multislice helical noncontrast CT, from top of the head to the ankles. The acquisition was obtained in helical mode, using 140 kV, 40 mA s and a 512512 matrix size, acquiring a field of view (FOV) of 867 mm in 22.5 s. This CT-based scan was used for attenuation correction purposes and to help in anatomic localization of FDG. Immediately after the CT, an emission PET scan was acquired in 2-D mode over the same anatomical regions starting at the level of the ankles for molecular/metabolic information. • Acquisition time was four minutes per bed position (35 slices/ bed) in eight beds, with a one-slice overlap at the borders of the FOV. PET emission scan was corrected by using segmented attenuation data of the CT scan. PET images were reconstructed with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets) using GE software release 5.0. All images were reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (eNtegra, GE Medical Systems, Haifa, Israel). • Semiquantitative analysis of the FDG uptake in the suspected lesions was based on calculation of standard uptake value (SUV), defined as the ratio of activity per milliliter of tissue to the activity in the injected dose corrected by decay and per patient_s body weight. Precision is greater than three significant digits for maximum SUV (SUVmax) value [6]. Regions of interest were placed around the regions of increased FDG uptake for SUVmax determination. <u>CT alone</u>
Reference standard (s)	<u>Pathology / clinical follow-up</u> • Specificity and sensitivity for PET, CT, and PET/CT in detection of melanoma were calculated by using the pathology results (91.5% of the patients) or clinical follow-up (8.5% of the cases) as the gold standard, using a 2x2 contingency table, with both a per-person and per-lesion analysis.
Subgroup analyses	Breslow thickness • 1-4mm • >4mm Stage III-IV melanoma

Study-level characteristics

	Study (N = 106)
% Female	35.9%
Mean age (SD)	56.8 (15.9) years
Mean (SD) FDG dose *(mCi)*	15.4 (1.8)
Mean Breslow thickness at diagnosis *(mm)*	3.56

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study was retrospective and reason for undergoing PET/CT is unclear. Protocol for giving PET/CT is also unclear.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(index test conducted prior to reference standard. Unclear whether test was conducted blind to other clinical characteristics.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Not all participants had the same follow-up (some underwent clinical follow-up to determine metastases, in others it was determined by pathology).Tests were*

Section	Question	Answer
		conducted unblinded, it is unclear whether this presents a risk of bias as the protocol for determining recurrence is unclear.)
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Unclear when the diagnosis was confirmed with reference standard in relation to index test.)*
Overall risk of bias and directness	Risk of Bias	High *(Unclear protocol for reference standard. Unclear protocol for giving PET-CT for re-staging at the study centre.)*
	Directness	Directly applicable

Helvind 2021

Helvind 2021

Bibliographic Reference	Helvind, N. M., Mardones, C. A. A., Hölmich, L. R., Hendel, H. W., Bidstrup, P. E., Sørensen, J. A., & Chakera, A. H. (2021). Routine PET-CT scans provide early and accurate recurrence detection in asymptomatic stage IIB-III melanoma patients. *European Journal of Surgical Oncology*.

Study Characteristics

Study type	Prospective cohort study

Study details	Study location • The Netherlands Setting • Two centres Study dates • 2016- 2017 Sources of funding • Funded by the Danish Cancer Society, The Danish Cancer Research Foundation and the Research Council at Herlev Gentofte Hospital
Inclusion criteria	• ≥18 years of age • IIB-III cutaneous melanoma • No history of invasive melanoma
Exclusion criteria	• follow-up in an individualized program without routine PET-CT scans (on patient's or physician's preference) • loss to follow-up (death or transfer to other specialty) • lack of routine scans performed at time of registration
Number of participants	138
Length of follow-up	Median follow-up time from primary treatment was 17.7 months (95%CI 5.8-32.6)
Surveillance strategy	Patients with stage IIB-III melanoma are followed with full skin examination and palpation of all major lymph node stations every three months for the first two years following diagnosis and every six months for an additional three years. At 6, 12, 24 and 36 months, a routine PET-CT scan is performed 1-2 weeks prior to the clinical examination. Additional PET-CT scans may be performed upon suspicion of recurrence or as a control following a prior equivocal scan. Baseline scans were generally performed in stage III patients and in T4 patients.

Index test(s)	Patients fasted 4-6 h prior to the PET-CT scan, received 4MBq/kg 18F-FDG i.v, and rested for 30-60 min before imaging. At HGH emission scans were obtained from the plantar surface of the feet to vertex of the head; at OUH emission scans ranged from the groin to vertex of the head, including lower limbs if relevant according to primary melanoma localization. At HGH, scans were performed using diagnostic dose CT with contrast enhancement (ceCT) from head to groin and low-dose CT (ldCT) for the lower extremities, with supplementary deep-inspiration breath-hold technique of the lungs [21]. OUH used ldCT only. The ceCT images were interpreted by an experienced onco-radiologist. The emission scans and the ldCT were interpreted by a specialist in nuclear medicine. Results of the combined scans were presented in one report in both centers.
Reference standard (s)	Scans were classified according to suspicion of melanoma recurrence and according to suspicion of other malignancy. If findings on routine PET-CT raised suspicion of malignancy, additional investigations were performed. Gold-standard verification was histolopathological confirmation, alternatively confirmation by other imaging modality. Results were classified as: True positive (TP): Suspicion of malignancy was confirmed within six months False positive (FP): Suspicion of malignancy was rejected within six months True negative (TN): No symptoms of malignancy and no scans or clinical examinations detected malignancy within 90 days False negative (FN): No suspicion of malignancy, but a scan or clinical examination detected malignancy within 90 days Equivocal (EQ): Suspicion of malignancy which could not be confirmed or rejected with histology or other imaging modalities within six months. If there were both TP and TN, FN or FP findings within the same scan, the scan was classified as TP. In case of uncertainty as how to classify findings, consensus was reached after discussion among the authors

Participant characteristics

	Study (N = 340)
Female	36.2%
Pathological stage	

	Study (N = 340)
IIB	26.1%
IIC	10.9%
IIIA	27.5%
IIIB	24.6%
IIIC	7.2%
III unclassifiable due to unknown T-stage	3.6%
Scanning intervals, underwent routine scan at:	
6-month	89.1%
12-month	63.0%
24-month	23.9%
Number of scans given overall	243

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Patients were prospectively enrolled).*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(There is a low level of completion of scans from 12 months onwards. This may bias the results if specific types of participants are missing scans.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Could be confirmed/excluded by histopathology or subsequent scanning. This is not optimal as the accuracy of these two methods differ. Additionally, there is the possibility that a recurrence developed after the index scan but before the reference scan.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low.
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(PET/CT scans were conducted prior to clinical exam and therefore it is unclear how many would have been captured by exam alone)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of bias due to missing data for post 6-month scans, variable reference standards and timing of index test).*

Section	Question	Answer
Overall risk of bias and directness	Directness	Directly applicable

Jansen 2021

Jansen 2021

Bibliographic Reference	Jansen, Y. J., Willekens, I., Seremet, T., Awada, G., Schwarze, J. K., De Mey, J., ... & Neyns, B. (2021). Whole-Body MRI for the Detection of Recurrence in Melanoma Patients at High Risk of Relapse. *Cancers*, *13*(3), 442

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Belgium Setting • Single centre Study dates • November 2014 until November 2019 Sources of funding • Funded by the Danish Cancer Society, The Danish Cancer Research Foundation and the Research Council at Herlev Gentofte Hospital
Inclusion criteria	• IIIb/c or IV (cohort A and B; according to AJCC 7th ed.)

	• disease-free following resection of macrometastases (cohort A). • in a durable complete response (CR) or partial response (PR) following systemic therapy (immunotherapy or targeted therapy) in stage IV disease (cohort B).
Exclusion criteria	• contra-indication for MRI (pacemaker, metallic foreign body in eye, recent operation with prosthetic material (<6weeks), claustrophobia, and metallic devices implanted such as hip prostheses altering the imaging quality
Number of participants	107
Length of follow-up	median follow-up of 32 months (95% CI, 20–45 months),
Surveillance strategy	All patients underwent whole-body MRI, including T1, short Tau Inversion Recovery, and DW imaging, every 4 months the first 3 years of follow-up and every 6 months in the following 2 years. A blood test, including liver chemistry, lactate dehydrogenase (LDH), and C-reactive protein (CRP), was performed on each visit. A total body skin examination by a dermatologist was performed every 6 months. After 5 years, all patients from cohort A were followed by their dermatologist on a yearly base. The follow-up after 5 years for patients in cohort B was dependent on their disease status and determined at the discretion of the treating physician.
Index test(s)	MRI • All whole-body MRI examinations were performed on a 3 Tesla scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with parallel radiofrequency transmission and phased-array surface coils. The MRI protocol included 3D TI weighted VIBE sequence, Short Tau Inversion Recovery (STIR) sequences, and diffusion-weighted imaging (DWI). We created a transverse series with the signal intensity of fat (fat-only), only water (water only), T1 in-phase, and T1 out-of-phase. The 3D T1 series were reconstructed in sagittal images. As T2-sequence, a coronal STIR sequence was used. Transverse DWI were acquired in eight stations (head/neck, thorax, abdomen, pelvis, upper legs, and lower legs) at b = 50 and b = 800 s/mm2. They were interpreted with the apparent diffusion coefficient (ADC) images. Post-processing of the eight stacks of images was required to have an excellent overview. These stacks are composed of one volume. This volume was reconstructed so that it could rotate along its cranio-caudal axis. 2.3. Imaging Analyses Two radiologists analyzed each MRI examination. Any clinical decision was based on the consensus of the two readers. The evaluation of the examination was based on morphological characteristics and DWI appearance. General radiological criteria for metastases were areas with a shape suggestive of a tumor, abnormal signal, hyperintensities on DWI, and corresponding ADC values. A lymph node was

	suspicious if it was round with a shortest diameter ≥10 mm. Lymph nodes <10mm, but hyperintense on T1 (suggestive of the presence of melanin) were also suspicious [27]. New subcutaneous lesions were detected on the DWI sequences
Reference standard (s)	• The result of a whole-body MRI was defined as true positive (TP) if metastatic disease was detected by the MRI and was confirmed by biopsy, surgical excision, or by PET/CT in case of multiple metastases. MRI finding was defined as true negative (TN) if the MRI was negative and no disease was detected in the following 4 months (on self-examination, additional consultation, or imaging due to symptoms or incidental finding). A false negative (FN) was defined as a negative MRI but with a relapse in the following 4 months. An MRI finding was defined as false positive (FP) if the possibility of metastatic disease was suspected based on active foci on the MRI, leading to biopsy, surgical management, or other radiological imaging not confirming relapse. • In all patients with a suspected relapse on MRI, supplementary imaging was performed before having a therapeutic impact. Clinical evident disease was defined as a disease causing symptoms such as pain, hemoptysis, dyspnea, etc.

Participant characteristics

	Cohort A (N = 68)	**Cohort B (N=39)**
Female	48.5%	56.4%
Median (range) age, years	58 (28–99)	57 (31–85)
Pathological stage		
Ia-IIc	19%	-
IIIA	28%	-
IIIB	18%	-
IIIC	26%	2%
IV-M1a	1%	3%

	Cohort A (N = 68)	Cohort B (N=39)
IV-M1b	-	13%
IV-M1c	-	46%
Unknown	7%	15%
Treatments		
Adjuvant high-dose IFN-α-2b	3%	21%
Anti-CTLA-4	13%	36%
Anti-PD-1	19%	13%
Anti-CTLA-4 and Anti-PD-1	4%	-
Other treatment	-	34%
BRAF mutant	58%	38%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Patients were prospectively enrolled. However, there was variance in disease stage in cohort A and variance in treatments received in cohort B).*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Could be confirmed/excluded by histopathology, subsequent scanning or consultation. This is not optimal as the accuracy of these two methods differ. Additionally, there is the possibility that a recurrence developed after the index scan but before the reference scan.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low.
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of bias due to use of composite reference standard.).*
Overall risk of bias and directness	Directness	Directly applicable

Koskivuo 2016

Koskivuo 2016

Bibliographic Reference	Koskivuo, I; Kemppainen, J; Giordano, S; Seppanen, M; Verajankorva, E; Vihinen, P; Minn, H; Whole body PET/CT in the follow-up of asymptomatic patients with stage IIB-IIIB cutaneous melanoma.; Acta oncologica (Stockholm, Sweden); 2016; vol. 55 (no. 11); 1355-1359

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Finland Setting Single centre Study dates 2004-2011 Sources of funding nr
Inclusion criteria	IIB-IIIB IIB-IIC (sentinel node-negative) or IIIA-IIIB (sentinel node-positive) SLNB All patients underwent sentinel node biopsy (SNB) with standard technique. Completion lymph node dissection (CLND) was performed in sentinel-positive patients.
Exclusion criteria	PET/CT at wrong timing following surgery All patients underwent whole body PET/CT, which was scheduled to be performed after an interval of six months after initial surgery. The patients were excluded, if PET/CT was performed earlier than three months or later than 12 months after surgery.
Number of participants	110
Length of follow-up	The median follow-up time of the patients was 56 months (4.6 years).

Index test(s)	PET-CT PET/CT was conducted between 3 and 12 months after surgery; No additional PET/CT scanning was routinely repeated if the patient remained asymptomatic and if there was no clinical suspicion of recurrent disease. For whole body 18F-FDG-PET/CT scan (Discovery STE or VCT, General Electric Medical Systems, Milwaukee, WI, USA) patients fasted for a minimum of six hours before the intravenous injection of 4 Mbq/kg 18F-FDG. Low-dose PET/CT (kV 120, Smart mA range 10–80) from calvarium to toes was performed after 50–60 minutes from injection. PET images were corrected for dead time, decay, and photon attenuation and were reconstructed with 128 128 matrix size in fully 3D mode using ML-OSEM reconstruction algorithm. Imaging analysis was performed using ADW 4.5 workstation. 18F-FDG PET/CT images were analyzed visually and semiquantitatively by calculating maximum standardized uptake value (SUVmax), defined as the ratio of activity per milliliter of tissue to activity in the injected dose corrected for decay and for the patient's body weight.
Reference standard (s)	Composite The follow-up protocol consisted of clinical examination every 3–6 months during the first five years. Routine chest x-ray and blood tests including liver chemistry were performed annually. No additional PET/CT scanning was routinely repeated if the patient remained asymptomatic and if there was no clinical suspicion of recurrent disease. The result of PET/CT was defined as true positive (TP), if metastatic disease was detected by the first scanning in an asymptomatic patient. PET/CT finding was defined as true negative (TN), if the first scanning was negative and no disease was detected during further follow-up. PET/CT result was defined as false negative (FN), if the first scanning was negative, but recurrent disease was detected during further follow-up. PET/CT finding was defined as false positive (FP), if the possibility of metastatic disease was suspected based on active foci in the scan leading to biopsy, surgical management, medical treatment, or repetitive PET scannings or other imagings.

Participant characteristics

	Study (N = 340)
Female	40.9%
Median (range) age	60 (19-87)

	Study (N = 340)
Tumour location	
Head/neck	10%
Trunk	52.7%
Extremities	37.3%
Ulceration	50.0%
Breslow thickness, mean (range)	4.1 (0.5-15.0) mm
Positive SLNB	60.9%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Patients were prospectively enrolled however there does not appear to be a prospective protocol for giving PET/CT after surgery.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Lack of clarity as to how a false positive was identified. Use of composite reference standard allows for variation between participants and the possibility of a newly developed recurrence (recurring shortly after the scan) resulting in the scan incorrectly being recorded as a false negative.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low.
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of bias due to reference standard and method of prospective enrolment.)*
Overall risk of bias and directness	Directness	Directly applicable

Lawal 2017

Lawal, 2017

Bibliographic Reference	Lawal, Ismaheel; Lengana, Thabo; Ololade, Kehinde; Boshomane, Tebatso; Reyneke, Florette; Modiselle, Moshe; Vorster, Mariza; Sathekge, Mike; 18F-FDG PET/CT in the detection of asymptomatic malignant melanoma recurrence.; Nuklearmedizin. Nuclear medicine; 2017; vol. 56 (no. 3); 83-89

Study Characteristics

Study type	Prospective cohort study - *Unclear study design, appears to be prospective*
Study details	Study location • South Africa Setting • Single centre Study dates • June 2010 - June 2016
Inclusion criteria	• Undergoing PET/ CT follow-up to detect asymptomatic recurrent metastatic disease *and had received a baseline FDG PET/CT scan acquired post-surgery that was negative for malignant lesions.* *The decision to refer patients for FDG PET/CT scan and the frequency of imaging were at the discretion of the managing physician.* • Confirmed melanoma in whom all malignant lesions (primary and nodal metastases) had been surgically excised
Exclusion criteria	• Residual malignant disease on baseline scan • Second malignant disease • Known recurrence • Stage IV disease • Adjuvant chemotherapy or radiotherapy.
Number of participants	313 scans in 144 patients
Length of follow-up	Median (IQR) follow-up: 50.50 (29.25–74.75) months

Index test(s)	PET-CT Interpretation • The images were analysed by two experienced nuclear medicine physicians. Disagreements were resolved by an independent third reviewer. Timing • Timing of scan is unclear Procedure • Imaging was acquired on a dedicated PET/CT scanner (Biograph 40, Siemens). Standard patient preparation was observed. • Briefly, all patients had a minimum of 4 hours of fasting, blood sugar was 11.0 mmol/l and activity of FDG injected was calculated based on weight using the formula: [(body weight ÷ 10) + 1] × 37 MBq. Vertex to mid-thigh imaging was commenced after 60 minutes of uptake time. • A separate lower limb imaging was one if the initial primary lesion was resected from the lower limb. This is based on reports that have shown that additional lower limb imaging does not increase lesion detection rate (10). • PET acquisition was in 3D mode at 3 minutes per bed position. Except where a contraindication existed, CT was done with intravenous contrast using non-ionic contrast material (Ultavist®, Bayer Vital GmbH) injected at a rate of 2 ml/s. Images were reconstructed using OSEM (ordered subsets expectation maximisation) to yield axial, sagittal and coronal slices of PET, CT and fused PET/CT images. Both attenuation corrected and non-corrected images were reviewed for interpretation.
Reference standard (s)	Composite

	• Findings on the images were verified using a combination of histological confirmation (42 patients) and follow- up FDG PET/CT imaging (102 patients).

Study-level characteristics

	Study (N = 144)
% Female	57.6
Mean age (SD)	53.93 (15)
Ethnicity	
White	84
Nominal	84
Black	16
Nominal	16
Tumour location	
head and neck	18.8
Trunk	30.6
extremities	47.9
Breslow thickness *(mm)*	

	Study (N = 144)
1 or less	16
1.01-2.00	16
2.01-4.00	19.4
>4.00	48.6
Median (IQR) follow-up period *(Months)*	50.5 (29.25 to 74.75)
% with recurrence	25.7
Median (IQR) time to recurrence *(Months)*	20 (5.75 to 37)
resection of nodes	56.3

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Unclear study design)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Unclear *(Unclear which test constitutes the index test.)*

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Not all participants had recurrence confirmed/ruled out by histopathology. Repeat scan with PET/CT is unlikely to be a sufficient gold standard test to confirm original scan. It is unclear how frequent scans were and how close in time they were. Unclear blinding.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Composite reference standard allowed for participants to receive different tests. It is unclear when during follow-up the tests were performed, or how frequent they were.)*
Overall risk of bias and directness	Risk of Bias	High *(Unclear blinding and study design. Composite reference standard allowed for variance between participants. Unclear timing of tests during follow-up)*
	Directness	Directly applicable

Lee 2018

Lee 2018

Bibliographic Reference	Lee, H.H.; Paeng, J.C.; Cheon, G.J.; Lee, D.S.; Chung, J.-K.; Kang, K.W.; Recurrence of Melanoma After Initial Treatment: Diagnostic Performance of FDG PET in Posttreatment Surveillance; Nuclear Medicine and Molecular Imaging; 2018; vol. 52 (no. 5); 327-333

Study Characteristics

Study type	Retrospective cohort study

Study details	• Study location
	  ○ South Korea
	• Setting
	  ○ Single centre
	• Study dates
	  ○ January 2005 to December 2014

Inclusion criteria	• biopsy proven melanoma I-IV • underwent PET/CT
Exclusion criteria	PET/CT performed for restaging of confirmed recurrence or for second primary cancer
Number of participants	76 (143 scans); Among 143 scans, 92 (64%) of 44 patients were performed for routine surveillance; the other 51 (36%) of 32 patients were performed for clinical suspicion of recurrence.
Length of follow-up	unclear; , the interval between repeated scans was 26.1 ± 20.6 months (range 4–122 months).
Index test(s)	PET-CT CT images were acquired for the whole body (from the vertex to the toe) for attenuation mapping and lesion localization (50 mA, 120 kVp, 5-mm section width, 4-mm collimation). After CT scan, PET images were acquired in three-dimensional mode for 6–7 bed positions (1 min per bed position). Images were reconstructed on 128 × 128 matrices using an iterative algorithm. The images were analyzed using a vendor-supplied analysis software package (Syngo.via, Siemens Healthcare). PET/CT images were retrospectively interpreted by consensus of two nuclear medicine specialists who were unaware of the final clinical outcome. Definitely abnormal lesions of FDG uptake (with excluding physiological or inflammatory uptake) were classified as positive for recurrence and, otherwise, classified as negative. Indeterminate lesions with borderline uptake increase were classified as negative.
Reference standard (s)	Composite Final diagnosis of a patient was determined by histologic confirmation of detected lesions and/or follow-up results based on image or clinical findings; if a patient without treatment did not exhibit disease progression for more than 6 months, the patient was deemed to be negative for recurrence. Based on the final diagnosis, PET/CT findings were classified as true positive (TP), false positive (FP), true negative (TN), or false negative (FN)

Participant characteristics

	Study (N = 76)
Female	43.4%
Tumour location	
Head/neck	23.7%
Trunk	10.5%
Extremities	59.2%
Other	6.6%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study was retrospective, unclear when participants would have undergone PET/CT during surveillance. Protocol for giving PET/CT during surveillance or for suspected recurrence at study centre is not reported. It is unclear whether other imaging modalities were more frequently used.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(Imaging records were independently reviewed by two blinded nuclear medicine specialists. However, actual surveillance strategy is unclear. It is likely that the study centre were advised to use NCCN guideline for follow-up however it is unclear how much deviation an variance there was in practice.)*

Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Use of composite reference standard allows for differences between participants. New recurrences (recurring shortly after PET/CT scan) would incorrectly be classified as a FN.).*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	High *(Variance in reference standard received. Study was retrospective and participants were not followed up in accordance with a standardised surveillance strategy. Time between scans and variance in frequency/intensity of imaging is unclear).*
Overall risk of bias and directness	Directness	Directly applicable

Leon-Ferre 2017

Leon-Ferre, 2017

Bibliographic Reference	Leon-Ferre, Roberto A; Kottschade, Lisa A; Block, Matthew S; McWilliams, Robert R; Dronca, Roxana S; Creagan, Edward T; Allred, Jacob B; Lowe, Val J; Markovic, Svetomir N; Association between the use of surveillance PET/CT and the detection of potentially salvageable occult recurrences among patients with resected high-risk melanoma.; Melanoma research; 2017; vol. 27 (no. 4); 335-341

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • USA Setting • Single centre Study dates • January 2008 and October 2012 Sources of funding • This study received a small grant from the Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA.
Inclusion criteria	• Completely resected stage III–IV cutaneous melanoma or melanoma of unknown primary • no visible residual disease following surgery • At least one PET/CT performed for surveillance purposes within 1 year from definitive surgery
Exclusion criteria	• Stage I or II melanoma • Ocular or mucosal primary • Visible disease following resection • PET/CT performed for staging *Defined as PET/CT performed between the diagnosis of melanoma and initial resection* • PET/CT performed for purposes other than surveillance • Underwent surveillance at a different institution • Records were not available for review

Number of participants	299
Length of follow-up	Median follow-up of 5.0 years
Index test(s)	PET-CT • PET-CT procedure was not described
Reference standard (s)	Composite • Biopsy; subsequent imaging throughout the surveillance period; management of first recurrence
Additional comments	Diagnostic accuracy reported by number of PET-CT scans (n=1687)

Study-level characteristics

	Study (N = 299)
% Female	39
Median age at diagnosis	56.2 years
Primary lesion *(%)*	
Cutaneous	86%
Melanoma of unknown primary	14%

	Study (N = 299)
Stage *(%)*	
IIIA	30
IIIB	33
IIIC	13
IV	23

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study is retrospective)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(PET-CT procedures were not described. Imaging records were independently reviewed by two blinded nuclear medicine specialists. However, actual surveillance strategy is unclear. It is likely that the study centre were advised to use NCCN guideline for follow-up however it is unclear how much deviation an variance there was in practice.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(No information on how reference standard was performed; it is likely that not all participants had the same reference standard)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Limited information on reference standards)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(No information about timing between reference test and reference standard)*
Overall risk of bias and directness	Risk of Bias	High *(Study is retrospective; no information on procedures for index test and reference standard (including timing between them); it is likely that not all participants had the same reference standard)*
	Directness	Directly applicable

Madu 2017

Madu, 2017

Bibliographic Reference	Madu, Max F; Timmerman, Pieter; Wouters, Michel W J M; van der Hiel, Bernies; van der Hage, Jos A; van Akkooi, Alexander C J; PET/CT surveillance detects asymptomatic recurrences in stage IIIB and IIIC melanoma patients: a prospective cohort study.; Melanoma research; 2017; vol. 27 (no. 3); 251-257

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • The Netherlands Setting • Single centre Study dates • between 1 January 2015 and 1 April 2016
Inclusion criteria	• fully resected high-risk (stage IIIB and IIIC) melanoma *Stage IIIB was defined as clinically detectable nodal metastasis or in-transit metastasis without nodal metastasis, leaving out sentinel node (SN)- positive patients with ulcerated primary tumors. Stage IIIC was defined as either in-transit metastasis combined with nodal metastasis, more than three metastatic lymph nodes, or an ulcerated primary tumor with clinically detectable lymph node metastases.* • underwent PET/CT surveillance imaging
Exclusion criteria	• PET/CT performed only for staging or restaging purposes in symptomatic patients • participation in clinical trials • stage IV disease before start of the surveillance period
Number of participants	51; 18 participants (32 scans) included in analysis (Thirty-three patients were excluded: 27 because they had received follow-up scans for restaging purposes after confirmation of locoregional or regional relapses, five because of elevated S100B before or during the follow-up scan, and one because the patient had not received scans according to the 6-monthly schedule).
Length of follow-up	Median (range): 15 (12-19) months
Index test(s)	PET-CT

	Timing • All stage IIIB and IIIC melanoma patients were staged with PET/CT before full resection of disease. After surgery, patients underwent 3-monthly physical examination in combination with S100B/lactate dehydrogenase testing. Surveillance PET/CT scans were performed in asymptomatic patients with a normal S100B every 6 months for the first 2 years after the startof follow-up and one final scan after 3 years. PET/CT scans were also performed in case of elevated tumor markers or symptoms, but these were not considered surveillance scans. Procedure • PET/CT scans were performed using a hybrid PET/CT scanner (Gemini II; Philips, Eindhoven, The Netherlands). Fluorine-18 fluorodeoxyglucose was administered intravenously at a dosage of 180–240 MBq after a fasting period of 6 h and adequate fluid intake. Whole-body acquisitions were performed according to standard acquisition protocols, with an acquisition time of 2 min per bed position. Low-dose CT images (40 mAs, 2–5mm slices) were acquired without intravenous contrast. PET was fused with the low-dose CT after correction for attenuation. PET/CT imaging characteristics, such as blood glucose levels, injected dose (MBq), and incubation period, were documented, along with the time interval between PET/CT and previous surgical or diagnostic procedures. The generated images were displayed using an Osirix Dicom viewer in a UNIX-based operating system (Macintosh OS X; Apple, Cupertino, California, USA). Experienced nuclear medicine physicians assessed all PET/CT scans by means of both visual and semiquantitative analysis. Interpretation • On the basis of these clinical reports lesions were categorized as negative, positive, or indeterminate.
Reference standard (s)	<u>Pathology / follow-up</u> • Locoregional recurrence was defined as local recurrence, satellite metastasis, or intransit metastasis. Regional recurrence was defined as lymph node recurrence in the treated regional lymph node basin. Distant recurrence was defined as a recurrence beyond the regional nodal basin (including distant cutaneous, subcutaneous, nodal, or visceral metastases). • PET/CT scans were considered true positive when there was pathological confirmation of metastasis or evidence of progression on subsequent imaging. When surveillance imaging showed suspected relapse, but pathological evaluation, clinical evaluation,

	or follow-up imaging showed no relapse, scans were scored as false positive. Scans were considered true negative if there was no relapse within 3 months of surveillance imaging. Scans were considered false negative if a relapse occurred within 3 months of imaging.

Study-level characteristics

	Study (N = 18)
% Female	50%
Tumour stage	
IIIB	50%
IIIC	50%
% ulceration	33%
Tumour location	
Head and trunk	6%
Trunk	39%
extremities	33%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Unclear blinding. Use of composite reference standard including follow-up is less optimal than a gold-standard test being employed immediately after PET/CT scan.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Various methodologies could be used to confirm recurrence, these differed between participants.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Use of composite reference standard meaning participants underwent different tests. Unclear blinding.)*
	Directness	Directly applicable

Malik 2019

Malik, 2019	
Bibliographic Reference	Malik, Dharmender; Sood, Ashwani; Mittal, Bhagwant Rai; Basher, Rajender Kumar; Bhattacharya, Anish; Singh, Gurpreet; Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in restaging and prognosis of recurrent melanoma after curative surgery.; World journal of nuclear medicine; 2019; vol. 18 (no. 2); 176-182

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • India Setting • Single centre Study dates • Unclear Sources of funding • nil
Inclusion criteria	• Melanoma • Suspected of recurrence • Underwent PET/CT at least 6 months post-surgery

Number of participants	54
Length of follow-up	mean follow-up period of 23.8 ± 18.1 months. Defined as the period from 18F-FDG PET/CT imaging to the last clinical review, and each patient had minimum follow-up of 6 months.
Index test(s)	<u>PET-CT</u> Interpretation • Two qualified nuclear medicine physicians retrospectively evaluated the studies in agreement without being aware of clinical/imaging findings. Any positive findings in the form of focal tracer uptake on 18F-FDG PET were anatomically localized on contrast-enhanced CT images. Maximum standardized uptake value (SUVmax) for semiquantitative analysis was obtained by assigning a region of interest over the lesion with highest tracer uptake. Procedure • 18F-FDG PET/CT studies were done in all the patients after minimum fasting for 6 h with blood glucose <150 mg/dl (8.3 mmol/l) and without any strenuous activity on or the day before the examination. Acquisition was performed at 45–60 min post-intravenous injection of 370 MBq (~10 mCi) of 18F-FDG on dedicated hybrid scanners (Discovery 710 or • Discovery STE-16; GE Healthcare, Milwaukee, Wisconsin, USA). A low-dose scout CT (120 kV, 10 mA) was acquired from vertex to toe. Contrast enhancement CT followed by 3D-PET acquisition was done in caudocranial direction with an acquisition period of 2 min per bed position using timeof-flight technique. The reconstructed attenuation-corrected • PET, CT, and fused images were reviewed in three planes (the axial, sagittal, and coronal) along with maximum intensity projections.
Reference standard (s)	<u>Composite</u> • The histopathological examination wherever available and clinical and imaging follow-up for the past 6 months (unclear timing of this relative to index test) were taken as the reference standard in the patients.

	• Any suspicious lesion with increase or decrease in size (posttreatment) at follow-up imaging was considered as true positive for recurrent disease.

Study-level characteristics

	Study (N = 54)
% Female	40.7%
Mean age (SD)	51.3 (16)
Tumour location	
head and neck	20%
Trunk	39%
extremities	41%
Pre-PET/CT treatment	
Surgery	81%
Surgery + CT	11%
Surgery + CT + radiotherapy	8%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(unclear what constituted suspicion of recurrence and whether PET/CT was routinely given for the patients.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear blinding)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(reference standard states that "clinical and imaging follow-up for the past 6 months were taken as the reference standard in the patients". The mean follow-up period is 23 months, with participants being seen every 3 months. This means that there is variance in the amount of follow-up imaging. Additionally it is possible for a recurrence to have occurred after PET/CT but prior to the last 6 months.)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding, potential for selection bias and issues with timing of reference standard.)*
	Directness	Directly applicable

Pfannenberg 2007

Pfannenberg 2007

Bibliographic Reference	Pfannenberg C; Aschoff P; Schanz S; Eschmann SM; Plathow C; Eigentler TK; Garbe C; Brechtel K; Vonthein R; Bares R; Claussen CD; Schlemmer HP; Prospective comparison of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma.; European journal of cancer (Oxford, England : 1990); 2007; vol. 43 (no. 3)

Study Characteristics

Study type	Prospective cohort study

Study details	• Study location
	  ○ Germany
	• Setting
	  ○ Referrals from a single centre
	• Study dates
	  ○ September 2004 to September 2005
	• Sources of funding
	  ○ nr

Inclusion criteria	• III-IV • presenting with potential evidence of metastatic spread • underwent wbMRI and PET/CT ○ indications for imaging included confirmation of local diseases before surgical resection in 9 patients, further characterisation of abnormal radiological, clinical and laboratory (S100 protein, lactic dehydrogenase) findings in 48 patients, routine melanoma surveillance in high risk patients in 7 patients

Number of participants	64 patients presented a total number of 420 lesions
Length of follow-up	Patients were observed in a regular three-month interval follow-up schedule for a mean follow-up time of 252.5 days (range, 99–474 days).
Index test(s)	PET-CT • "PET/CT imaging started 55– 65 min after intravenous administration of 370 MBq of 18FFDG and was performed using the Hi-Rez Biograph 16 (Siemens Medical Solutions, Knoxville, USA), consisting of a high-resolution 3D LSO PET and a state-of-the-art 16 row multi-slice CT. Emission data were acquired from the base of the skull to the lower legs with 3 min acquisition per bed position. Patients with BMI > 25 were examined 4 min per FOV. CT was operated with 120 kV, 120–160 mAs, rotation time of 0.5 s, collimation of 0.75 mm (thorax) and 1.5 mm (abdomen), respectively, table feed of 12/24 mm, and reconstructed slice thickness/increment 5/5 mm (axial) and 3/2 mm (coronal), respectively. Patients were positioned on the scanning table with their arms raised in order to reduce beam-hardening artifacts. To receive diagnostic CT data, in all patients a multi-phase CT protocol with an intravenous application of 120 ml iodinated contrast agent (Ultravist 370, Schering GmbH, Berlin, Germany) was performed. The intravenous contrast volume of 120 ml was administered with a flow of 2 ml/s. To prevent contrast-induced artefacts, we optimised the injection protocol with a 40 ml saline chaser. All patients were asked to drink 1000 ml Mannitol 2% as a negative oral contrast agent prior to scanning in order to distend the bowel. During preliminary studies, we tested different scanning and breathing protocols to optimise contrast-enhanced CT studies.19 According to the results of our tests, patients were asked to stop breathing in normal expiration during the contrast-enhanced CT scans for optimal co-registration. The attenuation-corrected PET data were iteratively reconstructed and co-registered with the CT data by commercial software (eSoft, Siemens, Erlangen, Germany). PET alone CT alone wbMRI • All wbMRI examinations were performed on a whole-body 1.5 T system using multiple phased-array surface coils and receiver channels together with integrated parallel acquisition technique (Avanto, Siemens AG, Erlangen, Germany). The total examination time lasted about 1 h. The examination protocol involved state-of-the-art MRI from head to toe, including axial and coronal scans before and after intravenous contrast administration as described in Re

Reference standard (s)	Composite • The data of the reference standard were collected by a physician unaware of the results of PET/CT and MRI imaging. • "The standard of reference for suspicious lesions was classified into three categories: (i) histology obtained by metastasectomy, (ii) imaging follow-up by PET/CT, CT, dedicated MRI, ultrasound, bone scan or radiography, (iii) clinical follow-up including tumour marker (S100, lactic dehydrogenase) and other laboratory and clinical tests. True positive (TP) means that a lesion was rated as malignant or probably malignant and malignancy was confirmed by histology or progression on follow-up. True negative (TN) was defined when a lesion was rated as benign or probably benign and was found to be benign on histology or failed to show progression on follow-up. False negative (FN) occurred either when one of the modalities failed to detect a lesion or when a lesion was falsely classified as benign or probably benign and the lesion was found to be malignant at histology or showed progression on follow-up. False positive (FP) occurred when a modality classified a lesion as malignant or probably malignant and the lesion was found to be benign on histology or failed to show progression on follow-up. Patients were observed in a regular three-month interval follow-up schedule for a mean follow-up time of 252.5 days (range, 99–474 days). The data of the reference standard were collected by a physician unaware of the results of PET/CT and MRI imaging."

Participant characteristics

	Study (N = 340)
Female	64.1%
Mean age (range)	57.8 (23-79) years
Breslow thickness	2.69 (0.6, 12.0) years
Stage III	39.1%
Stage IV	60.9%

Risk of bias

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study was prospective, with all patients suspected of metastatic progression being asked to*

		participate and undergo both imaging methods. However, there is a wide range of different reasons for referral, including confirmation of local diseases before surgical resection in 9 patients, further characterisation of abnormal radiological, clinical and laboratory (S100 protein, lactic dehydrogenase) findings in 48 patients, routine melanoma surveillance in high risk patients in 7 patients. It is unclear when the scans were conducted in relation to initial diagnosis)
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High *(analysis conducted on a per-lesion basis)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(use of a composite reference standard means that participants will have received different reference standards.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(classified as staging how the timing of scans in relation to initial diagnosis is unclear.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear timing of tests in relation to initial diagnosis. Use of composite reference standard. Numerous reasons for referral for imaging.)*
Overall risk of bias and directness	Directness	Partially applicable *(per-lesion analysis.)*

Rubaltelli 2011

Rubaltelli, 2011	
Bibliographic Reference	Rubaltelli L; Beltrame V; Tregnaghi A; Scagliori E; Frigo AC; Stramare R; Contrast-enhanced ultrasound for characterizing lymph nodes with focal cortical thickening in patients with cutaneous melanoma.; AJR. American journal of roentgenology; 2011; vol. 196 (no. 1)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Italy Setting • Single centre Study dates • June 2008 to December 2009
Inclusion criteria	• Melanoma • were being followed-up following surgery for melanoma • Underwent ultrasound of the regional lymph nodes as part of a follow-up program after surgery for cutaneous melanoma. • Focal cortical thickening required for contrast-enhanced US (identified on US)

Exclusion criteria	• common signs of malignancy on gray-scale ultrasound for example, changes in shape (a longitudinal- to-transverse diameter ratio of < 2) or structural changes, such as the cancellation or distortion of the central echogenic hilum and the presence of anomalous capsular vessels
Number of participants	460
Index test(s)	<u>US</u> • The axillary lymph nodes were examined in patients with melanomas of the upper limbs, the inguinal lymph nodes in patients with melanomas of the lower limbs, both axillary and inguinal lymph nodes in patients with melanomas of the trunk, and the cervical and supraclavicular lymph nodes in patients with melanomas of their head and neck. In all, 72 neck, 248 axillary, and 354 inguinal lymph node regions were examined. <u>Contrast-enhanced US</u> • All the lymph nodes considered were examined using equipment with state-of-the-art software for contrast-enhanced ultrasound (MyLab 25, Esaote). A 4.8-mL bolus was injected into a peripheral vein and followed by injection of 10 mL of physiologic saline solution. The lymph nodes were scanned immediately afterward at a rate of 15 frames per second. The apparatus used enables the recording and filing of images in a digital format, and all the dynamic stages of the examinations were memorized on this system. We assumed that the arterial phase lasted the first 5 seconds after the initial appearance of contrast medium in the lymph nodes, and the parenchymal phase from the 6th second to 20th second. The enhanced echogenicity after the injection of the contrast agent—that is, the expression of lymph node perfusion—was assessed by a single sonologist with 8 years of experience in contrast-enhanced ultrasound examination. Contrast enhancement in the arterial and parenchymal phases was classified as present or absent, scarce or intense, homogeneous or nonhomogeneous, and revealing or not revealing perfusion defects. Interpretation • At contrast-enhanced ultrasound examination, a homogeneous intense enhancement of the cortex was considered a benign sign; perfusion defects corresponding to the cortical focal thickening were considered a sign of malignancy.

Reference standard (s)	<u>FNAC, Lymphadenectomy, follow-up</u> Procedures • FNAC was performed on all lymph nodes considered in this study, focusing on the suspect area of focal thickening. FNAC was performed with a freehand technique using 21-gauge needles in the presence of the cytologist. Patients with positive FNAC findings underwent lymphadenectomy and subsequent histologic assessment of the resected lymph nodes. Patients with negative FNAC findings continued ultrasound follow-up for a period ranging between 6 and 16 months (median, 10 months). • Those with metastases identified by FNAC following contrast enhanced US also underwent lymphadenectomy to confirm diagnosis. • Those negative for metastases on FNAC following contrast enhanced US underwent US follow-up (6-16 months duration) Interpretation • Among the patients whose lymph nodes revealed perfusion defects on contrast-enhanced ultrasound, we considered those positive for metastases on cytology as true-positives, whereas those lacking cytologic evidence of metastatic spread were classified as false-positives. Among the lymph nodes showing intense and homogeneous contrast enhancement, those lacking cytologic evidence of metastases were considered true-negatives and those with cytologic signs of spread were classified as false-negatives.

Study-level characteristics

	Study (N = 460)
% Female	47.8%
Mean age (SD)	54 years
more than one lymph node with focal cortical thickening *(%)* of the 44 patients with focal cortical thickening	13.6%

		Study (N = 460)
Nominal		13.6
Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Participants were excluded from the study if US showed common signs of malignancy. People with signs already diagnostic for metastases were referred directly for FNAC.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(unclear blinding)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear blinding)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(not all participants underwent same reference standard. Those positive on FNAC had confirmation using CLD. Those negative underwent US follow-up, with limited*

Section	Question	Answer
		reporting of what this involved. In the wider population, follow-up for those node-negative participants is unclear.)
Overall risk of bias and directness	Risk of Bias	High *(Study excluded participants from the main cohort analysis if there were common signs of malignancy on first US. Participants had different reference standards depending on pathway. Follow-up is unclear for some participants.)*
	Directness	Directly applicable

Stahlie 2020

Stahlie 2020

Bibliographic Reference	Stahlie, E.H.A.; van der Hiel, B.; Stokkel, M.P.M.; Schrage, Y.M.; van Houdt, W.J.; Wouters, M.W.; van Akkooi, A.C.J.; The use of FDG-PET/CT to detect early recurrence after resection of high-risk stage III melanoma; Journal of Surgical Oncology; 2020; vol. 122 (no. 7); 1328-1336

Study Characteristics

Study type	Prospective cohort study

Study details	• Study location
	  ○ The Netherlands
	• Setting
	  ○ Single centre
	• Study dates
	  ○ Enrolled between January 2015 and December 2017

Inclusion criteria	• IIIB • IIIC

Number of participants	35
Length of follow-up	Median follow-up 33 (IQR 27-48) months
Index test(s)	PET-CT • After complete resection of disease, patients underwent a 3-monthly physical examination and assessment of serum S100B and lactate de-hydrogenase (LDH).17 If patients stayed asymptomatic and S100B was within normal values, a surveillance FDG-PET/CT scan was performed 6 months after surgery and every 6 months thereafter for 2 years, with one final scan after 3 years. So a total of five scans per patients could have been made per patient, depending on when he or she entered the surveillance protocol, but patients had to undergo at least one FDG-PET/ CT according to protocol to be included. Patients who received a FDG- PET/CT during follow-up for another indication, like restaging due to symptomatic and histologically or cytologically confirmed recurrence or for an increased serum S100B level, were excluded. Patients who participated in (neo-)adjuvant clinical trials were also excluded. • Whole body FDG-PET/CT imaging was conducted on a cross- calibrated Phillips Gemini TF time-of-flight 16 or Phillips Gemini TF big-bore PET/CT scanner (Philips, Cleveland). After fasting for 6 hours and adequate fluid intake, radioactive FDG was administered intravenously in a dosage of 180 to 240 MBq, depending on body mass index. Approximately 60 minutes after administration low-dose CT images (40 mAs, 2-5-mm slices) without intravenous contrast were obtained for attenuation correction and anatomic correlation, followed by whole body PET acquisitions with an acquisition time of 1 to 3 minutes per bed position. Abnormal FDG accumulation was evaluated according to location, size, and intensity.
Reference standard (s)	Composite • FDG-PET/CT scans were considered true positive when patients had a recurrence which was either confirmed with cytologic puncture or histologic biopsy, or sequential imaging with contrast-enhanced CT or MRI. In case of suspected recurrence on surveillance FDG-PET/CT, but no confirmation by pathology or sequential imaging, the scan was assessed as false positive (FP). In cohort 1, scans were considered true negative (TN) when patients had no recurrence within 2 months of surveillance FDG-PET/CT. When recurrence was found by physical examination but not detected by imaging or when patients suffered recurrence within 2 months after the surveillance FDG-PET/CT, the scan was considered false negative (FN). Incidental findings that were not related to melanoma were reported and assessed as TN

Participant characteristics

	Study (N = 340)
Female	60%
Median age (IQR)	60 (48-70) years
Tumour location	
Head/neck	3%
Trunk	34%
Extremities	46%
Breslow thickness >4mm	9%
Ulceration	29%
Stage IIIB	48%
Stage IIIC	52%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear blinding)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Use of composite reference standard means that some patients will have undergone more imaging than others)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Use of composite reference standard and unclear blinding)*
Overall risk of bias and directness	Directness	Directly applicable

Strobel 2007

Strobel, 2007

Bibliographic Reference	Strobel K; Skalsky J; Kalff V; Baumann K; Seifert B; Joller-Jemelka H; Dummer R; Steinert HC; Tumour assessment in advanced melanoma: value of FDG-PET/CT in patients with elevated serum S-100B.; European journal of nuclear medicine and molecular imaging; 2007; vol. 34 (no. 9)

Study Characteristics

Study type	Retrospective cohort study

Study details	Study location • Switzerland Setting • Single centre Study dates • January 2005 - January 2006
Inclusion criteria	• PET/CT during staging work-up *referred for FDG-PET/CT imaging after follow-up in accordance with Swiss national guidelines.* • high-risk melanoma *Breslow tumour thickness >4 mm, Clark level III or IV or known resected metastases in the case history* • elevated S-100B levels (>0.2 µg/l) *FDG-PET/ CT and S-100B measurement within an interval of not more than 2 weeks* • no treatment between PET/CT and tumour marker measurement • no systemic therapy before the PET/CT investigation.
Number of participants	47
Index test(s)	PET-CT All the data were acquired on a combined PET/CT in-line system (Discovery LS or Discovery ST), integrating a PET scanner (GE Advance Nxi) with a multislice helical CT (LightSpeed plus or Lightspeed 16) and permit the acquisition of co-registered CT and PET images in one session. Patients fasted for at least 4 h prior to the scanning, which started 60 min after the injection of 370–400 MBq of 18F-FDG. All patients were tested for a normal glucose level [range 80–120 mg/dl (4.4–6.7 mmol/l)] before scanning.

	Patients with elevated glucose levels were rescheduled and scanned with normal glucose levels. Oral CT contrast agent (Micropaque Scanner, Guerbet AG, Aulnay-sous-bois, France) was given 15 min before the injection of 18F-FDG. Patients were examined in the supine position. No intravenous contrast agent was given. Initially, the CT scan was acquired starting from the level of the head using the following parameters: 40 mAs, 140 kV, 0.5 s/tube rotation, slice thickness 4.25 mm, scan length 867 mm, data acquisition time 22.5 s. The CT scan was acquired during breath holding in the normal expiratory position. Immediately following the CT acquisition, a PET emission scan was acquired with an acquisition time of 3 min per cradle position with a one-slice overlap in 2D mode (matrix 128×128). The eight to nine cradle positions starting from the head to the knees resulted in an acquisition time of approximately 24–27 min. In the patients with primary tumours of the lower extremities, the scanning of the lower legs was added. The CT data were used for attenuation correction of the PET datasets and the images were reconstructed using a standard iterative algorithm (OSEM). The acquired images were viewed with software providing multiplanar reformatted images of PET alone, CT alone and fused PET/CT with linked cursors using a Xeleris workstation (GE Health Systems, Milwaukee, WI). PET/CT imaging was performed according to the recently published procedure guideline for tumour imaging with 18F-FDG PET/CT version 1.0. Lesions were interpreted as metastases if the FDG uptake was clearly greater than background. If a focal FDG-active lesion was detected, the exact anatomical localisation was determined on the fused PET/CT images. Lesions with 18F-FDG uptake in physiological sites or benign variants, e.g. muscles, brown fatty tissue or pulmonary infiltrations, were determined as benign.
Reference standard (s)	<u>Composite</u> • Lymph node or distant metastases were confirmed by a histopathological or cytological examination or other imaging modalities such as magnetic resonance imaging (MRI), PET/CT follow-up and clinical follow-up for a minimum of 6 months (range 6–18 months in all patients), including follow-up measurement of the serum S-100B. Interpretation • A false negative PET/CT diagnosis was determined if anotherimaging method (superior for the investigated region, such as brain MRI) showed metastases or if clinical findings raised the suspicion of metastases which were then

	proven by histology. A false positive PET/CT diagnosis was determined if histology of the lesion and/or clinical and PET/CT follow-up (complete disappearance of focal FDGactive lesion without therapy) ruled out metastases. FDGnegative, non-calcified lesions (for example in the lung) were determined as false positive if there was no change in lesion number or size on the follow-up PET/CT examinations 3 or 6 months later and no clinical suspicion of metastases arose >6 months after the scan.

Study-level characteristics

	Study (N =)
% Female	57.4%
Mean age (SD)	58.4 (20 to 83)

Risk of bias

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(However, note that study had restrictive inclusion criteria and only included high-risk (Breslow tumour thickness >4 mm, Clarklevel III or IV or known resected metastases in the case history) melanoma patients with elevated serum S-100B.)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(analysed by two experiencednuclear radiology physicians without knowledge of the resultsof other imaging studies or the level of serum S-100B. However, note that PET and CT result was determined by consensus instead of pre-specified criteria.)*

Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(unclear blinding when determining reference standard)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Multiple possible reference standards for confirming metastases. Participants did not all undergo each of the reference standards.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Differential use of reference standards and Index tests were confirmed by consensus rather than each reviewer judging in accordance with the pre-specified criteria, with a protocol in place for resolving conflicts.)*
	Directness	Directly applicable

Turner 2020

Turner 2020	
Bibliographic Reference	Turner, R. M., Dieng, M., Khanna, N., Nguyen, M., Zeng, J., Nijhuis, A. A., ... & Morton, R. L. (2021). Performance of long-term CT and PET/CT surveillance for detection of distant recurrence in patients with resected stage IIIA–D melanoma. *Annals of Surgical Oncology*, 1-9

Study Characteristics

Study type	Prospective cohort study
Associated papers	Dleng 2020

Study details	• Study location
	  ○ Australia
	• Setting
	  ○ (MIA) single centre
	• Study dates
	  ○ 2000 – 2017

Inclusion criteria	no evidence of disease following surgical treatment
Number of participants	332
Length of follow-up	median follow-up 61 months
Index test(s)	PET-CT 1) No imaging follow-up: No further routine imaging during follow-up. Clinical visit every 4 months for the first 3 years, every 6 months in years 4–5. Patients receive imaging if either the patient or doctor identifies signs/ symptoms suggesting recurrence 2) intensive follow-up: routine imaging every 3–4 months during the first 3 years, every 6 months in years 4–5. Clinical visit with a melanoma specialist at the time of each scan 3) Bi-annual imaging: Two PET/CT scans per year for 5 years. Clinical visit with a melanoma specialist at the time of each scan +every 3 months in between. 4) Annual imaging: One PET/CT scan per year for 5 years. Clinical visit with a melanoma specialist at the time of the scan

Reference standard (s)	Composite • The result of PET/CT imaging will be classified as true positive (TP), if metastatic disease was detected by the surveillance imaging. PET/CT findings will be defined as true negative (TN), if the scan was negative and no distant disease was detected during further follow-up. PET/CT results will be defined as false negative (FN), if the scan was negative, but recurrent disease was detected during 6-month follow-up by other tests or physical examination in clinical follow-up. PET/CT findings will be defined as false positive (FP), if the scan indicated melanoma or suspicion for melanoma, but the reference standard confirmed there was no melanoma.

Participant characteristics

	Study (N = 340)
Female	43%
Mean age (SD)	62 (8) years
Tumour location	
Head/neck	
Trunk	
Extremities	
Stage	
Extracapsular invasion	

	Study (N = 340)
Ulceration	
Breslow thickness	
LVI	
BRAF mutation	
Mitotic rate	
Previous recurrence	

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Unclear selection criteria for each of the surveillance strategies. No baseline characteristics and sample sizes are no given for any of the cohorts)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low

Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High *(index test was a strategy which allowed for surveillance scan using either CT or PET-CT, without disambiguation of these two modalities.)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Lack of clarity as to what the final reference standard is. Use of development of symptoms during follow-up as part of reference standard is not adequate as the metastasis could have developed after imaging was conducted.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Lack of clarity regarding inclusion criteria and reference standard)*
Overall risk of bias and directness	Directness	Directly applicable

Vensby 2017

Vensby, 2017

Bibliographic Reference	Vensby, P.H.; Schmidt, G.; Kjaer, A.; Fischer, B.M.; The value of FDG PET/CT for follow-up of patients with melanoma: A retrospective analysis; American Journal of Nuclear Medicine and Molecular Imaging; 2017; vol. 7 (no. 6); 255-262

Study Characteristics

Study type	Retrospective cohort study

Study details	Study location • Denmark Setting • Single institution Study dates • Jan. 1st 2009 to Dec. 31st 2011 Sources of funding • none reported
Inclusion criteria	• Melanoma • Received treatment for melanoma. It is unclear what constituted treatment. • At least 1 PET or PET/CT follow-up during 3 year period • Undergone treatment with curative intent • Unclear what constitutes treatment. Surgery is mentioned however it is not clear if this is always the case or what type of surgery. • PET/CT performed at least 3 months after surgery, either due to planned surveillance or suspected relapse • Two main cohorts of patients were included: Those who underwent imaging due to suspected relapse and those who underwent imaging follow-up due to being deemed high-risk at staging.
Exclusion criteria	PET/CT conducted earlier than 3 months after primary surgery
Number of participants	526 scans performed in 238 participants.

	121 scans were performed in the group suspected of relapse (29 due to Relapse being deemed likely based on the findings of tests conducted on another modality; 92 due to clinical suspicion of relapse). 352 scans performed during follow-up in people treated for melanoma who were deemed high risk at staging.
Loss to follow-up	15 scans in 8 participants
Index test(s)	PET-CT Timing • Patients underwent PET/CT scan either as part of surveillance following treatment or due to suspected relapse. Procedure • All patients were scanned on an integrated PET/CT scanner (Biograph TruePoint (16, 40 and 64 slice), Siemens Medical Solution, Malvern PA; Biography 64 mCT, Siemens Medical Solutions, Malvern PA or Discovery LS, 4 Slice, General Electric, Milwaukee, WI). • Patients fasted for at least 6 hours before intravenous administration of FDG. A dosage of 200-555 MBq FDG (4 MBq/kg) was administered and after 60 minutes of rest the scan was performed. PET scans were combined with a low dose CT for attenuation correction or a CT of diagnostic quality acquired at 120-140 Kilo electron volts (KeV) with or without iodine based intravenous contrast agent. • As routine, the scans are performed as a whole body examination (WB, skull base to proximal thigh), but at the discretion of the referring clinician an extended WB (from apex to toes) was performed. The attenuation corrected PET data were reconstructed iteratively using a 3D ordered-subset expectation-maximization algorithm (OSEM), for scans performed on the • Biography mCT this included point spread function and time of flight information. For initial reporting, all PET/CT scans were reviewed by a nuclear medicine physician and a radiologist. Interpretation

	• Original PET/CT reports were retrieved and reviewed by a nuclear medicine specialist blinded to other examinations and clinical follow-up. For each scan location of findinggs were registered and each finding classified as benign, equivocal or malignant and other clinically relevant findings were registered. • A true positive (TP) result was a PET/CT scan suggesting relapse, confirmed by pathology, MRI, or US within 6 months. • A false positive (FP) result was a PET/CT scan suggesting relapse, but disproved by pathology, MRI, or US within 6 months. • A true negative (TN) result was a PET/CT scan with no signs of relapse, and no relapse detected by pathology, MRI, US or at clinical follow-up for at least 6 months. • A false negative (FN) result was a PET/CT scan with no relapse, but where a relapse was later diagnosed by biopsy, MRI, US or at clinical follow-up within 6 months.
Reference standard (s)	Composite based on pathology reports, ultrasonography (US) and magnetic resonance imaging (MRI) as well as clinical follow-up for at least 6 months after PET/CT. Those with a negative PET/CT appear to have undergone less rigorous reference standard testing.

Study-level characteristics

	Study (N = 526)
% Female	50.8%
Median age (range) years	53 (11 to 89)
Tumour stage % of 238 participants; based on AJCC 8th edition	
IA	9.2%
IB	13%

	Study (N = 526)
IIA	10.9%
IIB	5.5%
IIC	3.4%
IIIA	22.7%
IIIB	16.8%
IIIC	3.4%
IV	9.2%
N/A	6.3%
Reason for referral	
Relapse likely based on another modality	5.5%
Evaluation after finding of solitary metastasis	8.7%
Treatment evaluation	1.1%
Clinical suspicion of relapse	17.5%
Planned control due to initial high-risk staging	66.9%
Patient's wish	0.2%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Retrospective review, it is likely that those selected for PET/CT screening differ from those patients not selected).*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Main analysis of those deemed at high-risk during staging, with scans conducted at follow-up: Unclear what constitutes high-risk or treatment with curative intent)* Low *(Analysis for those at risk of relapse will not be marked down for directness.)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(Imaging records were independently reviewed by two blinded nuclear medicine specialists. However, actual surveillance strategy is unclear. It is likely that the study centre were advised to use NCCN guideline for follow-up however it is unclear how much deviation an variance there was in practice.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(variance in reference standard received with some participants not having PET/CT scan confirmed during follow-up. Of those with a positive PET/CT, 75% were confirmed with histopathology and 6% were confirmed using MRI or US during follow-up. Inthe remaining 24 scans (19%) no other diagnosticconfirmation was sought, mainly due tofindings of multiple metastases clinically deemedas certain proof of relapse. Of those with a negative scan, 11% were notconfirmed or disproved based on clinical follow-up for 6 months. Unclear whether any of the tests were conducted blind to the results of other tests.)*

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low *(Note. scans were performed at least 3 months after primary surgery.)*
Overall risk of bias and directness	Risk of Bias	High *(Variance in reference standard received and unclear blinding. Study was retrospective and participants were not followed up in accordance with a standardised surveillance strategy. Time between scans and variance in frequency/intensity of imaging is unclear).*
	Directness	Partially applicable *(Main analysis of those deemed at high-risk during staging, with scans conducted at follow-up: Unclear what constitutes high-risk and what type of surgery was done. Analysis for those at risk of relapse will not be marked down for directness.)*

- 6.3 Brain metastases studies

Abdel-Rahman 2019

Abdel-Rahman, 2019

Bibliographic Reference	Abdel-Rahman, Omar; Population-based validation of the National Cancer Comprehensive Network recommendations for baseline imaging workup of cutaneous melanoma.; Melanoma research; 2019; vol. 29 (no. 1); 53-58

Study Characteristics

Study type	Retrospective cohort study

	retrospective review of prospective database
Study details	Study location Canada Setting Patients enrolled in SEER database Study dates 2010-2015
Inclusion criteria	Stage I-III melanoma complete information about TN stage and sites of metastases
Number of participants	109,971
Length of follow-up	n/a
Index test(s)	IIIC threshold for considering baseline brain imaging (I-IIIB not receiving imaging)
Reference standard (s)	Brain metastases status on record

Study-level characteristics

	Study (N = 109,971)
Female	41.2%
Non-white	5.5%
Aged <70 years	64.9%

	Study (N = 109,971)
Location	
Trunk	33.8%
Extremities	44.3%
Other	21.9%
Stage	
I-IIIB	95.9%
IIIC	4.1%

Risk of bias

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(Use of threshold as index test is inadequate as it is unclear what proportion of people across the different stages actually received brain imaging and why.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Final disease status (on record) is not an adequate reference standard. Ideally, all patients would have undergone brain imaging as to determine true status of brain metastases. NCCN guidelines to consider imaging only in IIIC means that this population is more likely to have undergone imaging.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(unclear timing of brain imaging relative to initial diagnosis.)*
Overall risk of bias and directness	Risk of Bias	High *(Limitations with index test and reference standard)*
	Directness	Directly applicable

Aukema 2010

Aukema, 2010

Bibliographic Reference	Aukema, T.S.; Valdes Olmos, R.A.; Wouters, M.W.J.M.; Klop, W.M.C.; Kroon, B.B.R.; Vogel, W.V.; Nieweg, O.E.; Utility of Preoperative 18F-FDG PET/CT and Brain MRI in Melanoma Patients with Palpable Lymph Node Metastases; Annals of Surgical Oncology; 2010; 1-6

Study Characteristics

Study type	Prospective cohort study

Study details	• Study location
	  ○ Netherlands
	  ○ Setting
	• PET/CT and brain MRI performed in melanoma patients

	• Study dates
	  ○ 2006 - 2009
	• Sources of funding
	  ○ Not reported

Inclusion criteria	• Cancer status
	  ○ Referred for imaging because of palpable and pathology-proven lymph node metastases. In these patients there were no signs of systemic metastases after the history had been taken and the physical examination had been performed.
	• Investigation status
	  ○ No other imaging modality was used prior to PET/CT.

Exclusion criteria	• Systemic Metastases ○ In these patients there were no signs of systemic metastases after the history had been taken and the physical examination had been performed.
Number of participants	70 melanoma patients
Length of follow-up	Observation period of 3 years
Loss to follow-up	not reported
Index test(s)	• FDG-PET A combined PET/CT device was used and FDG was administrated in a dosage of 180–240 MBq. PET/CT scans were performed after a fasting period of 6 hours. The body extension of the scan depended on the site of the primary lesion. Cranium or lower extremities were included only in patients with primary melanomas located in these areas. The interval between FDG administration and scanning was 60 ± 10 min. Low-dose CT images (40 mAs, 5-mm slices) were acquired without oral or intravenous contrast. PET was fused with the low-dose CT after correction for attenuation. Generated images (PET/CT, low-dose CT, and PET) were displayed using an Osirix Dicom viewer in a UNIX-based operating system and were evaluated on the basis of 2-dimensional orthogonal reslicing. PET/CT scans were reviewed by a panel of 3 experienced nuclear medicine physicians. • Brain MRI

	MRI of the brain was performed with a high-field strength 3.0 T scanner. The protocol consisted of precontrast transversal T2-weighted imaging, axial fluid attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging, and precontrast and postcontrast coronal T1-weighted 3D-FFE imaging.
Reference standard (s)	• Fine Needle Aspiration or histological biopsy where possible Proof of the nature of suspicious lesions on the PET/CT images was pursued by fine needle aspiration or histological biopsy when possible. If pathology results were not conclusive, additional images and/or the clinical course were used as the gold standard. PET/CT scans not showing metabolically active lesions (other than the involved regional lymph nodes) were considered true negative if patients remained without metastases detected by any method in the following 6 months. PET/CT was classified as false negative when the scan had been reviewed as normal but the patient developed evidence of metastatic melanoma within 6 months. True positive PET/CT scans demonstrated metastatic disease. PET/CT scans were classified as false positive if PET/CT suggested metastatic disease, but verification could not confirm dissemination within 6 months.

Study-level characteristics

	Study (N = 70)
Sample size	
% Female	45%
Mean age (SD)	58 (NR)
Primary melanoma site	
Upper extremity	6%
Lower extremity	53%
Trunk	27%
Head/neck	13%

	Study (N = 70)
Unknown primary	1%
Breslow thickness *(mm)*	3 (NR)

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(it appears that all patients who were referred and met criteria were included)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(unclear threshold for diagnosis for both FDG PET and MRI - however, this was an imaging device, therefore thresholds may be less appropriate.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(reference standard was different depending on the result of the imaging, therefore it was not interpreted in a stand-alone manner)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low *(approach to the reference standard seemed consistent, however may vary depending on the results of the imaging)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(recovery of the condition is unlikely with metastastes, deterioration is likely -*

Section	Question	Answer
		however unclear if 6 months is long enough to ensure capture of all false negatives)
Overall risk of bias and directness	Risk of Bias	Moderate
	Directness	Directly applicable

Daryanani 2005

Daryanani, 2005

Bibliographic Reference	Daryanani, Deepak; Plukker, John Th; de Jong, Mirjam A; Haaxma-Reiche, Hannie; Nap, Raoul; Kuiper, Hilde; Hoekstra, Harald J; Increased incidence of brain metastases in cutaneous head and neck melanoma.; Melanoma research; 2005; vol. 15 (no. 2); 119-24

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ The Netherlands
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ Between 1965 and 2000
	• Sources of funding
	  ○ The Groningen Melanoma Database was supported by a grant from the Research Foundation Ijsselmond, The Netherlands.

Inclusion criteria	Head / neck melanoma

Number of participants and recruitment methods	324 with head and neck melanoma 1379 additional patients with melanoma of trunk/extremities were included in tumour location analysis
Length of follow-up	median follow-up period of 24 months (range, 4–75 months)
Outcome(s) of interest	development of brain metastases. Follow-up protocol id not include laboratory controls or regularly scheduled computed tomography (CT) scans of the brain.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• tumour location • ulceration • mitotic rate
Covariates adjusted for in the multivariable regression modelling	multivariate model not reported in extractable format

Study-level characteristics

	Study (N = 324)
Female	47%
Median age (range)	57.5 (4.3 to 93.5)

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(potential for confounders)*
	Concerns for applicability for selection of participants domain	High *(stage I-IV melanoma)*

Section	Question	Answer
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(disease stage not adequately reported)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(imaging of the brain was not routine during follow-up. Unclear protocol for offering brain imaging.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(Multivariate model not reported in extractable format and did not include all predictors.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Potential for confounders not adequately adjusted for. Poor reporting for specific prognostic factors of relevant to this review. Unclear when brain imaging would have been conducted and this likely differed across the long time span of the study.)*
	Concerns for applicability	Moderate *(I-III melanoma)*

Frankel 2014

Frankel, 2014

Bibliographic Reference	Frankel, Timothy L; Bamboat, Zubin M; Ariyan, Charlotte; Coit, Daniel; Sabel, Michael S; Brady, Mary S; Predicting the development of brain metastases in patients with local/regional melanoma.; Journal of surgical oncology; 2014; vol. 109 (no. 8); 770-4

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Memorial Sloan-Kettering Cancer Center (MSKCC) and the University of Michigan Medical Center (UMMC).
	• Study dates
	  ○ unclear
	• Sources of funding
	  ○ none

Inclusion criteria	• Stage I-III melanoma • Developed distant metastases during follow-up ○ With or without brain mets
Exclusion criteria	Stage IV at time of diagnosis uveal or mucosal melanoma
Number of participants and recruitment methods	607
Length of follow-up	up to 10 years
Outcome(s) of interest	Development of brain metastases during follow-up up to 10 years. Routine CNS imaging was not employed, however, brain imaging (usually MRI) was routinely performed in patients diagnosed with stage IV disease.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age • Primary tumour location • Stage

	• Ulceration
Covariates adjusted for in the multivariable regression modelling	multivariate model conducted but results were not presented in extractable format

Study-level characteristics

	Study (N = 607)
Female	31.6%
Tumour stage	
I-II	50.1%
III	49.9%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	High *(potential for confounders)*
	Concerns for applicability for selection of participants domain	High *(Included people with stage I-III at diagnosis)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(multivariate model not reported in extractable format)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Inadequate adjustment for potential confounders)*
	Concerns for applicability	Partially applicable *(I-III at diagnosis)*

Haydu 2020

Haydu, 2020

Bibliographic Reference Haydu, L.E.; Lo, S.N.; McQuade, J.L.; Amaria, R.N.; Wargo, J.; Ross, M.I.; Cormier, J.N.; Lucci, A.; Lee, J.E.; Ferguson, S.D.; Saw, R.P.M.; Spillane, A.J.; Shannon, K.F.; Stretch, J.R.; Hwu, P.; Patel, S.P.; Diab, A.; Wong, M.K.K.; Glitza Oliva, I.C.; Tawbi, H.; Carlino, M.S.; Menzies, A.M.; Long, G.V.; Lazar, A.J.; Tetzlaff, M.T.; Scolyer, R.A.; Gershenwald, J.E.; Thompson, J.F.; Davies, M.A.; Cumulative incidence and predictors of CNS metastasis for patients with American Joint Committee on Cancer 8th Edition stage III melanoma; Journal of Clinical Oncology; 2020; vol. 38 (no. 13); 1429-1441

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected data
Study details	• Study location ○ USA/Australia • Study setting

	○ Clinicopathologic data were extracted from the melanoma clinical research databases of The University of Texas MD Anderson Cancer Center (MD Anderson) and Melanoma Institute Australia (MIA). • Study dates ○ 1998 - 2014
Inclusion criteria	• Aged 16 years or older • Stage III melanoma ○ AJCC 8th edition stage III melanoma arising from either an identifiable but previously untreated primary cutaneous tumor or an unknown primary site, with sufficient information to determine pathologic stage group (IIIA, IIIB, IIIC, or IIID). • Negative CNS imaging at baseline ○ including computed tomography (CT) and/or MRI of the brain, and/or positron emission tomography/CT of the whole body, within 4 months of diagnosis.
Number of participants and recruitment methods	1,918
Outcome(s) of interest	Development of brain metastases up 10 years
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Stage III substage • mitotic rate • Gender • age
Covariates adjusted for in the multivariable regression modelling	all factors were entered into multivariate model

Study-level characteristics

	Study (N = 1,918)
% Female	35.2%
Median age (range)	56 (16 to 95) years
Stage AJCC 8th ed.	
IIIA	22.2%
IIIB	28.8%
IIIC	44.7%
IIID	4.4%
melanoma subtype	
superficial spreading	34.4%
nodular	31.8%
Acral	5.8%
Other	4.6%
Unknown	23.4%
Median (range) Breslow thickness	2.7 (0.1 to 50) mm
% ulcerated	34.6%

	Study (N = 1,918)
17% N/A or unknown	
Location	
Scalp	6.1%
Head/neck melanoma	9.1%
Trunk	35.8%
Extremities	33.6%
Unknown	15.4%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Potential for confounders due to using database data)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Huismans 2014

Huismans, 2014

Bibliographic Reference	Huismans, Anna M; Haydu, Lauren E; Shannon, Kerwin F; Quinn, Michael J; Saw, Robyn P M; Spillane, Andrew J; Stretch, Jonathan R; Thompson, John F; Primary melanoma location on the scalp is an important risk factor for brain metastasis: a study of 1,687 patients with cutaneous head and neck melanomas.; Annals of surgical oncology; 2014; vol. 21 (no. 12); 3985-91

Study Characteristics

Study design	Retrospective cohort study Review of prospectively collected data

Study details	• Study location
	  ○ Austrailia
	• Study setting
	  ○ Melanoma Institute Australia database
	• Study dates
	  ○ 1980 - 2000

Inclusion criteria	• Melanoma diagnosis • AJCC stage I-II

Exclusion criteria	• Without follow-up data • Aged <14 years
Number of participants and recruitment methods	4,824 patients had sufficient follow-up for inclusion(main analyses conducted were on subgroup of patients with head/neck melanoma, n= 801)
Length of follow-up	At least 10 years, or had brain metastases within 10 years
Loss to follow up	Only 4,824 patients out of the original 12,751 patients had sufficient follow-up for inclusion in the risk review
Outcome(s) of interest	Development of brain metastases during follow-up
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Primary tumour location • Gender • T-stage • Ulceration • Breslow thickness • Mitotic rate
Covariates adjusted for in the multivariable regression modelling	Site, ulceration and t-stage were adjusted for in multivariate modelling

Arm-level characteristics

	HNM (N = 1687)	**TLM (N = 8795)**
Ulceration	20.5%	17.0%
T-stage		

		HNM (N = 1687)	TLM (N = 8795)
	t1	35.2%	46.5%
	t2	23.2%	24.3%
	t3	22.1%	16.0%
	t4	14.3%	7%
Mitotic rate <1		15.4%	18.4%
Female		35.3%	49.2%

Risk of bias

Section	Question	Answer
Selection of participants	Concerns for applicability for selection of participants domain	Low *(Exclusion criteria were applied to restrict bias (such as ensuring minimal length of follow-up, and disease stages to I-II only). However, it is possible that this will limit the generalisability of the included cohort.)*
Predictors or their assessment	Concerns for applicability for predictors or their assessment domain	High *(Moderately high proportion of patients (~20%) had missing data for the predictors ulceration and mitotic rate.)*
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Unclear *(Unclear protocol for follow-up during the study period)*

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	High *(Not all predictors entered into the multivariate model. Event data reported for all patients (including those deemed to have insufficient follow-up))*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Unclear follow-up protocol. Multivariate model did not adjust for all predictors. Univariate data not sufficiently reported.)*
	Concerns for applicability	Partially applicable *(participants were stage I-II)*

Lewin 2018

Lewin, 2018

Bibliographic Reference	Lewin, J.; Sayers, L.; Kee, D.; Walpole, I.; Sanelli, A.; Te Marvelde, L.; Herschtal, A.; Spillane, J.; Gyorki, D.; Speakman, D.; Estall, V.; Donahoe, S.; Pohl, M.; Pope, K.; Chua, M.; Sandhu, S.; McArthur, G.A.; McCormack, C.J.; Henderson, M.; Hicks, R.J.; Shackleton, M.; Surveillance imaging with FDG-PET/CT in the post-operative follow-up of stage 3 melanoma; Annals of Oncology; 2018; vol. 29 (no. 7); 1569-1574

Study Characteristics

Study type	Retrospective cohort study Although patients underwent prospective application of imaging surveillance, data were collected retrospectively and relied on clinical and imaging reports.
Study details	• Study location ○ Australia • Setting

	• Patients were identified from the institutional PET database.
	  ○ Study dates
	• 2009 to 2016
	• Sources of funding
	  ○ None declared

Inclusion criteria	• Cancer status • Proven melanoma • Investigation status • undergone a PET scan between 2009 and 2016

Exclusion criteria	• Relapse
	  ○ relapse before planned surveillance
	• Surveillance
	  ○ substantial deviation from recommended surveillance
	• Tumour type
	  ○ mucosal or uveal melanoma
	• Stage
	  ○ Stage 2 or 4 disease

Number of participants	170
Length of follow-up	retrospective - patients with a PET between 2009 and 2016 (7 years of observation)
Loss to follow-up	not applicable
Index test(s)	• FDG-PET

	After fasting, patients were injected with 3.6 MBq/kg (610%) of FDG and rested for 60min. Patients were scanned from vertex to proximal thighs unless the primary lesion was in a lower limb, in which case the scan was extended. A CT was acquired for attenuation correction and anatomical localization using 120 kV, 40-130 SMART mA, pitch 1.35, slice thickness 3.75mm and rotation time 0.5 s. The PET was acquired at 3 min per bed step.
Reference standard (s)	• Histological, radiological, or treatment with antimelanoma therapy True positive (TP) imaging relapses were confirmed histologically or radiologically, or treated with antimelanoma therapy. False positive (FP) findings were suspicious of melanoma relapse but found to be histologically benign or non-progressive on serial scans. Incidental findings unrelated to melanoma were negative results. True negative (TN) findings indicated melanoma non-recurrence at subsequent time points. Imaging findings were false negative (FN) if disease recurrence was confirmed subsequently at defined time points.

Study-level characteristics

	Study (N = 170)
% Female	36.5%
Mean age (SD)	61 (range: 21-83)
Stage	
3A	20%
3B	55%
3C	25%
Primary site	
Head and neck	21%
Lower limb	20%

	Study (N = 170)
Trunk	24%
Upper limb	19%
Unknown	16%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(however, one of the exclusion criteria was "inadequate documentation", this had an unclear definition)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(it is unclear if true positives were always confirmed without knowledge of reference standard (e.g. other radiological techniques or histology))*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(the reference standard was poorly defined and seemed to include histological, radiological techniques, or being treated with anti-melanoma therapy. Unclear if reference standard was interpreted without knowledge of the reference standard.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	High *(reference standard was vague and may differ between participants)*

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	High *(Unclear if there was an appropriate interval between the index test and reference standard, reference standard appeared influenced by index test and was not the same in every case,)*
Overall risk of bias and directness	Risk of Bias	High
	Directness	Partially applicable *(no brain-specific investigation was studied)*

Peuvrel 2014

Peuvrel, 2014

Bibliographic Reference Peuvrel, L; Saint-Jean, M; Quereux, G; Brocard, A; Khammari, A; Knol, A C; Dreno, B; Incidence and characteristics of melanoma brain metastases developing during treatment with vemurafenib.; Journal of neuro-oncology; 2014; vol. 120 (no. 1); 147-54

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ France
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ November 2010 - November 2013
	• Sources of funding
	  ○ None

Inclusion criteria	• Melanoma diagnosis • Treated with vemurafenib ○ The initial dose of vemurafenib was 960 mg twice daily, with adaptation in case of toxicity according to the recommendations of the Summary of Product Characteristics. • BRAF-V600 mutation
Exclusion criteria	• melanomas with brain involvement before treatment initiation • The absence of the first assessment scan in patients treated for less than 2 months
Number of participants and recruitment methods	86
Length of follow-up	9-month median follow-up (1–26 months)
Outcome(s) of interest	development of brain metastases during treatment
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• histological type • breslow thickness • Ulceration • Unknown primary melanoma • no. previous therapeutic lines • no. metastatic sites at time of starting treatment
Covariates adjusted for in the multivariable regression modelling	None

Arm-level characteristics

	With brain metastases (N = 17)	**Without brain metastases (N = 69)**
Ulceration		

	With brain metastases (N = 17)	Without brain metastases (N = 69)
Mean age (SD)	55 (11.3) years	59.6 (7.3) years
Mean Breslow thickness (SD)	3.7 mm (3.7)	4.8 mm (4)
Condition status X		
Mean number of previous therapeutic lines	0.41 (0.71)	0.54 (1.02)
Mean number of metastatic sites at vemurafenib initiation	3.18 (1.7)	2.28 (1.22)

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Patients underwent systematic tumor assessment through brain, chest, abdominal and pelvic scan before vemurafenib initiation, at month 2, and every 3 months thereafter. Brain imaging was also performed at the onset of neurological symptoms. Diagnosis of brain metastases was based on scan findings, sometimes completed with a MRI in case of doubt or stereotactic radiotherapy indication)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for confounders.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(no adjustment for confounders)*
	Concerns for applicability	Low

Qian 2013

Qian, 2013

Bibliographic Reference	Qian, Meng; Ma, Michelle W; Fleming, Nathaniel H; Lackaye, Daniel J; Hernando, Eva; Osman, Iman; Shao, Yongzhao; Clinicopathological characteristics at primary melanoma diagnosis as risk factors for brain metastasis.; Melanoma research; 2013; vol. 23 (no. 6); 461-7

Study Characteristics

Study design	Prospective cohort study
Study details	• Study location

	○ USA • Study setting ○ New York University Medical Center, enrolled in either the Melanoma Cooperative Group (MCG) (November 1972–November 1982) [12] or the Interdisciplinary Melanoma Cooperative Group (IMCG) (August 2002–December 2009)
Inclusion criteria	Cutaneous melanoma stage I-IV
Number of participants and recruitment methods	2,341
Length of follow-up	patients were followed through October 1993 and December 2011, for cohorts 1 and 2 respectively. Median follow-up 98 months
Outcome(s) of interest	development of brain metastases during follow-up
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • ulceration • stage mitosis • location

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Potential for confounders. Treatment received was not accounted for. The two cohorts are separated by large time periods however results are presented separately for each.)*
	Concerns for applicability for selection of participants domain	High *(Stage I-III)*

Section	Question	Answer
Predictors or their assessment	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(unclear protocol for detecting brain mets)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(multivariate analysis conducted for brain metastasis-free survival but not for development of brain metastases)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Potential for confounders not adequately adjusted for. Unclear follow-up protocol)*
	Concerns for applicability	Partially applicable *(Stage I-III)*

Samlowski 2017

Samlowski, 2017

Bibliographic Reference	Samlowski, Wolfram E; Moon, James; Witter, Merle; Atkins, Michael B; Kirkwood, John M; Othus, Megan; Ribas, Antoni; Sondak, Vernon K; Flaherty, Lawrence E; High frequency of brain metastases after adjuvant therapy for high-risk melanoma.; Cancer medicine; 2017; vol. 6 (no. 11); 2576-2585

Study Characteristics

Study design	Retrospective cohort study

	retrospective review of study records from a large prospective randomized multi-institutional clinical trial

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ participants in the Southwest Oncology Group S0008 RCT which randomized patients to receive either HDI or biochemotherapy consisting of dacarbazine, cisplatin, vinblastine, interleukin-2, IFN alfa-2b (IFN--2b) and granulocyte colony-stimulating factor given every 21 days for three cycles.
	• Study dates
	  ○ Patient accrual took place between 1 August 2000 and 15 November 2007

Inclusion criteria	• IIIAN2a-IIIC disease
	  ○ adequate wide excision of the primary
	• SLNB
	  ○ Sentinel lymph node biopsy was required. A complete regional lymphadenectomy was performed if there was any lymph node involvement.
	• Adequate Zubrod performance 0–1, adequate renal, hepatic, hematologic, cardiac, and pulmonary function testing were also required.
	• Baseline brain CT/MRI imaging
	• Baseline CT or MRI brain imaging was required and it was suggested that this be repeated every 3 months during protocol participation

Exclusion criteria	resected or active distant metastases
Number of participants and recruitment methods	402
Length of follow-up	Suggested patient imaging included a brain CT or MRI every 3 months. Use of contrast for imaging was not specified in study protocol. Surviving patients were followed up for 10 years.
Outcome(s) of interest	Development of brain metastases

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration • Tumour site • Metastases • stage
Covariates adjusted for in the multivariable regression modelling	none

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	Low *(study used data from an RCT trial.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(Note. Analysis for ulceration will be marked down once due to high level or missing data.)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Suggested patient imaging included a brain CT or MRI every 3 months)*
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	Low *(Study used data from an RCT. Treatments arms did not significantly differ in the development of brain metastases)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Wang 2014

Wang, 2014

Bibliographic Reference	Wang, Jennifer; Wei, Caimiao; Noor, Rahat; Burke, Anahit; McIntyre, Susan; Bedikian, Agop Y; Surveillance for brain metastases in patients receiving systemic therapy for advanced melanoma.; Melanoma research; 2014; vol. 24 (no. 1); 54-60

Study Characteristics

Study design	Retrospective cohort study
Associated papers	Davies 2005

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Institutional Review Board-approved clinical trials of systemic therapies from 1986 to 2004 in the Department of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center
	• Study dates
	  ○ 1986 - 2004

Inclusion criteria	• Stage IV melanoma • chemotherapy naive
Number of participants and recruitment methods	685
Outcome(s) of interest	Development of brain metastases: All patients underwent staging MRI or computed tomography scans, including scans of the brain, every 6 weeks as part of the study protocols. Incidence of brain metastases: reported in 12-week periods up to 60 weeks.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Site of primary melanoma • Breslow thickness • Stage (within stage IV) • Number of distant metastatic sites • LDH • Presence of liver metastases
Covariates adjusted for in the multivariable regression modelling	Model 1: adjusted for site of primary melanoma and number of metastatic sites Model 2: adjusted for site of primary melanoma and stage at diagnosis

Study-level characteristics

	Study (N = 685)
% Female	35.0%
Median age (range)	47 (18 to 78)

	Study (N = 685)
% brain metastases	46%
Site of primary tumour	
head and neck	17.2%
Trunk	42%
extremities	23.6%
Breslow thickness	
≤2	9.9%
2-4	23.1%
>4	34.6%
IV sub-stage at diagnosis	
M1a	20.6%
M1b	22.5%
M1c	56.9%
Number of distant metastatic sites	
None	20%
1 site	43.2%

	Study (N = 685)
>1 site	36.8%
% elevated LDH	36.6%
% with liver metastases	30.4%

Risk of bias

Section	Question	Answer
Selection of participants	Concerns for applicability for selection of participants domain	High *(Participants were recruited from numerous clinical trials. All participants were chemotherapy naive and stage IV at time of diagnosis however treatments received during the trial differed.)*
Predictors or their assessment	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low *(Prespecified and detailed protocol for follow-up scans for brain metastases)*
Analysis	Overall risk of bias for analysis domain	High *(treatments received were not controlled for)*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(potential for confounders not adequately adjusted for)*
	Concerns for applicability	Low

Zhang 2019

Zhang, 2019

Bibliographic Reference	Zhang, Dongxiao; Wang, Zhe; Shang, Dongping; Yu, Jinming; Yuan, Shuanghu; Incidence and prognosis of brain metastases in cutaneous melanoma patients: a population-based study.; Melanoma research; 2019; vol. 29 (no. 1); 77-84

Study Characteristics

Study design	Retrospective cohort study Review of prospectively collected SEER database

Study details	• Study location
	  ○ International
	• Study setting
	  ○ SEER database
	• Study dates
	  ○ 2010 – 2015

Inclusion criteria	• Melanoma diagnosis • Known brain metastasis status
Number of participants and recruitment methods	116,119
Outcome(s) of interest	Presence of brain metastases at baseline
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender (male vs. female) • Age (≤40, 40-60, 60-80, ≥80) • Race • Marital status • Insurance status

	• Primary site • Histologic type • T-stage • N-stage (for baseline BM analysis only) • Ulceration (for baseline BM analysis only) • extracranial metastasis sites (for baseline BM analysis only) • Surgery (for overall survival analysis only) • no. extracranial metastases (for overall survival analysis only)
Covariates adjusted for in the multivariable regression modelling	All univariate factors were entered into the multivariate model
Additional comments	Subgroup analysis available for those participants with metastatic disease

Study-level characteristics

	Study (N = 116,119)
% Female	37.7%
% brain metastases	1.3%

Risk of bias

Section	**Question**	**Answer**
Selection of participants	Overall risk of bias for selection of participants domain	Low *(Not all patients had known brain metastases status and were excluded from the analysis however this was a small proportion of the original cohort.)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	High *(multiple predictors had high degree of missing data.)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Concerns for applicability for outcome or its determination domain	Unclear *(Unclear protocol for screening for brain metastases)*
Analysis	Overall risk of bias for analysis domain	Low *(multivariate analysis conducted adjusting for all predictor variables, for both outcomes)*
Overall Risk of bias and Applicability	Risk of bias	High *(important confounders such as disease stage, time of scan and treatment received were not captured by database. Lack of clarity surrounding protocol for offering brain scan.)*
	Concerns for applicability	Low

Zukauskaite 2013

Zukauskaite, 2013

Bibliographic Reference	Zukauskaite, Ruta; Schmidt, Henrik; Asmussen, Jon T; Hansen, Olfred; Bastholt, Lars; Asymptomatic brain metastases in patients with cutaneous metastatic malignant melanoma.; Melanoma research; 2013; vol. 23 (no. 1); 21-6

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ Denmark
	• Study setting
	  ○ Two university hospitals
	• Study dates
	  ○ Between 1995 and 2009

Inclusion criteria	• metastatic skin melanoma referred to first-line IL-2-based immunotherapy • Asymptomatic for brain metastases
Number of participants and recruitment methods	763
Length of follow-up	None
Outcome(s) of interest	Asymptomatic brain metastases at time of starting IL-2 therapy. contrast-enhanced CT brain was given to all patients.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Location
Covariates adjusted for in the multivariable regression modelling	None

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	Low
	Concerns for applicability for selection of participants domain	Unclear *(Unclear disease stage - likely stage IV)*
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all patients underwent screening for brain metastases)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no multivariate modelling however cohort was very specific.)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

- 6.4 Surveillance strategies for stage IV (and unresectable stage III) disease

CHECKMATE-037

CHECKMATE-037

Bibliographic Reference	Larkin, James; Minor, David; D'Angelo, Sandra; Neyns, Bart; Smylie, Michael; Miller, Wilson H Jr; Gutzmer, Ralf; Linette, Gerald; Chmielowski, Bartosz; Lao, Christopher D; Lorigan, Paul; Grossmann, Kenneth; Hassel, Jessica C; Sznol, Mario; Daud, Adil; Sosman, Jeffrey; Khushalani, Nikhil; Schadendorf, Dirk; Hoeller, Christoph; Walker, Dana; Kong, George; Horak, Christine; Weber, Jeffrey; Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2018; vol. 36 (no. 4); 383-390

Study details

Trial registration number and/or trial name	CheckMate 037 trial NCT01721746
Study type	Randomised controlled trial (RCT)
Study location	Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, UK, US
Study setting	Multicentre
Study dates	2012 - 2016
Sources of funding	The study was funded by Bristol-Myers Squibb.
Inclusion criteria	Age • 18 years or older Melanoma • histologically confirmed, unresectable stage IIIC or IV metastatic melanoma Eastern Cooperative Oncology Group performance status (ECOG PS) • 0 or 1

	Progressed after anti-CTLA-4 treatment • BRAF wild-type tumours patients must have had progression after anti-CTLA-4 treatment, such as ipilimumab • $BRAFV^{600}$ mutation-positive tumour patients must have had progression on anti-CTLA-4 treatment and a BRAF inhibitor
Exclusion criteria	• Active brain metastases • Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies • Those who had grade 4 toxic effects • Used infliximab to manage adverse events from previous ipilimumab treatment • Patients with a primary ocular melanoma
Intervention(s)	Nivolumab
Comparator	Investigator's choice chemotherapy (either dacarbazine or carboplatin plus paclitaxel)
Outcome measures	• Progression free survival o Defined as the time from randomization to first documented disease progression as determined by the independent radiological review committee • Overall survival o Defined as the time from randomisation to death • Health related quality of life o Assessed at baseline, every cycle (ICC), or every other cycle (nivolumab) for the first 6 months, then every 6 weeks and at follow-up and survival visits; assessments were EORTC QLQ-C30 version 3 and EuroQoL EQ-5D summary index and visual analog scale. • Serious adverse events
Subgroup analysis	Melanoma stage Overall survival at 2 years follow-up was reported by melanoma stage • M0 • M1A

	• M1B • M1C
Number of participants	405
Duration of follow-up	2 years
Loss to follow-up	1

Study arms

Nivolumab (N = 272) 3 mg/kg every 2 weeks
Investigator's choice chemotherapy (N = 133) either dacarbazine 1000 mg/m² every 3 weeks or carboplatin area under the curve 6 plus paclitaxel 175 mg/m² every 3 weeks, by intravenous infusion

Participant characteristics

	Nivolumab (N = 272)
% Female	35%
Median age (range)	59 (23-88)
Stage M1c at study entry	75%
AJCC stage IV at study entry	96%

	Nivolumab (N = 272)
History of brain metastases	20%
BRAF mutant	22%
Tumour size at baseline	96 (10-422) mm
Number of previous systemic treatments In metastatic disease setting	
1	28%
2	51%
>2	21%
Type of previous treatment In metastatic disease setting	
Ipilimumab	99%
Vemurafenib	18%
Chemotherapy	53%
Other immunotherapy Excluding previous ipilimumab treatment (documented previous interferon α2a and b, interleukin 2 and 21, and T-cell infusion immunotherapies)	14%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data were only extracted from the nivolumab arm ensuring all patients received the same treatment).*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

CHECKMATE-064

CHECKMATE-064

Bibliographic Reference	Weber, Jeffrey S; Gibney, Geoff; Sullivan, Ryan J; Sosman, Jeffrey A; Slingluff, Craig L Jr; Lawrence, Donald P; Logan, Theodore F; Schuchter, Lynn M; Nair, Suresh; Fecher, Leslie; Buchbinder, Elizabeth I; Berghorn, Elmer; Ruisi, Mary; Kong, George; Jiang, Joel; Horak, Christine; Hodi, F Stephen; Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial.; The Lancet. Oncology; 2016; vol. 17 (no. 7); 943-955

Study details

Trial registration number and/or trial name	CheckMate 064 NCT01783938
Study type	Randomised controlled trial (RCT)
Study location	US
Study setting	Academic medical centres
Study dates	2013 - 2020
Sources of funding	Bristol-Myers Squibb
Inclusion criteria	Age • at least 18 years of age Melanoma • histologically confirmed unresectable stage III or stage IV melanoma Eastern Cooperative Oncology Group performance status (ECOG PS)

	• 0 or 1 Know BRAF mutation status or consent to BRAFV600E mutation testing during the screening period Measurable disease by CT or MRI scan • within 28 days prior to randomisation as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria Previously untreated or had progressed after no more than one previous systemic therapy Criteria for determining progression on previous systemic therapy were based on investigator-assessed radiographic imaging Suitable lesions available for biopsies at baseline and at week 13 (eg, assessment of PD-L1)
Exclusion criteria	Active brain metastases Previous treatment with anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies Active autoimmune disease Condition requiring corticosteroids or immunosuppressive medication
Intervention(s)	Nivolumab followed by ipilimumab
Comparator	Ipilimumab followed by nivolumab
Outcome measures	Overall survival
Subgroup analysis	Melanoma stage Overall survival by melanoma stage at study entry • M1a/M1b • M1c

Number of participants	140
Duration of follow-up	2 years
Loss to follow-up	Not reported
Additional comments	The time interval between drug sequences was 2 weeks for nivolumab followed by ipilimumab whereas it was 3 weeks for ipilimumab followed by nivolumab (dosing intervals were different for the two strategies because the agents have different frequencies of administration). After induction, all patients in both groups who completed the second induction period with the second immunotherapy agent and had clinical benefit were eligible to enter the continuation period and receive nivolumab 3 mg/kg every 2 weeks for up to 2 years or longer until progression, unacceptable toxicity, or withdrawal of consent.

Study arms

Nivolumab followed by ipilimumab (N = 70)
Nivolumab at 3 mg/kg as a 60-min intravenous infusion every 2 weeks for up to six doses during weeks 1 to 13 in the first induction period, followed by a planned switch to ipilimumab 3 mg/kg as a 90-min intravenous infusion every 3 weeks for up to four doses during weeks 13–25 in the second induction period

Duration of follow-up	Median follow-up in the nivolumab followed by ipilimumab group was 19.8 months (IQR 12.8–25.7)

Ipilimumab followed by nivolumab (N = 70)
Ipilimumab 3 mg/kg as a 90-min intravenous infusion every 3 weeks for up to four doses during weeks 1 to 13 in the first induction period, followed by a planned switch to nivolumab at 3 mg/kg as a 60-min intravenous infusion every 2 weeks for up to six doses during weeks 13–25 in the second induction period

Duration of follow-up	Median follow-up in the ipilimumab followed by nivolumab group was 14.7 months (5.6–23.9)

Arm-level characteristics

	Nivolumab followed by ipilimumab (N = 70)	Ipilimumab followed by nivolumab (N = 70)
% Female	32%	34%
Mean age (SD)	60.5 (46.5-70)	63 (52-73)
AJCC stage at study entry		
III	9%	17%
IV	91%	83%
M stage		
M0	0%	4%
M1a	4%	10%
M1b	21%	11%
M1c	66%	61%
Not reported	9%	13%
BRAF status		
BRAFV600E mutant	28%	29%
Wild type	65%	61%
Not reported	7%	10%

	Nivolumab followed by ipilimumab (N = 70)	Ipilimumab followed by nivolumab (N = 70)
History of brain metastases		
Yes	13%	3%
No	78%	86%
Not reported	9%	11%
Any previous systemic therapy for metastatic disease	15%	11%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data are presented separately for the two arms, allowing for evaluation of the effect of treatment on each risk factors predictive ability. Data for the two arms were combined for the purposes of this analysis).*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

CHECKMATE-067

CHECKMATE-067

Bibliographic Reference	Larkin, James; Chiarion-Sileni, Vanna; Gonzalez, Rene; Grob, Jean-Jacques; Rutkowski, Piotr; Lao, Christopher D; Cowey, C Lance; Schadendorf, Dirk; Wagstaff, John; Dummer, Reinhard; Ferrucci, Pier F; Smylie, Michael; Hogg, David; Hill, Andrew; Marquez-Rodas, Ivan; Haanen, John; Guidoboni, Massimo; Maio, Michele; Schoffski, Patrick; Carlino, Matteo S; Lebbe, Celeste; McArthur, Grant; Ascierto, Paolo A; Daniels, Gregory A; Long, Georgina V; Bastholt, Lars; Rizzo, Jasmine I; Balogh, Agnes; Moshyk, Andriy; Hodi, F Stephen; Wolchok, Jedd D; Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma.; The New England journal of medicine; 2019; vol. 381 (no. 16); 1535-1546

Study details

Trial registration number and/or trial name	CheckMate 067 trial NCT01844505
Study type	Randomised controlled trial (RCT)
Study location	Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Spain, Sweden, Switzerland, UK, US
Study setting	Multicentre
Study dates	2013 - 2018
Sources of funding	This study was funded by Bristol-Myers Squibb (Princeton, NJ, USA).

Inclusion criteria	• Age
	  ○ 18 years or older
	• Melanoma
	  ○ histologically confirmed, unresectable stage III or stage IV metastatic melanoma
	• No prior systemic therapy for advanced disease
	• Eastern Cooperative Oncology Group performance status (ECOG PS)
	  ○ 0 or 1
	• Know BRAF mutation status (WT or M)
	• Measurable disease by CT or MRI scan

	• in accordance with Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 • Sufficient tumour tissue available for biomarker analyses • assessment of PD-L1 expression
Exclusion criteria	• Active brain metastases • Pregnancy or breastfeeding • Leptomeningeal metastases • Ocular melanoma • mucosal melanoma was allowed • Active autoimmune disease • Condition requiring corticosteroids or immunosuppressive medication ○ within 14 days of study drug administration
Intervention(s)	Nivolumab plus ipilimumab
Comparator	Nivolumab plus ipilimumab-matched placebo Ipilimumab plus nivolumab-matched placebo

Outcome measures	• Progression free survival
	  ○ defined as time from randomisation to progression or death from any cause, whichever occurred first
	• Overall survival
	  ○ defined as time from randomisation to death from any cause
	• Health related quality of life
	  ○ HRQoL was collected, as available, in all randomised patients and assessed at weeks 1 and 5 of each 6-week cycle for the first 6 months and then once every 6 weeks thereafter as well as at two visits in the follow-up period. Secondary end-point assessment was European Organisation for Research and Treatment of Cancer

	(EORTC) QLQ-C30 Questionnaire Version 3; European Quality of Life-5 Dimensions (EQ-5D) Summary Index and Visual Analogue Scale (VAS). • Serious adverse events

Subgroup analysis	• Melanoma stage
	• Progression free survival and overall survival at 5 years follow-up were reported by melanoma stage
	  • M0/M1a/M1b
	  • M1c

Number of participants	945
Duration of follow-up	5 years
Additional comments	Previous adjuvant or neoadjuvant treatment for melanoma was allowed if it was completed at least 6 weeks before randomisation, and all treatment-related adverse events had either returned to baseline or had stabilised.

Study arms

Nivolumab plus ipilimumab (N = 314)
intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses (induction phase), then nivolumab 3 mg/kg every 2 weeks

Duration of follow-up	Median follow-up was 54.6 months
Loss to follow-up	None

Nivolumab plus ipilimumab-matched placebo (N = 316)
intravenous nivolumab 3 mg/kg every 2 weeks plus ipilimumab-matched placebo

Duration of follow-up	Median follow-up was 36.0 months
Loss to follow-up	1

Ipilimumab plus nivolumab-matched placebo (N = 315)
intravenous ipilimumab 3 mg/kg every 3 weeks for four doses plus nivolumab-matched placebo

Duration of follow-up	Median follow-up was 18.6 months
Loss to follow-up	None

Arm-level characteristics

	Nivolumab plus ipilimumab (N = 314)	Nivolumab plus ipilimumab-matched placebo (N = 316)	Ipilimumab plus nivolumab-matched placebo (N = 315)
% Female	34%	36%	36%
Mean age (SD)	Median 61 years (range 18 to 88)	Median 60 years (range 25 to 90)	Median 62 years (range 18 to 89)
M stage			
M1c	58%	58%	58%
M0, M1a, or M1b	42%	42%	42%
Brain metastases at baseline			
Yes	4%	2%	5%

	Nivolumab plus ipilimumab (N = 314)	Nivolumab plus ipilimumab-matched placebo (N = 316)	Ipilimumab plus nivolumab-matched placebo (N = 315)
No	97%	98%	95%
BRAF status			
Mutant	32%	32%	31%
Wild-type	68%	68%	69%
Sum of reference diameters of target lesions (mm)	Median 54.5 (range 10 to 372)	Median 54.0 (range 10 to 384)	Median 55.0 (range 10 to 283)
Number of lesion sites			
1	28%	25%	27%
2-3	53%	56%	54%
≥3	19%	19%	19%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*

Section	Question	Answer
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data re presented separately for the three arms, allowing for evaluation of the effect of treatment on each risk factors predictive ability. Data for the three arms were combined for the purposes of this analysis).*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

COLUMBUS

COLUMBUS trial

Bibliographic Reference	Ascierto, Paolo A; Dummer, Reinhard; Gogas, Helen J; Flaherty, Keith T; Arance, Ana; Mandala, Mario; Liszkay, Gabriella; Garbe, Claus; Schadendorf, Dirk; Krajsova, Ivana; Gutzmer, Ralf; de Groot, Jan Willem B; Loquai, Carmen; Gollerkeri, Ashwin; Pickard, Michael D; Robert, Caroline; Update on tolerability and overall survival in COLUMBUS: landmark analysis of a randomised phase 3 trial of encorafenib plus binimetinib vs vemurafenib or encorafenib in patients with BRAF V600-mutant melanoma.; European journal of cancer (Oxford, England : 1990); 2020; vol. 126; 33-44

Study details

Trial registration number and/or trial name	COLUMBUS trial NCT01909453
Study type	Randomised controlled trial (RCT)
Study location	Argentina, Australia, Brazil, Canada, Colombia, Czechia, France, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Mexico, Netherlands, Norway, Poland, Portugal, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, Switzerland, Turkey, UK, US
Study setting	Multicentre
Study dates	2013 - 2018
Sources of funding	This study was sponsored by Pfizer Inc. (formerly Array BioPharma, Inc).
Inclusion criteria	• Age ○ at least 18 years of age • Melanoma

	○ histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous melanoma or unknown primary melanoma classified as American Joint Committee on Cancer (AJCC) stage IIIB, IIIC or IV • Eastern Cooperative Oncology Group performance status (ECOG PS) ○ 0 or 1 • BRAFV^{600} mutation-positive tumour ○ BRAF V600E or BRAF V600K mutation or both in tumour tissue as ascertained by central genetic mutation analysis with the bioMerieux THxID BRAF diagnostic test before enrolment • Treatment naive or had progressed on or after previous first-line immunotherapy • Adequate bone marrow • Adequate organ function • Adequate laboratory parameters • At least one measurable lesion • in accordance with guidelines based on Response Evaluation Criteria in Solid Tumors
Exclusion criteria	• Leptomeningeal metastases • Untreated central nervous system lesions • Uveal melanoma • Mucosal melanoma • Gilbert syndrome • History, current evidence or risk of retinal vein occlusion • Previous BRAF inhibitor treatment • Previous MEK inhibitor treatment • Previous use of systemic chemotherapy • Extensive radiotherapy • An investigational agent other than previous immunotherapy for locally advanced, unresectable or metastatic melanoma
Intervention(s)	• Encorafenib plus binimetinib
Comparator	• Encorafenib

	• Vemurafenib
Outcome measures	• Progression free survival ○ defined as the time from randomisation to first documented progression or death from any cause (whichever occurred first) • Overall survival
Number of participants	577
Duration of follow-up	Median follow-up for overall survival was 48.8 months Median follow-up for progression free survival was 16.6 months
Loss to follow-up	Lost to follow-up was reported combined with protocol violation and new therapy for study indication

Study arms

Encorafenib plus binimetinib (N = 192)
encorafenib 450 mg once a day plus binimetinib 45 mg twice daily

Loss to follow-up	2 (1.0%) which included lost to follow-up, protocol violation and new therapy for study indication

Encorafenib (N = 194)
encorafenib 300 mg once a day

Loss to follow-up	1 (0.5%) which included lost to follow-up, protocol violation and new therapy for study indication

Vemurafenib (N = 191)

vemurafenib 960 mg twice daily	
Duration of follow-up	
Loss to follow-up	1 (0.5%) which included lost to follow-up, protocol violation and new therapy for study indication

Arm-level characteristics

	Encorafenib plus binimetinib (N = 192)	Encorafenib (N = 194)	Vemurafenib (N = 191)
% Female	40%	44%	42%
Mean age (SD)	56 (14)	55 (13)	55 (14)
BRAF mutation status			
BRAFV600E	89%	89%	88%
BRAFV600K	11%	10%	12%
AJCC tumour stage at study entry			
IIIB/IIIC	5%	3%	6%
IVM1a	14%	15%	13%
IVM1b	18%	20%	16%
IVM1c	64%	62%	65%
Number of organs involved			
1	24%	29%	24%

	Encorafenib plus binimetinib (N = 192)	Encorafenib (N = 194)	Vemurafenib (N = 191)
2	30%	27%	31%
≥3	45%	44%	46%
Previous immunotherapy	30%	30%	30%
Ipilimumab	4%	5%	4%
Ipilimumab adjuvant	1%	1%	1%
Ipilimumab advance or metastatic	3%	5%	3%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders however inclusion criteria is very specific and data re presented separately for the three arms, allowing for evaluation of the effect of treatment on each risk factors predictive ability. Data for the three arms were combined for the purposes of this analysis).*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

Faries 2017

Faries, 2017

Bibliographic Reference	Faries, Mark B; Mozzillo, Nicola; Kashani-Sabet, Mohammed; Thompson, John F; Kelley, Mark C; DeConti, Ronald C; Lee, Jeffrey E; Huth, James F; Wagner, Jeffrey; Dalgleish, Angus; Pertschuk, Daniel; Nardo, Christopher; Stern, Stacey; Elashoff, Robert; Gammon, Guy; Morton, Donald L; MMAIT-IV Clinical Trial, Group; Long-Term Survival after Complete Surgical Resection and Adjuvant Immunotherapy for Distant Melanoma Metastases.; Annals of surgical oncology; 2017; vol. 24 (no. 13); 3991-4000

Study Characteristics

Study design	RCTs o randomized, double-blind study enrolled subjects
Study details	• Study location • Study setting • Study dates • Enrolment between May 1998 and April 2005
Inclusion criteria	• Resected IV o AJCC 5th edition stage IV melanoma (1998 staging guidelines), and no clinical evidence of disease after complete resection of distant soft tissue or lymph node metastases or metastases in deep iliac/obturator nodes (AJCC stage IV M1a) and/or distant lung or other visceral metastases (AJCC 5th ed. stage IV M1b). o Pre study computed tomography (CT) of chest, abdomen and pelvis, magnetic resonance imaging (MRI) or CT of the brain, and bone scan confirmed no evident disease at trial entry. Exclusion criteria included abnormal liver function and LDH [1.5 times the upper limit of normal. Patients could have no more than five metastases in no more than two visceral organ sites at the time of definitive surgery and were required to start study drug 14–90 days after surgery
Number of participants and recruitment methods	The study was an RCT randomising 496 patients to adjuvant therapy (post-resection) of Canvaxin plus bacillus Calmette Guerin (BCG) or BCG alone. Median duration of drug administration was 8.1 months for both arms.
Length of follow-up	Up to 132 months.
Outcome(s) of interest	Overall survival
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Treatment administered • M stage (1b vs 1a) • Number of lesions (1 vs >1)

	• Age (60+ years) • Gender • Time from primary diagnosis to randomization • Previous treatment for stage IV • ECOG • LDH • Previous stage III disease
Covariates adjusted for in the multivariable regression modelling	all prognostic factors entered into model.

Participant characteristics

	Study (N = 496)
Female	39%
Mean age (SD)	54.1 (0.58)
ECOG status 0	88%
Prior diagnosis of stage III disease	56%
Elevated LDH	12%
M1a	43%
M1b	57%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(risk factors likely comorbid)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low *(all risk factors entered into model)*
Overall Risk of bias and Applicability	Risk of bias	Low
	Concerns for applicability	Low

KEYNOTE-002

KEYNOTE-002

Bibliographic Reference	Hamid, Omid; Puzanov, Igor; Dummer, Reinhard; Schachter, Jacob; Daud, Adil; Schadendorf, Dirk; Blank, Christian; Cranmer, Lee D; Robert, Caroline; Pavlick, Anna C; Gonzalez, Rene; Hodi, F Stephen; Ascierto, Paolo A; Salama, April K S; Margolin, Kim A; Gangadhar, Tara C; Wei, Ziwen; Ebbinghaus, Scot; Ibrahim, Nageatte; Ribas, Antoni; Final analysis of a randomised trial comparing pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory advanced melanoma.; European journal of cancer (Oxford, England : 1990); 2017; vol. 86; 37-45

Study details

Trial registration number and/or trial name	KEYNOTE-002 trial NCT01704287
Study type	Randomised controlled trial (RCT)
Study location	Argentine, Australia, France, Germany, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, US
Study setting	Multicentre
Study dates	2012 - 2019
Sources of funding	Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
Inclusion criteria	Age • 18 years or older Melanoma • histologically or cytologically confirmed unresectable stage III or stage IV melanoma not amenable to local therapy Eastern Cooperative Oncology Group performance status (ECOG PS) • 0 or 1 Measurable disease

	• per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) Previous BRAF inhibitor therapy or MEK inhibitor therapy or both (if BRAFV600 mutant-positive) Confirmed disease progression • within 24 weeks of the last ipilimumab dose (minimum two doses, 3 mg/kg once every 3 weeks) Resolution or improvement of ipilimumab-related adverse events to grade 0–1 Prednisone dose 10 mg/day or less for at least 2 weeks before the first dose of study drug Values within the prespecified range for absolute neutrophil count (≥1500 cells per mL), platelets (≥100 000 cells per mL), haemoglobin (≥90 g/L), serum creatinine (≤1·5 upper limit of normal [ULN]), serum total bilirubin (≤1·5 ULN or direct bilirubin ≤ULN for patients with total bilirubin concentrations >1·5 ULN), aspartate and alanine aminotransferases (≤2·5 ULN or ≤5 ULN for patients with liver metastases), international normalised ratio or prothrombin time (≤1·5 ULN if not using anticoagulants), and activated partial thromboplastin time (≤1·5 ULN if not using anticoagulants)

Exclusion criteria	• Active brain metastases
	  ○ or carcinomatous meningitis
	• Active autoimmune disease
	• Active infection requiring systemic therapy
	• Known history of HIV infection
	• Active hepatitis B virus or hepatitis C virus infection
	• History of grade 4 ipilimumab-related adverse events
	  ○ or grade 3 ipilimumab-related adverse events lasting longer than 12 weeks
	• Previous treatment with any other anti-PD-1 or anti-PD-L1 therapy

Intervention(s)	• Pembrolizumab 2mg/kg

	• Pembrolizumab 10mg/kg
Comparator	• Chemotherapy
Outcome measures	Progression free survival time from randomisation to first documented disease progression per RECIST v1.1 by independent central review or death from any cause, whichever occurred first. Overall survival • time from randomisation to death from any cause. Health related quality of life European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 instrument (QLQ-C30) Serious adverse events †Results in death; or †is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or †results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or †results in or prolongs an existing inpatient hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation) (Note: Hospitalization [including hospitalization for an elective procedure] for a pre-existing condition which has not worsened does not constitute a serious adverse experience.); or †is a congenital anomaly/birth defect (in offspring of subject/patient taking the product regardless of time to diagnosis); or is a new cancer; (that is not a condition of the study) or is an overdose (Whether accidental or intentional). Other important medical events that may not result in death, not be life threatening, or not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Number of participants	540

Duration of follow-up	Median follow-up 28 months (range 24.1 to 35.5)
Loss to follow-up	Not reported
Additional comments	Patients had a washout period of at least 4 weeks between the last dose of the most recent therapy and the first dose of pembrolizumab. Patients in the chemotherapy group with documented and verified disease progression at or after week 12 who met the relevant eligibility criteria could cross over to receive pembrolizumab after a washout period of at least 28 days from the last dose of chemotherapy; patients who crossed over were randomly assigned to one of the two pembrolizumab doses in a double-blind manner.

Study arms

Pembrolizumab 2mg/kg (N = 180) Pembrolizumab 2 mg/kg intravenously every 3 weeks
Pembrolizumab 10mg/kg (N = 181) Pembrolizumab 10 mg/kg intravenously every 3 weeks
Chemotherapy (N = 179) Investigator-choice chemotherapy (paclitaxel plus carboplatin, paclitaxel, carboplatin [eliminated with protocol amendment one], dacarbazine, or oral temozolomide)

Arm-level characteristics

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
% Female			
Sample Size	n = 76 ; % = 42	n = 72 ; % = 40	n = 65 ; % = 36
Mean age (SD)			
Custom value	Median 62 years (range 15 to 87)	Median 60 years (range 27 to 89)	Median 63 years (range 27 to 87)
BRAFV600 status			
Mutant			
Sample Size	n = 44 ; % = 24.4	n = 40 ; % = 22.1	n = 42 ; % = 23.5
Wild type			
Sample Size	n = 136 ; % = 75.6	n = 141 ; % = 77.9	n = 137 ; % = 76.5
Tumour size			
Custom value	Median 99.4 mm (range 10 to 428)	Median 98.6 mm (range 12 to 560)	Median 101.3 mm (range 11 to 568)
Metastatic stage			
M0			
Sample Size	n = 2 ; % = 1.1	n = 2 ; % = 1.1	n = 2 ; % = 1.1
M1a			

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
Sample Size	n = 8 ; % = 4.4	n = 13 ; % = 7.2	n = 15 ; % = 8.4
M1b			
Sample Size	n = 22 ; % = 12.2	n = 17 ; % = 9.4	n = 15 ; % = 8.4
M1c			
Sample Size	n = 148 ; % = 82.2	n = 149 ; % = 82.3	n = 147 ; % = 82.1
Number of lines of previous systemic therapies			
None Patients with no previous systemic therapies received neoadjuvant or adjuvant therapy only			
Sample Size	n = 1 ; % = 0.6	n = 0	n = 0
one			
Sample Size	n = 40 ; % = 22.2	n = 55 ; % = 30.4	n = 47 ; % = 26.3
two			
Sample Size	n = 79 ; % = 43.9	n = 65 ; % = 35.9	n = 78 ; % = 43.6
three			
Sample Size	n = 32 ; % = 17.8	n = 36 ; % = 19.9	n = 32 ; % = 17.9
Four			

	Pembrolizumab 2mg/kg (N = 180)	Pembrolizumab 10mg/kg (N = 181)	Chemotherapy (N = 179)
Sample Size	n = 12 ; % = 6.7	n = 18 ; % = 9.9	n = 11 ; % = 6.1
≥5			
Sample Size	n = 16 ; % = 18.9	n = 7 ; % = 3.9	n = 11 ; % = 6.1
Previous therapy			
Ipilimumab			
Sample Size	n = 180 ; % = 100	n = 181 ; % = 100	n = 179 ; % = 100
Interleukin 2			
Sample Size	n = 21 ; % = 12	n = 16 ; % = 9	n = 12 ; % = 7
Immunotherapy, excluding ipilimumab and interleukin 2			
Sample Size	n = 25 ; % = 14	n = 18 ; % = 10	n = 23 ; % = 13
Chemotherapy			
Sample Size	n = 90 ; % = 50	n = 84 ; % = 46	n = 86 ; % = 48
BRAF or MEK inhibitor			
Sample Size	n = 46 ; % = 26	n = 45 ; % = 25	n = 43 ; % = 24

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Participants were prospectively enrolled and specific inclusion/exclusion criteria ensured a level of homogeneity between participants. However, there is still the potential for risk factors to be comorbid.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(All predictors were assessed at baseline)*
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(all participants underwent standardised follow-up protocol outlined in the RCT).*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for potential confounders. For the purposes of this analysis, data for those receiving immunotherapy is not separable from those receiving investigators choice of chemotherapy).*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Potential for confounders (particularly choice of treatment) to influence events.*

Section	Question	Answer
	Concerns for applicability	Low

- Miscellaneous studies referenced in committee discussions

The following papers were protocol deviations, made in an attempt to fill evidence gaps in the following areas:

- Risk of lymph node recurrence in SLNB positive patients
- The utility of ultrasound scanning of the lymph node basins during follow-up
- The risk of recurrence during follow-up of people with stage IIB-III melanoma

DeCOG-SLT

DeCOG-SLT

Bibliographic Reference	Leiter, Ulrike; Stadler, Rudolf; Mauch, Cornelia; Hohenberger, Werner; Brockmeyer, Norbert H; Berking, Carola; Sunderkotter, Cord; Kaatz, Martin; Schatton, Kerstin; Lehmann, Percy; Vogt, Thomas; Ulrich, Jens; Herbst, Rudolf; Gehring, Wolfgang; Simon, Jan-Christoph; Keim, Ulrike; Verver, Danielle; Martus, Peter; Garbe, Claus; German Dermatologic Cooperative Oncology, Group; Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2019; vol. 37 (no. 32); 3000-3008

Study details

Other publications associated with this study included in review	Leiter 2017
Trial registration number and/or trial name	DeCOG-SLT NCT02434107

Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Multicentre: 41 German skin cancer centres
Study dates	Recruitment occurred from between Jan 1, 2006, and Dec 1, 2014
Sources of funding	German Cancer Aid
Inclusion criteria	Age aged between 18 and 75 years Clinical features of melanoma Primary cutaneous melanoma of the torso, arms, or legs and a tumour thickness of at least 1 mm Metastases micrometastasis in the sentinel lymph node, including single cells
Exclusion criteria	Metastases Evidence of satellite, in-transit, or distant metastatic disease, or involvement of the entire lymph node with capsular perforation (regional macrometastasis) Location of skin tumour Patients with melanoma of the head and neck region Past medical history Patients with a history of previous or concurrent (ie, second primary) invasive melanoma, solid tumours, or haematological malignancy during the past 5 years (except non-melanoma skin cancer), treated with oral or parenteral immunosuppressive agents during study participation or within 6 months before enrolment) Pregnancy

	pregnant or lactating women Allergies patients allergic to vital blue dye or any radio colloid
Outcome measures	Disease-free survival Secondary endpoints included recurrence-free survival (defined as time between randomisation and the date of diagnosis of first recurrence, the date of last follow-up visit, or date of death by any cause), and recurrence of regional lymph node metastases. Distant-metastases-free survival The primary endpoint was distant metastasis-free survival, calculated from the date of randomisation to the date of diagnosis of first distant metastases, date of latest follow-up visit, or date of death by any cause. Overall survival overall survival (time between randomisation and date of last follow-up visit or date of death by any cause), Adverse events For patients allocated to the complete lymph node dissection group, adverse events and surgical complications were collected immediately postoperatively and 3 and 6 months after complete lymph node dissection. Grade 3 and 4 adverse events of surgical complications were reported in the complete lymph node dissection group during the entire follow-up. Grade 3 and 4 events were delayed wound healing (grade 3 moderate, >2 months; grade 4 severe, >3 months); infection (grade 3 moderate, cellulitis; grade 4 severe, sepsis); seroma (grade 3 moderate, seroma size of >7 cm; grade 4 severe, seroma size of >10 cm); lymph fistula (grade 3 moderate, >3 months; grade 4 severe, persistent); lymphoedema (grade 3 moderate, >3 months; grade 4 severe, persistent); and persistent staining of the skin due to injection of patent vital blue dye (grade 3 moderate, <9 months; grade 4 severe, persistent).
Number of participants	483
Duration of follow-up	3 year and 6 year follow up
Loss to follow-up	10 were lost to follow up, 8 in the observation group and 2 in the CLND group

Methods of analysis	Intention to treat
Additional comments	

Study arms

Observation group (N = 233)
Identical follow-up schedules were applied for both study groups. Physical examinations (whole body and palpation of primary scar to and including the regional lymph node basin), lymph node sonography (primary scar to and including regional lymph node basin), and blood tests with serum S100b were done every 3 months. Every 6 months, patients received section diagram imaging, such as whole body CT scan, MRI, or PET-CT, or a chest x-ray and abdomen sonography at minimum. This procedure was done during the entire 3-year follow-up from the date of randomisation.

Completion Lymph Node Dissection (N = 240)
Randomisation and complete lymph node dissection in patients who were randomly assigned to the complete lymph node dissection group had to be completed within 120 days after the sentinel lymph node biopsy. Standard operating procedures for the sentinel lymph node biopsy, for the complete lymph node dissection, and for the histopathological processing of the lymph nodes were done.

Characteristics

Arm-level characteristics

	Observation group (N = 233)	**Completion Lymph Node Dissection (N = 240)**
Sex (male)		
Sample Size	n = 150 ; % = 64	n = 141 ; % = 59
Median age at diagnosis		

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
MedianIQR	56 (45 to 66)	57 (47 to 67.8)
Body site of tumour		
Trunk		
Sample Size	n = 119 ; % = 51	n = 128 ; % = 53
Upper extremity		
Sample Size	n = 31 ; % = 13	n = 35 ; % = 15
Lower extremity		
Sample Size	n = 83 ; % = 36	n = 77 ; % = 32
Median tumour thickness (mm)		
MedianIQR	2.4 (1.5 to 3.85)	2.4 (1.6 to 4)
Ulceration present		
Sample Size	n = 95 ; % = 41	n = 90 ; % = 38
Sentinel node biopsy positives per patient		
one		
Sample Size	n = 213 ; % = 91	n = 222 ; % = 93
two or more		

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
Sample Size	n = 20 ; % = 9	n = 16 ; % = 7
not applicable		
Sample Size	n = 0 ; % = 0	n = 2 ; % = 1
Positive sentinel node biopsies per patient		
Histological criteria		
Haematoxylin and eosin stain positive		
Sample Size	n = 144 ; % = 62	n = 140 ; % = 58
Immunhistochemistry positive (S100, HMB45, Melan A)		
Sample Size	n = 73 ; % = 31	n = 77 ; % = 32
Size of metasteses in the sentinel lymph node biopsy		
Single cells or <0.5		
Sample Size	n = 76	n = 68
0.5 to 1.0		
Sample Size	n = 82	n = 85
1.01 - 2.0		
Sample Size	n = 43	n = 48

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
2.01 to 5.0		
Sample Size	n = 12	n = 11
more than 5		
Sample Size	n = 4	n = 3
no size specified		
Sample Size	n = 16	n = 25
Adjuvant interferon-a		
No therapy		
Sample Size	n = 82 ; % = 35	n = 103 ; % = 43
Low dose		
Sample Size	n = 105 ; % = 45	n = 89 ; % = 37
High dose		
Sample Size	n = 40 ; % = 17	n = 37 ; % = 15
Pegylated interferon		
Sample Size	n = 6 ; % = 3	n = 11 ; % = 5

Risk of Bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Yes/Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes

Section	Question	Answer
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate *(36 participants in the CLND group requested to be in the observation arm and 3 in the observation arm asked for CLND. These patients were included in the ITT analysis but excluded from the per-protocol analysis.)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low *(nearly all data was available at follow up for ITT analysis)*
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No

Section	Question	Answer
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups)*
	Overall Directness	Directly applicable

Ibrahim 2020

Ibrahim, 2020

Bibliographic Reference	Ibrahim, A.M.; Le May, M.; Bosse, D.; Marginean, H.; Song, X.; Nessim, C.; Ong, M.; Imaging Intensity and Survival Outcomes in High-Risk Resected Melanoma Treated by Systemic Therapy at Recurrence; Annals of Surgical Oncology; 2020; vol. 27 (no. 10); 3683-3691

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ Canada
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ 1 January 2006 and 1 January 2016

Inclusion criteria	• IIB-IIIC • Resection of primary lesion • SLNB and/or CLND • imaging results beyond initial consultation

Number of participants and recruitment methods	353
Length of follow-up	5 years
Surveillance strategy	local practice guidelines have supported regular surveillance imaging protocols, with stage III patients imaged every 6 months, and stage IIB–IIC patients imaged between 6- and 12-month intervals for up to 5 years.
Outcome(s) of interest	Recurrence (asymptomatic, symptomatic), post-recurrence survival.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Gender • Age • Location • Stage • Surveillance modality • Adjuvant
Covariates adjusted for in the multivariable regression modelling	Post-recurrence survival adjusted for asymptomatic surveillance detected recurrence, LHD level, sites of metastatic disease, age, brain metastases and time period of recurrence (Pre vs post 2013).
Additional comments	Use of adjuvant therapies: "The time period selected encompasses a cohort of patients with access to novel systemic therapies in Ontario (i.e. ICIs ipilimumab and nivolumab/pembrolizumab, and TTs vemurafenib/dabrafenib and cobimetinib/trametinib)".

Participant characteristics

	Study (N = 353)
Female	65%

	Study (N = 353)
Aged >65 years	45%
Tumour location	
Head/neck	16%
Trunk	35%
Extremities	45%
Stage	
IIB	24%
IIC	18%
IIIA	27%
IIIB	16%
IIIC	14%
CT used in surveillance	62%
PET-CT used In surveillance	26%
CXR/US only used in surveillance	3%
Combination used in surveillance	9%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(retrospective study with potential for selection bias as patients are likely to have comorbid risk factors. Surveillance strategy will likely have been influenced by presence of risk factors and this may impact upon likelihood of outcome. Variance in treatments received will also affect outcomes.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(surveillance strategy was recommended only and it is unclear how often it was conducted accordingly. It is unclear* whether people with certain risk factors underwent a more rigorous follow-up. There is variation in imaging modality used during follow-up)
	Concerns for applicability for outcome or its determination domain	Low

Section	Question	Answer
Analysis	Overall risk of bias for analysis domain	High *(Multivariate analysis done for post-recurrence survival but not for recurrence.)*
Overall Risk of bias and Applicability	Risk of bias	Moderate/Low *(Moderate for recurrence; low for post-recurrence survival)*
	Concerns for applicability	Low

Lee 2017

Lee, 2017

Bibliographic Reference	Lee, Ann Y; Droppelmann, Nicolas; Panageas, Katherine S; Zhou, Qin; Ariyan, Charlotte E; Brady, Mary S; Chapman, Paul B; Coit, Daniel G; Patterns and Timing of Initial Relapse in Pathologic Stage II Melanoma Patients.; Annals of surgical oncology; 2017; vol. 24 (no. 4); 939-946

Study Characteristics

Study design	• Retrospective cohort study ○ review of prospectively maintained database

Study details	• Study location
	  ○ USA
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ between January 1993 and December 2013

Inclusion criteria	• Stage II • underwent pathologic nodal staging by SLNB or LND

Number of participants and recruitment methods	738
Length of follow-up	Median follow-up was 52.1 months for non-relapsing survivors
Surveillance strategy	Standard follow-up included evaluation by a surgical oncologist, medical oncologist, or dermatologist every three to six months for the first two years, then every six to twelve months thereafter. Serum laboratory values were rarely used for surveillance. CT scans and chest x-rays were performed in asymptomatic patients at the treating physician's discretion. Synchronous initial relapses were scored by the most advanced site (systemic sites outranked nodal sites, which outranked local/in-transit). Second primary melanomas were not recorded as relapses. Appropriate symptoms reported at the same time as a corresponding image-detected relapse were recorded as patient-detected.
Outcome(s) of interest	Synchronous initial relapses were scored by the most advanced site (systemic sites outranked nodal sites, which outranked local/in-transit). Second primary melanomas were not recorded as relapses. Appropriate symptoms reported at the same time as a corresponding image-detected relapse were recorded as patient-detected.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	How recurrence was detected: Physician detected, patient detected or imaging
Covariates adjusted for in the multivariable regression modelling	None

Participant characteristics

	Study (N = 738)
Female	38.5%
Median (range)	62 (17-91) years
Tumour location	

	Study (N = 738)
Head/neck	19.2%
Trunk	35.8%
Extremities	45%
Ulceration	53.1%
Breslow thickness >4mm	27.5%
Mitotic rate 1+	79%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Surveillance strategy will have been influenced by patient characteristics and risk factors)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low

Section	Question	Answer
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear variance in surveillance frequency/intensity and in how often imaging was employed)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	High *(Unclear variance in surveillance strategy, which likely differed according to risk. Differences in strategy will have affected ability to detect outcome)*
	Concerns for applicability	Low

Leon-Ferre 2017

Leon-Ferre, 2017

Bibliographic Reference	Leon-Ferre, Roberto A; Kottschade, Lisa A; Block, Matthew S; McWilliams, Robert R; Dronca, Roxana S; Creagan, Edward T; Allred, Jacob B; Lowe, Val J; Markovic, Svetomir N; Association between the use of surveillance PET/CT and the detection of potentially salvageable occult recurrences among patients with resected high-risk melanoma.; Melanoma research; 2017; vol. 27 (no. 4); 335-341

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location

	• USA Setting • Single centre Study dates • January 2008 and October 2012 Sources of funding • This study received a small grant from the Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA.
Inclusion criteria	• Completely resected stage III–IV cutaneous melanoma or melanoma of unknown primary • no visible residual disease following surgery • At least one PET/CT performed for surveillance purposes within 1 year from definitive surgery
Exclusion criteria	• Stage I or II melanoma • Ocular or mucosal primary • Visible disease following resection • PET/CT performed for staging *Defined as PET/CT performed between the diagnosis of melanoma and initial resection* • PET/CT performed for purposes other than surveillance • Underwent surveillance at a different institution • Records were not available for review
Number of participants	299
Length of follow-up	Median follow-up of 5.0 years

Surveillance strategy	Patients have routinely undergone surveillance PET/CT following resection of stage III or IV melanoma for a period of 5 years. PET/CT is obtained at various intervals at the discretion of the treating oncologist
Additional comments	Diagnostic accuracy reported by number of PET-CT scans (n=1687)

Study-level characteristics

	Study (N = 299)
% Female	39
Median age at diagnosis	56.2 years
Primary lesion *(%)*	
Cutaneous	86%
Melanoma of unknown primary	14%
Stage *(%)*	
IIIA	30
IIIB	33
IIIC	13
IV	23

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Surveillance strategy will have been influenced by patient characteristics and risk factors)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Unclear *(Unclear variance in surveillance frequency/intensity and in how often imaging was employed)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(No adjustment for confounders)*
Overall Risk of bias and Applicability	Risk of bias	High *(Unclear variance in surveillance strategy, which likely differed according to risk. Differences in strategy will have affected ability to detect outcome)*
	Concerns for applicability	Low

Lim 2018

Lim, 2018

Bibliographic Reference	Lim, K.H.J.; Spain, L.; Barker, C.; Georgiou, A.; Walls, G.; Gore, M.; Turajlic, S.; Board, R.; Larkin, J.M.; Lorigan, P.; Contemporary outcomes from the use of regular imaging to detect relapse in high-risk cutaneous melanoma; ESMO Open; 2018; vol. 3 (no. 2); e000317

Study Characteristics

Study design	Retrospective cohort study

Study details	• Study location
	  ○ UK
	• Study setting
	  ○ 3 cancer centres
	• Study dates
	  ○ From July 2013 to June 2015
	• Sources of funding
	  ○ none declared

Inclusion criteria	• <50% 5 year OS risk ○ The high-risk cohort was broadly defined as patients with a predicted OS of less than 50% at 5years, encompassing those with Stages IIC, IIIB and IIIC disease as per the seventh edition of the American Joint Committee on Cancer TNM staging system.12 13 Some patients with thick Stage IIB melanoma (>4mm Breslow thickness) and Stage IIIA were also included at clinician discretion.
Exclusion criteria	• unresectable Stage III disease • Mucosal or ocular melanoma • any patients who received adjuvant systemic treatment, i

Number of participants and recruitment methods	173
Length of follow-up	The median duration of follow-up was 23.3±8.4months.
Surveillance strategy	The recommended surveillance schedule consisted of CT thorax, abdomen and pelvis or positron emission tomography (PET)-CT scans, as well as MRI of the brain, at baseline postoperatively, and then at 6-monthly intervals for 3years, followed by annual scans to 5years.
Outcome(s) of interest	Recurrence;
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	How recurrence was detected (patient, physician or imaging)
Covariates adjusted for in the multivariable regression modelling	None

Participant characteristics

	Study (N = 173)
Female	40.5%
Mean age (SD)	62.5 (14.9) years
Tumour location	
Head/neck	6.9%

	Study (N = 173)
Trunk	32.9%
Extremities	50.2%
Stage	
IIB	1.7%
IIC	18.5%
IIIA	0.6%
IIIB	50.9%
IIIC	28.3%
Ulceration	65.7%
Breslow thickness, median (IQR)	3.5mm (2.0-5.6)
Mitosis	89.3%
BRAF mutated	34.8%

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(patients were not prospectively enrolled, follow-up strategy was only recommended and it is likely that clinical gestalt influenced actual surveillance strategies)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	High *(Attempts were made to assess compliance with recommended follow-up strategy, comparing the number of actual scans performed against the number of theoretical scans which would be performed if the surveillance strategy was adhered to fully. There was a good level of compliance for scans overall but a low level for brain imaging. In addition, there is no attempt to assess variations in physical examinations.)*
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Unclear
	Concerns for applicability	Low

MSLT-II

MSLT-II

Bibliographic Reference Faries, Mark B; Thompson, John F; Cochran, Alistair J; Andtbacka, Robert H; Mozzillo, Nicola; Zager, Jonathan S; Jahkola, Tiina; Bowles, Tawnya L; Testori, Alessandro; Beitsch, Peter D; Hoekstra, Harald J; Moncrieff, Marc; Ingvar, Christian; Wouters, Michel W J M; Sabel, Michael S; Levine, Edward A; Agnese, Doreen; Henderson, Michael; Dummer, Reinhard; Rossi, Carlo R; Neves, Rogerio I; Trocha, Steven D; Wright, Frances; Byrd, David R; Matter, Maurice; Hsueh, Eddy; MacKenzie-Ross, Alastair; Johnson, Douglas B; Terheyden, Patrick; Berger, Adam C; Huston, Tara L; Wayne, Jeffrey D; Smithers, B Mark; Neuman, Heather B; Schneebaum, Schlomo; Gershenwald, Jeffrey E; Ariyan, Charlotte E; Desai, Darius C; Jacobs, Lisa; McMasters, Kelly M; Gesierich, Anja; Hersey, Peter; Bines, Steven D; Kane, John M; Barth, Richard J; McKinnon, Gregory; Farma, Jeffrey M; Schultz, Erwin; Vidal-Sicart, Sergi; Hoefer, Richard A; Lewis, James M; Scheri, Randall; Kelley, Mark C; Nieweg, Omgo E; Noyes, R Dirk; Hoon, Dave S B; Wang, He-Jing; Elashoff, David A; Elashoff, Robert M; Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma.; The New England journal of medicine; 2017; vol. 376 (no. 23); 2211-2222

Study details

Trial registration number and/or trial name	MSLT-II NCT00297895
Study type	Randomised controlled trial (RCT)
Study location	USA

Study setting	An international, multicenter trial conducted in 63 settings
Study dates	The trial opened in December 2004 and was registered on February 27, 2006.
Sources of funding	Supported by grants (CA189163 and CA29605, to Dr. Faries) from the National Cancer Institute and by funding from the Borstein Family Foundation, the Amyx Foundation, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, and the John Wayne Cancer Institute Auxiliary.
Inclusion criteria	Age 18 to 75 years of age Clinical features of melanoma Clinically localized cutaneous melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with 0 indicating an absence of disability and higher numbers indicating greater disability) Life expectancy a non–melanoma-related life expectancy of 10 years or more Metastases Tumor-positive sentinel node.
Outcome measures	Melanoma-specific survival For the primary end point, melanoma-specific survival, authors used the log-rank test to compare the rates among patients in the dissection group and the observation group in the intention-to-treat population with three-year follow up from the point of randomisation. Melanoma-specific survival was determined at the time of melanoma-related death. Disease-free survival Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up. Disease-free survival was the time to any recurrence. Survival without nodal recurrence was the time to recurrence within the draining nodal basin Distant-metastases-free survival

	Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up. Overall survival Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up.
Number of participants	1939
Duration of follow-up	3 years
Loss to follow-up	4 and 1 (in the treatment and observation group, respectively) were ineligible for analysis in the ITT analysis, 147 and 37 were not eligible for per protocol analysis
Methods of analysis	Intention to treat
Additional comments	

Study arms

Completion Lymph Node Dissection (N = 971) Follow-up of the dissection group involved the same schedule as in the observation group (see below), but without protocol-mandated nodal ultrasonography.
Observation (N = 968) Patients who were assigned to the observation group were monitored by means of clinical examination every 4 months during the first 2 years, every 6 months during years 3 through 5, and then annually. Nodal ultrasonographic assessment of the sentinel-node basin occurred at each visit

for the first 5 years; findings were considered to be abnormal on the basis of a length:depth ratio of less than 2, a hypoechoic center, an absence of hilar vessels, or focal nodularity with increased vascularity.

Arm-level characteristics

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
Sex (male)		
Sample Size	n = 478 ; % = 58	n = 549 ; % = 59
Age		
Smoking status		
Current		
Sample Size	n = 147 ; % = 18.3	n = 158 ; % = 17.4
Previous		
Sample Size	n = 193 ; % = 24	n = 227 ; % = 25
Never		
Sample Size	n = 463 ; % = 57.7	n = 522 ; % = 57.6
Breslow thickness (mm)		
Mean/SD	2.76 (2.34)	2.7 (2.11)
Primary site		

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
Arm or Leg		
Sample Size	n = 327 ; % = 39.7	n = 382 ; % = 41
Head or neck		
Sample Size	n = 113 ; % = 13.7	n = 128 ; % = 13.7
Trunk		
Sample Size	n = 384 ; % = 46.6	n = 421 ; % = 45.2
Ulceration present		
Sample Size	n = 316 ; % = 38.3	n = 353 ; % = 37.9
Number of positive sentinel lymph nodes		
0, RT-RCT positive		
Sample Size	n = 80 ; % = 9.7	n = 111 ; % = 11.9
one		
Sample Size	n = 596 ; % = 72.3	n = 643 ; % = 69.1
two		
Sample Size	n = 121 ; % = 14.7	n = 162 ; % = 17.4
three		
Sample Size	n = 18 ; % = 2.2	n = 10 ; % = 1.1

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
more than 3		
Sample Size	n = 9 ; % = 1.1	n = 5 ; % = 0.5
Diameter of sentinel lymph node metastases		
Mean/SD	1.07 (*empty data*)	1.11 (*empty data*)
Receieved adjuvant treatment		
Sample Size	n = 66 ; % = 8.1	n = 60 ; % = 6.5
Age		
Mean/SD	52.5 (12.9)	53.2 (13.6)
Size of sentinel lymph node metastases (mm)		
<0.1 mm		
Sample Size	n = 45 ; % = 8	n = 65 ; % = 10.4
0.1 - 1.0 mm		
Sample Size	n = 333 ; % = 58.8	n = 343 ; % = 55.1
>1.0 mm		
Sample Size	n = 188 ; % = 33.2	n = 215 ; % = 34.5

Risk of bias

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Moderate *(Unclear if allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information

Section	Question	Answer
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate *(In the treatment arm 140 Declined dissection 3 Did not undergo dissection for unknown reason. In the observation group, 9 Declined observation 7 Did not undergo observation for unknown reason. It does not appear that deviations from the intended treatment were due to the experimental context - however this was not stated directly. Intent-to-treat analysis was used.)*
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate *(little evidence was provided on "adherence to intervention" among those who had received surgery)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably no

Section	Question	Answer
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Moderate *(Risk of bias was high for per protocol analysis but low for intent to treat. Many more declined intervention in the treatment group, however this is unlikely to be related to the risk of survival. 4 and 1 (in the treatment and observation group, respectively) were ineligible for analysis in the ITT analysis, 147 and 37 were not eligible for per protocol analysis)*
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no

Section	Question	Answer
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Moderate *(all aspects of the trial were unblinded)*
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Unclear if allocation concealment. A large proportion of those randomised to the surgery group did not consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed.)*

Section	Question	Answer
	Overall Directness	Directly applicable

Podlipnik 2016

Podlipnik, 2016

Bibliographic Reference	Podlipnik, Sebastian; Carrera, Cristina; Sanchez, Marcelo; Arguis, Pedro; Olondo, Maria L; Vilana, Ramon; Rull, Ramon; Vidal-Sicart, Sergi; Vilalta, Antonio; Conill, Carles; Malvehy, Josep; Puig, Susana; Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study.; Journal of the American Academy of Dermatology; 2016; vol. 75 (no. 3); 516-524

Study Characteristics

Study design	Prospective cohort study

Study details	• Study location
	  ○ Spain
	• Study setting
	  ○ Single centre
	• Study dates
	  ○ from January 2003 to July 2013
	• Sources of funding
	  ○ supported in part by grants from Fondo de Investigaciones Sanitarias P.I. 09/01393 and P.I. 12/00840; CIBER on Rare Disease, Instituto de Salud Carlos III, co-funded by ‘‘Fondo Europeo de Desarrollo Regional, Union Europea, Una manera de hacer Europa’’; AGAUR 2009 SGR1337 and AGAUR 2014 SGR603 of the Catalan Government; a grant from ‘‘Fundacio La Marato de TV3, 201331-30,’’ Catalonia; the European Commission under the Sixth Framework Program, contract no. LSHC-CT-2006-018702 (GenoMEL), under the Seventh Framework Program (Diagnoptics), and by the National Cancer Institute of the US National Institutes of Health (CA83115)

Inclusion criteria	• IIB-III

	• disease free
Number of participants and recruitment methods	435; 290 after applying inclusion/exclusion criteria
Length of follow-up	10 years; a median of 2.5 years in all patients (interquartile range [IQR] 1.1-4.6)
Surveillance strategy	All patients underwent a baseline computed tomography (CT) scan and brain magnetic resonance imaging (MRI) as part of this protocol to rule out metastatic disease at presentation. Total body CT (thorax, abdomen, and pelvic) and brain MRI were performed every 6 mo from the beginning of the study until the fifth year, and then just an annual chest x-ray up to the tenth year. Physical exam and laboratory tests every 3 months for years 1-2, every 6 months for years 3-5 then annually thereafter. Periodic consultations were performed by a dermatoncologist working at a melanoma referral center and consisted of physical examination of the skin including palpation of lymph nodes and the primary scar, dermoscopy, and digital dermoscopy when needed. Laboratory tests were scheduled with the same frequency as clinic visits and consisted of a complete blood cell count, biochemical profile, lactate dehydrogenase, serum S100B protein, melanoma-inhibitoryaactivity protein, and beta-2 microglobulin.
Outcome(s) of interest	Recurrence
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	How recurrence was detected: Patient, physician or laboratory

Participant characteristics

		Study (N = 290)
Female		43%
Median age (IQR)		56 (16-87)
Stage		
	IIB	25.9%
	IIC	11.0%
	III	63.1%
Breslow thickness, mean (SD) mm		5.02 (5.14)

Risk of bias

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	High *(Study was prospectively conducted with patients undergoing a standardized follow-up protocol, common to all included disease stages, which included routine imaging. However, there was variance in follow-up suggesting that differences in participant characteristics may have influenced surveillance strategy.)*
	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low

Section	Question	Answer
	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low
	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	High *(no adjustment for risk factors (including breakdown of stage III subgroups))*
Overall Risk of bias and Applicability	Risk of bias	Moderate *(Prospectively designed study however variance in follow-up suggests that strategy may have been influenced by clinical characteristics (which were not controlled for))*
	Concerns for applicability	Low

Appendix E - Forest plots

- Risk factors for recurrence/progression (6.1 and 6.4)

Figure 1 Gender as a predictor of recurrence during follow-up (hazard ratios)

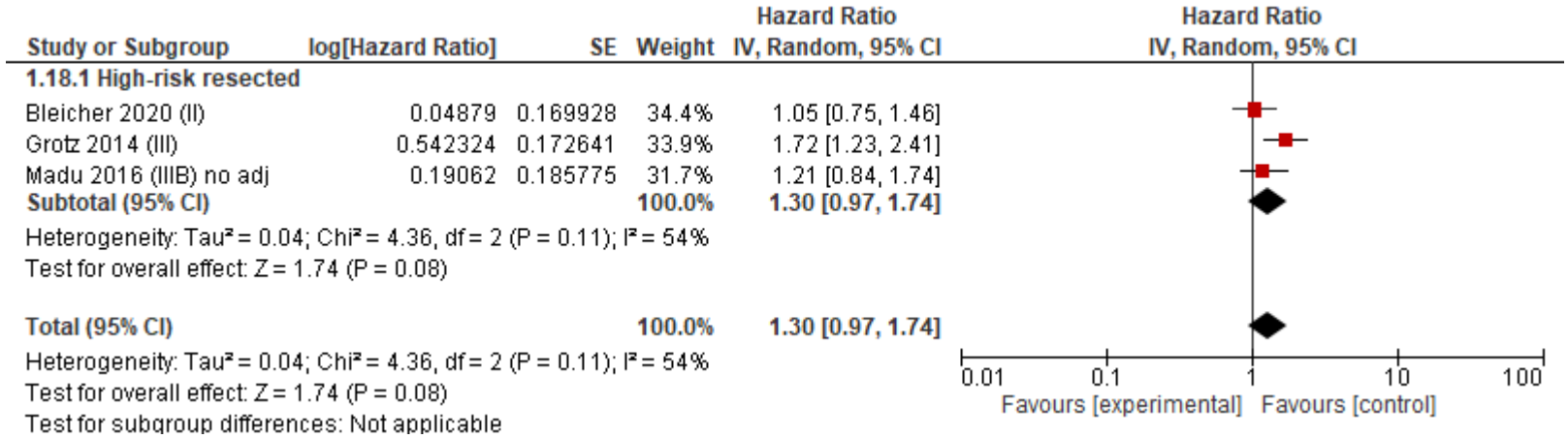
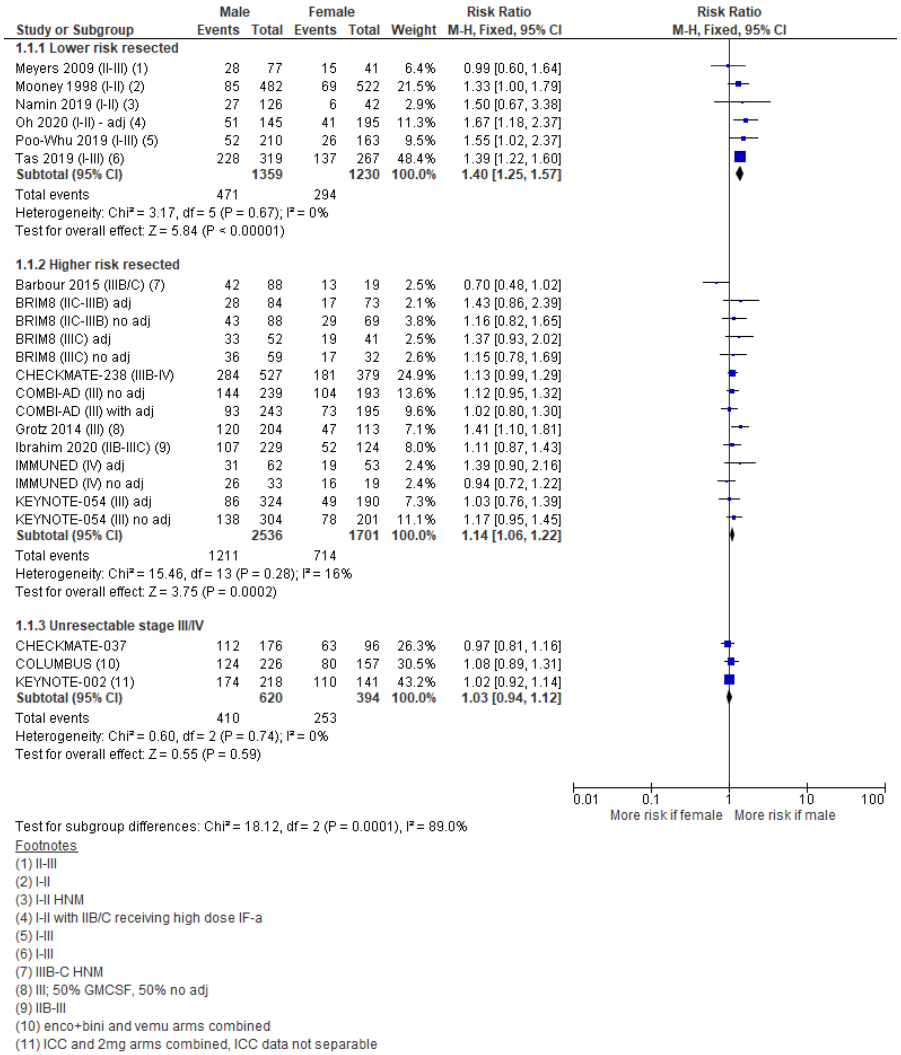


Figure 2 Gender as a predictor of recurrence during follow-up (risk ratios)



Test for subgroup differences: Chi² = 18.12, df = 2 (P = 0.0001), I² = 89.0%

Footnotes

(1) II-III
(2) I-II
(3) I-II HNM
(4) I-II with IIB/C receiving high dose IF-a
(5) I-III
(6) I-III
(7) IIIB-C HNM
(8) III; 50% GMCSF, 50% no adj
(9) IIB-III
(10) enco+bini and vemu arms combined
(11) ICC and 2mg arms combined, ICC data not separable

Figure 3: Age as a predictor of recurrence during follow-up (hazard ratios)

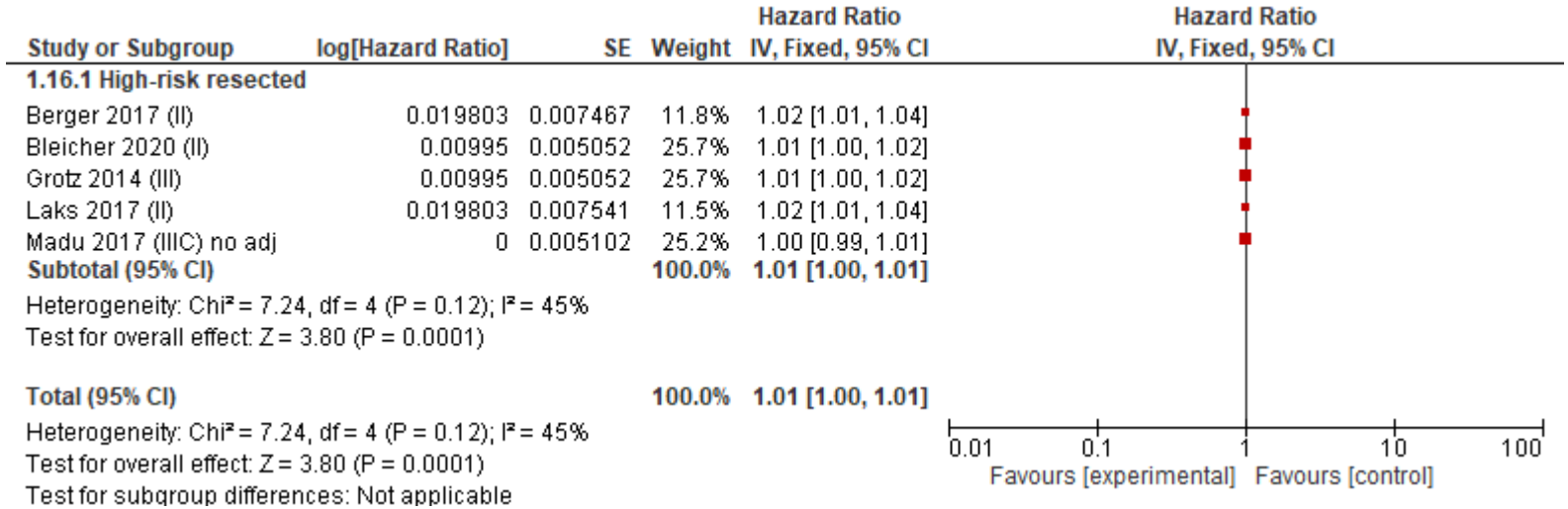
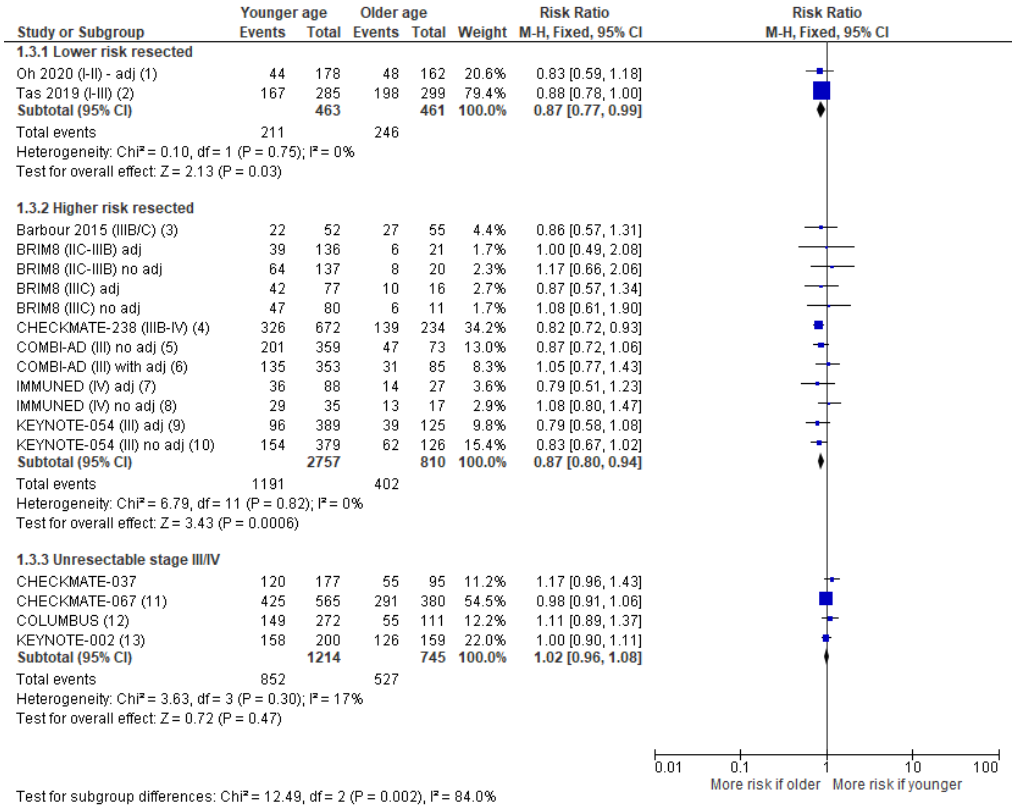


Figure 4: Age as a predictor of recurrence during follow-up (risk ratios)



Test for subgroup differences: Chi² = 12.49, df = 2 (P = 0.002), I² = 84.0%

Footnotes

(1) <60 v 60+; IIB/C received high dose IF-a
(2) <50 v 50+; I-III
(3) <60 vs >60; IIIB-C HNM
(4) <65 v 65+
(5) <65 v 65+
(6) <65 v 65+
(7) <65 v 65+
(8) <65 v 65+
(9) <65 v 65+
(10) <65 v 65+
(11) <65 v 65+; ipi-nivo, ipi only and nivo only arms combined
(12) <65 v 65+; enco+bini and vemu arms combined
(13) <65 v 65+; ICC and pembro 2mg combined, ICC data not separable

Figure 5: Breslow thickness (continuous variable, per mm) as a predictor of recurrence during follow-up (hazard ratio)

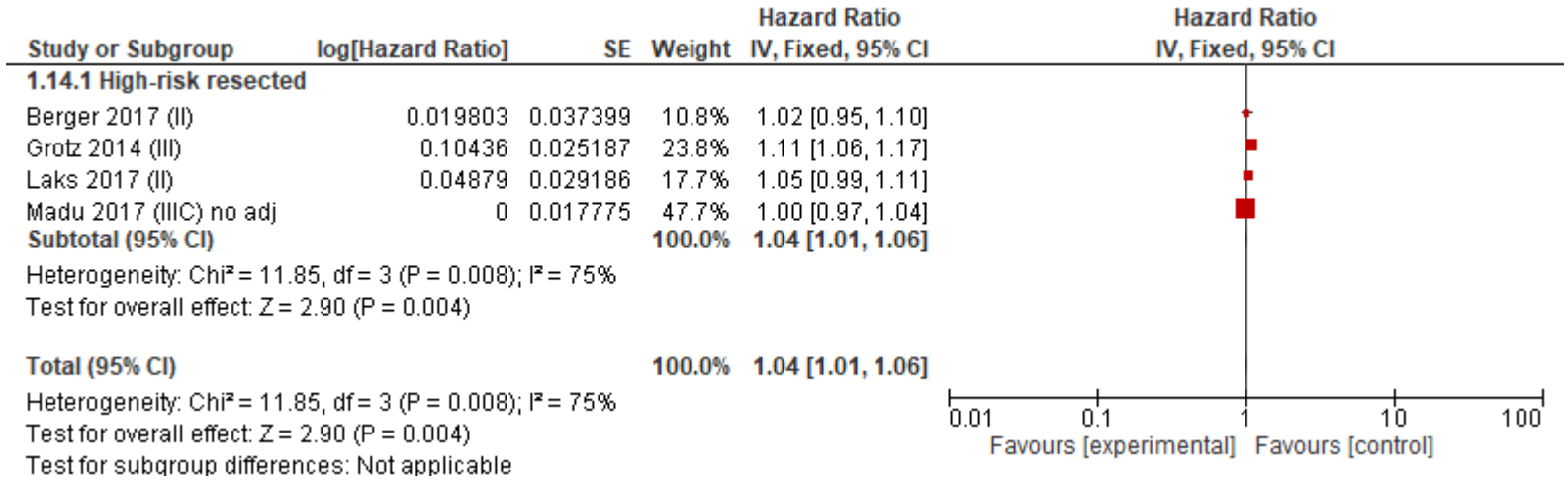
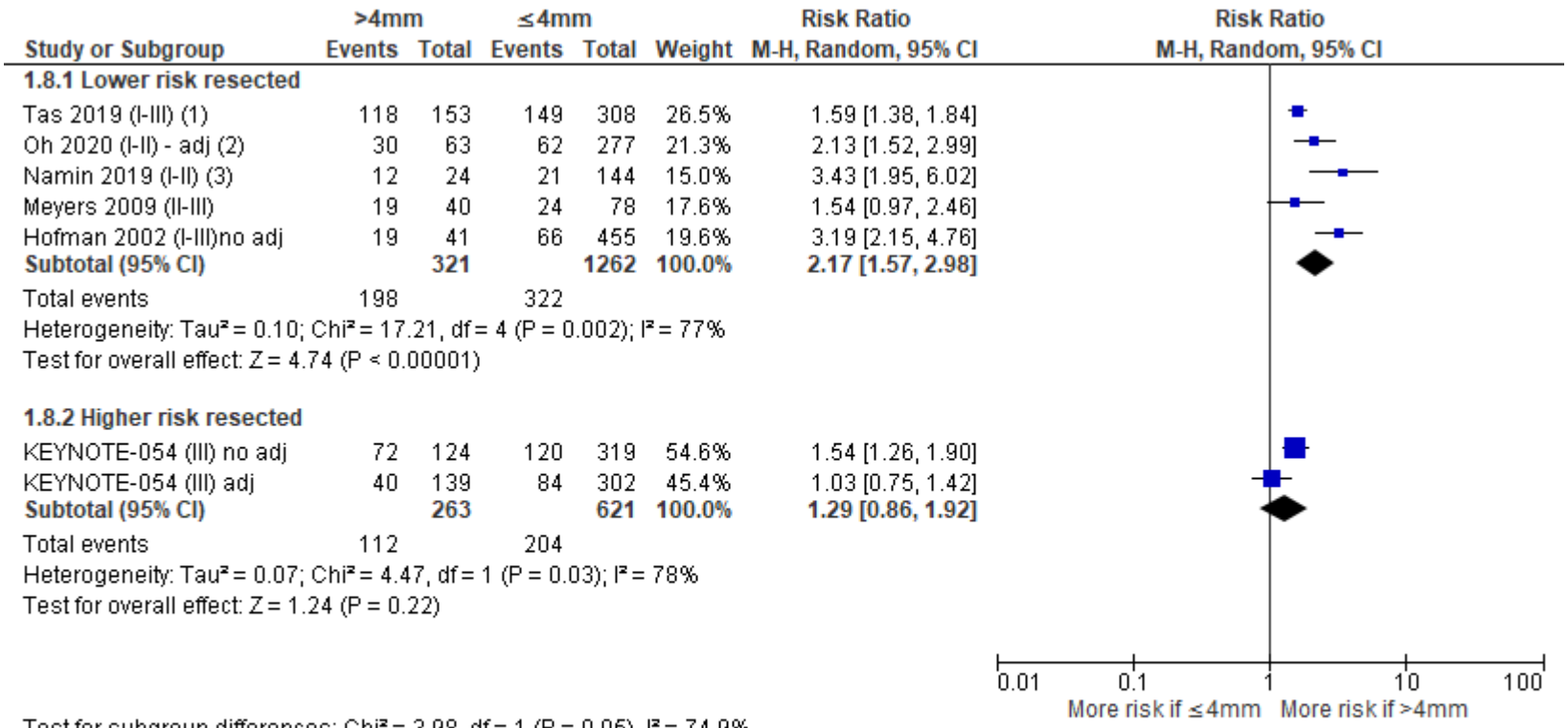


Figure 6: Breslow thickness as a predictor of recurrence developing during follow-up (risk ratios)



Test for subgroup differences: Chi² = 3.98, df = 1 (P = 0.05), I² = 74.9%

Footnotes

(1) I-III

(2) IIB/C received high dose IF-a

(3) I-II HNM

Figure 7: LVI as a predictor of brain metastases developing during follow-up

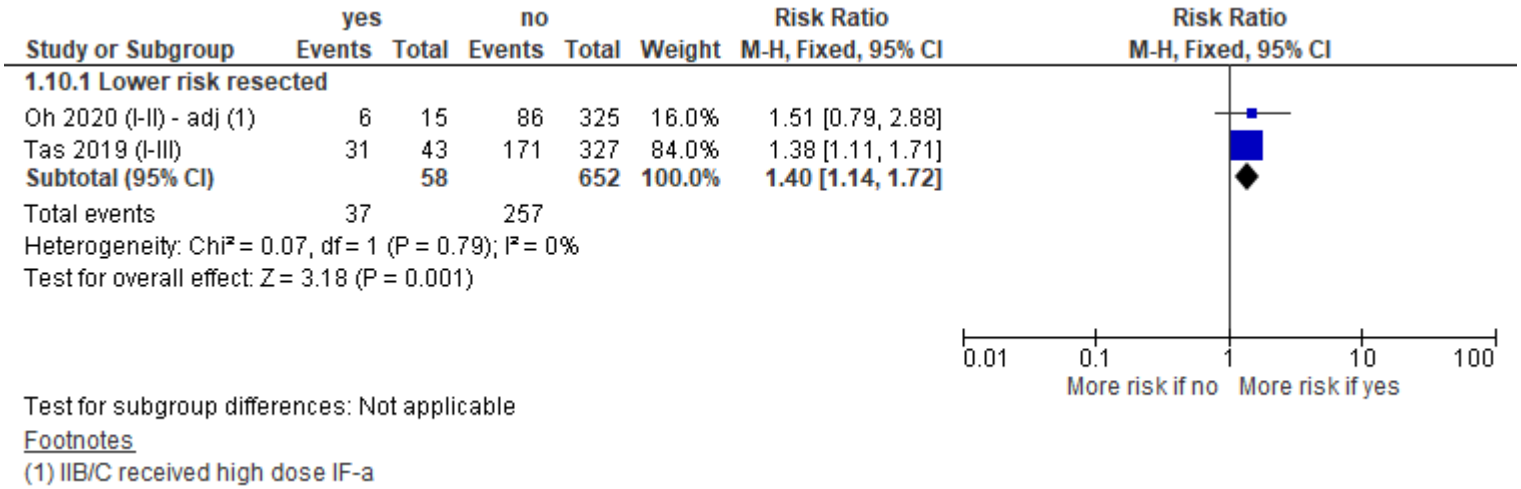


Figure 8: LDH as a predictor of recurrence during follow-up

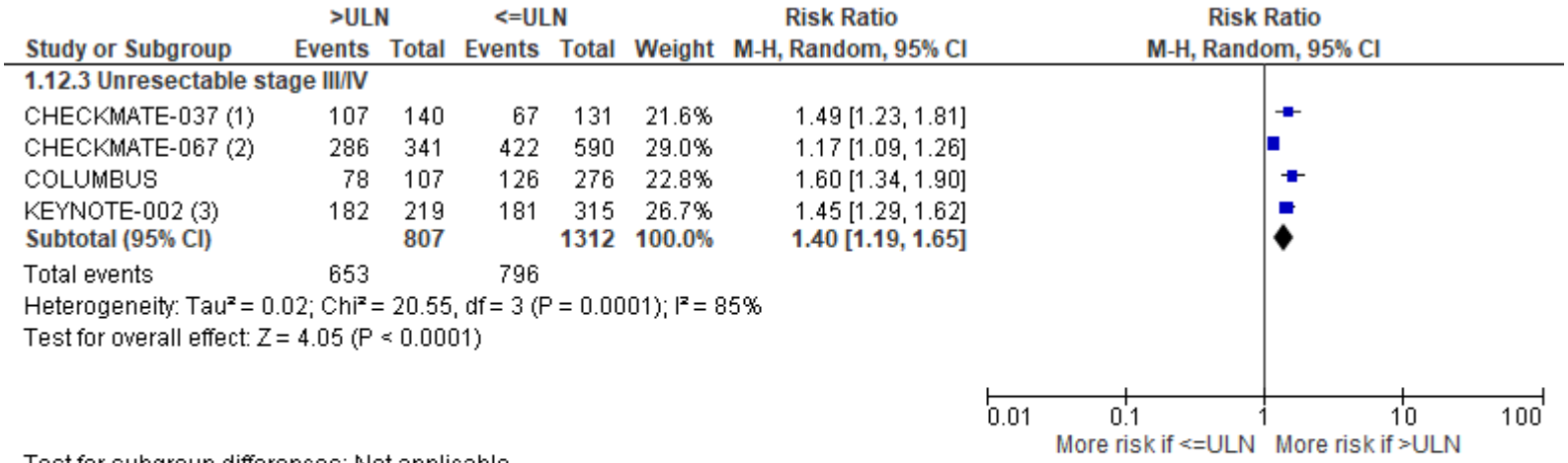


Figure 9: ECOG status ≥1 as a predictor of recurrence during follow-up of high-risk patients

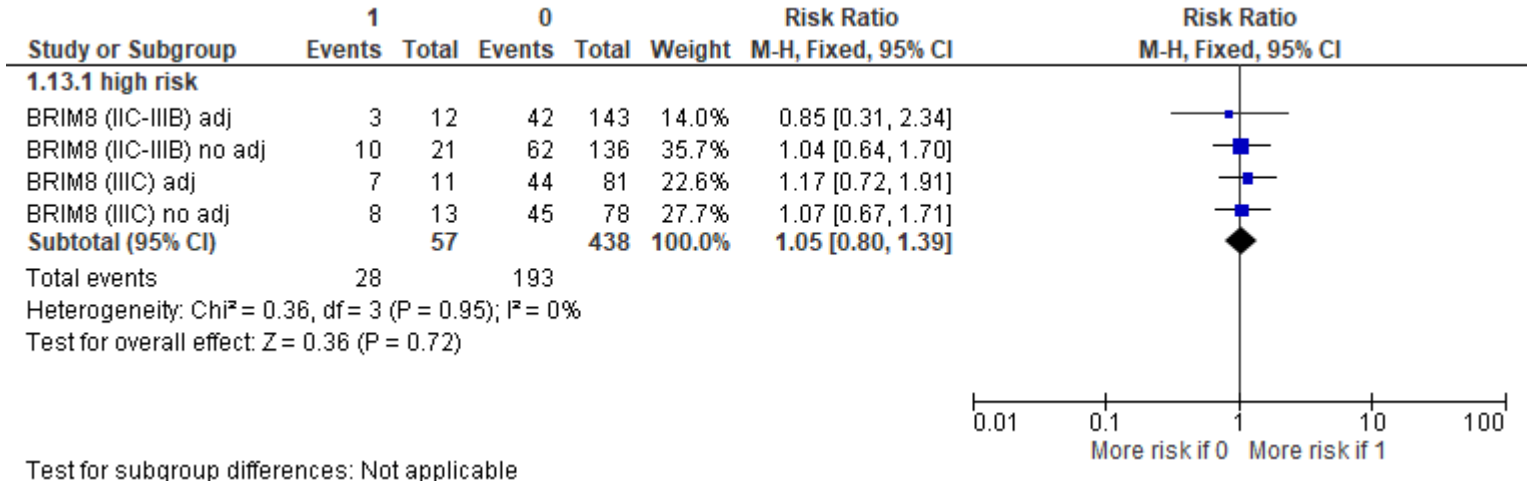
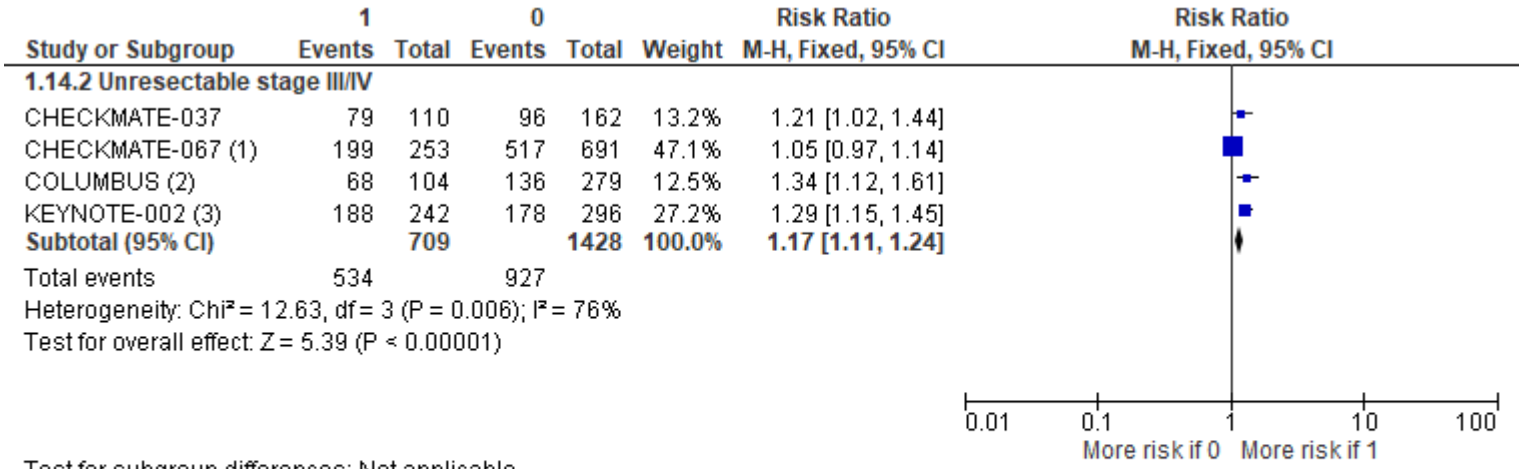


Figure 10: ECOG status ≥1 as a predictor of recurrence during follow-up of stage IV/unresectable stage III



Test for subgroup differences: Not applicable

Footnotes

(1) ipi-nivo, ipi only and nivo only arms combined

(2) enco+bini and vemu arms combined

(3) ICC, pembro 2mg and 10mg arms combined, ICC data not separable

Figure 11: Ulceration as a predictor of recurrence during follow-up of stage II melanoma (hazard ratios)

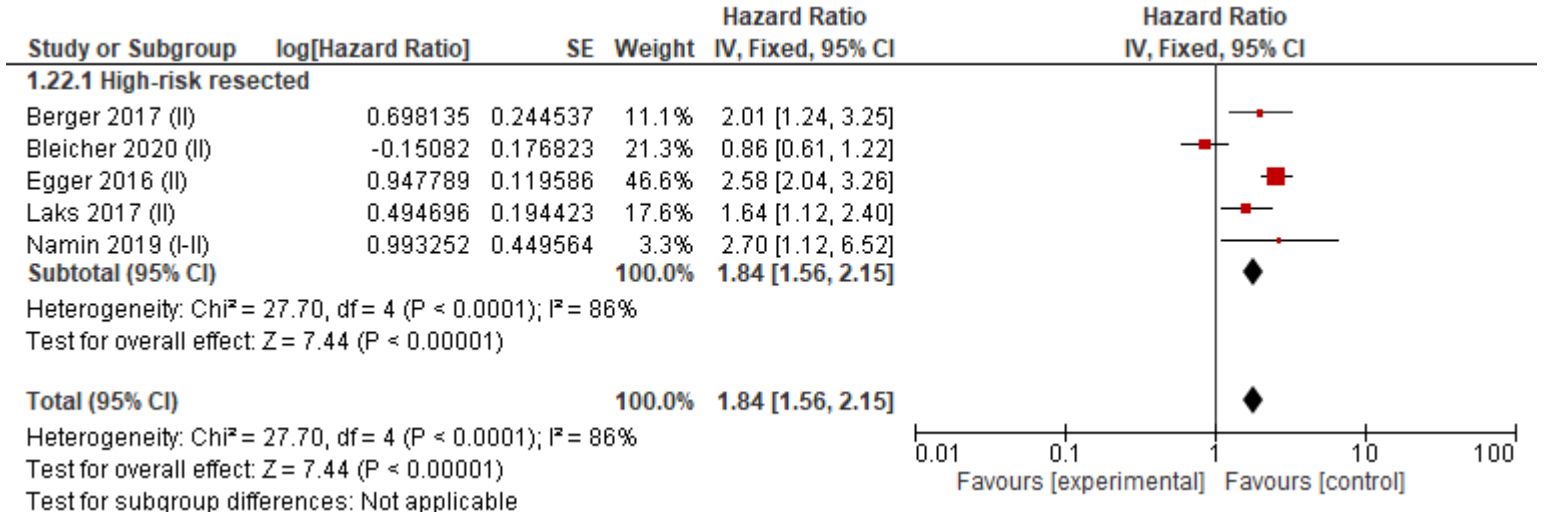


Figure 12: Ulceration as a predictor of recurrence during follow-up of stage IIIB/C melanoma (hazard ratios)

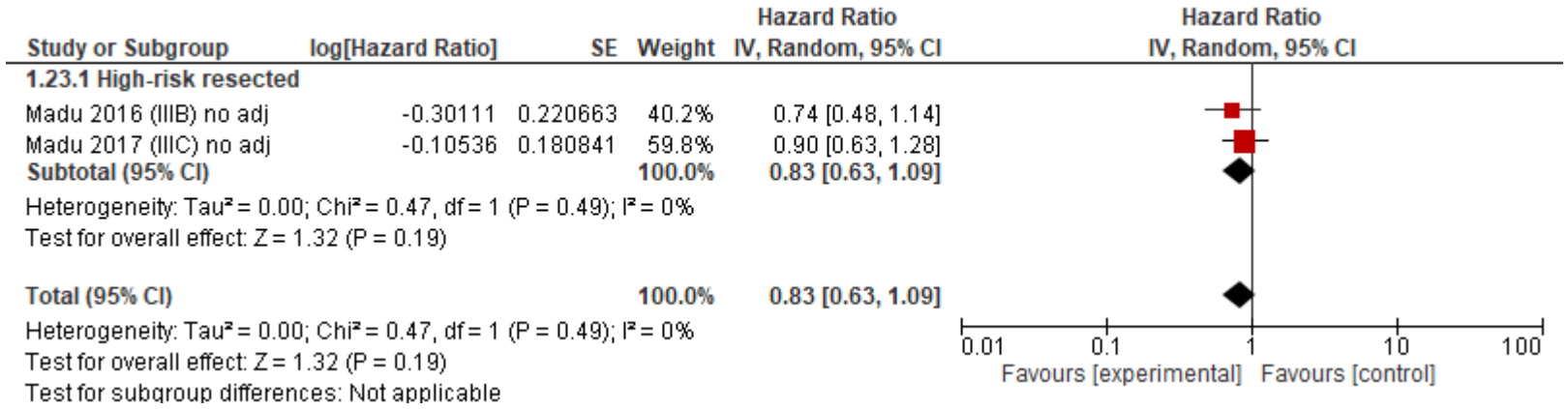
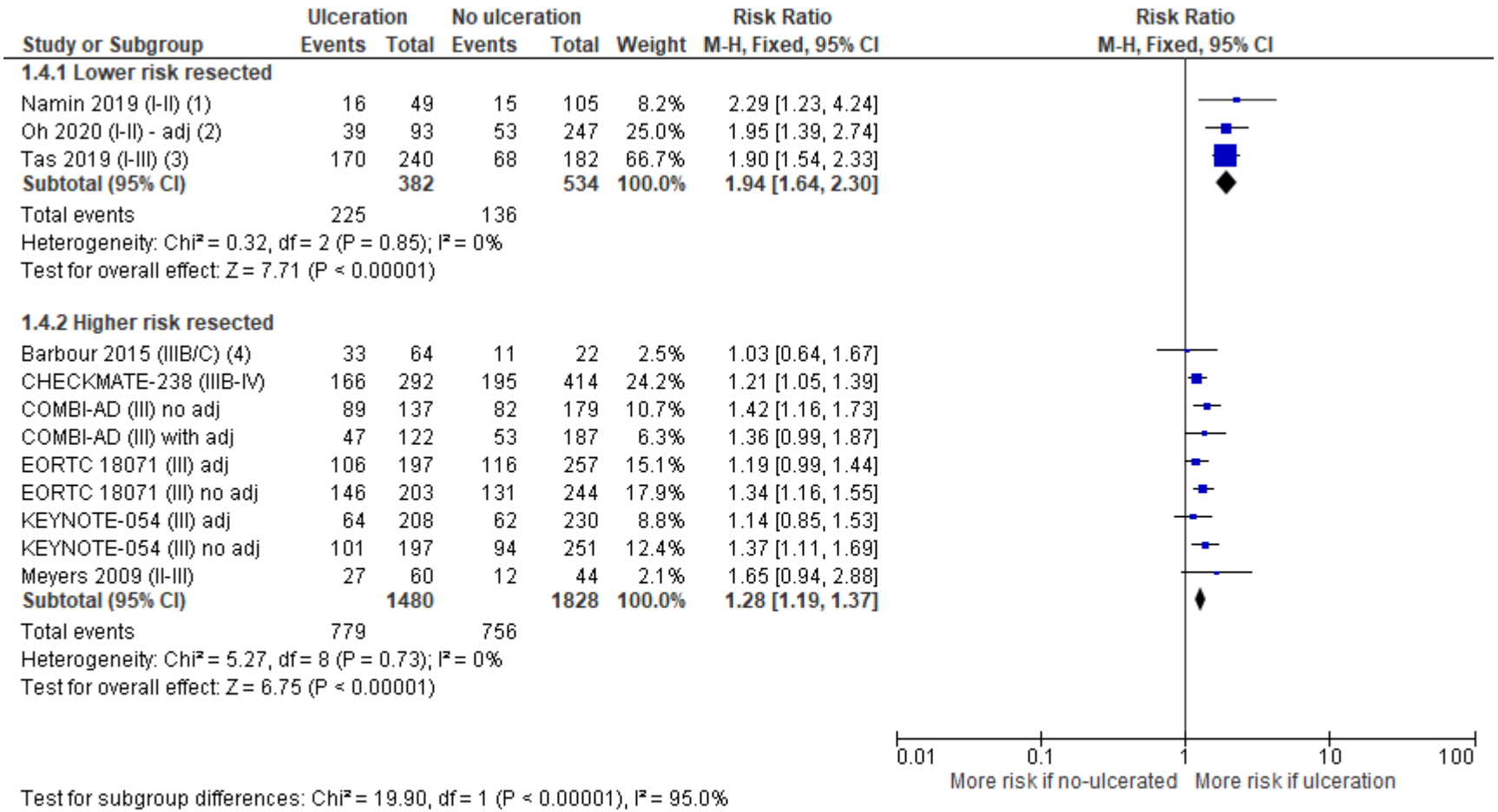


Figure 13: Ulceration as a predictor of recurrence during follow-up (risk ratios)



Test for subgroup differences: Chi² = 19.90, df = 1 (P < 0.00001), I² = 95.0%

Footnotes

(1) I-II HNM

(2) IIB/C received high dose IF-a; assumes no missing data for ulceration status

(3) I-III

(4) IIIB-C HNM

Figure 14: Location (trunk vs extremities) as a predictor of recurrence during follow-up (hazard ratios)

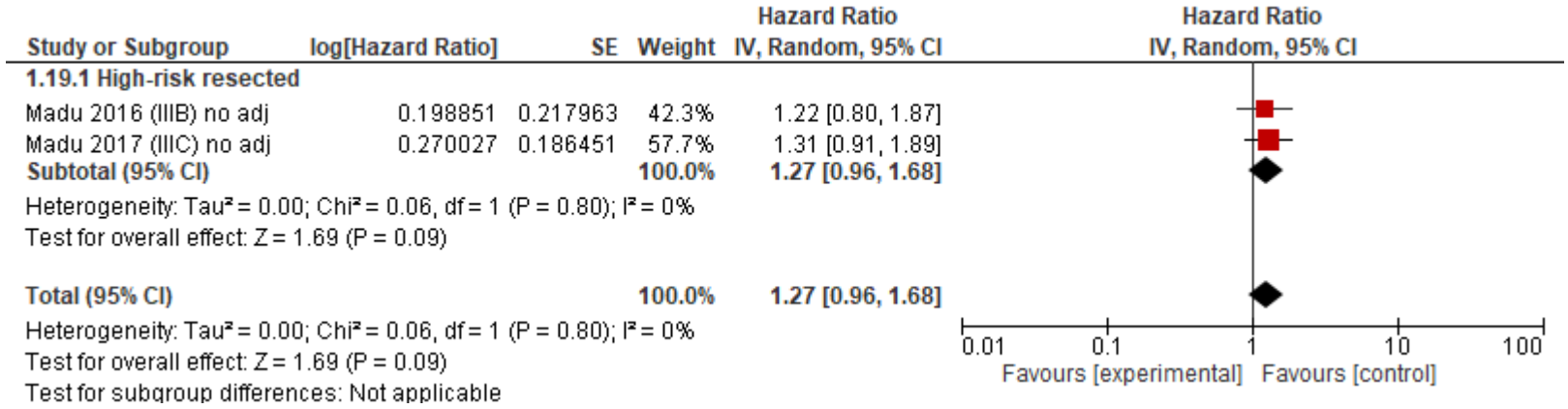


Figure 15: Location (head/neck melanoma vs extremities) as a predictor of recurrence during follow-up (hazard ratios)

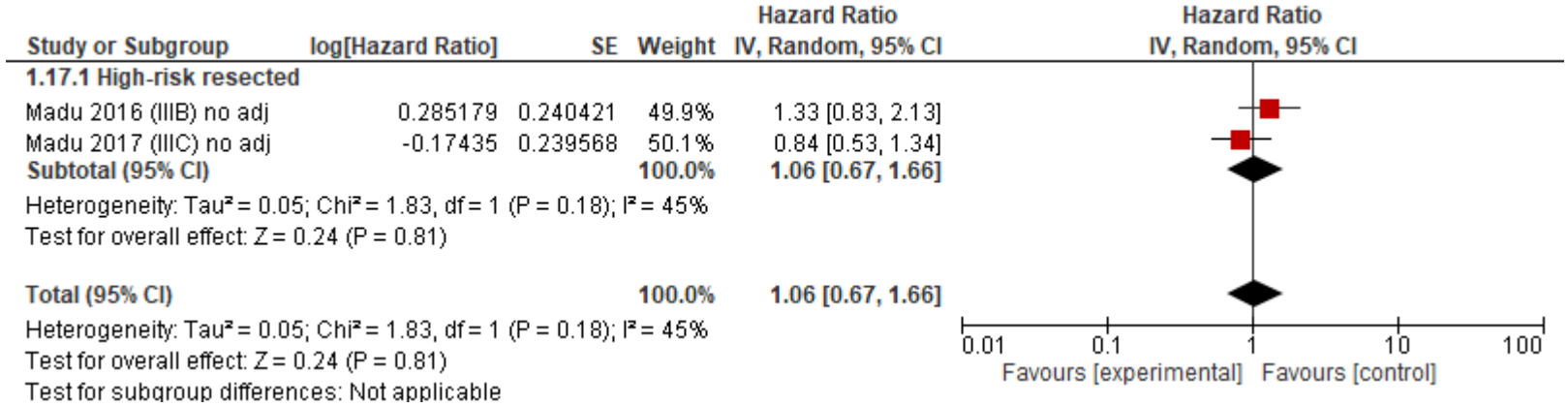


Figure 16: Location (head/neck/trunk vs extremities) as a predictor of recurrence during follow-up of low-risk patients (risk ratios

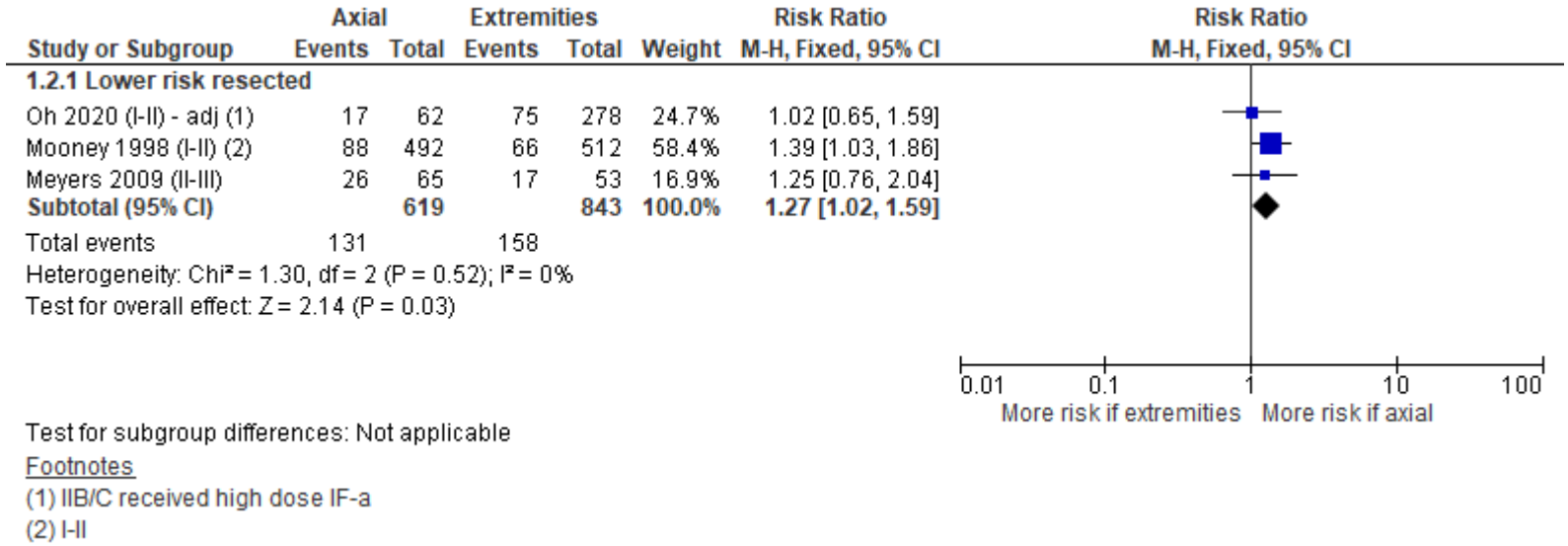


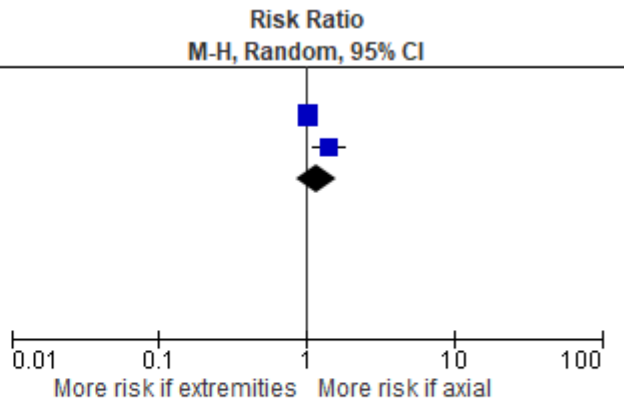
Figure 17: Location (head/neck/trunk vs extremities) as a predictor of recurrence during follow-up of high-risk patients (risk ratios)

The follow up of people with melanoma

Study or Subgroup	Axial Events	Total	Extremities Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.2 Higher risk resected						
Tan 2019 (IIC-IIIA) (1)	204	324	153	249	55.6%	1.02 [0.90, 1.17]
Ibrahim 2020 (IIB-IIIC) (2)	93	181	58	159	44.4%	1.41 [1.10, 1.81]
Subtotal (95% CI)		**505**		**408**	**100.0%**	**1.18 [0.86, 1.62]**
Total events	297		211			

Heterogeneity: Tau² = 0.04; Chi² = 5.14, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 1.03 (P = 0.30)



Test for subgroup differences: Not applicable

Footnotes

(1) IIIC-IIA

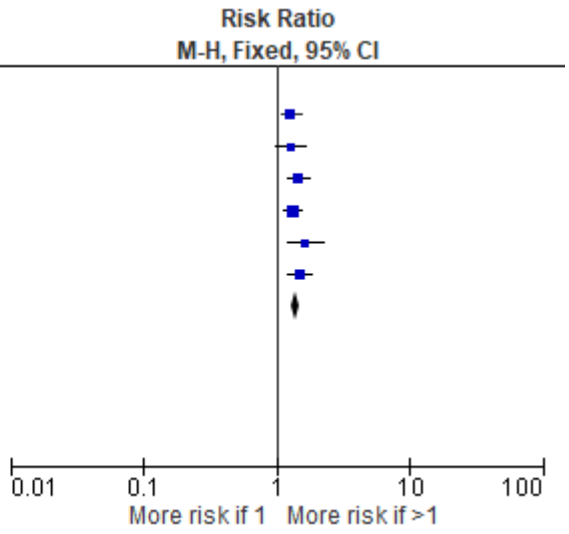
(2) IIB-III

Figure 18: number of positive lymph nodes as predictor of recurrence during follow-up

Study or Subgroup	2+ Events	Total	1 Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.28.2 Higher risk resected						
COMBI-AD (III) no adj	144	222	93	183	19.6%	1.28 [1.07, 1.52]
COMBI-AD (III) with adj	97	231	58	177	12.6%	1.28 [0.99, 1.66]
EORTC 18071 (III) adj	148	258	86	217	18.0%	1.45 [1.19, 1.76]
EORTC 18071 (III) no adj	178	256	116	220	24.0%	1.32 [1.14, 1.53]
KEYNOTE-054 (III) adj	91	287	44	227	9.5%	1.64 [1.19, 2.24]
KEYNOTE-054 (III) no adj	136	268	80	237	16.3%	1.50 [1.21, 1.86]
Subtotal (95% CI)		**1522**		**1261**	**100.0%**	**1.39 [1.28, 1.51]**
Total events	794		477			

Heterogeneity: Chi² = 3.49, df = 5 (P = 0.62); I² = 0%

Test for overall effect: Z = 7.75 (P < 0.00001)



Test for subgroup differences: Not applicable

Figure 19: Macrometastases as a predictor of recurrence during follow-up

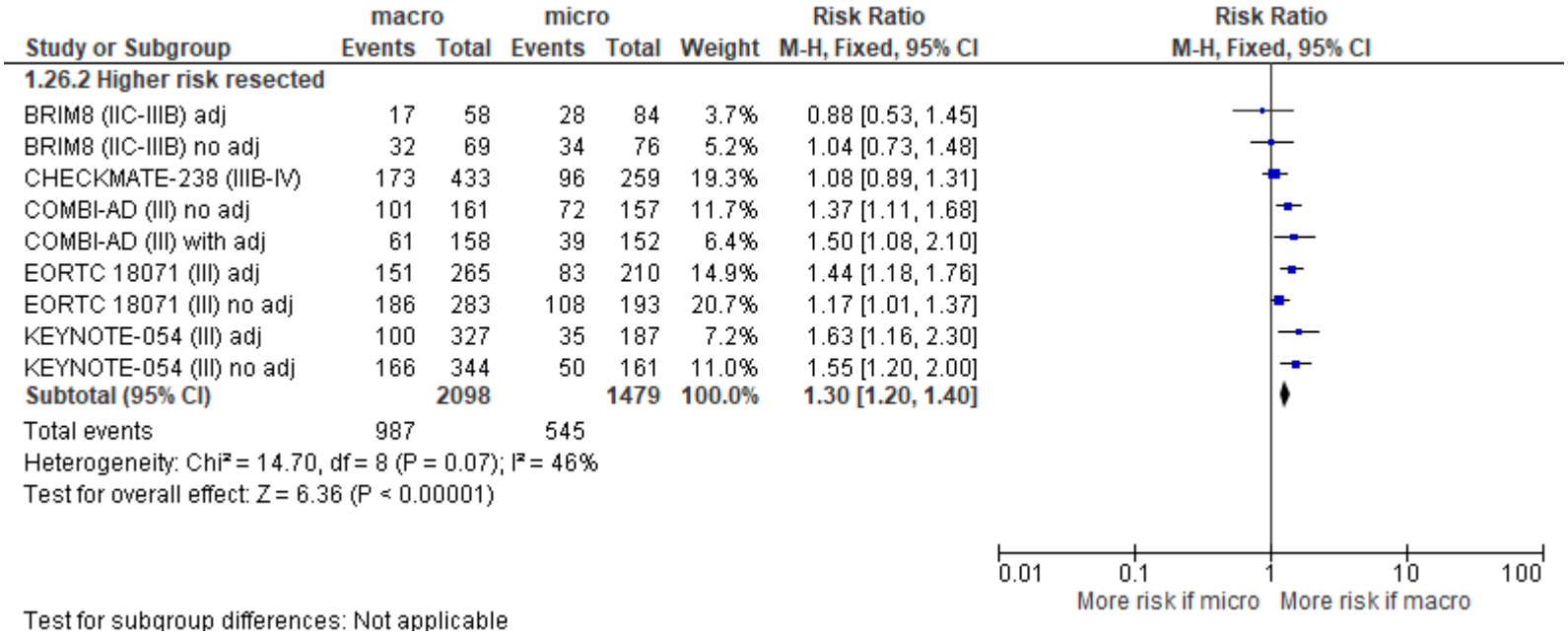
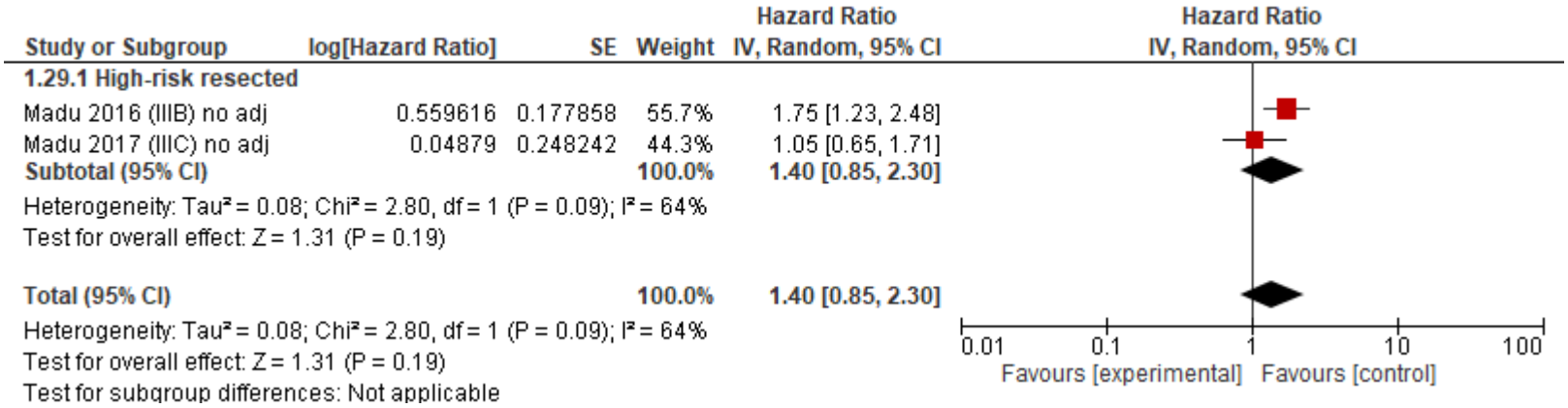


Figure 20: N-stage as a predictor of recurrence during follow-up



- Risk factors for all-cause mortality (6.1 and 6.4)

Figure 21: Gender as a predictor of melanoma-specific mortality during follow-up (hazard ratios)

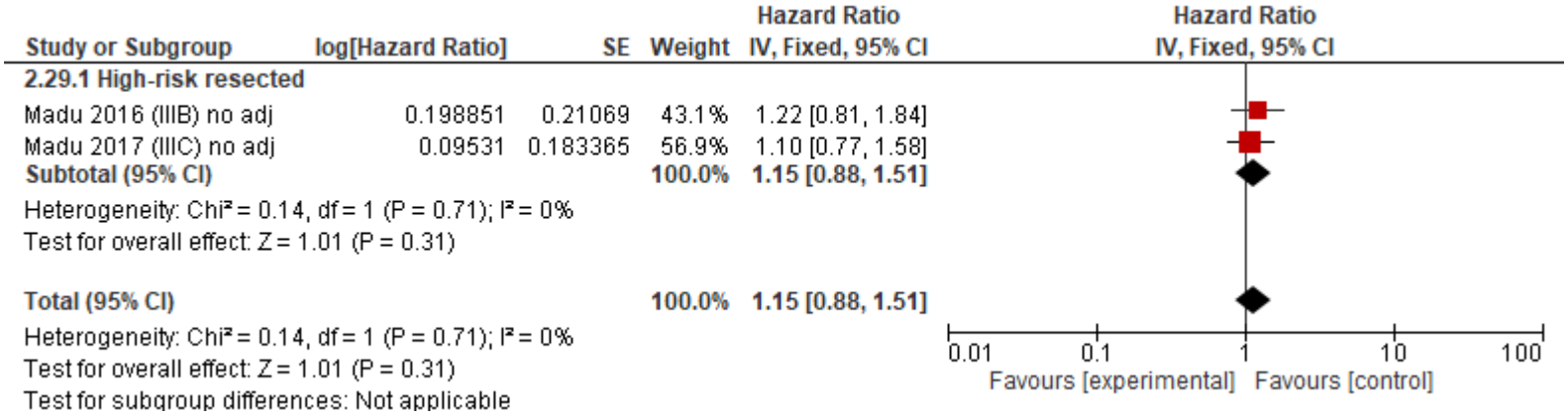


Figure 22: Gender as a predictor of overall survival during follow-up (risk ratios)

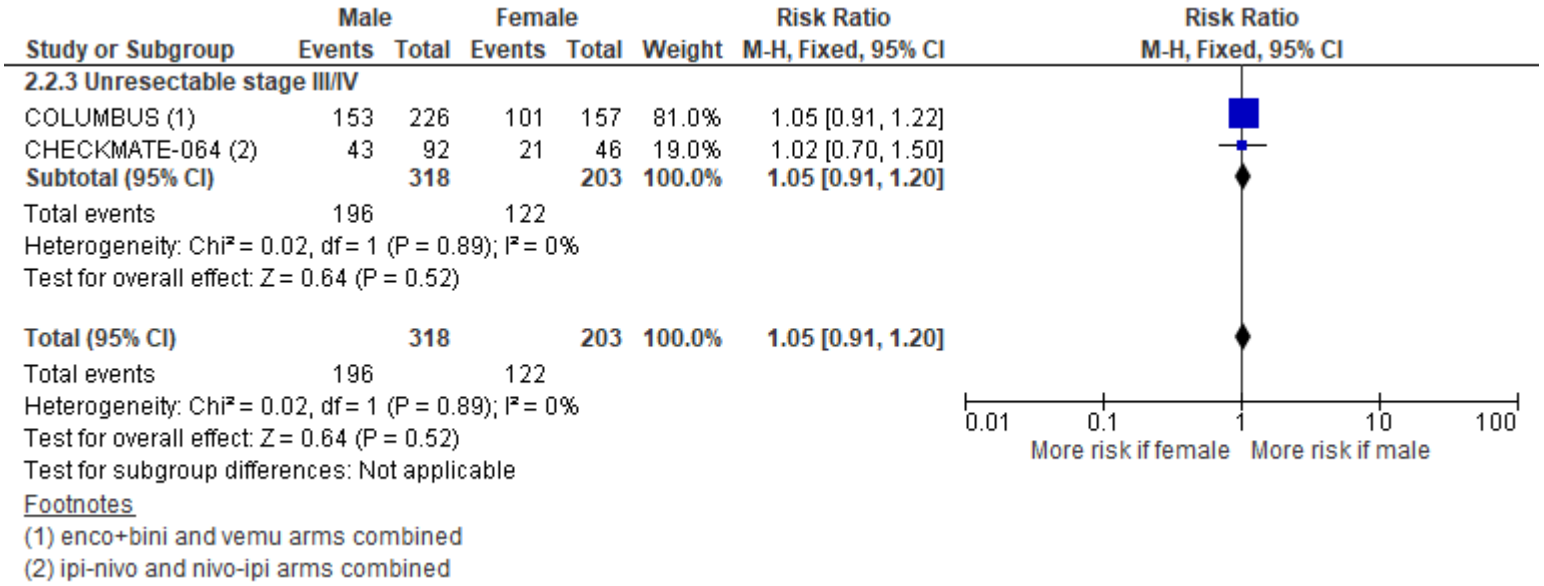


Figure 23: Age as a predictor of overall survival during follow-up

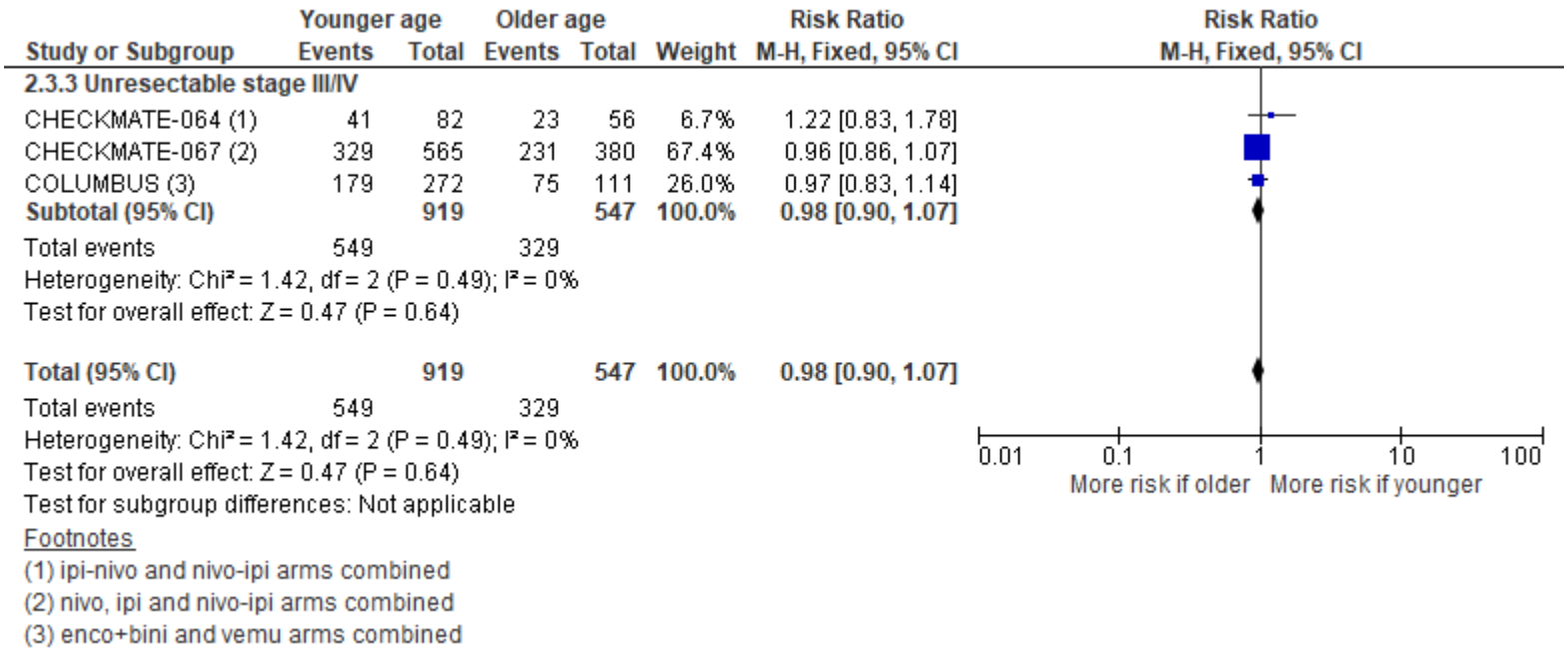
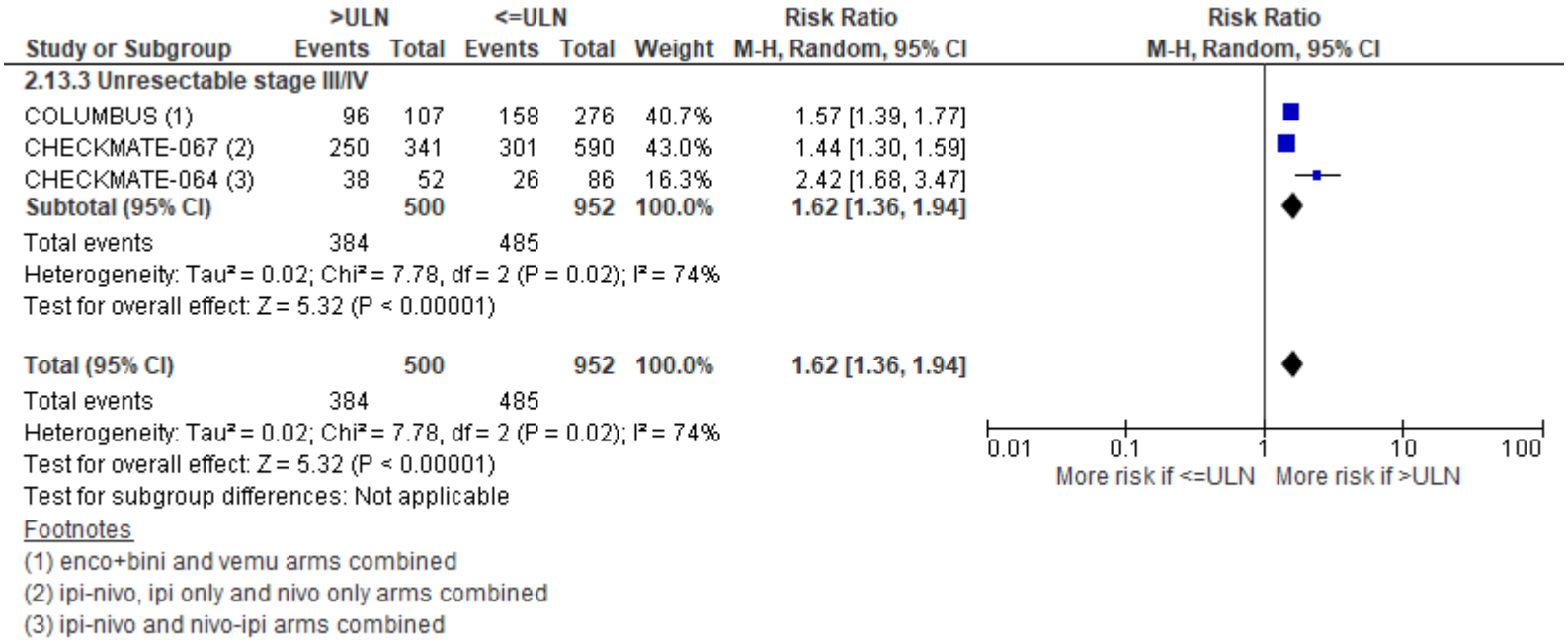


Figure 24: LDH as a predictor of overall survival during follow-up



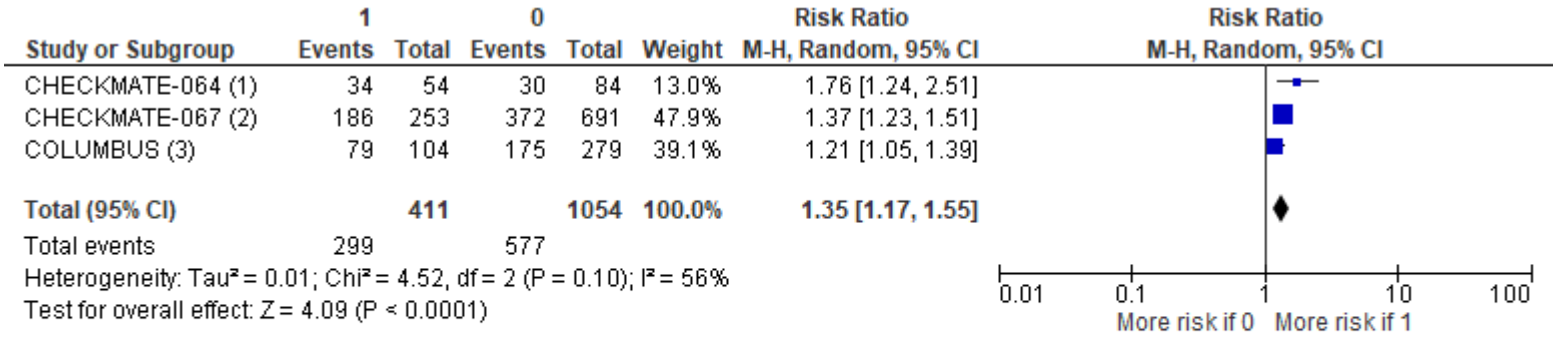
Footnotes

(1) enco+bini and vemu arms combined

(2) ipi-nivo, ipi only and nivo only arms combined

(3) ipi-nivo and nivo-ipi arms combined

Figure 25: ECOG status ≥1 as a predictor of overall survival during follow-up



Footnotes
(1) ipi-nivo and nivo-ipi arms combined
(2) ipi-nivo, ipi only and nivo only arms combined
(3) enco+bini and vemu arms combined

Figure 26: Trunk tumour location as a predictor of overall survival during follow-up

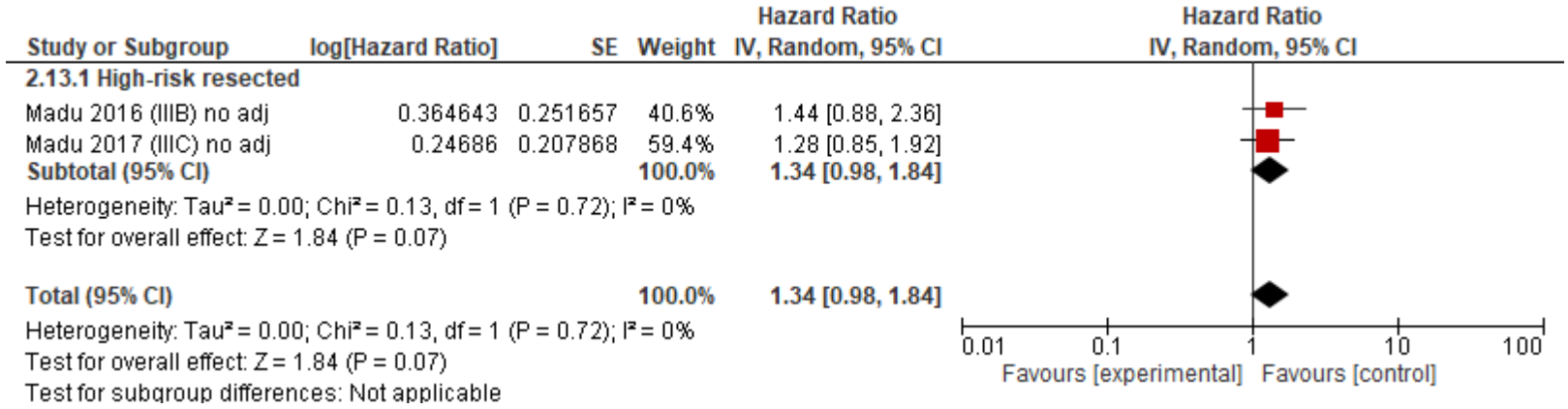


Figure 27: Head/neck tumour location as a predictor of overall survival during follow-up

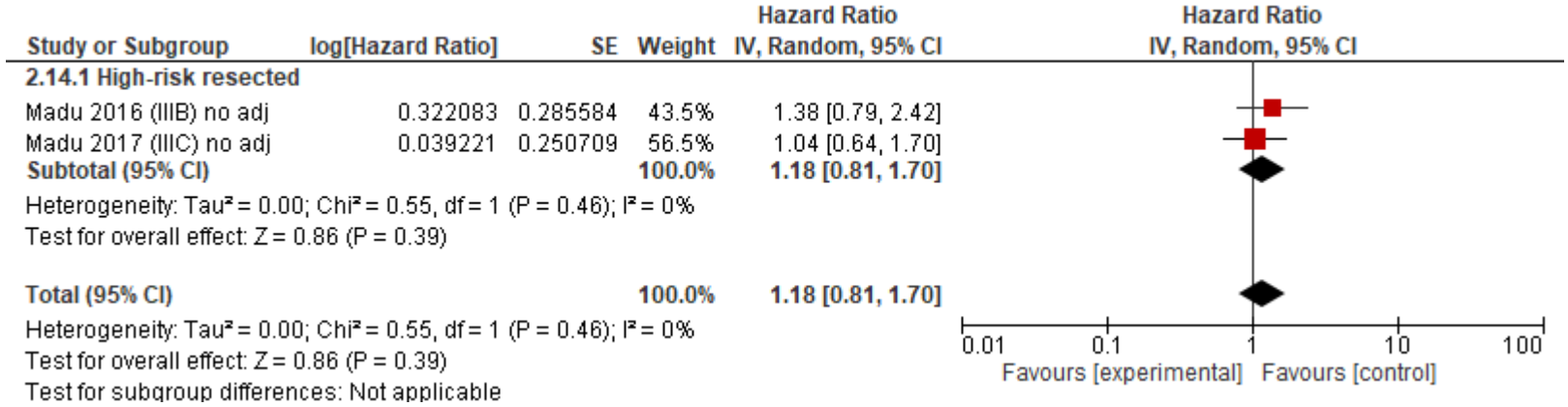


Figure 28: Ulceration as a predictor of overall survival during follow-up

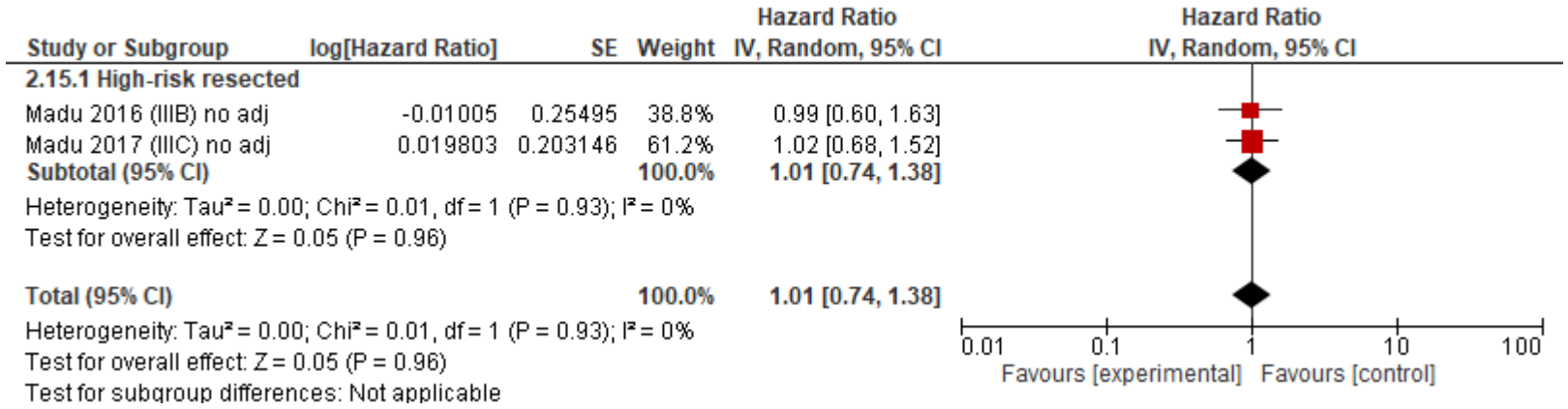
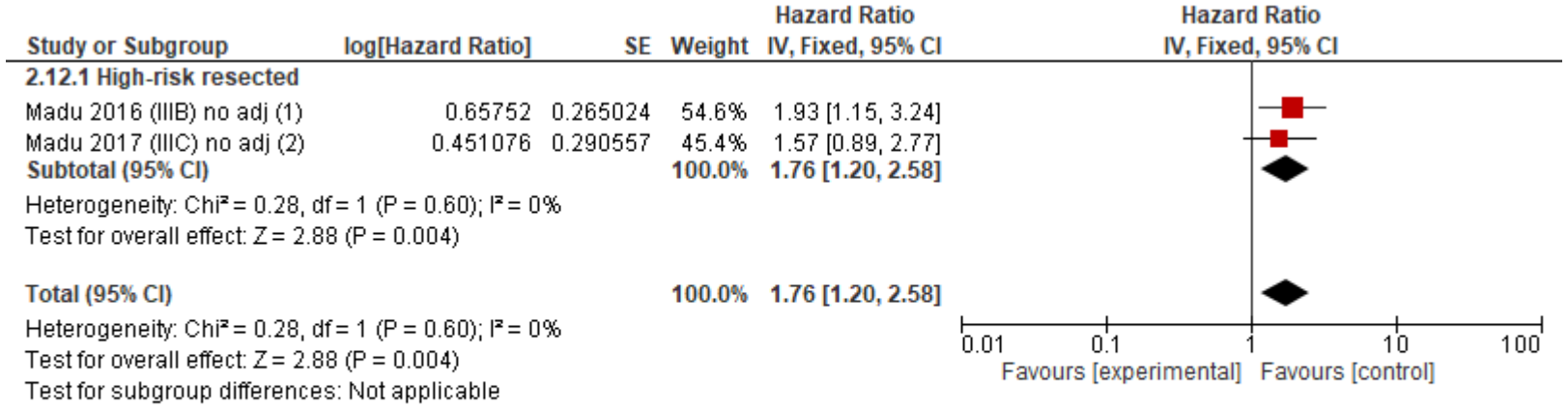


Figure 29: N-stage as a predictor of overall survival during follow-up



Footnotes

(1) adjusted for Breslow thickness, N-stage, sex, ASA classification, location, tumour histology, Breslow thickness, ulceration, type of operation,...

(2) adjusted for gender, age, location, Breslow thickness, Ulceration, Operation site, type of nodal involvement, time to LND, number of positive...

- Risk factors for brain metastases (6.3)

Figure 30: Disease stage as a predictor of brain metastases developing during follow-up

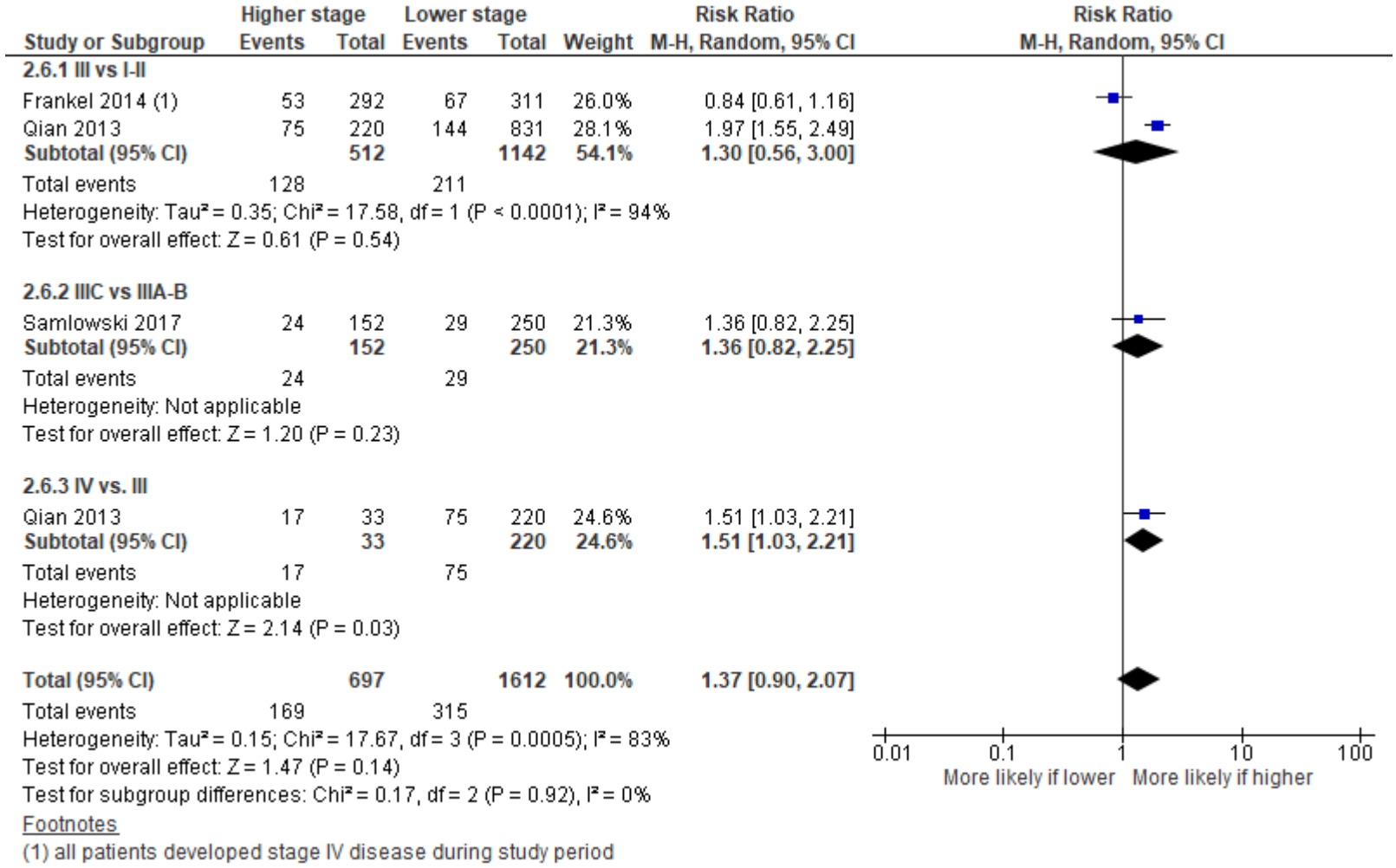


Figure 31: Gender as a predictor of brain metastases being present at baseline

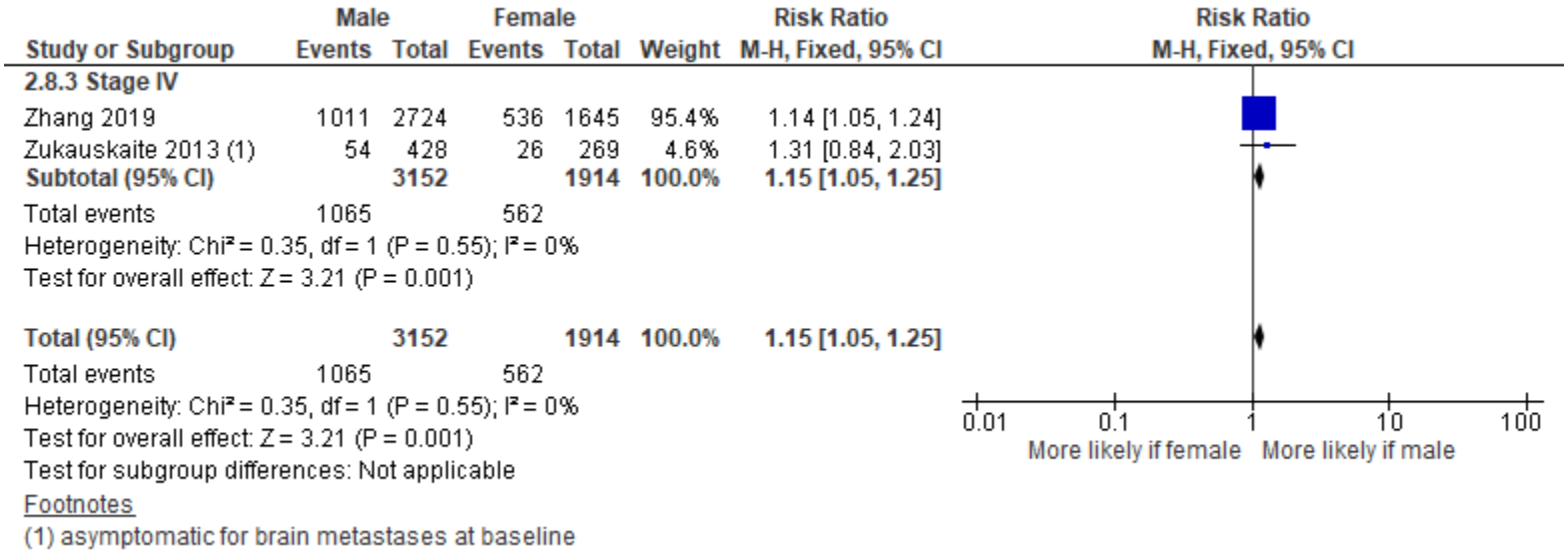
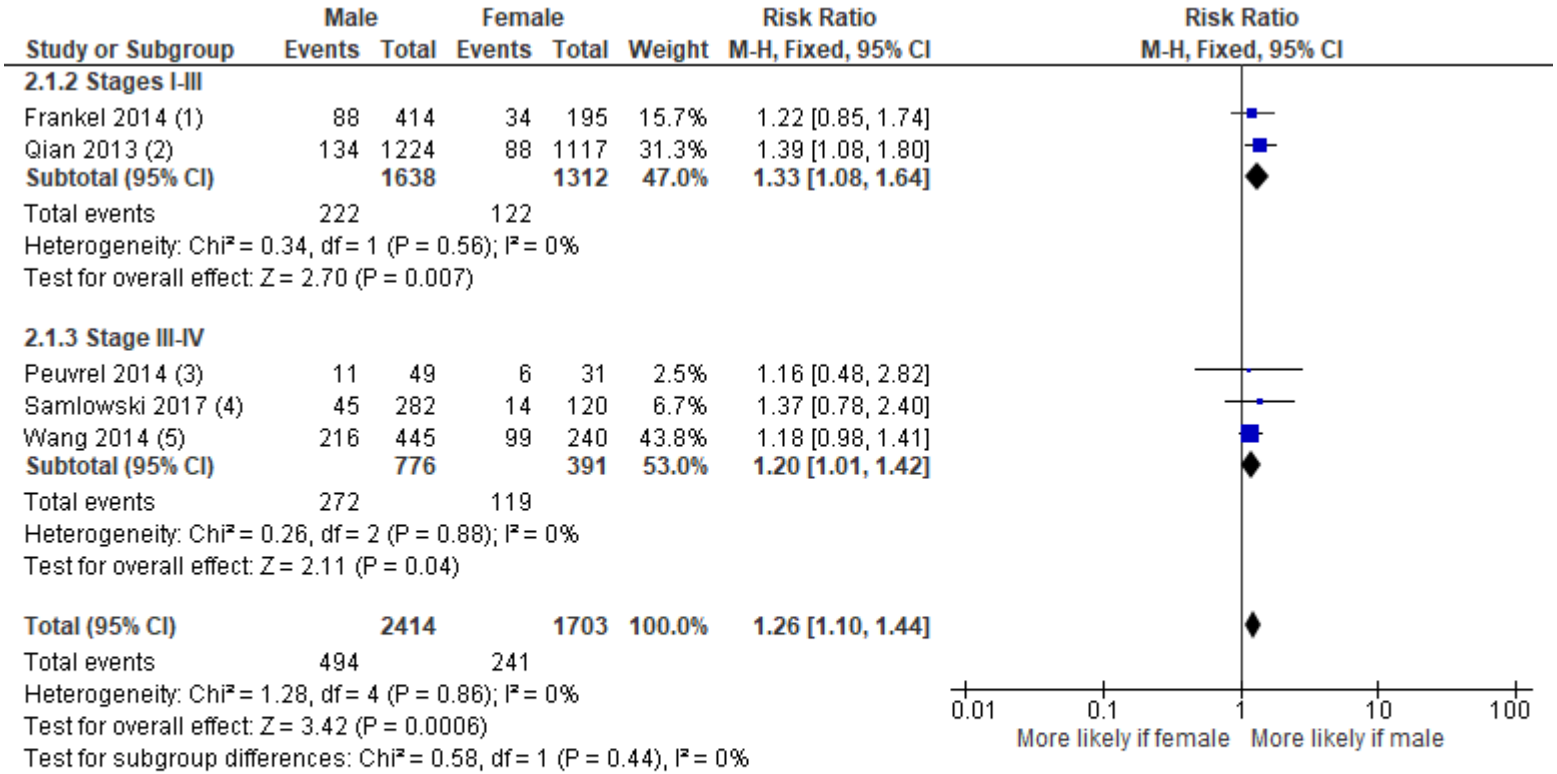


Figure 32: Gender as a predictor of brain metastases developing during follow-up



Footnotes

(1) I-III; 50% III

(2) 85% stage I-II

(3) stage III-IV BRAF-positive patients treated with vemurafenib

(4) Stage IIIA-IIIC, WLE + regional lymphadenectomy + received either adjuvant biochemo or high-dose interferon alpha-2B

(5) Chemotherapy naive stage IV patients

Figure 33: Head/neck primary tumour location as a predictor of brain metastases being present at baseline

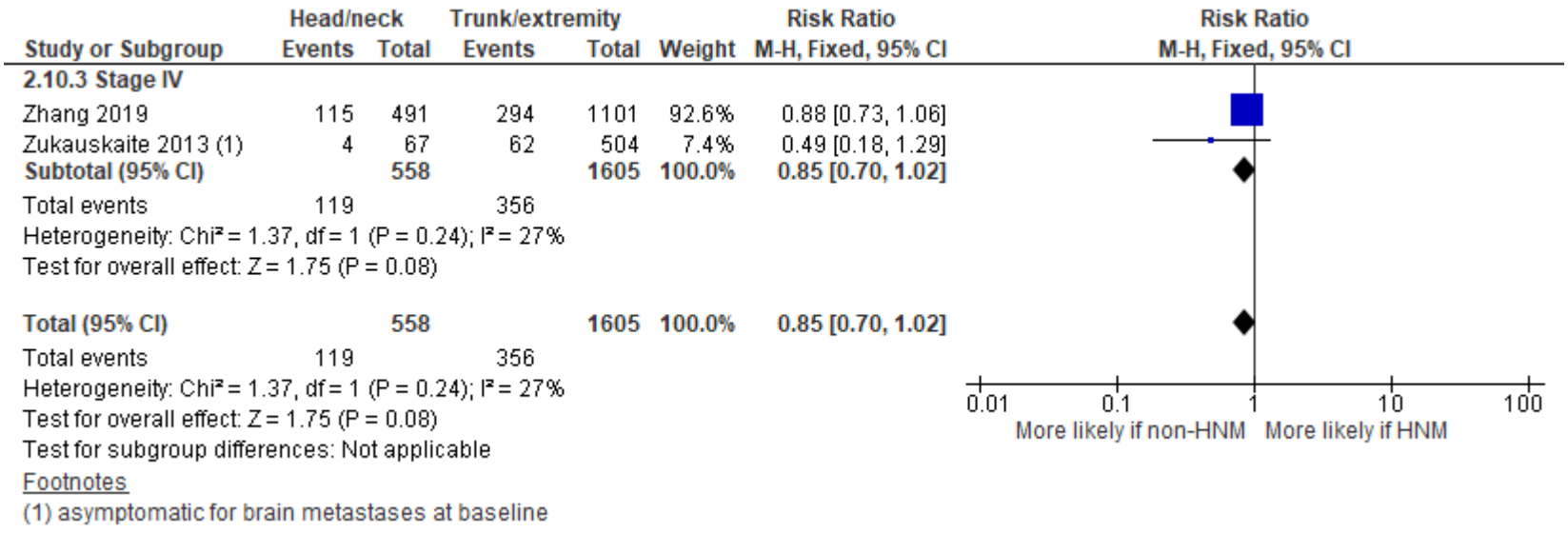


Figure 34: Trunk primary tumour location as a predictor of brain metastases being present at baseline

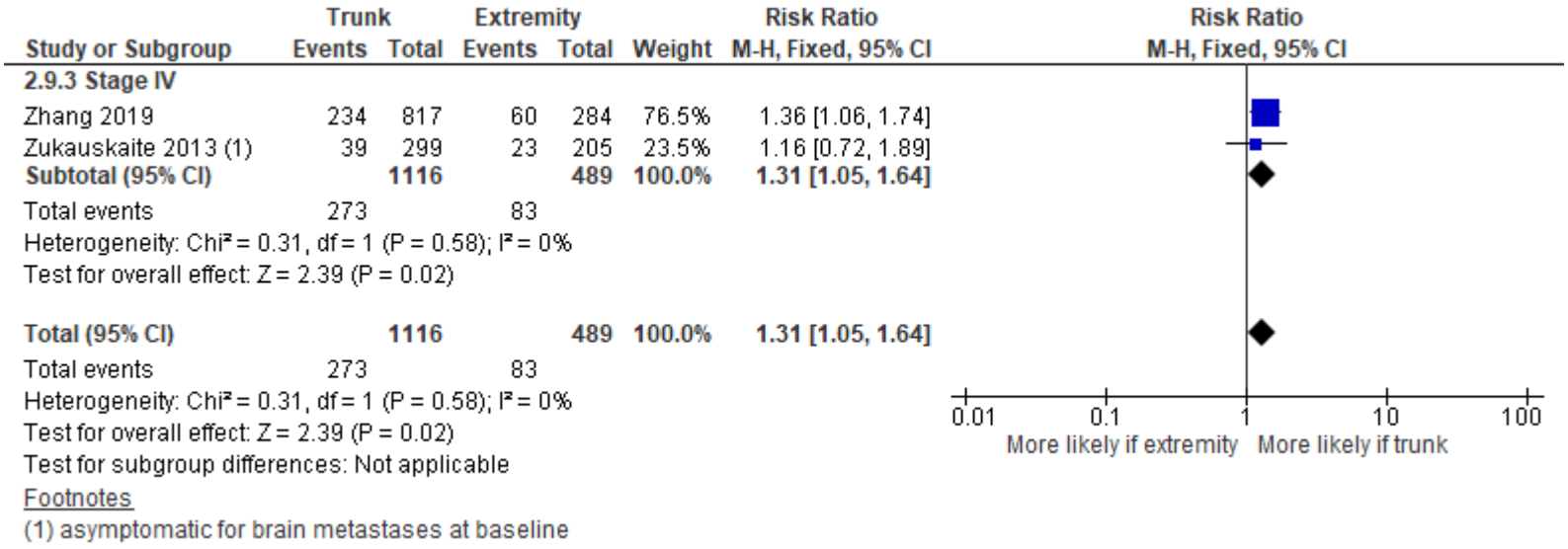
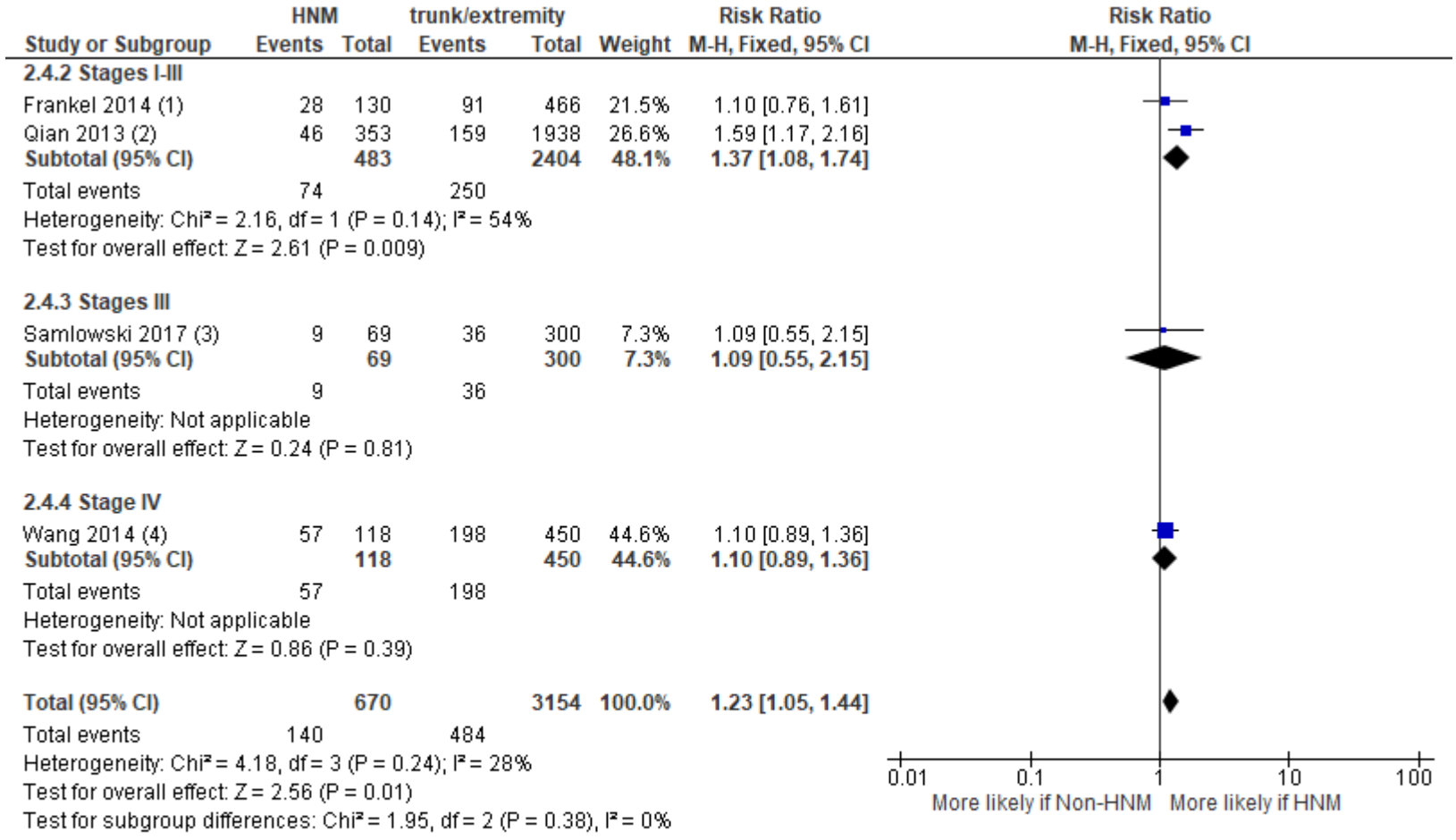


Figure 35: Head/neck primary tumour location as a predictor of brain metastases developing during follow-up



Footnotes

(1) I-III; 50% III

(2) 85% stage I-II

(3) Stage IIIA-IIIC, WLE + regional lymphadenectomy + received either adjuvant biochemo or high-dose interferon alpha-2B

(4) Chemotherapy naive

Figure 36: Trunk primary tumour location as a predictor of brain metastases developing during follow-up

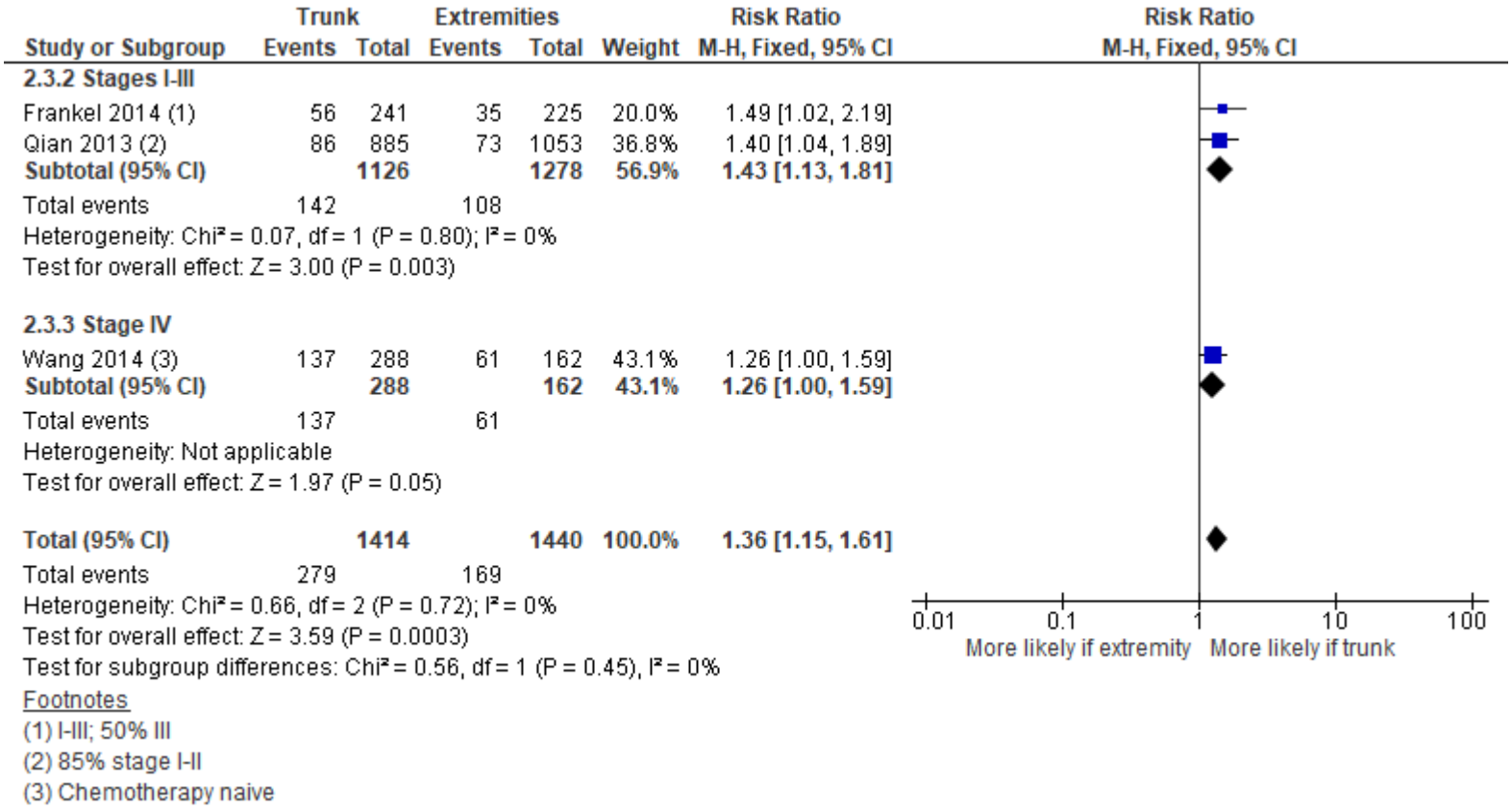
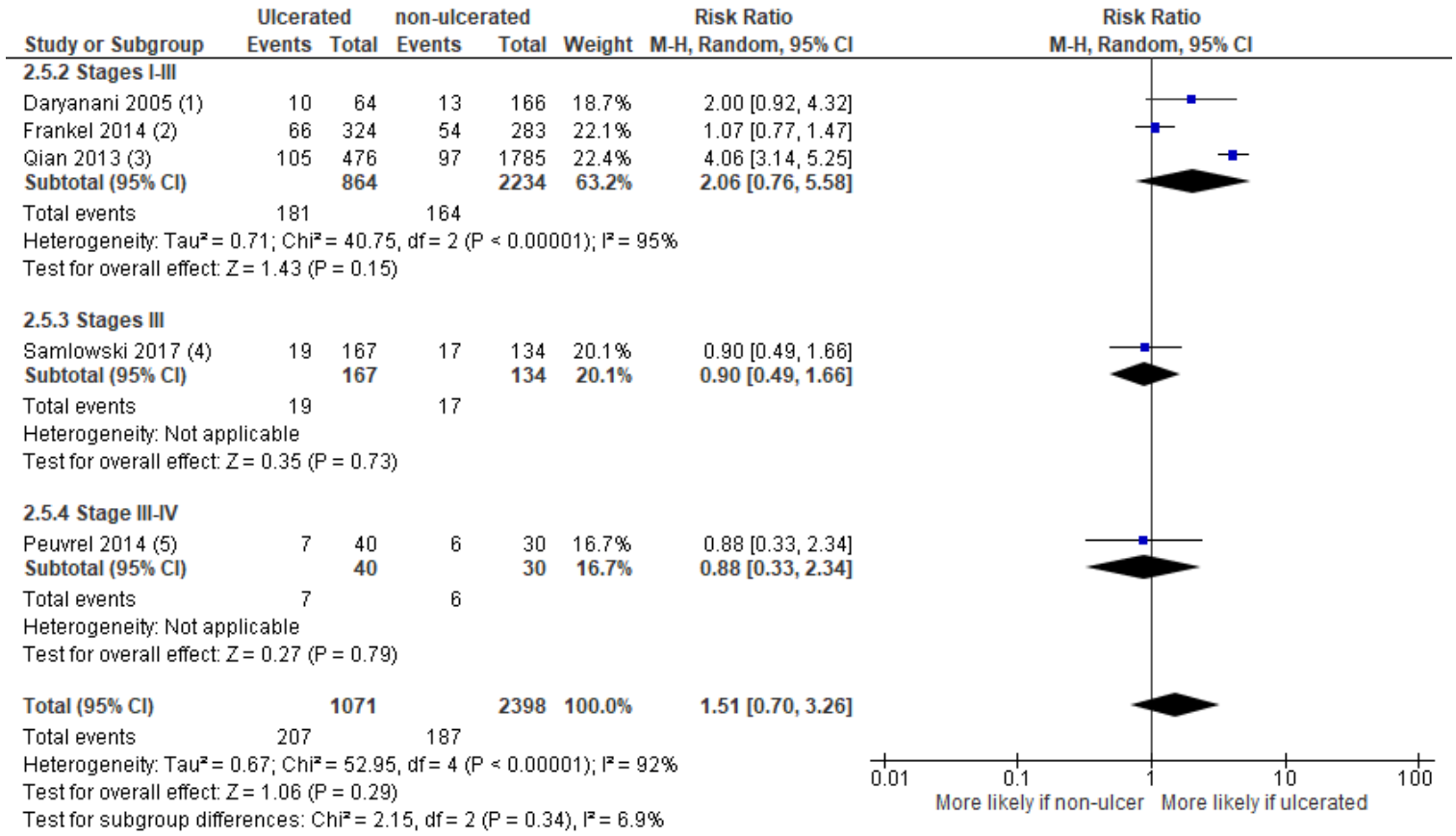


Figure 37: Ulceration as a predictor of brain metastases developing during follow-up



Footnotes

(1) I-III

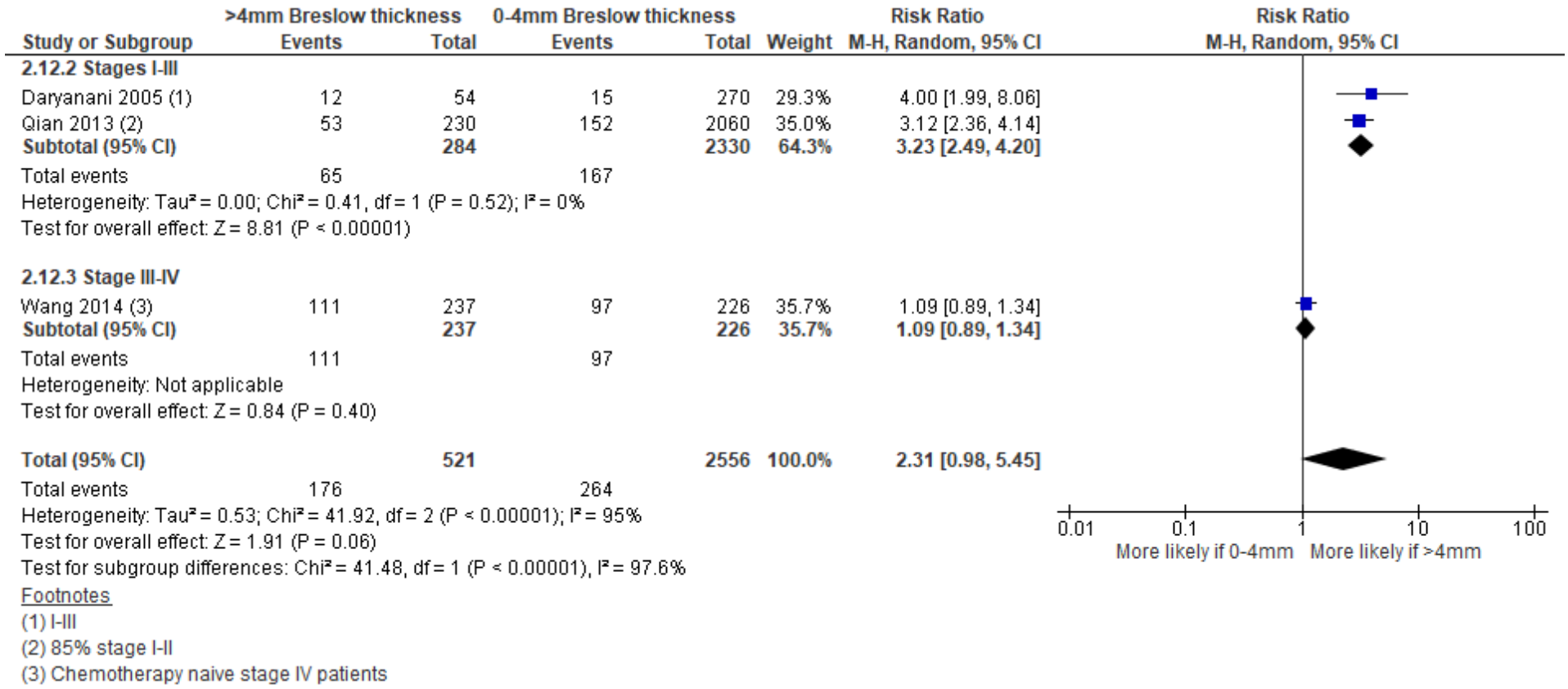
(2) I-III; 50% III

(3) 85% stage I-II

(4) Stage IIIA-IIIC, WLE + regional lymphadenectomy + received either adjuvant biochemo or high-dose interferon alpha-2B

(5) BRAF-positive patients treated with vemurafenib

Figure 38: Breslow thickness as a predictor of brain metastases developing during follow-up (random effects)



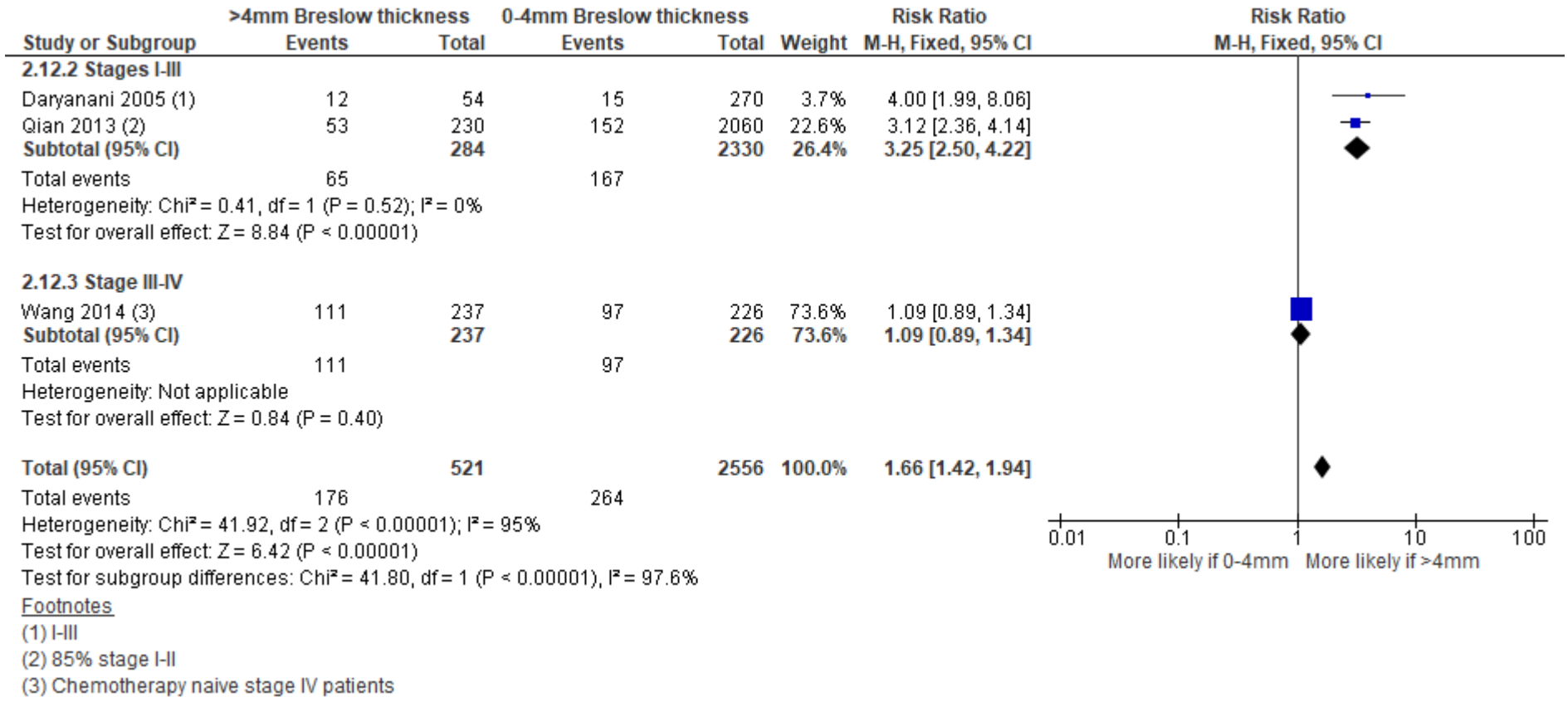
Footnotes

(1) I-III

(2) 85% stage I-II

(3) Chemotherapy naive stage IV patients

Figure 39: Breslow thickness as a predictor of brain metastases developing during follow-up (fixed effects)



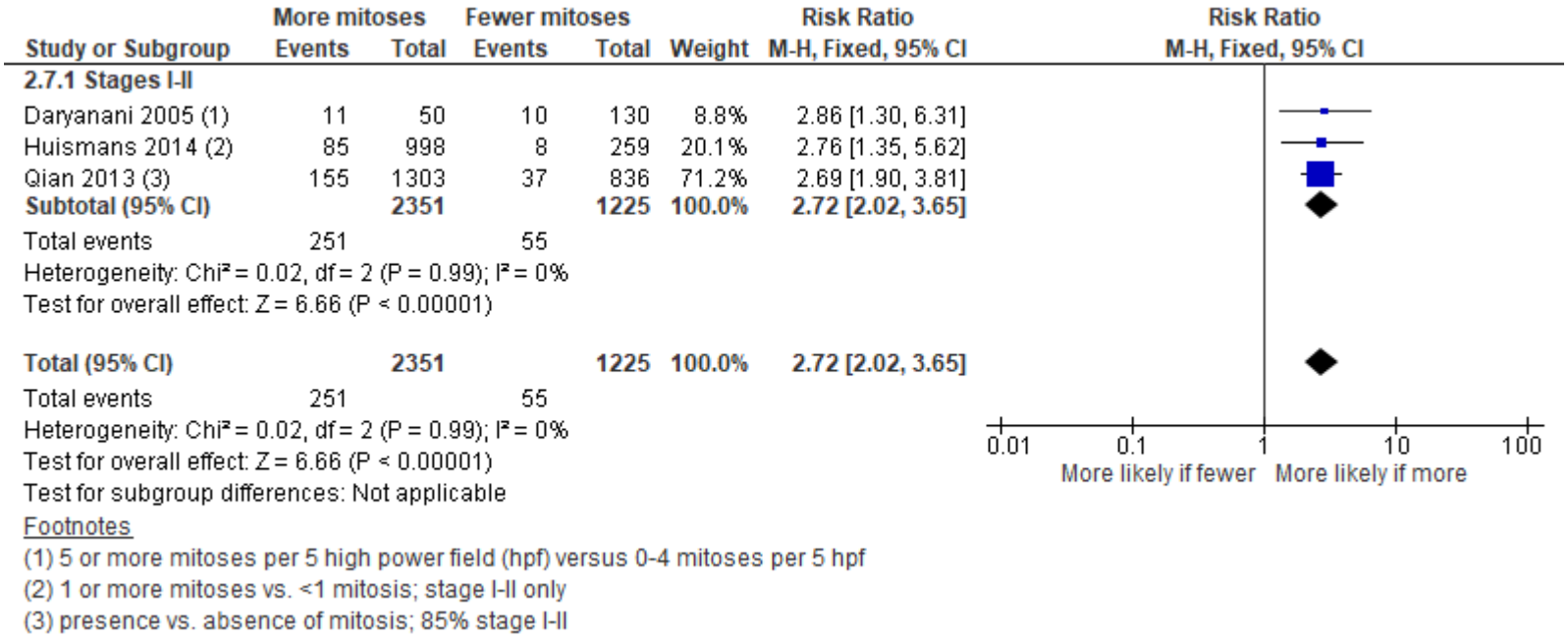
Footnotes

(1) I-III

(2) 85% stage I-II

(3) Chemotherapy naive stage IV patients

Figure 40: Mitotic rate as a predictor of brain metastases developing during follow-up



Footnotes

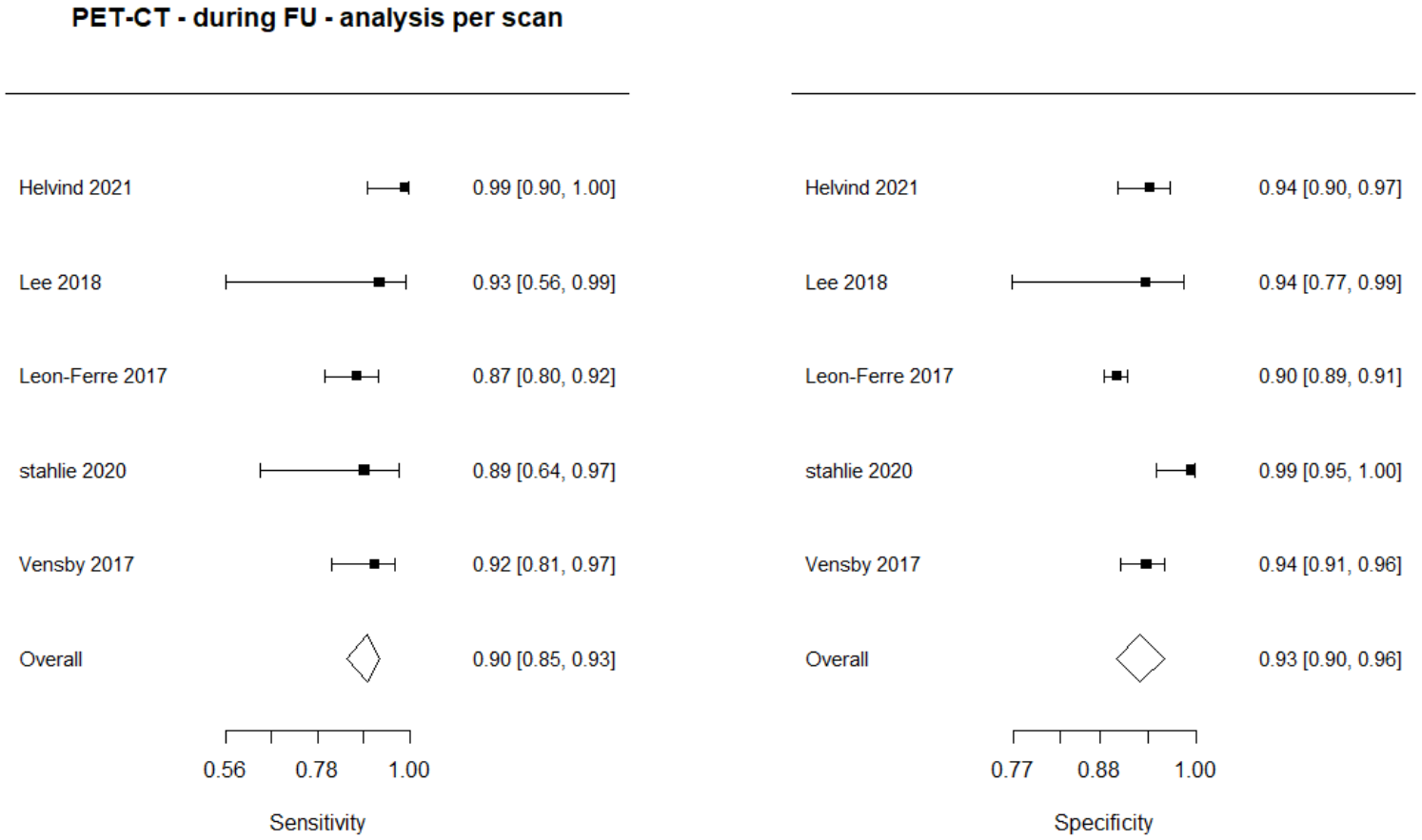
(1) 5 or more mitoses per 5 high power field (hpf) versus 0-4 mitoses per 5 hpf

(2) 1 or more mitoses vs. <1 mitosis; stage I-II only

(3) presence vs. absence of mitosis; 85% stage I-II

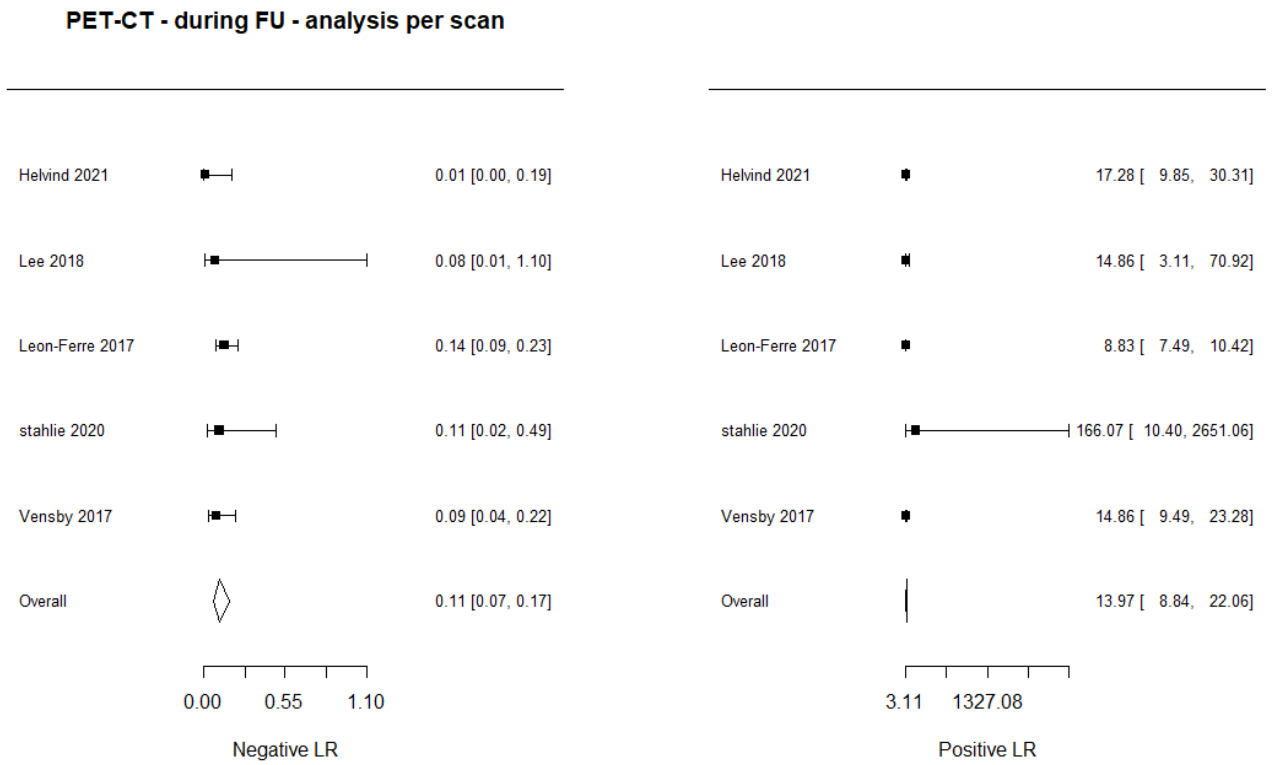
- Diagnostic accuracy of imaging during follow-up (6.2)

Figure 41: Sensitivity/specificity of PET-CT during follow-up of high-risk melanoma (per scan analysis)



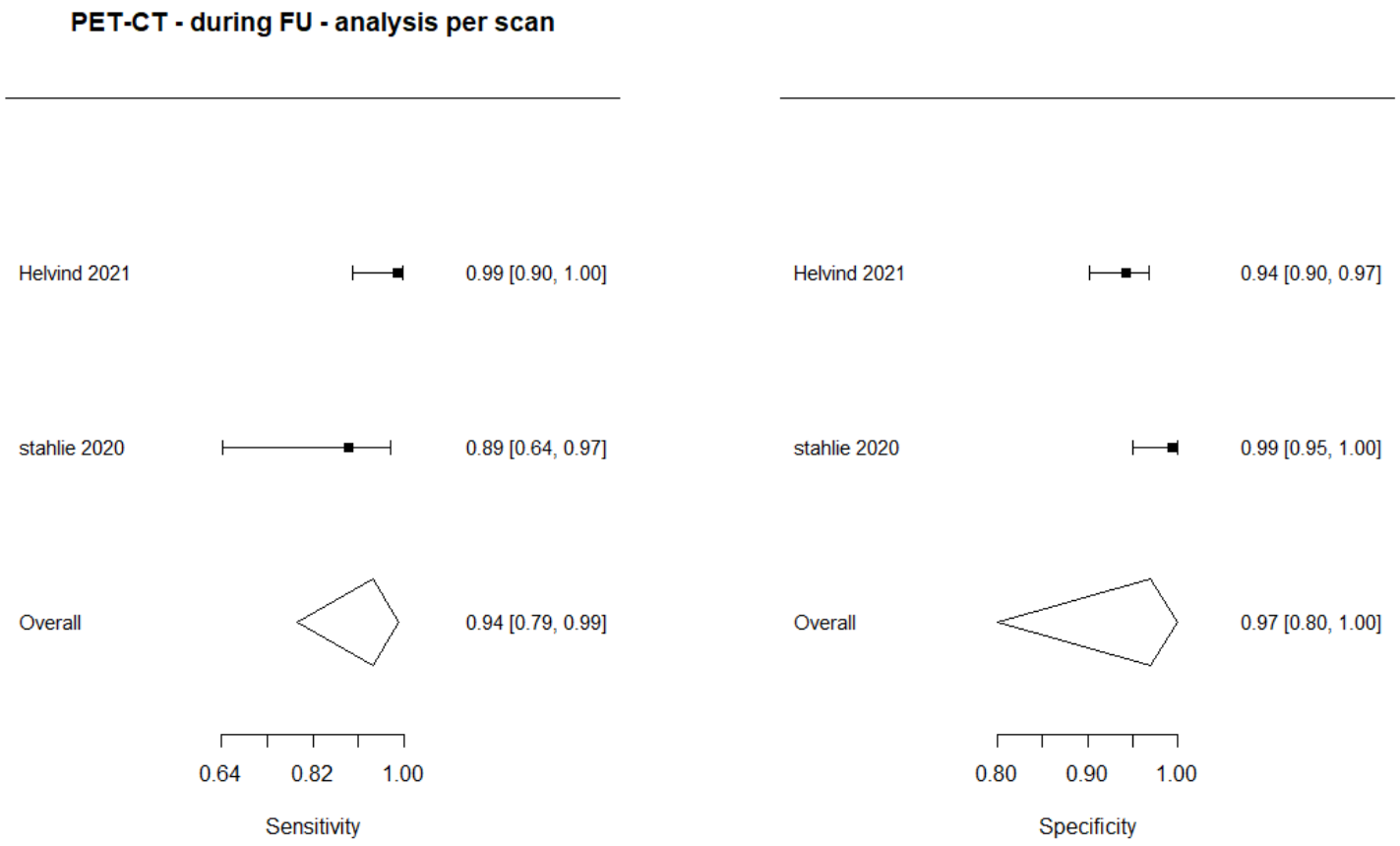
Sensitivity I^2= 0% Specificity I^2= 65.7%

Figure 42: Likelihood ratios of PET-CT during follow-up of high-risk melanoma (per scan analysis)



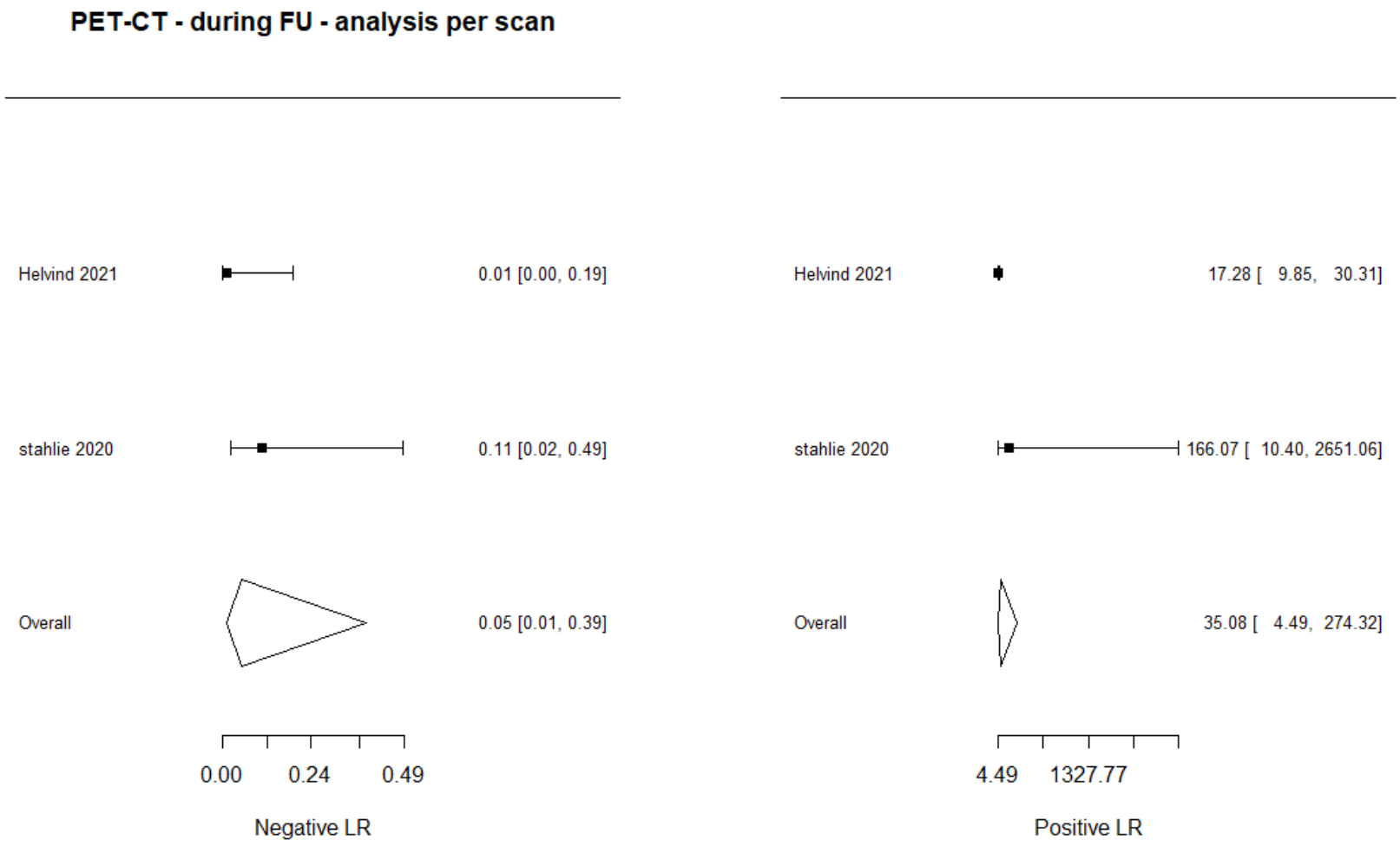
Negative LR I^2= 0.0% Positive LR I^2= 69.7%

Figure 43: Sensitivity/specificity of PET-CT during follow-up of high-risk melanoma (per scan analysis)



Sensitivity I^2= 49.7% Specificity I^2= 64.0%

Figure 44: Likelihood ratios of PET-CT during follow-up of high-risk melanoma (per scan analysis)

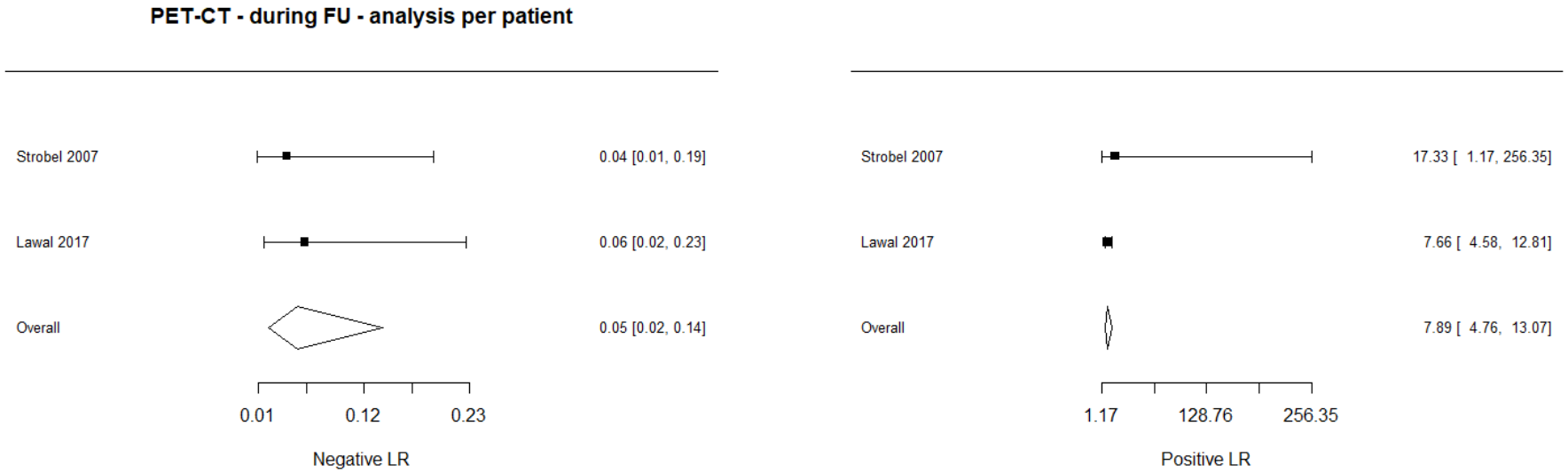


Negative LR I^2= 46.4% Positive LR I^2= 59.4%

Figure 45: Sensitivity/specificity of PET-CT during follow-up of melanoma (per patient analysis)

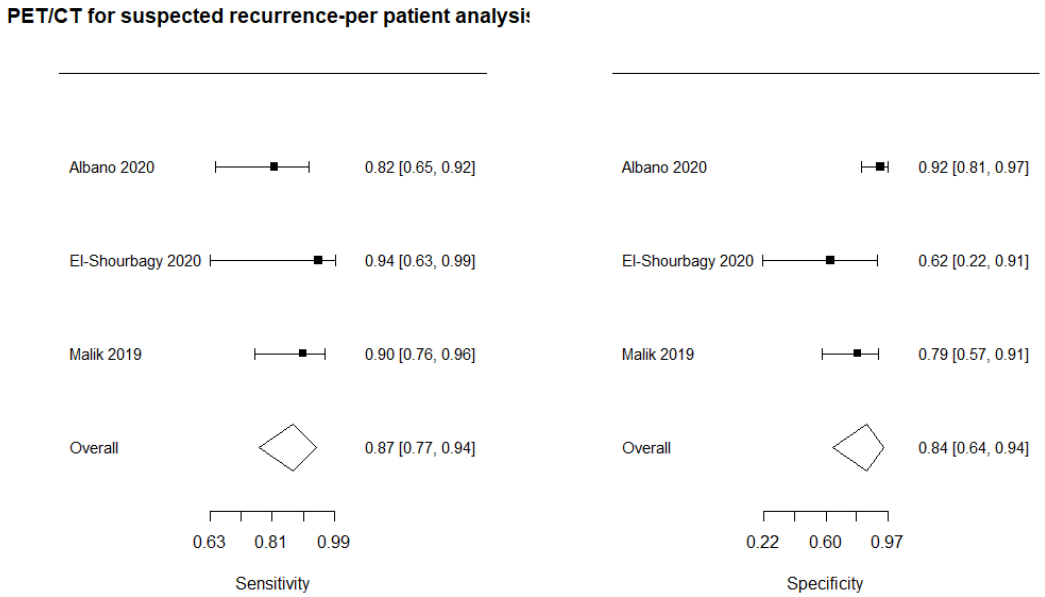
Sensitivity I^2=0% Specificity I^2=0%

Figure 46: Likelihood ratios of PET-CT during follow-up of high-risk melanoma (per patient analysis)



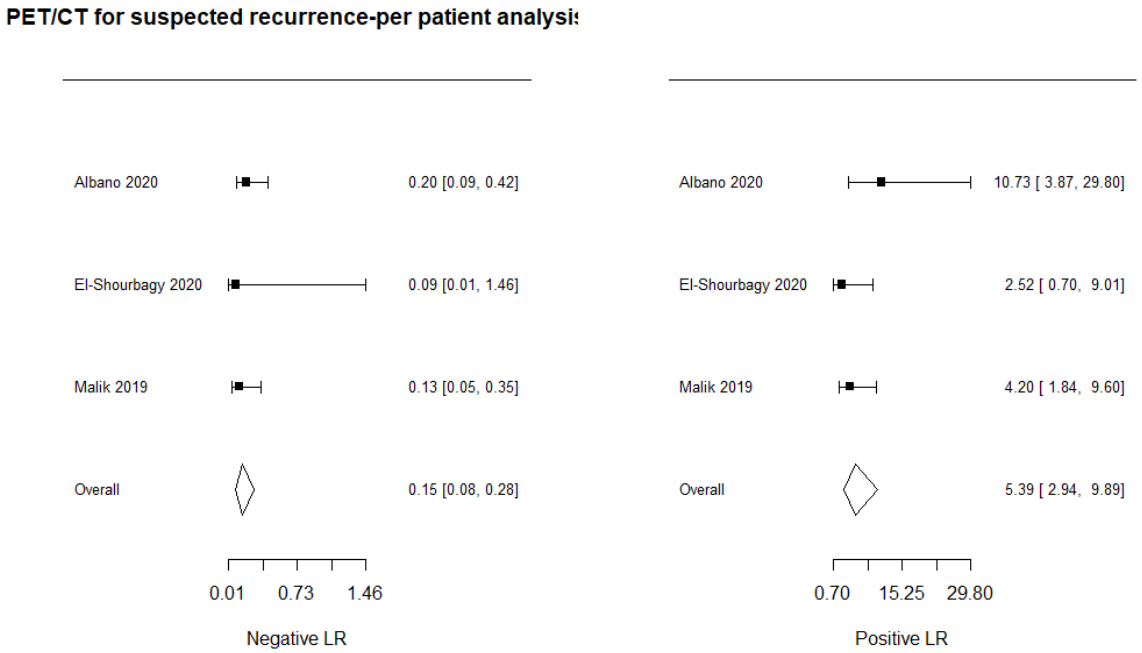
Negative LR I^2=0% Positive LR I^2=0%

Figure 47: Sensitivity and specificity for PET/CT for suspected recurrence (per patient analysis)



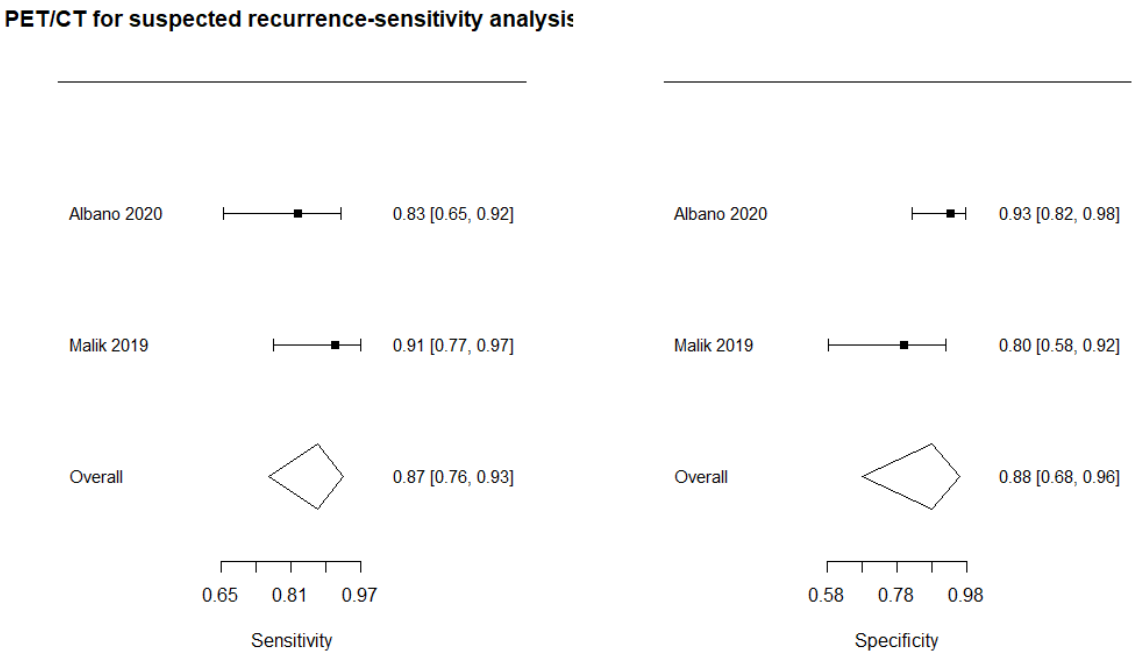
Sensitivity I^2=0% Specificity I^2=50.9%

Figure 48: Likelihood ratios for PET/CT for suspected recurrence (per patient analysis)



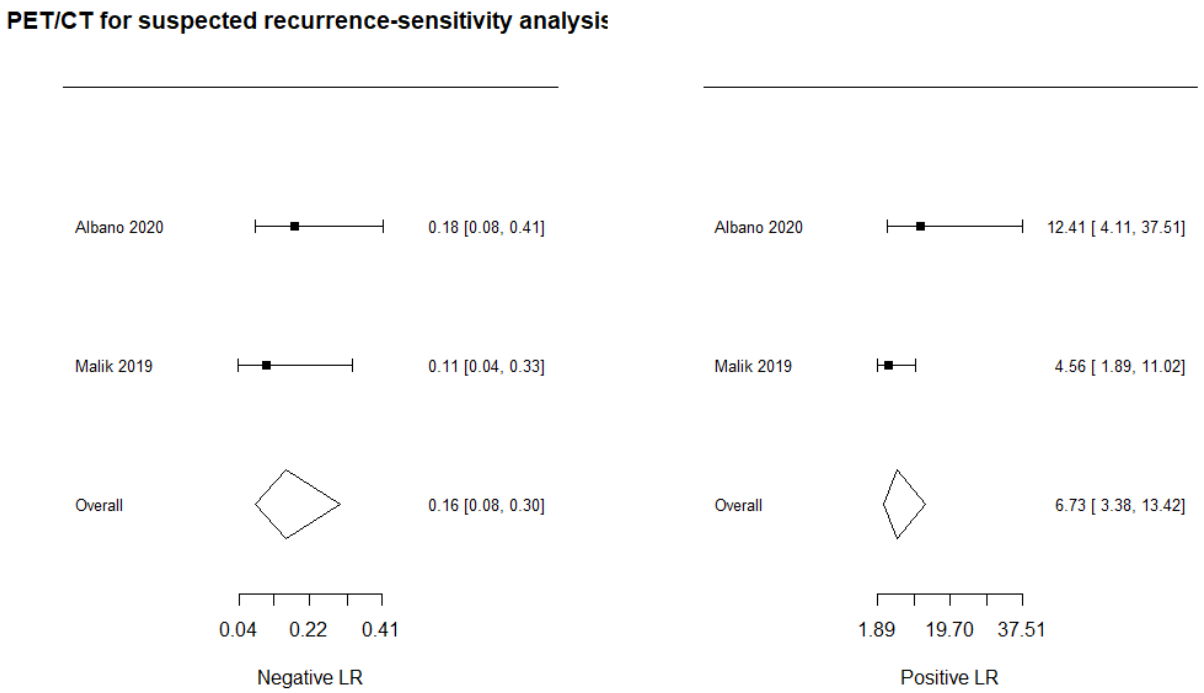
Negative LR I^2=0% Positive LR I^2= 45.8%

Figure 49: Sensitivity and specificity for PET/CT for suspected recurrence (per patient analysis) - *sensitivity analysis excluding high risk of bias studies*



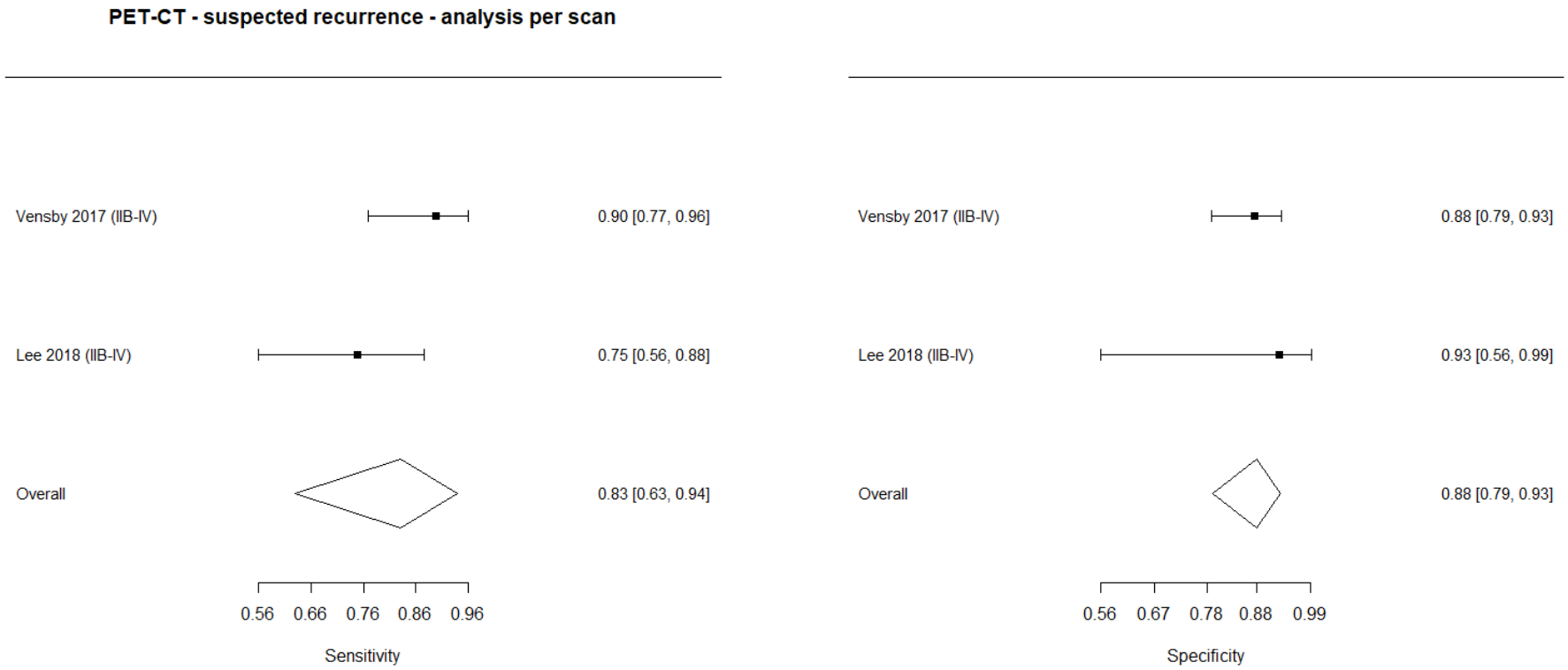
Sensitivity I^2=0% Specificity I^2=57.3%

Figure 50: Likelihood ratios for PET/CT for suspected recurrence (per patient analysis) - *sensitivity analysis excluding high risk of bias studies*



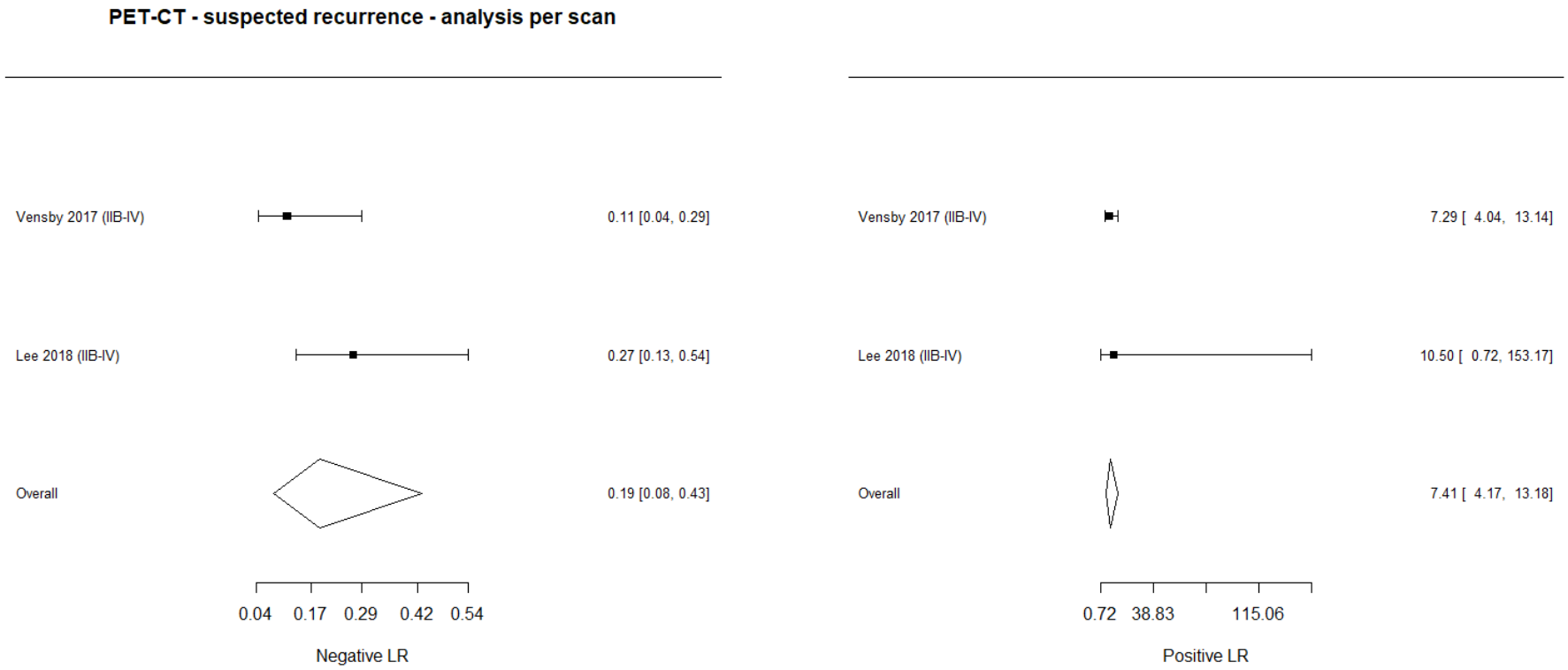
Negative LR I^2= 0% Positive LR I^2=48.1%

Figure 51: Sensitivity and specificity for PET/CT for suspected recurrence (per scan analysis)



Sensitivity I^2=85.5%% Specificity I^2=0.0%

Figure 52: Likelihood ratios for PET/CT for suspected recurrence (per scan analysis)



Negative LR I^2= 99.7% Positive LR I^2=0.0%

Appendix F GRADE tables

6.1 Surveillance strategies following surgery

- Risk stratified vs conventional follow-up for IB-IIC

Table 35 Efficacy of risk-stratified surveillance schedule (RCTs)

Outcome	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Risk-stratified	Conventional					
Recurrences detected during follow-up: RR>1 indicates greater risk in risk-stratified follow-up arm										
3 years	Melfo study: UK	207	RR 1.05 (0.56, 1.97)	17/104	16/103	Not serious	Not serious	N/A	Very serious[2]	Low
3 years	Melfo study: The Netherlands	180	RR 1.60 (0.76, 3.38)	15/93	10/87	Not serious	Not serious	N/A	Very serious[2]	Low
All-cause mortality during follow-up: RR>1 indicates greater risk in risk-stratified follow-up arm										
3 years	Melfo study: UK	207	RR 0.81 (0.35, 1.87)	9/104	11/103	Not serious	Not serious	N/A	Very serious[2]	Low
3 years	Melfo study: The Netherlands	180	RR 1.07 (0.42, 2.72)	8/87	8/93	Not serious	Not serious	N/A	Very serious[2]	Low
Missed visits during follow-up: RR>1 indicates greater risk in risk-stratified follow-up arm										
1 year (melanoma clinic)	Melfo study: UK	207	RR 0.23 (0.09, 0.57)	5/104	22/103	Not serious	Not serious	N/A	Not serious	High
2-3 years (melanoma clinic)	Melfo study: UK	207	RR 1.10 (0.47, 2.60)	10/104	9/103	Not serious	Not serious	N/A	Very serious[2]	Low
3 years (outpatient clinic)	Melfo study: The Netherlands	110	RR 0.59 (0.18, 1.91)	4/54	7/56	Not serious	Not serious	N/A	Very serious[2]	Low

Outcome	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Risk-stratified	Conventional					
Extra visits during follow-up: RR>1 indicates greater risk in risk-stratified follow-up arm										
1 year (melanoma clinic)	Melfo study: UK	207	RR 2.34 (1.22, 4.48)	26/104	11/103	Not serious	Not serious	N/A	Serious[3]	Moderate
2-3 years (melanoma clinic)	Melfo study: UK	207	RR 1.52 (0.84, 2.74)	23/104	15/103	Not serious	Not serious	N/A	Serious[3]	Moderate
3 years (outpatient clinic)	Melfo study: The Netherlands	110	RR 2.67 (1.21, 5.87)	18/54	7/56	Not serious	Not serious	N/A	Not serious	High
3 years (GP+hospital appointments)	Melfo study: The Netherlands	110	RR 1.01 (0.84, 1.23)	43/54	44/56	Not serious	Not serious	N/A	Not serious	High
State-trait anxiety inventory: Positive MD indicates greater anxiety in risk-stratified follow-up arm										
3 years	Melfo study: UK	170	MD: 1.50 (-4.43, 7.43)	35 (22.9)	33.5 (15.9)	Serious[1]	Not serious	N/A	Not serious	Moderate
	Melfo study: The Netherlands	110	MD: 0.10 (-3.14, 3.34)	30.4 (7.9)	30.3 (9.4)	Serious[1]	Not serious	N/A	Not serious	Moderate
Cancer worry scale: Positive MD indicates more worries in risk-stratified follow-up arm										
3 years	Melfo study: UK	170	MD: -0.30 (-0.90, 0.30)	6.5 (2.0)	6.8 (2.0)	Serious[1]	Not serious	N/A	Not serious	Moderate
	Melfo study: The Netherlands	110	MD: -0.20 (-0.74, 0.34)	3.8 (1.0)	4.0 (1.8)	Serious[1]	Not serious	N/A	Not serious	Moderate
Impact-of-event scale: Positive MD indicates higher level of stress response symptoms in risk-stratified follow-up arm										

Outcome	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Risk-stratified	Conventional					
3 years	Melfo study: UK	170	MD: 1.10 (-1.18, 3.38)	20.6 (8.1)	19.5 (7)	Serious[1]	Not serious	N/A	Not serious	Moderate
	Melfo study: The Netherlands	110	MD -7.80 (-12.80, -2.80)	6.2 (8.5)	14 (17)	Serious[1]	Not serious	N/A	Serious[4]	Moderate
RAND-36 (mental component): Positive MD indicates greater mental functioning in risk-stratified follow-up arm										
RAND-36 mental component	Melfo study: UK	170	MD: 0.00 (-2.32, 2.32)	53 (8.4)	53 (9.3)	Serious[1]	Not serious	N/A	Not serious	Moderate
	Melfo study: The Netherlands	110	MD: 0.80 (-1.79, 3.39)	54.3 (5.3)	53.5 (8.3)	Serious[1]	Not serious	N/A	Not serious	Moderate
RAND-36 (physical component): Positive MD indicates greater physical functioning in risk-stratified follow-up arm										
RAND-36 physical component	Melfo study: UK	170	MD: -0.50 (-3.43, 2.42)	50.4 (9.1)	50.9 (10.3)	Serious[1]	Not serious	N/A	Not serious	Moderate
	Melfo study: The Netherlands	110	MD: -2.10 (-5.68, 1.48)	50.3 (10.6)	52.4 (8.4)	Serious[1]	Not serious	N/A	Serious[5]	Low

1. This outcome was marked down once for risk of bias due to differences between groups in baseline scores for this outcome.
2. 95% CIs cross both line of the MID (0.8, 1.25)
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. 95% Cis cross one line of the MID (half the SD of the conventional follow-up arm: 8.5)
5. 95% Cis cross one line of the MID (half the SD of the conventional follow-up arm; 4.2)

- Cross-sectional imaging use in follow-up of II-III disease

Table 36 Efficacy of imaging in follow-up of stage II-III disease

Timepoint	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Surveillance with imaging	Surveillance without imaging					
Recurrences detected during follow-up: RR>1 indicated greater number of recurrences detected among those who underwent imaging										
Minimum of 12 months (follow-up length varied between groups)	Ravichandran 2020	179	RR 1.10 (0.75, 1.60)	74/143	17/36	Very serious[1]	Not serious	N/A	Very serious[2]	Very low
Imaging detected recurrences during follow-up: RR>1 indicated greater number of recurrences detected among those who underwent imaging										
Minimum of 12 months (follow-up length varied between groups)	Ravichandran 2020	180	RR 16.11 (2.31, 112.24)	64/143	1/36	Very serious[1]	Not serious	N/A	Very serious[2]	Very low

1. Study was at high risk of bias
2. 95% CIs cross both line of the MID (0.8, 1.25)

- Predictors of recurrence/progression during follow-up of resected disease
  - *Nomograms to predict all recurrences*

Table 37 nomograms

Disease stage(s)	No. Studies	Sample size	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
EORTC nomogram								

Disease stage(s)	No. Studies	Sample size	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
SLN negative	El Sharouni 2021	8,795	C-statistic: 0.70 (0.68, 0.71)	Serious[1]	Not serious	N/A	Serious[2]	Low
	Ipenburg 2019	4,235	C-statistic: 0.69 (0.67, 0.71)	Serious[1]	Not serious	N/A	Serious[2]	Low
EORTC-DeCOG nomogram								
SLN positive	Verver 2020	692	C-statistic: 0.70 (0.67, 0.74)	Serious[1]	Not serious	N/A	Serious[2]	Low

1. Study was at moderate risk of bias.
2. C-statistic confidence intervals cross one boundary of interpretation (0.70).

- *Effect of stage IIC - IIIC*

Table 38 Stage to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Increased risk of recurrence alongside disease stage before and after correcting for other risk factors										
IIIC vs IIIA	Grotz 2014[1]	317	Unadjusted HR 3.81 (2.52,5.77)	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
			Adjusted HR 3.96 (2.48,6.33)[2]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
IIIB vs IIIA	Grotz 2014[1]	317	Unadjusted HR 1.89 (1.25,2.85)	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
			Adjusted HR 2.20 (1.43,3.40)[2]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate

1. Patients were randomised to receive adjuvant GMCSF or no adjuvant therapy.
2. Adjusted for Gender, age, stage or Breslow depth.
3. Study was at moderate risk of bias.

- *Gender*

Table 39 Gender to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect sizes >1 indicated greater risk if male (Figure 1 and Figure 2)										
Lower risk (most patients were stage I-II)	6	2,589	RR 1.40 (1.25, 1.57)	471/1359	294/1230	Serious[1]	Not serious	Not serious	Not serious	Moderate
Higher risk (IIC-IV)	14	4,237	RR 1.14 (1.06, 1.22)	1211/2536	714/1701	Not serious	Not serious	Not serious	Not serious	High
Higher risk (II-III)	3	1,083	Unadjusted HR 1.30 (0.97, 1.74)	N/A	N/A	Serious[1]	Not serious	Serious[4]	Serious[3]	Very low
IIB-C	Jang 2020	1,174	Adjusted OR 0.88 (0.68, 1.15)[5]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
IIIA	Jang 2020	142	Adjusted OR 0.46 (0.21, 0.99)[5]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
III	Grotz 2014	317	Adjusted HR 2.38 (1.56,3.64)[6]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN+ III	Tas 2021	389	Unadjusted HR 1.25 (0.93, 1.68)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
SLN negative	Egger 2016	1,998	Adjusted HR 1.03 (0.80, 1.33)[7]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
SLN negative	Verver 2018	3,180	Adjusted HR 1.20 (0.99,1.45)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
SLN negative <1mm BT	Kim 2021	209	Unadjusted HR 1.30 (0.50, 3.33)	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Moderate
I-III	Liang 2020	731	Adjusted HR 1.22 (0.93, 1.36)[9]	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Moderate

1. >33.3% of studies were at moderate/high risk of bias.
2. Study was at moderate risk of bias.

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					

3. 95% CIs cross one line of the MID (0.8, 1.25).
4. I^2 >33.3%.
5. Adjusted for age, gender, race, marital status, geographical location, histological type, T4 vs T3, ulceration, Charleston comorbidity index, time to resection and use. of adjuvant therapy.
6. Patients were randomised to receive adjuvant GMCSF or no adjuvant therapy. Adjusted for Gender, age, stage or Breslow depth.
7. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
8. Adjusted for age. Gender, Breslow thickness, ulceration, Clark level, Anatomical location, histology, no. of SNs, multiple SN fields.
9. Adjusted for sex, tumour size, location, stage, extended resection, surgical margin, adjuvant therapy use.

- *Age*

Table 40 Age to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Effect sizes >1 indicated greater risk if younger (Figure 3 and Figure 4)										
Lower risk (most patients were stage I-II)	2	924	RR 0.87 (0.77, 0.99)	211/463	246/461	Serious[1]	Not serious	Not serious	Serious[2]	Low
Higher risk (IIC-IV)	12	3,567	RR 0.87 (0.80, 0.94)	1191/2757	402/810	Not serious	Not serious	Not serious	Not serious	High
II-III (per year of age)	5	1,948	Unadjusted HR 1.01 (1.00, 1.02)	N/A	N/A	Serious[1]	Not serious	Serious[3]	Not serious	Low
SLN positive III (≥50 vs <50)	Tas 2021	389	Unadjusted HR 1.19 (0.89, 1.59)	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low
IIB-C (65-75 vs <65)	Jang 2020	1,174	Adjusted OR 0.87 (0.45, 1.68)[7]	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low

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Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
IIIA (65-75 vs <65)	Jang 2020	142	Adjusted OR 1.22 (0.38, 3.91)[7]	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low
IIB-C (>75 vs 65-75)	Jang 2020	1,174	Adjusted OR 1.85 (1.42, 2.43)[7]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate
IIIA (>75 vs 65-75)	Jang 2020	142	Adjusted OR 0.82 (0.35, 1.90)[7]	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low
III (≥49 vs <49)	Najjar 2019	928	Adjusted HR 1.20 (0.99–1.46)[4]	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low
SLN positive (≥65 vs <65)	Mitra 2021	215	Adjusted HR 1.87 (1.06–3.30)[15]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
SLN negative (≥45 vs <45)	Egger 2016	1,998	Adjusted HR 0.67 (0.50, 0.89)[8]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate
SLN negative (per year of age)	Laks 2017	273	Adjusted HR 1.01 (1.00,1.03)[12]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate
SLN negative (per year of age)	Verver 2018	3,180	Adjusted HR 1.06 (0.82, 1.36)[14]	N/A	N/A	Serious[5]	Not serious	N/A	Serious[6]	Low
IIIB (≥51 vs <50)	Madu 2016	186	Adjusted HR 1.58 (1.07–2.34)[10]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
IIIC (per year of age)	Madu 2017	205	unadjusted HR 1.00 (0.99–1.01)[11]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate

The follow up of people with melanoma

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
I-IV HNM (>2 vs ≤2 per mm2)	Kim 2020	191	Adjusted OR 1.00 (0.97-1.02)[16]	N/A	N/A	Very Serious[1][7]	Not serious	N/A	Not serious	Low
II (per year of age)	Berger 2017	581	Adjusted HR: 1.02 (1.01-1.04)[13]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate
II (per year of age)	Bleicher 2020	585	Adjusted HR 1.01 (1.00 1.02)[9]	N/A	N/A	Serious[5]	Not serious	N/A	Not serious	Moderate
SLN negative <1mm (per year of age)	Kim 2021	209	Unadjusted HR 1.01 (0.98, 1.04)	N/A	N/A	Not serious	Not serious	N/A	Serious[6]	Moderate
I-III	Liang 2020	731	Unadjusted HR 1.01 (1.00, 1.01)	N/A	N/A	Serious[1][8]	Not serious	N/A	Not serious	Moderate

1. >33.3% of studies were at moderate or high risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. I^2 >33.3%
4. Patients were randomly assigned to high dose interferon-alpha or no treatment. Adjusted for treatment, ulceration, recurrence disease, age and white blood cell count.
5. Study was at moderate risk of bias
6. 95% Cis cross the line of no effect (1.0)
7. Adjusted for age, gender, race, marital status, geographical location, histological type, T4 vs T3, ulceration, Charleston comorbidity index, time to resection and use of adjuvant therapy.
8. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
9. Adjusted for age and stage
10. Adjusted for Breslow thickness, N-stage, Gender, ASA classification, location, tumour histology, Breslow thickness, ulceration, type of operation, lymph node ratio, maximum node diameter, extracapsular extension, use of adjuvant radiotherapy and Age.
11. Adjusted for gender, age, location, Breslow thickness, Ulceration, Operation site, type of nodal involvement, time to LND, number of positive lymph nodes, lymph node ratio, maximum lymph node diameter, extracapsular extension, adjuvant radiotherapy, locoregional recurrence prior to or at time of LND.

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					

12. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.
13. Adjusted for stage, regression, ulceration and age.
14. Adjusted for age. Gender, Breslow thickness, ulceration, Clark level, Anatomical location, histology, no. of SNs, multiple SN fields.
15. Adjusted for Adjusted for microsatellite lesions, age, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage, age, perineal invasion, ≥20 mitosis/mm2, and extracapsular extension.
16. Adjusted for regression, Breslow thickness, mitoses, nodular melanoma, age at diagnosis, ulceration
17. Study at high risk of bias
18. Study at low risk of bias overall but marked down once for this predictor due to it not being included in the multivariate model.

- *Breslow thickness*

Table 41 Breslow thickness to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker (>4mm)	Thinner (<4mm)					
Effect sizes > 1 indicated greater risk if thicker melanoma (Figure 5 and Figure 6)										
Lower risk (most patients were stage I-II)	5	1,583	RR 2.17 (1.57, 2.98)	198/321	322/1262	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
IIB-IIC	Jang 2020	1,174	Adjusted OR 1.92 (1.44, 2.54)[5]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
IIIA	Jang 2020	142	Adjusted OR 1.31 (0.58, 2.99)[5]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
III not using adjuvant therapy	KEYNOTE-054	443	RR 1.54 (1.26, 1.90)	72/124	120/319	Not serious	Not serious	N/A	Not serious	High

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker (>4mm)	Thinner (<4mm)					
III using adjuvant therapy	KEYNOTE-054	441	RR 1.03 (0.75, 1.42)	40/139	84/302	Not serious	Not serious	N/A	Not serious	High
II-III	4	1,369	Unadjusted HR: 1:04 (1.01, 1.06)[1]	N/A	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
II (>4 vs <2mm)	Bleicher 2020	585	Unadjusted HR 1.69 (1.26–2.29)	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
SLN positive III (≥2 vs <2mm)	Tas 2021	389	Unadjusted HR 1.34 (0.93, 2.15)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
IIIB (>2mm vs <2mm)	Madu 2016	183	Unadjusted HR 1.30 (0.87–1.93)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
IIIC (continuous)	Madu 2017	205	Unadjusted HR 1.00 (0.97-1.04)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
I-IV HNM (>1 vs ≤1)	Kim 2020	191	Adjusted OR 2.17 (0.84-5.55)[12]	N/A	N/A	Very Serious[13]	Not serious	N/A	Serious[11]	Very low
I-II HNM (>4 vs 0-1mm)	Namin 2019	170	Unadjusted HR 20.00 (5.00, 100.00) *Error in reporting of adjusted HR*	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
I-II HNM	Namin 2019	71	Adjusted HR: 5.88 (2.00, 16.67)[8]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker (>4mm)	Thinner (<4mm)					
(>4 vs 1.01-2mm)										
I-II HNM (>4 vs 2.01-4mm)	Namin 2019	172	Adjusted HR: 2.17 (0.93, 5.00)[8]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
SLN negative (>2 vs <2mm)	Egger 2016	1,998	Adjusted HR: 1.84 (1.42, 2.38)[6]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
SLN negative (per mm)	Laks 2017	273	Adjusted HR: 1.02 (0.93,1.13)[7]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
SLN negative (IQR 3.0 vs 1.1mm)	Verver 2018	3,180	Adjusted HR 2.47 (1.94, 3.13)[9]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
SLN negative (per mm)	Bertolli 2019	1,213	Adjusted HR 1.11 (1.05,1.17)[10]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
SLN negative <1mm (per 0.1mm thickness)	Kim 2021	209	Adjusted HR 1.35 (0.92, 1.97)[14]	N/A	N/A	Not serious	Not serious	N/A	Serious[6]	Moderate

1. >33.3% of studies were at moderate/high risk of bias
2. I^2 >66.6%
3. Study was at moderate risk of bias
4. 95% Cis cross the line of no effect (1.0)
5. Adjusted for age, gender, race, marital status, geographical location, histological type, T4 vs T3, ulceration, Charleston comorbidity index, time to resection and use of adjuvant therapy.

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker (>4mm)	Thinner (<4mm)					

6. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
7. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.
8. Adjusted for location, ulceration, lymph node status and Breslow thickness.
9. Adjusted for Gender, age, stage or Breslow depth.
10. Adjusted for Breslow thickness, ulceration, microsatellites and Ki67.
11. 95% Cis cross one line of the MID (0.8, 1.25)
12. Adjusted for regression, Breslow thickness, mitoses, nodular melanoma, age at diagnosis, ulceration
13. Study at high risk of bias
14. Adjusted for location, Breslow thickness, ulceration and mitotic rate

- *Mitotic rate*

Table 42 Mitotic rate to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher	Lower					
Effect sizes >1 indicate greater risk if mitotic rate is higher (studies varied considerably in the cut-offs they used for comparing low vs. high mitotic rate)										
SLN positive III (>3 vs 0-3 per mm2)	Tas 2021	389	Adjusted HR 1.63 (1.11–2.38)[8]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
I-II (≥1.69 vs <1.69 per mm2)	Oh 2020	227	RR 1.88 (1.22, 2.87)	28/74	31/153	Serious[1]	Not serious	N/A	Not serious	Moderate
I-III (>1 vs 0-1)	Tas 2019	398	RR 2.32 (1.69, 3.20)	193/295	29/103	Serious[1]	Not serious	N/A	Not serious	Moderate
I-IV HNM	Kim 2020	191	Adjusted OR 2.71 (1.11-6.75)[5]	N/A	N/A	Very Serious[6]	Not serious	N/A	Serious[4]	Very low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher	Lower					
(>2 vs ≤2 per mm2)										
II SLN negative (continuous variable)	Laks 2017	267	Unadjusted HR 1.03 (1.01,1.05)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
			Adjusted HR 1.02 (1.00,1.04)[3]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
IIC-IIIA (>5 vs 0-5)	Tan 2019	131	Unadjusted HR 2.59 (1.21–5.53)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN positive III (>3 vs ≤3mm)	Tas 2021	389	Unadjusted HR 1.69 (1.16, 2.46)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
II (>1 vs 0 per mm2)	Bleicher 2020	587	Unadjusted HR 2.42 (0.34–17.36)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
II (1 vs 0 per mm2)	Bleicher 2020	588	Unadjusted HR 2.51 (0.34–18.79)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN negative (per mm)	Bertolli 2019	1,213	Unadjusted HR 1.06 (1.03,1.10)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[3]	Low
SLN negative <1mm (per mm2)	Kim 2021	209	Adjusted HR 1.39 (1.09, 1.76)[7]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Study was at moderate risk of bias
2. 95% Cis cross the line of no effect (1.0)
3. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.
4. 95% Cis cross one line of the MID (0.8, 1.25)

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher	Lower					
5. Adjusted for regression, Breslow thickness, mitoses, nodular melanoma, age at diagnosis, ulceration 6. Study at high risk of bias 7. Adjusted for location, Breslow thickness, ulceration and mitotic rate 8. Adjusted for mitotic rate and number of positive lymph nodes										

- *Recurrence prior to surgery*

Table 43 Prior recurrence to predict recurrence

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Hazard ratios										
III	Najjar 2019	928	Adjusted HR 1.33 (1.09–1.63)[3]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
IIIC Locoregional recurrence prior to surgery	Madu 2017	205	Unadjusted HR 0.97 0.70-1.34	N/A	N/A	Not serious	Not serious	N/A	Serious[1]	Moderate
1. Study was at moderate risk of bias 2. 95% Cis cross the line of no effect (1.0) 3. Adjusted for treatment, ulceration, recurrence disease, age and white blood cell count										

- *ECOG performance status ≥1*

Table 44 ECOG to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				1+	0					
Effect sizes >1 indicate a greater risk of recurrence if ECOG ≥1 (Figure 9)										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				1+	0					
Higher risk (IIC-IIIC)	1 study reporting on 4 cohorts	495	RR 1.05 (0.80, 1.39)	28/57	193/438	Not serious	Not serious	Not serious	Serious[2]	Moderate
III (≥1 vs 0)	Grotz 2014	317	Unadjusted HR 1.50 (0.94, 2.38)[1]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low

1. Patients were randomly assigned to GMCSF.
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. Study was at moderate risk of bias
4. 95% Cis cross the line of no effect (1.0)

- *Lymphovascular invasion*

Table 45 LVI to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					
Effect sizes >1 indicated greater risk of recurrence if LVI is present (Figure 7)										
I-II	2	710	RR 1.40 (1.14, 1.72)	37/58	257/652	Serious[1]	Not serious	Not serious	Serious[2]	Low
SLN positive	Mitra 2021	215	HR 2.36 (1.32–4.23)[5]	N/A	N/A	Not serious	Not serious	Not serious	Not serious	High
SLN positive III	Tas 2021	389	Unadjusted HR 1.07 (0.67, 1.71)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
SLN negative II	Egger 2016	1,998	Unadjusted HR 1.10 (0.65, 1.73)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low

1. >33% of studies were at moderate or high risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. Study was at moderate risk of bias
4. 95% CIs cross the line of no effect (1.0)

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					
5. Adjusted for Adjusted for microsatellite lesions, age, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage, age, perineal invasion, ≥20 mitosis/mm2, and extracapsular extension.										

- *Ulceration*

Table 46 Ulceration to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					
Risk ratios (Figure 11: Ulceration as a predictor of recurrence during follow-up of stage II melanoma (hazard ratios)										

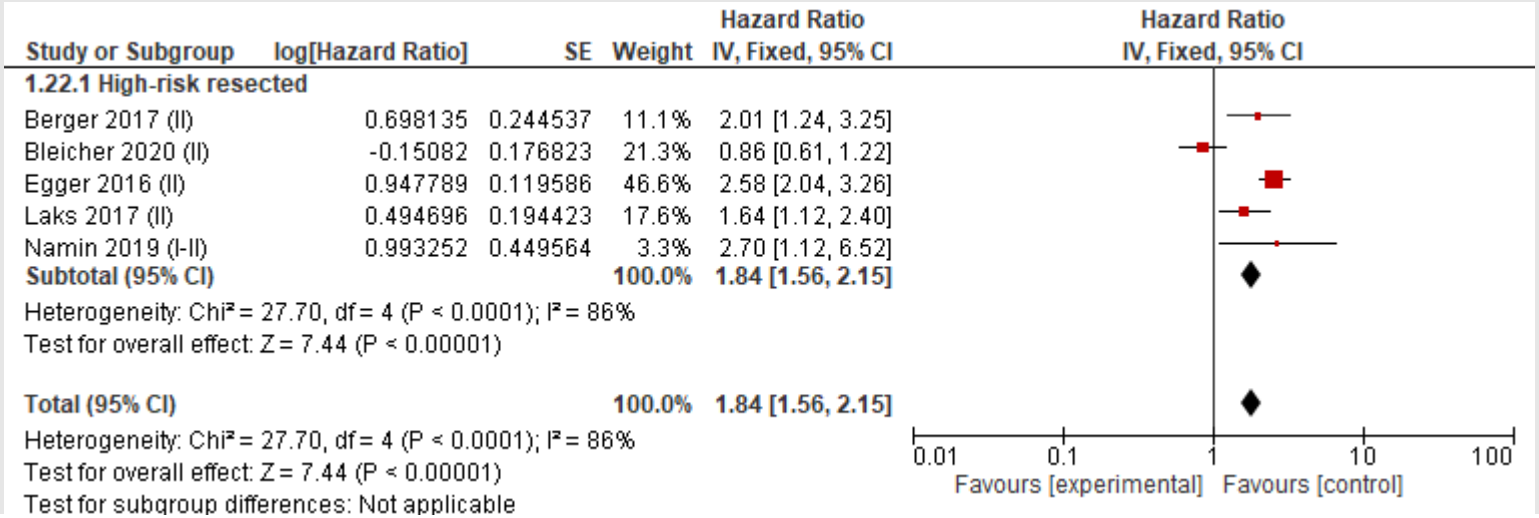

Figure 12: Ulceration as a predictor of recurrence during follow-up of stage IIIB/C melanoma (hazard ratios)

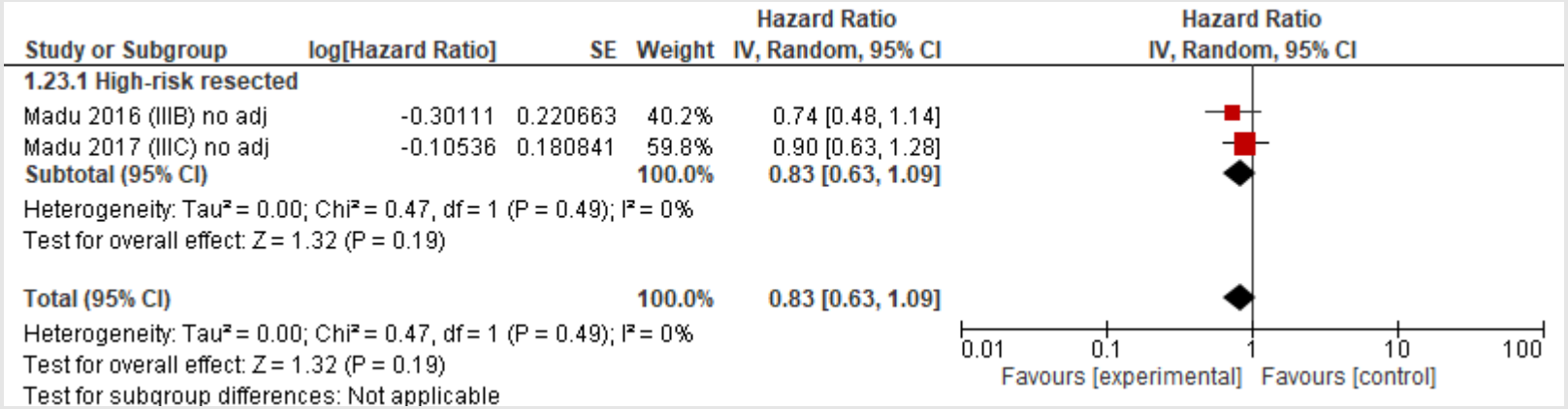

Figure 13, Figure 11 and Figure 12)

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred Yes	No. recurred No	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Lower risk (most patients stage I-II)	3	916	RR 1.94 (1.64, 2.30)	225/382	136/534	Serious[1]	Not serious	Not serious	Not serious	Moderate
Higher risk (IIC-IV)	9	3,308	RR 1.28 (1.19, 1.37)	779/1480	756/1828	Not serious	Not serious	Not serious	Serious[3]	Moderate
IIIB/C	2	393	Unadjusted HR 0.83 (0.63, 1.09)	N/A	N/A	Not serious	Not serious	Not serious	Serious[5]	Moderate
IIB-IIC	Jang 2020	1,174	Adjusted OR 1.77 (1.29, 2.43)[6]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN positive III	Tas 2021	389	Unadjusted HR 1.57 (1.07, 2.30)	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
II	5	3,592	Unadjusted HR 1.84 (1.56, 2.15)	N/A	N/A	Serious[1]	Not serious	Very serious[4]	Not serious	Very low

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Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					
III	Najjar 2019	928	Adjusted HR 1.34 (1.10–1.65)[11]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN negative	Egger 2016	1,998	Adjusted HR 2.04 (1.58, 2.61)[7]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN negative	Laks 2017	273	Adjusted HR 1.82 (1.20,2.75)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN negative	Verver 2018	3,180	Adjusted HR 1.84 (1.50, 2.26)[12]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-IV HNM	Kim 2020	191	Adjusted OR 0.82 (0.3-2.16)[15]	N/A	N/A	Very Serious[16]	Not serious	N/A	Very serious[14]	Very low
II	Berger 2017	581	Adjusted HR 2.02 0.96-4.25[9]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[5]	Low
I-II HNM	Namin 2019	168	Adjusted HR 1.25 (0.58, 2.70)[10]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[5]	Low
SLN negative (per mm)	Bertolli 2019	1,213	Adjusted HR 3.43 (2.29,5.13)[13]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN negative <1mm (per mm2)	Kim 2021	209	Adjusted HR 10.77 (3.00, 38.71)[17]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. >33% of studies were at moderate or high risk of bias
2. Study was at moderate risk of bias
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. I^2 >66.6%
5. 95% Cis cross the line of no effect (1.0)
6. Adjusted for age, gender, race, marital status, geographical location, histological type, T4 vs T3, ulceration, Charleston comorbidity index, time to resection and use of adjuvant therapy.
7. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
8. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					

9. Adjusted for stage, regression, ulceration and age.
10. Adjusted for location, ulceration, lymph node status and Breslow thickness
11. Adjusted for treatment, ulceration, recurrence disease, age and white blood cell count
12. Adjusted for age. Gender, Breslow thickness, ulceration, Clark level, Anatomical location, histology, no. of SNs, multiple SN fields.
13. Adjusted for Breslow thickness, ulceration, microsatellites and Ki67.
14. 95% Cis cross one line of the MID (0.8, 1.25)
15. Adjusted for regression, Breslow thickness, mitoses, nodular melanoma, age at diagnosis, ulceration
16. Study at high risk of bias
17. Adjusted for location, ulceration, breslow thickness and mitotic rate

- *Location*

Table 47 Location to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Axial vs extremities (Figure 16 and Figure 17)										
Lower risk (most patients I-II)	3	1,462	RR 1.27 (1.02, 1.59)	131/619	158/843	Serious[1]	Not serious	Not serious	Serious[2]	Low
Higher risk after definitive surgery (IIC-IV)	2	913	RR 1.18 (0.86, 1.62)	297/505	211/408	Serious[1]	Not serious	Very serious[13]	Serious[2]	Very low
SLN positive III (≥50 vs <50)	Tas 2021	389	Unadjusted HR 0.98 (0.71, 1.37)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
SLN negative	Egger 2016	1,998	Adjusted HR 1.46 (1.13, 1.88)[6]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
Trunk vs extremities (Figure 14)										
IIIB/C	2	388	Unadjusted HR 1.27 (0.96, 1.68)	N/A	N/A	Not serious	Not serious	Not serious	Serious[4]	Moderate
SLN negative	Laks 2017	270	Unadjusted HR 1.25 (0.79,1.98)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
SLN negative (trunk vs arms)	Verver 2018	3,180	Adjusted HR 1.54 (1.15, 2.07)[8]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
II	Bleicher 2017	580	Unadjusted HR 0.89 (0.59–1.35)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
I-III[12]	Liang 2020	731	Adjusted HR 1.12 (0.86, 1.47)[11]	N/A	N/A	Not serious	Not serious	N/A	Serious[4]	Moderate
Scalp vs other head/neck melanomas										
IIIB/C	Barbour 2015	107	RR 1.48 (0.99, 2.21)	15/24	35/83	Serious[3]	Not serious	N/A	Serious[2]	Low
I-II HNM	Namin 2019	168	Adjusted HR 2.33 (1.11, 5.00)[7]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
Head/neck melanoma vs. extremities (Figure 15)										
IIIB-IIIC	2	389	Unadjusted HR 1.06 (0.67, 1.66)	N/A	N/A	Not serious	Not serious	Serious[5]	Serious[4]	Low
SLN negative	Laks 2017	270	Unadjusted HR 1.47 (0.98,2.21)	N/A	N/A	Not serious	Not serious	N/A	Serious[4]	Moderate
SLN negative (head/neck vs arms)	Verver 2018	3,180	Adjusted HR 2.12 (1.45, 3.11)[8]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
II	Bleicher 2017	580	Unadjusted HR 1.04 (0.66, 1.64)	N/A	N/A	Not serious	Not serious	N/A	Serious[4]	Moderate
SLN negative <1mm (per mm2)[9]	Kim 2021	209	Adjusted HR 3.52 (1.17, 10.57)[10]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. >33% of studies were at moderate or high risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. Study was at moderate risk of bias
4. 95% Cis cross the line of no effect (1.0)
5. I^2 >33.3%
6. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
7. Adjusted for location, ulceration, lymph node status and Breslow thickness
8. Adjusted for age. Gender, Breslow thickness, ulceration, Clark level, Anatomical location, histology, no. of SNs, multiple SN fields.
9. Head/neck compared to extremities/trunk
10. Adjusted for location, ulceration, Breslow thickness and mitotic rate.
11. Adjusted for sex, tumour size, location, stage, extended resection, surgical margin, adjuvant therapy use.
12. Trunk compared to lower extremity.
13. I^2 >66.6%

- *Lymph node involvement*

Table 48 Lymph node involvement to predict recurrence/ progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
Number of positive nodes (Figure 18)**: Effect sizes >1 indicate greater risk if ≥2 positive lymph nodes**										
III	6	2,783	RR 1.39 (1.28, 1.51)	794/1522	477/1261	Not serious	Not serious	Not serious	Not serious	High
>1mm nodal deposit: Effect sizes >1 indicate greater risk if >1mm nodal deposit										
SLNB +	Mitra 2021	215	Adjusted HR 2.29 (1.23–4.22)[5]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
N-stage: Effect sizes >1 indicate greater risk if stage ≥2										
IIIB/C (2-3 vs 1)	Barbour 2015	107	RR 1.68 (1.13, 2.48)	25/40	25/67	Serious[2]	Not serious	N/A	Serious[3]	Low
III SLN positive (2-3 vs 1)	Tas 2021	389	Adjusted HR 1.54 (1.08 – 2.20)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
IIIC (N2 vs 1)	Madu 2017	205	Adjusted HR 0.91 (0.52, 1.60)[1]	N/A	N/A	Not serious	Not serious	N/A	Serious[4]	Moderate
IIIC (N3 vs 1)	Madu 2017	205	Adjusted HR 2.34 (1.47, 3.71)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
IIIB (N2 vs 1)	2	388	Unadjusted HR 1.40 [0.85, 2.30]	N/A	N/A	Serious[2]	Not serious	Not serious	Serious[4]	Low
Lymph node status (Macrometastases vs micrometastases) (Figure 19**): Effect sizes >1 indicate greater risk if macro-metastatic**										
IIC-III	9	3,577	RR 1.30 (1.20, 1.40)	987/2098	545/1479	Not serious	Not serious	Not serious	Serious[3]	Moderate

1. Adjusted for gender, age, location, Breslow thickness, Ulceration, Operation site, type of nodal involvement, time to LND, number of positive lymph nodes, lymph node ratio, maximum lymph node diameter, extracapsular extension, adjuvant radiotherapy, locoregional recurrence prior to or at time of LND.
2. Study was at moderate risk of bias.
3. 95% CIs cross one line of the MID (0.8, 1.25).
4. 95% CIs cross the line of no effect (1.0).
5. Adjusted for Adjusted for microsatellite lesions, age, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage, age, perineal invasion, ≥20 mitosis/mm2, and extracapsular extension.
6. Adjusted for mitotic rate and number of involved lymph nodes.

- Predictors of regional/lymph node recurrence in follow-up of resected disease
  - *Lymph node involvement*

Table 49 Lymph node involvement to predict nodal recurrence

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
Number of positive nodes: Effect sizes >1 indicate greater risk if ≥2 positive lymph nodes										
SLN positive	Mitra 2021	215	Adjusted HR 2.14 (1.07–4.26)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
>1mm nodal deposit: Effect sizes >1 indicate greater risk if >1mm nodal deposit										
SLN positive	Mitra 2021	215	Adjusted HR 2.21 (1.00–4.92)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Adjusted for microsatellite lesions, ulceration, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage and extracapsular extension.

  - *Lymphovascular invasion*

Table 50 LVI to predict nodal recurrence

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect size >1 indicates greater risk if LVI										
SLN positive	Mitra 2021	215	Adjusted HR 3.84 (1.90–7.76)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Adjusted for microsatellite lesions, ulceration, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage and extracapsular extension.

- Predictors of distant progression in follow-up of resected disease
    - *Nomograms to predict recurrence*

Table 51 nomograms

Disease stage(s)	No. Studies	Sample size	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
EORTC-DeCOG								
SLN positive	Verver 2020	692	C-statistic: 0.72 (0.68, 0.75)	Serious[1]	Not serious	N/A	Serious[2]	Low

1. Study was at moderate risk of bias.
2. C-statistic confidence intervals cross one boundary of interpretation (0.70)

    - *Effect of stage IIC - IIIC*

Table 52 Stage to predict distant progression in resected disease

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Increased risk of recurrence in stage IIC compared to IIIA. Adjusted values not reported but notes that difference becomes non-significant after adjusting for mitotic: HR >1 indicates greater risk if IIC										
IIC vs IIIA	Tan 2019	133	Unadjusted HR 2.67 (1.36–5.25)[1]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

1. 7% of IIC patients and 69% of IIIA patients received adjuvant interferon therapy. Although adjusted HR are not provided. The author notes that after adjusted for mitosis, there is no longer a significant difference in progression between stage IIIA and IIC
2. Study was at moderate risk of bias

- *Gender*

Table 53 Gender to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect sizes >1 indicates greater risk of progression if male										
III	Groen 2019	73	RR 2.31 (0.78, 6.84)	9/36	4/37	Serious[1]	Not serious	N/A	Very serious[2]	Very low
III	Turner 2021	332	RR 0.95 (0.69, 1.31)	70/215	40/117	Serious[1]	Not serious	N/A	Very serious[2]	Very low
SLN negative II	Egger 2016	1,998	Adjusted HR 1.09 (0.80, 1.50)[6]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLN negative	Echanique 2021	152	Unadjusted HR 2.27 (0.53, 10.00)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
IIC-IIIA	Tan 2019	129	Unadjusted HR 0.89 (0.46–1.73)[4]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
III	Grotz 2014	317	Adjusted HR 2.38 (1.56,3.64)[5]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative <1mm (per mm2)[9]	Kim 2021	209	Unadjusted HR 1.01 (0.31, 3.33)	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Moderate

1. Study was at moderate risk of bias
2. 95% Cis cross both lines of the MID (0.8, 1.25)
3. 95% Cis cross the line of no effect (1.0)
4. 47% of IIC patients and 69% of IIIA patients received adjuvant interferon therapy.
5. Patients were randomised to receive adjuvant GMCSF or no adjuvant therapy.
6. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.

- *Age*

Table 54 Age to predict progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Effect sizes >1 indicate greater risk of progression if younger age										
SLN negative II (≥45 vs <45)	Egger 2016	1,998	Adjusted HR 1.51 (1.07, 2.18)[3]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
IIC-IIIA (>55 vs ≤55)	Tan 2019	128	Unadjusted HR 1.96 (1.00–3.87)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
III (age entered as continuous variable)	Grotz 2014	317	Adjusted HR 1.03 (1.01,1.04)[2]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative II (age entered as continuous variable)	Laks 2017	273	Adjusted HR 1.04 (1.02,1.05)[4]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative (age entered as continuous variable)	Echanique 2021	152	Unadjusted HR 1.02 (0.99, 1.05)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[5]	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
SLN negative <1mm (per mm2)[9]	Kim 2021	209	Unadjusted HR 1.00 (0.96, 1.04)	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Moderate

1. Study was at moderate risk of bias
2. Patients were randomized to either adjuvant GMCSF or no treatment.
3. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
4. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.
5. 95% Cis cross the line of no effect.

- *Breslow thickness*

Table 55 Breslow thickness to predict progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				>4mm	<4mm					
Risk of distant metastases at baseline: RR >1 indicates greater risk of progression if >4mm										
III (>4mm vs 0-4mm)	Groen 2019	73	RR 2.26 (0.83, 6.15)	4/12	9/61	Serious[1]	Not serious	N/A	Serious[2]	Low
Risk of progression to distant metastases during follow-up: Effect sizes >1 indicate greater risk if thicker melanoma										
III (>4mm vs 0-4mm)	Turner 2021	332	RR 1.34 [0.95, 1.88]	30/73	66/215	Serious[1]	Not serious	N/A	Serious[2]	Low
II SLNB negative (>2mm vs <2mm)	Egger 2016	1,998	Adjusted HR: 1.92 (1.41, 2.62)[3]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				>4mm	<4mm					
SLN negative HNM (per mm)	Echanique 2021	152	Unadjusted HR 1.50 (1.25, 1.80)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative <1mm (per 0.1mm thickness)	Kim 2021	209	Adjusted HR 1.35 (0.92, 1.97)[4]	N/A	N/A	Not serious	Not serious	N/A	Serious[6]	Moderate

1. Study was at moderate risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
4. Adjusted for location, ulceration, Breslow thickness and mitotic rate.

- *Ulceration*

Table 56 Ulceration to predict progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Risk of distant metastases at baseline: Effect sizes >1 indicate greater risk if ulcerated										
III	Groen 2019	73	RR 0.37 (0.09, 1.54)	2/24	11/49	Serious[1]	Not serious	N/A	Very serious[4]	Very low
Risk of distant metastases developing during follow-up: Effect size >1 indicates greater risk if ulcerated										
III	Turner 2021	332	RR 1.45 [1.05, 2.01]	44/105	51/177	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN negative II	Egger 2016	1,998	Adjusted HR: 2.80 (2.11, 3.70)[4]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
SLN negative HNM	Echanique 2021	152	Adjusted HR 1.74 (0.63, 4.84)[5]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLN negative <1mm (per 0.1mm thickness)	Kim 2021	209	Adjusted HR 10.77 (3.00, 38.71)[14]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Study was at moderate risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. 95% CIs cross both lines of the MID (0.8, 1.25)
4. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type
5. Adjusted for ulceration, stage, mitotic rate, perineural invasion and scalp location.
6. Adjusted for location, ulceration, Breslow thickness and mitotic rate.

- *Mitotic rate*

Table 57 Mitotic rate to predict distant progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Risk of distant metastases developing during follow-up: Effect size >1 indicates greater risk if mitotic rate (per mm^2) is ≥1										
SLN negative	Echanique 2021	152	Adjusted HR 3.60 (0.89, 14.58)[5]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLN negative <1mm (per 0.1mm thickness)	Kim 2021	209	Adjusted HR 1.39 (1.09, 1.76)[6]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Study was at moderate risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. 95% CIs cross both lines of the MID (0.8, 1.25)

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					

4. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type
5. Adjusted for ulceration, stage, mitotic rate, perineural invasion and scalp location.
6. Adjusted for location, ulceration, Breslow thickness and mitotic rate.

- *Location*

Table 58 Location to predict progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Arm 1	Arm 2					
Effect size >1 indicates greater risk if located on the axial plane (compared to extremities)										
III	Turner 2021	332	RR 1.12 (0.80, 1.57)	58/166	38/122	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN negative II (>2mm vs <2mm)	Egger 2016	1,998	Adjusted HR 2.15 (1.60, 2.93)[3]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
Effect size >1 indicates greater risk if located on the head/neck (compared to trunk/extremities)										
SLN negative <1mm (per 0.1mm thickness)	Kim 2021	209	Adjusted HR 3.52 (1.17, 10.57)[5]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
Effect size >1 indicates greater risk if located on the scalp (compared to non-scalp)										
SLN negative HNM	Echanique 2021	152	Adjusted HR 6.49 (2.36, 17.81)[4]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Arm 1	Arm 2					
4. Adjusted for ulceration, stage, mitotic rate, perineural invasion and scalp location.										
5. Adjusted for location, ulceration, Breslow thickness and mitotic rate.										

- *Lymph node involvement*

Table 59 Lymph node involvement to predict distant progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
Number of positive nodes: Effect sizes >1 indicate greater risk if ≥2 positive lymph nodes										
SLN positive	Mitra 2021	215	Adjusted HR 2.51 (1.15–5.48)[1]	N/A	N/A	Not serious	Not serious	Not serious	Not serious	High
>1mm nodal deposit: Effect sizes >1 indicate greater risk if >1mm nodal deposit										
SLN positive	Mitra 2021	215	Adjusted HR 2.51 (1.00–6.60)[1]	N/A	N/A	Not serious	Not serious	Not serious	Not serious	High
1. Adjusted for Adjusted for microsatellite lesions, age, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage and extracapsular extension.										

- *Lymphovascular invasion*

Table 60 LVI to predict distant progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect size >1 indicates greater risk if LVI										
IIC-IIIA	Tan 2019	129	Unadjusted HR 1.50 (0.64–3.52)[2]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
SLN negative II (>2 vs <2mm)	Egger 2016	1,998	Unadjusted HR 1.02 (0.52, 1.78)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
SLN negative HNM	Echanique 2021	152	Unadjusted HR 2.07 (0.47, 9.12)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLN positive	Mitra 2021	215	Adjusted HR 2.29 (1.23–4.22)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Adjusted for Adjusted for microsatellite lesions, age, LVI, >1mm nodal deposit, ≥2 lymph nodes positive, disease stage and extracapsular extension.
2. 47% of IIC patients and 69% of IIIA patients received adjuvant interferon therapy.
3. Study was at moderate risk of bias.
4. 95% CIs cross the line of no effect (1.0)

- Predictors of survival in follow-up of resected disease

Predicting overall survival unless otherwise stated

- *Nomograms to predict melanoma specific survival*

Table 61 nomograms

Disease stage(s)	No. Studies	Sample size	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
EORTC nomogram								
SLN negative	Ipenburg 2019	4,235	C-statistic: 0.69 (0.66, 0.72)	Serious[1]	Not serious	N/A	Serious[2]	Low
EORTC-DeCOG nomogram								
SLN positive	Verver 2020	692	C-statistic: 0.74 (0.71, 0.78)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias.
2. C-statistic confidence intervals cross one boundary of interpretation (0.70)

- *Effect of stage IIC - IIIC*

Table 62 Stage to predict overall survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Increased risk of death in IIIBC compared to IIIA both before and after correcting for other risk factors: HR >1 indicated greater risk associated with the higher disease stage										
IIIC vs IIIA	Grotz 2014[1]	317	Unadjusted HR 3.28 (1.98,5.41)	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
			Adjusted HR 3.29 (1.87,5.77)	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
IIIB vs IIIA	Grotz 2014[1]	317	Unadjusted HR 1.17 (0.68,2.00)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
			Adjusted HR 1.37 (0.78,2.42)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
Increased risk of death in IIC compared to IIIA, adjusted values not provided however it is noted that difference becomes non-significant after adjusted for mitotic rate: HR>1 indicates greater risk of mortality if stage IIIA										
IIC vs IIIA	Tan 2019	133	Unadjusted HR 2.70 (1.35, 5.26)[3]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

1. Patients were randomised to receive adjuvant GMCSF or no adjuvant therapy.
2. Study was at moderate risk of bias
3. 7% of IIC patients and 69% of IIIA patients received adjuvant interferon therapy. Although adjusted HR are not provided. The author notes that after adjusted for mitosis, there is no longer a significant difference in progression between stage IIIA and IIC
4. 95% Cis cross the line of no effect (1.0)

- *Gender*

Table 63 Gender to predict survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Adult population (Melanoma-specific survival): Effect sizes > 1 indicate greater risk of mortality if male (Figure 21)										
IIIB/C	2	378	Unadjusted HR 1.15 (0.88, 1.51)	N/A	N/A	Serious[2]	Not serious	Not serious	Serious[4]	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Adult population (Overall survival): Effect sizes > 1 indicate greater risk if male										
II	Berger 2017	581	RR 1.45 (1.14, 1.84)	151/360	64/221	Serious[2]	Not serious	N/A	Serious[4]	Low
IIIB/C	Barbour 2015	107	RR 3.09 (1.07, 8.93)	43/88	3/19	Serious[2]	Not serious	N/A	Serious[4]	Low
IIC-IIIA	Tan 2019	136	Unadjusted HR 1.55 (0.81–2.98)[1]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[5]	Low
SLN positive III	Tas 2021	389	Unadjusted HR 1.29 (0.92, 1.81)	N/A	N/A	Serious[3]	Not serious	N/A	Serious[5]	Low
SLN positive	Huang 2020	530	Unadjusted HR 1.67 (1.07, 2.59)	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN negative II	Egger 2016	1,998	Adjusted HR 1.22 (0.97, 1.55)[7]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[5]	Low
I-IV	Yang 2019	77,508	Adjusted HR 1.23 (1.18, 1.32)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Paediatric population (Overall survival): Effect sizes > 1 indicate greater risk if male										
I-II	Brecht 2015	268	RR 0.74 (0.25, 2.19)	5/123	8/145	Very serious[3]	Not serious	N/A	Very serious[6]	Very low
Mixed population (15-40) (Overall survival): Effect sizes > 1 indicate greater risk of mortality if male										
I-III	Yang 2021	19,887	Adjusted HR 1.32 (1.12, 1.54)[9]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (cancer-specific survival): Effect sizes > 1 indicate greater risk of mortality if male										
I-III	Yang 2021	19,887	Adjusted HR 1.37 (1.15, 1.61)[9]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					

1. 47% of IIC patients and 69% of IIIA patients received adjuvant interferon therapy.
2. Study was at moderate risk of bias
3. Study was at high risk of bias
4. 95% CIs cross one line of the MID (0.8, 1.25)
5. 95% CIs cross the line of no effect (1.0)
6. 95% CIs cross both lines of the MID (0.8, 1.25)
7. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type
8. Adjusted for age, gender, location, SEER stage, AJCC stage, insurance status, median family income, marital status.
9. Adjusted for age, gender, race, tumour location, histologic subtype, Clark level, ulceration, Breslow thickness, N stage.

- *Age*

Table 64 Age to predict survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Adult population (Melanomas-specific survival): Effect sizes >1 indicates greater risk if younger age										
IIIB (≥51 vs <50)	Madu 2016	186	Adjusted HR 0.59 (0.35–0.99)[4]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
IIIC (continous)	Madu 2017	205	Unadjusted HR 0.99 (0.98-1.01)[6]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[2]	Low
Adult population (Post-recurrence survival): Effect sizes >1 indicates greater risk if younger age										
IIB-IIIC Post-recurrence survival	Ibrahim 2020	353	HR 1.01 (0.99, 1.02)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
(age entered as continuous variable)										
Adult population (overall survival): Effect sizes >1 indicates greater risk if younger age										
IIIB/C	Barbour 2015	107	RR 0.48 (0.31, 0.76)	16/52	35/55	Serious[1]	Not serious	N/A	Not serious	Moderate
Each year	Berger 2017	581	HR 1.02 (1.01-1.04)[1]	NA	NA	Serious[1]	Not serious	N/A	Not serious	Moderate
IIC-IIIA (>55 vs ≤55)	Tan 2019	128	Unadjusted HR 5.23 (2.51–10.90)	NA	NA	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN positive III (≥50 vs <50)	Tas 2021	389	Unadjusted HR 1.09 (0.79, 1.51)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN positive	Huang 2020	530	Adjusted HR 0.46 (0.31, 0.68)[8]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative II (≥45 vs <45)	Egger 2016	1,998	Adjusted HR 1.41 (1.09, 1.84)[5]	NA	NA	Serious[1]	Not serious	N/A	Not serious	Moderate
I-IV (per year of age)	Yang 2019	77,508	Adjusted HR 1.02 (1.01, 1.02)[7]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (overall survival): Effect sizes > 1 indicate greater risk of mortality if 26-40 years old										
I-III	Yang 2021	19,887	Adjusted HR 1.64 (1.32, 2.04)[9]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
(26-40 vs 15-25)										
Mixed population (15-40) (cancer-specific survival): Effect sizes > 1 indicate greater risk of mortality if 26-40 years old										
I-III (26-40 vs 15-25)	Yang 2021	19,887	Adjusted HR 1.70 (1.33, 2.19)[9]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias
2. 95% Cis cross the line of no effect (1.0).
3. Study was at low risk of bias but was marked down for this outcome as only univariate analyses were reported
4. Adjusted for Breslow thickness, N-stage, Gender, ASA classification, location, tumour histology, Breslow thickness, ulceration, type of operation, lymph node ratio, maximum node diameter, extracapsular extension, use of adjuvant radiotherapy and Age.
5. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type
6. Adjusted for gender, age, location, Breslow thickness, Ulceration, Operation site, type of nodal involvement, time to LND, number of positive lymph nodes, lymph node ratio, maximum lymph node diameter, extracapsular extension, adjuvant radiotherapy, locoregional recurrence prior to or at time of LND.
7. Adjusted for age, gender, location, SEER stage, AJCC stage, insurance status, median family income, marital status.
8. Adjusted for age, location, ulceration and number of lymph nodes.
9. Adjusted for age, gender, race, tumour location, histologic subtype, Clark level, ulceration, Breslow thickness, N stage.

- *Breslow thickness*

Table 65 Breslow thickness to predict survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker	Thinner					
Paediatric population (overall survival): Effect sizes > 1 indicate greater risk if thicker melanoma										
I-II Paediatric population	Brecht 2015	251	RR 6.24 (2.07, 18.78)	7/46	5/205	Very serious[2]	Not serious	N/A	Not serious	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker	Thinner					
(>2 vs 0-2mm)										
Adult population (overall survival): Effect sizes > 1 indicate greater risk if thicker melanoma										
SLN positive (>2mm vs ≤2mm)	Huang 2020	530	Unadjusted HR 2.13 (1.43, 3.18)	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN positive III (≥2 vs <2mm)	Tas 2021	389	Unadjusted HR 1.30 (0.75, 2.24)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLN negative II (per mm)	Laks 2017	273	Adjusted HR: 1.02 (0.93,1.13)[7]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
SLNB negative II (>2mm vs <2mm)	Egger 2016	1,998	Adjusted HR: 1.90 (1.50, 2.40)[6]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
Adult population (melanoma-specific survival): Effect sizes > 1 indicate greater risk if thicker melanoma										
IIIB (>2mm vs 0-2mm)	Madu 2016	186	Adjusted HR 2.04 (1.25–3.35)[5]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
III (per mm)	Grotz 2014	317	Adjusted HR: 1.10 (1.02,1.18)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker	Thinner					
IIIC (continous)	Madu 2017	205	Unadjusted HR 1.01 (0.98-1.05)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Low
Mixed population (15-40) (overall survival): Effect sizes > 1 indicate greater risk of mortality if thicker melanoma										
I-III (1.01-2.0 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 3.09 (2.43, 3.95)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (2.01-4 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 4.71 (3.59, 6.18)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (>4 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 7.50 (5.57, 10.10)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (cancer-specific survival): Effect sizes > 1 indicate greater risk of mortality if thicker melanoma										
I-III (1.01-2.0 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 3.54 (2.68, 4.68)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (2.01-4 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 4.87 (3.58, 6.63)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (>4 vs 0-1mm)	Yang 2021	19,887	Adjusted HR 8.04 (5.77, 11.20)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias
2. Study was at high risk of bias
3. 95% Cis cross the line of no effect (1.0)
4. Study was at low risk of bias but was marked down for this outcome as only univariate analyses were reported

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Thicker	Thinner					
5. Adjusted for Breslow thickness, N-stage, Gender, ASA classification, location, tumour histology, Breslow thickness, ulceration, type of operation, lymph node ratio, maximum node diameter, extracapsular extension, use of adjuvant radiotherapy and Age. 6. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type 7. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate. 8. Adjusted for age, gender, race, tumour location, histologic subtype, Clark level, ulceration, Breslow thickness, N stage.										

- *Mitotic rate*

Table 66 Mitotic rate to predict overall survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher	Lower					
Effect sizes >1 indicate greater risk if mitotic rate is high										
SLN positive III (>3 vs 0-3 per mm2)	Tas 2021	389	Unadjusted HR 1.61 (1.04–2.49)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative II (continuous variable)	Laks 2017	267	Unadjusted HR 1.02 (1.00,1.05)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
			Adjusted HR 1.02 (1.00,1.05)[2]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN positive	Huang 2020	530	Unadjusted HR 2.08 (1.17, 3.71)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
IIC-IIIA (>5 v 0-5)	Tan 2019	138	Adjusted HR 3.47 (1.62–7.42)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
1. Study was at moderate risk of bias										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher	Lower					
2. Adjusted for age, Breslow thickness, T stage, ulceration and mitotic rate.										

- *LVI*

Table 67 LVI to predict overall survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect sizes >1 indicate greater risk if LVI is present										
IIC-IIIA	Tan 2019	129	Unadjusted HR 1.31 (0.53–3.24)[1]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN positive III	Tas 2021	389	Unadjusted HR 1.52 (0.92, 2.54)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low
SLN positive	Huang 2020	530	Unadjusted HR 2.12 (1.42, 3.16)	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN negative II (>2 vs <2mm)	Egger 2016	1,998	Unadjusted HR 1.41 (0.93, 2.04)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[2]	Low
1. Study was at moderate risk of bias 2. 95% Cis cross the line of no effect (1.0)										

- *Ulceration*

Table 68 Ulceration to predict survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Paediatric population (overall survival): risk of developing recurrence: Effect sizes >1 indicate greater risk if ulcerated										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
I-II Paediatric population	Brecht 2015	199	RR 64.24 (8.20, 502.89)	6/17	1/182	Very serious[3]	Not serious	N/A	Not serious	Low
Adult population (overall survival): risk of developing recurrence: Effect sizes >1 indicate greater risk if ulcerated										
IIIB/C	Barbour 2017	86	RR 0.97 (0.59, 1.58)	31/64	11/22	Serious[2]	Not serious	N/A	Very serious[4]	Very low
II	Berger 2017	581	HR 1.46 (0.85-2.50)[1]	NA	NA	Serious[2]	Not serious	N/A	Serious[5]	Low
II Ulceration and >4mm	Berger 2017	581	HR 3.00 (1.50-6.01)	NA	NA	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN positive	Huang 2020	530	Adjusted HR 1.67 (1.17, 2.40)[7]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
SLN positive III	Tas 2021	389	Unadjusted HR 1.45 (0.94, 2.25)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[5]	Low
SLN negative II	Egger 2016	1,998	Adjusted 2.41 (1.94, 3.01)[6]	N/A	N/A	Serious[1]	Not serious	N/A	Serious[5]	Low
Adult population (overall survival): risk of developing recurrence: Effect sizes >1 indicate greater risk if ulcerated (Figure 28)										
IIIB/C	2	388	unadjusted HR 1.01 (0.74, 1.38)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[5]	Low
Mixed population (15-40) (overall survival): Effect sizes > 1 indicate greater risk of mortality if ulcerated										
I-III	Yang 2021	19,887	Adjusted HR 2.55 (2.13, 3.06)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (cancer-specific survival): Effect sizes > 1 indicate greater risk of mortality if ulcerated										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
I-III	Yang 2021	19,887	Adjusted HR 2.77 (2.28, 3.37)[8]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

1. Adjusted for age, regression, stage and ulceration.
2. Study was at moderate risk of bias.
3. Study was at high risk of bias.
4. 95% CIs cross both lines of the MID (0.8, 1.25).
5. 95% Cis cross the line of no effect (1.0).
6. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type.
7. Adjusted for age, location, ulceration and number of positive lymph nodes.
8. Adjusted for age, gender, race, tumour location, histologic subtype, Clark level, ulceration, Breslow thickness, N stage.

- *N-stage*

Table 69 N-stage to predict recurrence/ progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
Adult population (overall survival) N-stage: Effect sizes >1 indicate greater risk if N-stage is higher (Figure 29)										
IIIB/C (N2 vs N1)	2	388	Adjusted HR 1.76 (1.20, 2.58)	N/A	N/A	Not serious	Not serious	Not serious	Not serious	High
IIIC (N3 vs N1)	Madu 2017	205	Adjusted HR 2.51 (1.54, 4.08)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
SLN positive III (N2/3 vs N1)	Tas 2021	389	Unadjusted HR 1.40 (1.01, 1.94)	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
Adult population (overall survival) N-stage: Effect sizes >1 indicate greater risk if N-stage is higher										
SLN positive	Huang 2020	530	Adjusted HR 1.57 (1.11, 2.23)[2]	N/A	N/A	Serious[3]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (overall survival): Effect sizes > 1 indicate greater risk of mortality if N-stage is higher										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥2	1					
I-III (N1 vs N0)	Yang 2021	19,887	Adjusted HR 2.23 (1.80, 2.76)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (N2 vs N0)	Yang 2021	19,887	Adjusted HR 3.12 (2.43, 4.01)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (N3 vs N0)	Yang 2021	19,887	Adjusted HR 7.50 (5.57, 10.10)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Mixed population (15-40) (cancer-specific survival): Effect sizes > 1 indicate greater risk of mortality if N-stage is higher										
I-III (N1 vs N0)	Yang 2021	19,887	Adjusted HR 2.30 (1.83, 2.89)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (N2 vs N0)	Yang 2021	19,887	Adjusted HR 3.43 (2.64, 4.46)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
I-III (N3 vs N0)	Yang 2021	19,887	Adjusted HR 5.63 (4.17, 7.59)[4]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate

1. Adjusted for gender, age, location, Breslow thickness, Ulceration, Operation site, type of nodal involvement, time to LND, number of positive lymph nodes, lymph node ratio, maximum lymph node diameter, extracapsular extension, adjuvant radiotherapy, locoregional recurrence prior to or at time of LND.
2. Adjusted for age, location, ulceration and >1 positive lymph node.
3. Study was at moderate risk of bias
4. Adjusted for age, gender, race, tumour location, histologic subtype, Clark level, ulceration, Breslow thickness, N stage.

- *Location*

Table 70 Location to predict overall survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Scalp vs other head/neck location: Effect sizes >1 indicate greater risk if located on scalp										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
IIIB/C	Barbour 2015	107	RR 1.68 (1.14, 2.47)	16/24	33/83	Serious[2]	Not serious	N/A	Serious[3]	Low
Scalp/neck vs face location: Effect sizes >1 indicate greater risk if located on scalp										
SLN positive	Huang 2020	530	Adjusted HR 1.48 (1.04, 2.11)[7]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Axial vs extremities location: Effect sizes >1 indicate greater risk if located on axial plane										
SLN negative II	Egger 2016	1,998	Adjusted 1.65 (1.31, 2.09)[5]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate
SLN positive III	Tas 2021	389	Unadjusted HR 0.98 (0.71– 1.37)	N/A	N/A	Serious[1]	Not serious	N/A	Serious[3]	Low
Trunk vs extremities: Effect sizes >1 indicate greater risk if located on trunk (Figure 26)										
SLNB negative II	Laks 2017	277	Unadjusted HR 1.39 (0.83,2.33)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
IIIB/C (melanoma specific survival)	2	388	unadjusted HR 1.34 (0.98, 1.84)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
Head/neck melanoma vs. extremities: Effect sizes >1 indicate greater risk if located on head/neck (Figure 27)										
SLN negative II	Laks 2017	277	Unadjusted HR 1.41 (0.89,2.25)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
IIIB/C (melanoma specific survival)	2	388	unadjusted HR 1.18 (0.81, 1.70)	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
Head/neck melanoma vs. lower limb: Effect sizes >1 indicate greater risk if located on head/neck										
I-IV	Yang 2019	77,508	Adjusted HR 0.87 (0.80, 0.94)[6]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Head/neck melanoma vs. upper limb: Effect sizes >1 indicate greater risk if located on head/neck										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
I-IV	Yang 2019	77,508	Adjusted HR 0.75 (0.70 0.82)[6]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Head/neck melanoma vs. trunk: Effect sizes >1 indicate greater risk if located on head/neck										
I-IV	Yang 2019	77,508	Adjusted HR 0.89 (0.83, 0.96)[6]	N/A	N/A	Serious[2]	Not serious	N/A	Not serious	Moderate
Paediatric population: Axial vs extremities: Effect sizes >1 indicate greater risk if located on axial plane										
I-II paediatric	Brecht 2015	266	RR 0.64 (0.21, 1.97)	5/140	7/126	Serious[1]	Not serious	N/A	Serious[3]	Low

1. Study was at high risk of bias
2. Study was at moderate risk of bias
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. 95% Cis cross the line of no effect (1.0)
5. Adjusted for Breslow thickness, age, gender, Clark level, ulceration, location and histological type
6. Adjusted for age, gender, location, SEER stage, AJCC stage, insurance status, median family income, marital status.
7. Adjusted for age, location, ulceration and number of positive lymph nodes.

- *ECOG performance status ≥1*

Table 71 ECOG to melanoma-specific survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥1	0					
Effect sizes >1 indicate greater risk if ECOG ≥1										
III Melanoma-specific survival (≥1 vs 0)	Grotz 2014	317	Unadjusted HR 1.88 (1.06,3.34)[1]	N/A	N/A	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Patients were randomly assigned to GMCSF.

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥1	0					
2. Study was at moderate risk of bias										

- Predictors of recurrence/progression during the interval between resection and start of adjuvant therapy in stage IIIB/IIIC

Table 72 Risk factors to predict rapid recurrences in resected IIIB/C

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				N/A	N/A					
Gender: RR >1 indicates greater risk of recurrence if male										
IIIB/C	Bloemendal 2019	120	RR 1.97 (0.78, 4.97)	Male: 17/76	Female: 5/44	Serious[1]	Not serious	N/A	Very serious[2]	Very low
Breslow Thickness: RR>1 indicated greater risk of recurrence if ≥4mm										
IIIB/C	Bloemendal 2019	120	RR 1.52 (0.71, 3.27)	≥4mm: 9/36	<4mm: 12/73	Serious[1]	Not serious	N/A	Very serious[2]	Very low
Ulceration: RR>1 indicated greater risk of recurrence if ulcerated										
IIIB/C	Bloemendal 2019	120	RR 0.90 (0.40, 2.01)	Ulcerated: 7/38	Not ulcerated: 15/73	Serious[1]	Not serious	N/A	Very serious[2]	Very low
Location: RR>1 indicated greater risk of recurrence if located on axial plane										
IIIB/C	Bloemendal 2019	120	RR 1.08 (0.50, 2.31)	axial: 13/63	extremities : 9/47	Serious[1]	Not serious	N/A	Very serious[2]	Very low
Number of positive lymph nodes: RR>1 indicated greater risk of recurrence if >1 positive lymph node										
IIIB/C	Bloemendal 2019	120	RR 1.72 (0.72, 4.07)	≥2:	0-1:	Serious[1]	Not serious	N/A	Very serious[2]	Very low

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				N/A	N/A					
				16/73	6/47					

1. Patients were randomised to receive adjuvant GMCSF or no adjuvant therapy.
2. 95% CIs cross both lines of the MID (0.8, 1.25)

6.2 Diagnostic accuracy of imaging used during follow-up

Surveillance (asymptomatic) – all recurrences

CT

Table 73 Diagnostic accuracy of CT during follow-up

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CT or PET-CT (most scans were CT only) for follow-up of stage IIB-IIIB melanoma after resection (per patient analysis) – patients received 6-12 months PET-CT scans: accuracy of first scan (6-12 months after surgery)										
Turner 2020	Prospective	332	0.75 (0.59, 0.86)	0.84 (0.80, 0.88)	LR+ 4.72 (3.42, 6.52)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR+ 0.30 (0.17, 0.52)	Serious[1]	Not serious	N/A	Serious[1]	Low
CT or PET/CT for follow-up of stage IIB-IIIB melanoma after resection (per patient analysis) – patients received 6-12 months PET-CT scans: accuracy of fourth (6-12 months after surgery)										
Turner 2020	Prospective	172	0.86 (0.57, 0.96)	0.88 (0.82, 0.92)	LR+ 7.13 (4.44, 11.44)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.16 (0.05, 0.59)	Serious[1]	Not serious	N/A	Serious[1]	Low

1. Study at moderate risk of bias
2. 95% Cis cross one line of the MID (0.5, 1, 2.0)

- PET-CT

Table 74 Diagnostic accuracy of PET-CT during follow-up

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PET-CT during follow-up of high-risk resected patients (primarily stage III-IV) (per-scan analysis) (Figure 41 and Figure 42)										
5	Cohort studies	2,416	0.90 (0.85, 0.93)	0.93 (0.90, 0.96)	LR+ 13.97 (8.84, 22.06)	Serious[2]	Not serious	Very serious[6]	Not serious	Very low
					LR- 0.11, (0.07, 0.17)	Serious[2]	Not serious	Not serious	Not serious	Moderate
Sensitivity analysis: PET/CT during follow-up of high-risk resected patients (primarily stage III-IV) (per-scan analysis) (Figure 43 and Figure 44)										
2	Prospective cohort study	348	0.94 (0.79, 0.99)	0.97 (0.80, 1.00)	LR+ 35.08 (4.49, 274.32)	Serious[2]	Not serious	Serious[3]	Not serious	Moderate
					LR- 0.05, (0.01, 0.39)	Serious[2]	Not serious	Serious[3]	Not serious	Moderate
PET-CT during follow-up of resected melanoma of an unclear stage (per-patient analysis) (Figure 45 and Figure 46)										
2	Cohort studies	191	0.96 (0.88, 0.98)	0.88 (0.81, 0.93)	LR+ 7.89 (4.76, 13.07)	Serious[2]	Not serious	Serious[3]	Not serious	Low
					LR- 0.05, (0.02, 0.14)	Serious[2]	Not serious	Not serious	Not serious	Moderate
Sensitivity analysis (excluding high risk of bias studies): PET/CT during follow-up after completing therapy (per patient analysis)										
Strobel 2007	Retrospective cohort study	47	0.96 (0.83, 0.99)	0.94 (0.50, 0.99)	LR+ 17.33 (1.17, 256.35)	Serious[2]	Not serious	N/A	Serious[4]	Low
					LR- 0.04 (0.01, 0.19)	Serious[2]	Not serious	N/A	Not serious	Moderate
Follow-up of stage IV										
El-Shourbagy 2020	Retrospective cohort study	18	0.97 (0.65, 1.00)	0.63 (0.18, 0.93)	LR+ 2.58 (0.73, 9.18)	Very serious[5]	Not serious	N/A	Very serious[7]	Very low
					LR- 0.05 (0.00, 0.85)	Very serious[5]	Not serious	N/A	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PET/CT for follow-up of stage IIB-IIIB melanoma after resection (per patient analysis) – single scan given 3-12 months after surgery, accuracy assessed 6 months after PET/CT scan										
Koskivuo 2016	Prospective	110	0.79 (0.51, 0.93)	0.84 (0.76, 0.90)	LR+ 5.03 (2.93, 8.62)	Serious[5]	Not serious	N/A	Not serious	Moderate
					LR- 0.25 (0.09, 0.70)	Serious[5]	Not serious	N/A	Serious[4]	Low
PET/CT for follow-up of stage IIB-IIIB melanoma after resection (per patient analysis) – single scan given 3-12 months after surgery, accuracy assessed 12 months after PET/CT scan										
Koskivuo 2016	Prospective	110	0.46 (0.28, 0.65)	0.83 (0.73, 0.89)	LR+ 2.63 (1.40, 4.95)	Serious[5]	Not serious	N/A	Serious[4]	Low
					LR- 0.66 (0.45, 0.96)	Serious[5]	Not serious	N/A	Serious[4]	Low
PET/CT for follow-up of stage IIB-IIIB melanoma after resection (per patient analysis) – single scan given 3-12 months after surgery, accuracy assessed 36 months after PET/CT scan										
Koskivuo 2016	Prospective	110	0.31 (0.18, 0.47)	0.80 (0.69, 0.87)	LR+ 1.51 (0.77, 2.94)	Serious[5]	Not serious	N/A	Very serious[7]	Very low
					LR- 0.87 (0.68, 1.11)	Serious[5]	Not serious	N/A	Not serious	Moderate
PET/CT for follow-up of stage III melanoma after resection (per patient analysis) – single scan given 3-12 months after surgery, accuracy assessed 60 months after PET/CT scan										
Koskivuo 2016	Prospective	110	0.26 (0.15, 0.41)	0.78 (0.67, 0.86)	LR+ 1.19 (0.60, 2.34)	Serious[5]	Not serious	N/A	Very serious[7]	Very low
					LR- 0.95 (0.76, 1.18)	Serious[5]	Not serious	N/A	Not serious	Moderate

1. Iagaru 2007 conducted scan for restaging after completion of therapy, El-Shourbagy 2020 conducted scan for follow-up of stage IV patients after resection and/or 6 months course of chemotherapy/radiotherapy, Strobel 2009 conducted scan for follow-up of high-risk patients.
2. >33.3% of weighted data from studies at moderate or high risk of bias
3. i-squared >33.3%
4. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5,1, 2)
5. Study at moderate risk of bias
6. i-squared >66.6%

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
7. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5,1, 2)										

Table 75 Diagnostic accuracy of PET-CT during follow-up (subgroup analysis by Breslow thickness)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
PET/CT for re-staging after completing therapy: Breslow <1.0 mm (per lesion)										
Iagaru 2007	Retrospective	7	0.75 (0.23, 0.96)	0.66 (0.15, 0.95)	LR+ 2.25 (0.41, 12.28)	Very serious[1]	Serious[3]	N/A	Very serious[2]	Very low
					LR- 0.37 (0.05, 2.44)	Very serious[1]	Serious[3]	N/A	Very serious[2]	Very low
PET/CT for re-staging after completing therapy: Breslow 1.0-4.0 mm (per lesion)										
Iagaru 2007	Retrospective	73	0.92 (0.79, 0.97)	0.87 (0.71, 0.95)	LR+ 7.41 (2.95, 18.61)	Very serious[1]	Serious[3]	N/A	Not serious	Very low
					LR- 0.08 (0.02, 0.25)	Very serious[1]	Serious[3]	N/A	Not serious	Very low
PET/CT for re-staging after completing therapy: Breslow >4.0 mm (per lesion)										
Iagaru 2007	Retrospective	21	0.81 (0.55, 0.93)	0.60 (0.20, 0.90)	LR+ 2.03 (0.67, 6.09)	Very serious[1]	Serious[3]	N/A	Very serious[2]	Very low
					LR- 0.31 (0.09, 1.08)	Very serious[1]	Serious[3]	N/A	Very serious[2]	Very low

1. Study at high risk of bias
2. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)
3. Study was only partially applicable to the review question as data were reported on a per-lesion basis.

- PET alone

Table 76 Diagnostic accuracy of PET-alone for follow-up of stage III disease

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Surveillance strategy (per patient analysis): IIIA: PET scans at 6 and 18 months; IIIB/C: 6 monthly PET scans for first 2 years + scan at 36 months. IIIC: MRI brain recommended at 6 and 12 months.										
Lewin 2018[1]	Retrospective cohort study	156	0.69 (0.57, 0.79)	0.89 (0.81, 0.93)	LR+ 6.06 (3.47, 10.57)	Very serious[2]	Serious[3]	N/A	Not serious	Very low
					LR- 0.35 (0.24, 0.50)	Very serious[2]	Serious[3]	N/A	Not serious	Very low

1. 2x2 data backcalculated using RevMan
2. >33.3% of weighted data from studies at moderate or high risk of bias
3. i-squared >33%

- MRI

Table 77 Diagnostic accuracy of whole-body MRI for follow-up of melanoma

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Surveillance strategy (per scan analysis; following surgical resection): every 4 months the first 3 years of follow-up and every 6 months in the following 2 years.										
Jansen 2021	Prospective cohort study	68 (373 scans)	0.63 (0.40, 0.81)	0.98 (0.95, 0.99)	LR+ 27.95 (12.99, 60.14)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.38 (0.21, 0.68)	Serious[1]	Not serious	N/A	Serious[2]	Low
Surveillance strategy (per scan analysis; following systemic treatment): every 4 months the first 3 years of follow-up and every 6 months in the following 2 years.										
Jansen 2021	Prospective cohort study	39 (201 scans)	0.43 (0.14, 0.77)	0.99 (0.96, 1.00)	LR+ 29.14 (7.10, 119.59)	Serious[1]	Not serious	N/A	Not serious	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					LR- 0.58 (0.31, 1.10)	Serious[1]	Not serious	N/A	Very serious[3]	Very low

1. Study at moderate risk of bias.
2. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)
3. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)

- US

Table 78 Diagnostic accuracy of US during follow-up

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
US during follow-up after surgery (per patient)										
Rubaltelli 2011	Retrospective	460	0.98 (0.82, 0.99)	0.92 (0.89, 0.94)	LR+ 13.28 (9.47, 18.62)	Very serious[1]	Not serious	N/A	Not serious	Low
					LR- 0.01 (0.00, 0.22)	Very serious[1]	Not serious	N/A	Not serious	Low
US-CE during follow-up after surgery (per patient)										
Rubaltelli 2011	Retrospective	460	0.98 (0.82, 0.99)	0.99 (0.98, 0.99)	LR+ 167.36 (48.60, 576.32)	Very serious[1]	Not serious	N/A	Not serious	Low
					LR- 0.01 (0.00, 0.20)	Very serious[1]	Not serious	N/A	Not serious	Low

1. Study at high risk of bias

- Surveillance – lymph node recurrences

Table 79 Diagnostic accuracy during follow-up

No. of studies	Study design	Studies (sample)	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CT										
Xing 2010	Meta-analysis of both prospective and retrospective studies	3 (439)	0.61 (0.15, 0.93)	0.97 (0.70, 1.00)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
PET-CT										
Xing 2010	Meta-analysis of both prospective and retrospective studies	5 (571)	0.65 (0.20, 0.93)	0.99 (0.92, 1.00)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
PET alone										
Xing 2010	Meta-analysis of both prospective and retrospective studies	22 (1,531)	0.87 (0.67, 0.96)	0.98 (0.93, 1.00)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
US										
Xing 2010	Meta-analysis of both prospective and retrospective studies	22 (7,087)	0.96 (0.85, 0.99)	0.99 (0.95, 1.00)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low

1. Study was at moderate risk of bias

No. of studies	Study design	Studies (sample)	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2. Tests of heterogeneity are not reported										

- Surveillance – distant progression/recurrence

Table 80 Diagnostic accuracy during follow-up

No. of studies	Study design	Studies (sample)	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CT										
Xing 2010	Meta-analysis of both prospective and retrospective studides	3 (439)	0.63 (0.46, 0.77)	0.78 (0.58, 0.90)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
PET-CT										
Xing 2010	Meta-analysis of both prospective and retrospective studides	2 (324)	0.86 (0.76, 0.93)	0.91 (0.79, 0.97)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
PET alone										
Xing 2010	Meta-analysis of both prospective and retrospective studies	4 (454)	0.82 (0.72, 0.88)	0.83 (0.70, 0.91)	N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					N/A	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
1. Study was at moderate risk of bias 2. Tests of heterogeneity are not reported										

- Suspected recurrence (symptomatic)
  - PET-CT

Table 81 Diagnostic accuracy of PET-CT for suspected recurrence

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Stage III-IV suspected of distant progression (per lesion analysis)										
Pfannenberg 2007	Prospective	64 (420 lesions)	0.91 (0.87, 0.93)	0.77 (0.69, 0.84)	LR+ 3.98 (2.87, 5.52)	Serious[2]	Not serious	N/A	Not serious	Moderate
					LR- 0.12 (0.09, 0.18)	Serious[2]	Not serious	N/A	Not serious	Moderate
PET/CT for suspected recurrence (per patient analysis) (Figure 47 and Figure 48)										
3	Retrospective	139	0.87 (0.77, 0.94)	0.84 (0.64, 0.94)	LR+ 5.39 (2.94, 9.89)	Serious[2]	Not serious	Serious[3]	Not serious	Low
					LR- 0.15 (0.08, 0.28)	Serious[2]	Not serious	Not serious	Not serious	Moderate
Sensitivity analysis (excluding high risk of bias studies): PET/CT for suspected recurrence (per patient analysis) (Figure 49 and Figure 50)										
2	Retrospective	128	0.87 (0.76, 0.93)	0.88 (0.68, 0.96)	LR+ 6.73 (3.38, 13.42)	Serious[2]	Not serious	Serious[3]	Not serious	Low
					LR- 0.16 (0.08, 0.30)	Serious[2]	Not serious	Not serious	Not serious	Moderate
PET/CT for suspected recurrence (per scan analysis) (Figure 51 and Figure 52)										
2	Retrospective	152	0.83 (0.63, 0.94)	0.88 (0.79, 0.93)	LR+ 7.41 (4.17, 13.18)	Serious[1]	Not serious	Not serious	Not serious	Moderate
					LR- 0.19 (0.08, 0.43)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low

1. Study was at moderate risk of bias
2. >33.3% of weighted data from studies at moderate or high risk of bias
3. i-squared >33.3%
4. i-squared >66.6%

- PET

Table 82 Diagnostic accuracy of PET-CT for suspected recurrence

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Stage III-IV suspected of distant progression (per lesion analysis)										
Pfannenberg 2007	prospective	64 (420 lesions)	0.70 (0.65, 0.75)	0.84 (0.76, 0.89)	LR+ 4.33 (2.88, 6.51)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.35 (0.29, 0.43)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study was at moderate risk of bias

- CT

Table 83 Diagnostic accuracy of PET-CT for suspected recurrence

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Stage III-IV suspected of distant progression (per lesion analysis)										
Pfannenberg 2007	prospective	64 (420 lesions)	0.77 (0.72, 0.82)	0.70 (0.61, 0.77)	LR+ 2.56 (1.94, 3.38)	Serious[1]	Not serious	N/A	Serious[2]	Low
					LR- 0.33 (0.26, 0.42)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)

- wbMRI

Table 84 Diagnostic accuracy of PET-CT for suspected recurrence

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Stage III-IV suspected of distant progression (per lesion analysis)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Pfannenberg 2007	prospective	64 (420 lesions)	0.80 (0.75, 0.84)	0.76 (0.68, 0.83)	LR+ 3.39 (2.45, 4.68)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.26 (0.21, 0.34)	Serious[1]	Not serious	N/A	Not serious	Moderate
1. Study was at moderate risk of bias										

- Restaging
  - CT

Table 85 Diagnostic accuracy of CT for re-staging after completion of therapy

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
CT for restaging after completing therapy (per patient analysis)										
Iagaru 2007	Retrospective	106	0.67 (0.54, 0.78)	0.94 (0.83, 0.98)	LR+ 11.31 (3.72, 34.38)	Very serious[1]	Not serious	N/A	Not serious	Low
					LR- 0.34 (0.23, 0.50)	Very serious[1]	Not serious	N/A	Not serious	Low
1. Study at high risk of bias										

  - PET-CT

Table 86 Diagnostic accuracy of PET-CT during follow-up

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Staging strategy - Detection of in-transit or distant metastases: palpable + lymph node metastatic patients referred for total body PET/CT and brain MRI imaging										
Aukema 2010[1]	Prospective cohort study	70	0.87 (0.70, 0.95)	0.97 (0.84, 1.00)	LR+ 33.97 (4.88, 236.23)	Serious[3]	Serious[3]	N/A	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					LR- 0.13 (0.05, 0.33)	Serious[3]	Serious[3]	N/A	Not serious	Low
Restaging after completing therapy (per patient analysis)										
Iagaru 2007	Retrospective	106	0.89 (0.78, 0.95)	0.88 (0.76, 0.95)	LR+ 7.44 (3.49, 15.85)	Very serious[1]	Not serious	N/A	Not serious	Low
					LR- 0.12 (0.06, 0.26)	Very serious[1]	Not serious	N/A	Not serious	Low

1. i-squared >33%
2. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2)
3. Study at moderate risk of bias
4. Study only partially applicable to the review question.
5. I-squared >66%
6. >33.3% of weighted data from studies only partially applicable to the review question

6.3 Brain imaging

- Diagnostic accuracy of imaging protocols which include brain imaging
  - *Stage IIIC threshold*

Table 87 Diagnostic accuracy of imaging strategies (which include brain scans) for stage III patients

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Surveillance strategy - Detection of brain metastases: Utility of using IIIC as a threshold for considering brain scans during surveillance										
Abdel-Rahman 2019[1]	Retrospective review of prospective database	109,971	0.32 (0.26, 0.38)	0.96 (0.96, 0.96)	LR+ 8.33 (6.89, 10.07)	Very serious[2]	Not serious	N/A	Not serious	Low
					LR- 0.71 (0.65, 0.78)	Very serious[2]	Not serious	N/A	Not serious	Low
Surveillance strategy - Detection of any suspected recurrence: IIIA: PET scans at 6 and 18 months; IIIB/C: 6 monthly PET scans for first 2 years + scan at 36 months. IIIC: MRI brain recommended at 6 and 12 months.										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Lewin 2018[1]	Retrospective cohort study	156	0.69 (0.57, 0.79)	0.89 (0.81, 0.93)	LR+ 6.06 (3.47, 10.57)	Very serious[2]	Serious[3]	N/A	Not serious	Very low
					LR- 0.35 (0.24, 0.50)	Very serious[2]	Serious[3]	N/A	Not serious	Very low
Staging strategy - Detection of in-transit or distant metastases: palpable + lymph node metastatic patients referred for total body PET/CT and brain MRI imaging										
Aukema 2010[1]	Prospective cohort study	70	0.87 (0.70, 0.95)	0.97 (0.84, 1.00)	LR+ 33.97 (4.88, 236.23)	Serious[3]	Serious[3]	N/A	Not serious	Low
					LR- 0.13 (0.05, 0.33)	Serious[3]	Serious[3]	N/A	Not serious	Low

1. 2x2 data not reported by study. 2x2 table was back-calculated using revman.
2. Study was at high risk of bias.
3. Study was only partially applicable to the review question (outcome was any relapse, not specifically brain metastases).
4. Study was at moderate risk of bias

- Predictors of brain metastases
  - *Stage*

Table 88 Stage to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher stage	Lower stage					
Time to development of brain metastases in stage III-IV patients: HR >1 =higher disease stage has greater risk of developing brain metastases										
IIIB vs. IIIA	Haydu (2020)	949	HR 2.07 (1.35, 3.17)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
IIIC vs. IIIA	Haydu (2020)	1,239	HR 2.46 (1.65, 3.67)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Higher stage	Lower stage					
IIID vs. IIIA	Haydu (2020)	489	HR 3.17 (1.75, 5.74)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
Development of brain metastases during follow-up: RR >1 = males have greater risk of developing brain metastases (Figure 30)										
Overall higher versus lower stages	3	2,309	RR 1.37 (0.90, 2.07)	169/697	315/1612	Serious[3]	Serious[5]	Very serious[4]	Serious[6]	Very low
III vs I-II	2	1,656	RR 1.30 (0.56, 3.00)	128/512	211/1142	Serious[3]	Serious[5]	Very serious[4]	Very serious[7]	Very low
IIIC vs IIIA-B	Samlowski 2017	402	RR 1.36 (0.82, 2.25)	24/152	29/250	Not serious	Not serious	N/A	Serious[6]	Moderate
IV vs III	Qian 2013	253	RR 1.51 (1.03, 2.21)	17/33	75/220	Serious[2]	Not serious	N/A	Serious[6]	Low

1. Adjusted for enrolment institution, age, Gender tumour stage III subgroup, and mitotic rate
2. Study was at moderate risk of bias
3. >33.3% of studies were at moderate or high risk of bias
4. I^2 >66.6%
5. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease).
6. 95% CIs cross one line of the MID (0.8, 1.25)
7. 95% CIs cross both lines of the MID (0.8, 1.25)

- *Gender*

Table 89 Gender to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Time to development of brain metastases in stage III-IV patients: HR >1 = males have greater risk of developing brain metastases										

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
III	Haydu (2020)	1,918	HR 1.53 (1.18, 1.99)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
IV (unresectable)	Wang (2014)	665	HR 1.25 (0.95, 1.65)[2]	N/A	N/A	Serious[4]	Not serious	N/A	Serious[5]	Low
Development of brain metastases during follow-up: RR >1 = males have greater risk of developing brain metastases (Figure 32)										
All combined	6	4,117	RR 1.26 (1.10, 1.44)	494/2414	241/1703	Serious[6]	Serious[7]	Not serious	Serious[3]	Very low
I-III combined	2	2,828	RR 1.33 [1.08, 1.64]	222/1638	122/1312	Serious[6]	Serious[7]	Not serious	Serious[3]	Very low
III-IV combined	3	665	RR 1.20 [1.01, 1.42]	272/776	119/391	Serious[6]	Not serious	N/A	Serious[3]	Low
Presence of brain metastases at baseline: RR >1 = males have greater risk of developing brain metastases (Figure 31)										
IV	2	5,066	RR 1.15 (1.05, 1.25)	1065/3152	562/1914	Serious[6]	Not serious	N/A	Serious[3]	Low

6. Adjusted for enrolment institution, age, tumour stage subgroup and mitotic rate
7. Unadjusted
8. 95% CIs cross one line of the MID (0.8, 1.25)
9. Study was at moderate risk of bias
10. 95% Cis cross the line of no effect (1.0)
11. >33% of studies were at moderate or high risk of bias
12. >33.3% of studies were only partially applicable to the review question (due to large proportion of study sample being in early stages of disease).

- *Age*

Table 90 Age to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				<60 years	≥60 years					
Time to development of brain metastases: HR >1 = risk of brain metastases increases with age										
III	Haydu (2020)	1,918	Per 10 years HR 0.90 (0.83, 0.97)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				<60 years	≥60 years					
IV (unresectable)	Wang (2014)	665	HR 1.00 (0.99, 1.00)[2]	N/A	N/A	Serious[3]	Not serious	N/A	Serious[4]	Low
Presence of brain metastases at baseline: RR >1 = People aged <60 years have greater risk of having brain metastases										
IV	Zhang (2019)	4,369	RR 1.25 (1.15, 1.35)	617/1516	930/2853	Serious[3]	Not serious	N/A	Serious[5]	Low

1. Adjusted for enrolment institution, Gender, tumour stage subgroup and mitotic rate
2. Unadjusted
3. Study was at moderate risk of bias
4. 95% CIs cross the line of no effect (1.0,)
5. 95% CIs cross one line of the MID (0.8, 1.25)

- *Location: Scalp versus other locations*

Table 91 scalp location of primary tumour to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Scalp	Other					
Time to development of brain metastases: HR >1 = risk of brain metastases increases if location is scalp										
III	Haydu (2020)	1,918	Vs. other head/neck locations: HR 1.72 (1.05, 2.86)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
			Vs. upper extremity: HR 2.56 (1.54, 4.35)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
			Vs. lower extremity: HR 2.00 (1.33, 3.03) [1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
			Vs.trunk: HR 1.59 (1.07, 2.32)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
Development of brain metastases: RR >1 = risk of brain metastases increases if location is scalp										
I-II	Huismans (2018)	1,599	Vs. other head/neck locations:	37/258	88/1341	Serious[2]	Serious[3]	N/A	Not serious	Low

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Scalp	Other					
			RR 2.19 (1.52, 3.13)							

1. Adjusted for enrolment institution, age, tumour stage subgroup and Gender
2. Study was at moderate risk of bias
3. Study was only partially applicable to the review question

- *Location: Head and neck versus trunk/limbs*

Table 92 head/neck location of primary tumour to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				HNM	Trunk or Limb melanoma					
Time to development of brain metastases: HR >1 = risk of brain metastases increases if location is Head/neck										
IV only	Wang (2014)	568	HR 1.16 [0.77, 1.76][1]	N/A	N/A	Serious[2]	Not serious	N/A	Serious[4]	Low
Development of brain metastases: RR >1 = risk of brain metastases increases if location is head/neck (Figure 35)										
All stages combined	3	3,824	RR 1.23 [1.05, 1.44]	140670	484/3154	Serious[3]	Serious[6]	Not serious	Serious[5]	Very low
I-III only	2	2,887	RR 1.35 [0.94, 1.92]	74/483	250/2404	Serious[3]	Serious[6]	Very serious	Serious[5]	Very low
III only	Samlowski (2017)	369	RR 1.09 [0.55, 2.15]	9/69	36/300	Not serious	Not serious	N/A	Very serious[7]	Low
IV only	Wang (2014)	568	RR 1.10 [0.89, 1.36]	57/118	198/450	Serious[2]	Not serious	N/A	Serious[5]	Low
Presence of brain metastases at baseline: RR >1 = risk of brain metastases increases if location is head/neck (Figure 33)										
IV	2	2,163	RR 0.85 [0.70, 1.02]	119/558	356/1605	Serious[3]	Not serious	Not serious	Serious[5]	Low

1. Adjusted for M-stage and compared head and neck melanomas specifically to limb melanomas
2. Study was at moderate risk of bias
3. >33.3% of studies were at moderate or high risk of bias

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				HNM	Trunk or Limb melanoma					
4. 95% CIs cross the line of no effect (1.0) 5. 95% CIs cross one line of the MID (0.8, 1.25) 6. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease). 7. 95% CIs cross both lines of the MID (0.8, 1.25)										

- *Location: Trunk versus limbs*

Table 93 Trunk location of primary tumour to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Trunk	Limbs					
Time to development of brain metastases: HR >1 = risk of brain metastases increases if location is trunk										
IV only	Wang (2014)	450	HR 1.37 (0.98, 1.91)[1]	N/A	N/A	Serious[2]	Not serious	Not serious	Serious[5]	Low
Development of brain metastases: RR >1 = risk of brain metastases increases if location is trunk (Figure 36)										
All stages combined	3	2,854	RR 1.36 (1.15, 1.61)	279/1414	169/1440	Serious[3]	Serious[4]	Not serious	Serious[6]	Very low
I-III only	2	2,404	RR 1.43 (1.13, 1.81)	142/1126	108/1278	Serious[3]	Serious[4]	Not serious	Serious[6]	Very low
IV only	Wang (2014)	450	RR 1.26 (1.00, 1.59)	137/288	61/162	Serious[2]	Not serious	Not serious	Serious[6]	Low
Presence of brain metastases at baseline: RR >1 = risk of brain metastases increases if location is trunk (Figure 34)										
IV	2	1,599	RR 1.31 (1.05, 1.64)	273/1116	83/489	Serious[3]	Not serious	Not serious	Serious[6]	Low
1. Model adjusted for M-stage 2. Study was at moderate risk of bias 3. >33.3% of studies were at moderate or high risk of bias 4. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease).										

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Trunk	Limbs					
5. 95% CIs cross the line of no effect (1.0) 6. 95% CIs cross one line of the MID (0.8, 1.25)										

- *Ulceration*

Table 94 Ulceration to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Ulcerated	Non-ulcerated					
Development of brain metastases during follow-up: RR >1 = ulceration has greater risk of developing brain metastases (Figure 37)										
All combined	5	3,469	RR 1.51 (0.70, 3.26)	207/1071	187/2398	Serious[1]	Serious[2]	Very serious	Very serious[4]	Very low
I-III combined	3	3,098	RR 2.06 (0.76, 5.58)	181/864	164/2234	Serious[1]	Serious[2]	Very serious	Very serious[4]	Very low
III	Samlowski 2017	301	RR 0.90 (0.49, 1.66)	19/167	17/134	Not serious	Not serious	N/A	Very serious[4]	Very low
III-IV combined	Peuvrel 2014	70	RR 0.88 (0.33, 2.34)	7/40	6/30	Serious[3]	Not serious	N/A	Very serious[4]	Very low
Presence of brain metastases at baseline: RR >1 = ulceration has greater risk of developing brain metastases										
IV	Zhang 2019	1,003	RR 1.01 [0.80, 1.28]	149/644	82/359	Serious[3]	Not serious	N/A	Serious[5]	Low
1. >33.3% of studies were at moderate or high risk of bias 2. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease). 3. Study was at moderate risk of bias 4. 95% CIs cross both lines of the MID (0.8, 1.25) 5. 95% CIs cross one line of the MID (0.8, 1.25)										

- *Breslow thickness*

Table 95 Breslow thickness (>4mm versus ≤4mm) to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				>4mm	≤4mm					
Development of brain metastases during follow-up: RR >1 = males have greater risk of developing brain metastases (Figure 38 and Figure 39)										
All combined	3	3,257	RR 2.31 (0.98, 5.45)	176/521	264/2556	Serious[1]	Serious[2]	Very serious[5]	Serious[3]	Very low
I-III combined	2	2,614	RR 3.25 (2.50, 4.22)	65/284	167/2330	Serious[1]	Serious[2]	Not serious	Not serious	Low
III-IV combined	Wang (2014)	463	RR 1.09 (0.89, 1.34)	111/237	97/226	Serious[4]	Not serious	N/A	Serious[3]	Low
Presence of brain metastases at baseline: RR >1 = males have greater risk of developing brain metastases										
IV	Zhang (2019)	5,066	RR 0.97 (0.78, 1.21)	106/469	139/597	Serious[4]	Not serious	N/A	Serious[3]	Low

1. >33.3% of studies were at moderate or high risk of bias
2. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease).
3. 95% CIs cross one line of the MID (0.8, 1.25)
4. Study was at moderate risk of bias
5. I^2 > 66.6%

- *Mitosis*

Table 96 Mitosis (per mm^2) to predict brain metastases

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				More mitosis	Fewer /no mitosis					
Time to development of brain metastases in stage III-IV patients: HR >1 = males have greater risk of developing brain metastases										
III	Haydu (2020)	1,918	5-9 vs 0-4 mitoses: HR 1.77 (1.30, 2.41)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High
			>9 vs 0-4 mitoses:	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

Disease stage(s)	No. Studies	Sample size	Effect size	No. brain mets		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				More mitosis	Fewer /no mitosis					
			HR 2.18 (1.60, 2.98)[1]							
Development of brain metastases during follow-up: RR >1 = males have greater risk of developing brain metastases (Figure 40)										
I-III combined	3	3,576	RR 2.72 [2.02, 3.65][2]	251/2351	55/1225	Serious[3]	Serious[4]	Not serious	Not serious	Low

1. Adjusted for enrolment institution, age, Gender, tumour stage subgroup and mitotic rate
2. Daryanani (2005) compared 5 or more mitoses per 5 high power field (hpf) versus 0-4 mitoses per 5 hpf; Huismans (2014) compared 1 or more mitoses vs. <1 mitosis; Qian (2013) compared presence vs. absence of mitosis.
3. >33.3% of studies were at moderate or high risk of bias
4. >33.3% of studies were only partially applicable to the review question (due to study population having large proportion of sample in lower stages of disease).

6.4 Surveillance strategies for stage IV disease

- Predictors of relapse in stage IV (and unresectable stage III) melanoma
  - *Gender*

Table 97 Gender to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect sizes >1 indicate greater risk if male (Figure 2)										
Unresectable stage III/IV	3	1,014	RR 1.03 (0.94, 1.12)	410/620	253/394	Not serious	Not serious	Not serious	Not serious	High

- *Age*

Table 98 Age to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Risk ratios (Figure 4)										
Unresectable stage III/IV	4	1,959	RR 1.02 (0.96, 1.08)	852/1214	527/745	Not serious	Not serious	Not serious	Not serious	High

- *LDH*

Table 99 LVI to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Elevated	Normal					
Effect sizes >1 indicate greater risk if LDH is elevated (Figure 8)										
Unresectable III/IV	4	2,119	RR 1.40 (1.19, 1.65)	653/807	796/1312	Not serious	Not serious	Very serious[1]	Not serious	Low

1. I^2 >66.6%

- *ECOG performance status ≥1*

Table 100 ECOG to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				1+	0					
Risk ratios (Figure 10)										
Unresectable III/IV	4	2,137	RR 1.17 (1.11, 1.24)	534/709	927/1428	Not serious	Not serious	Not serious	Not serious	High

- Predictors of survival in stage IV (and unresectable stage III) melanoma

Predicting overall survival unless otherwise stated

- *Prior diagnosis of stage III disease*

Table 101 prior stage III disease to predict recurrence/ progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Yes	No					
Effect size >1 indicates greater risk of mortality if patient had prior diagnosis of stage III disease										
Resected IV	Faries 2017	499	Adjusted HR 1.37 (1.03–1.84)[1]	N/A	N/A	Not serious	Not serious	N/A	Not serious	High

1. Patients received adjuvant vaccination. Adjusted for vaccine received, M-status, number of lesions (>1 vs 1), Age 60 years or older, gender, time from primary diagnosis to randomisation, previous treatment for stage IV, ECOG performance status, elevated LDH, previous stage III disease.

- *Gender*

Table 102 Gender to predict survival

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Male	Female					
Effect sizes >1 indicate greater risk if male (Figure 22)										
Unresectable III/IV	2	521	RR 1.05 (0.91, 1.20)	196/318	122/203	Not serious	Not serious	Not serious	Not serious	High
IV	Faries 2017	496	Adjusted HR 0.99 (0.75–1.31)[2]	N/A	N/A	Not serious	Not serious	N/A	Serious[1]	Moderate

1. 95% Cis cross the line of no effect (1.0).
2. Patients received adjuvant vaccination. Adjusted for vaccine received, M-status, number of lesions (>1 vs 1), Age 60 years or older, gender, time from primary diagnosis to randomisation, previous treatment for stage IV, ECOG performance status, elevated LDH, previous stage III disease.

- *Age*

Table 103 Age to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Effect sizes >1 indicate greater risk if younger age (Figure 23)										

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Younger age	Older age					
Unresectable III/IV	3	1,466	RR 0.98 (0.90, 1.07)	549/919	329/547	Not serious	Not serious	Not serious	Not serious	High
IV (≥60 vs <60 year)	Faries 2017	497	Unadjusted HR 0.96 (0.72–1.29)[2]	NA	NA	Not serious	Not serious	N/A	Serious[1]	Moderate

1. Adjusted for age, regression, stage and ulceration
2. Patients received adjuvant vaccination. Adjusted for vaccine received, M-status, number of lesions (>1 vs 1), Age 60 years or older, gender, time from primary diagnosis to randomisation, previous treatment for stage IV, ECOG performance status, elevated LDH, previous stage III disease.

- *LDH*

Table 104 LVI to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				Elevated	Normal					
Effect sizes >1 indicate greater risk if LDH is elevated (Figure 24)										
Unresectable III/IV	3	1,452	RR 1.62 (1.36, 1.94)	384/500	485/952	Not serious	Not serious	Very serious[1]	Not serious	Low

1. I^2 >66.6%

- *ECOG performance status ≥1*

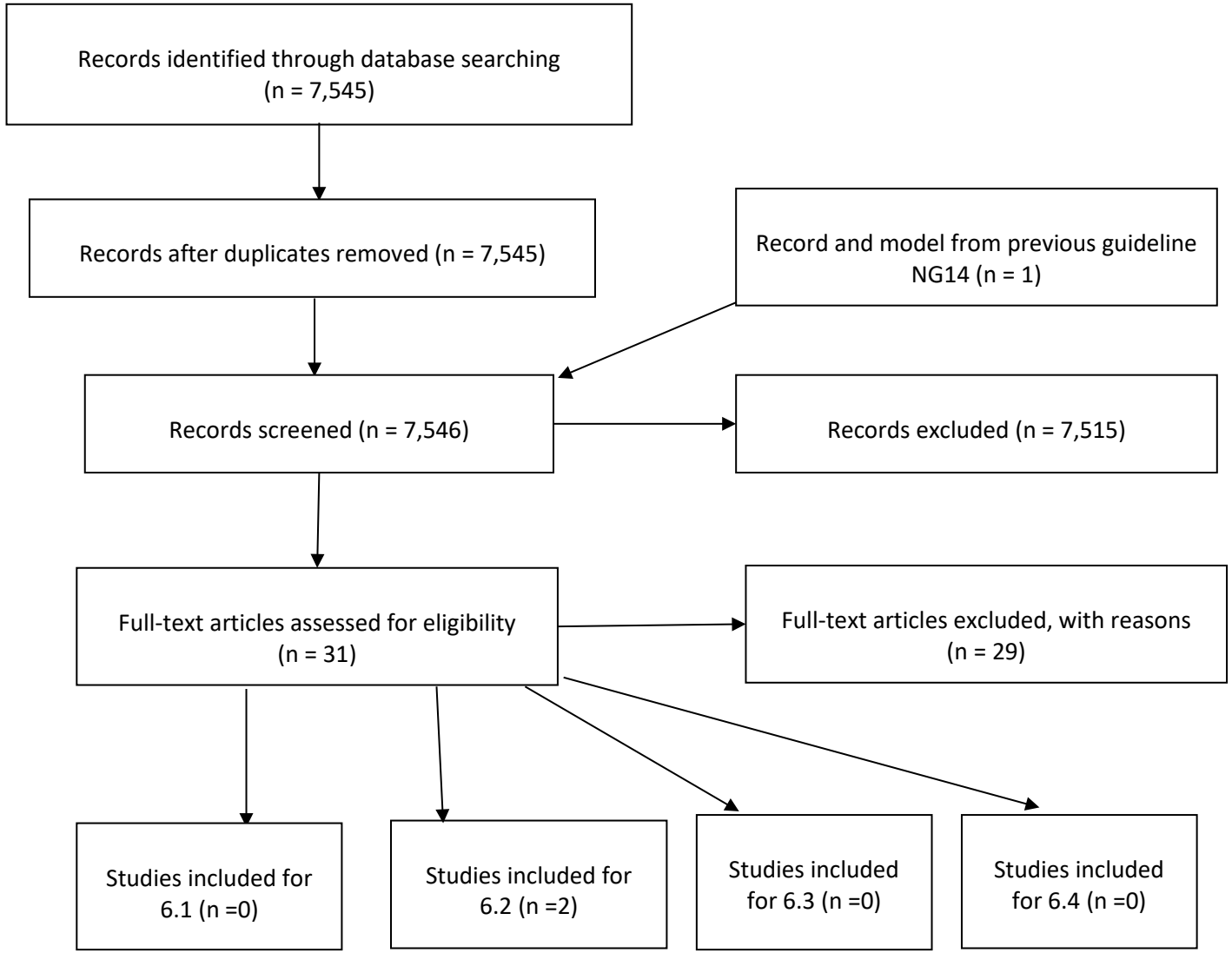
Table 105 Gender to predict recurrence/progression

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥1	0					
Effect sizes >1 indicate greater risk if ECOG ≥1 (Figure 25)										
Unresectable III/IV	3	1,465	RR 1.35 (1.17, 1.55)	534/709	927/1428	Not serious	Not serious	Serious[1]	Serious[2]	Low
IV (1 vs 0)	Faries 2017	498	Adjusted HR 0.80 (0.52–1.23)[4]	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Moderate

Disease stage(s)	No. Studies	Sample size	Effect size	No. recurred		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
				≥1	0					

1. I^2 >33.3%
2. 95% CIs cross one line of the MID (0.8, 1.25)
3. 95% Cis cross the line of no effect (1.0)
4. Patients received adjuvant vaccination. Adjusted for vaccine received, M-status, number of lesions (>1 vs 1), Age 60 years or older, gender, time from primary diagnosis to randomisation, previous treatment for stage IV, ECOG performance status, elevated LDH, previous stage III disease.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 106 Economic Evidence Table

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
NG14 Model (2014)	Cost utility study Markov model	UK Hospital National healthcare system	Standard follow-up (consisting of clinical reviews – 3 monthly years 1-3, 6 monthly years 4-5, annually years 6-10) Standard follow up with the addition of Imaging (MRI head, CT chest, abdomen and pelvis) every 6 months during the first 3 years	Patients with Stage III (different recurrence rates were assigned to patients with stage IIIA, IIIB and IIIC) melanoma who were rendered free of the disease. Age:57 Male:64%	**Health states:** no evidence of disease, loco-regional recurrence, distant recurrence, treatment for distant recurrence, death from melanoma, death from other causes **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) *Effectiveness* – based on the literature (cohort studies) *Costs* – NHS reference costs *Utilities* – from the literature or assumed based on other values included **Time horizon:** 20 years **Discount rates:** 3.5%	Costs[1]: Standard follow-up: £34,026 Imaging: £35,854 QALYs: Standard follow-up:5.7468 Imaging:5.8674 Incremental: Costs: £1,828 QALYs: 0.1206 ICER: £15,163	**Deterministic:** Lowering the probability of moving from loco-regional disease to distant disease makes imaging less cost effective. **Probabilistic:** At £20,000/QALY threshold standard follow-up was preferred in 61.75% of iterations. The addition of imaging was preferred over 50% of the time only when the threshold was £25,000/QALY	**Source of funding:** Built as part of the 2014 update to NG14 **Authors' conclusions:** Under the base case assumptions the addition of imaging is cost effective however, nearly two thirds of iterations in the probabilistic sensitivity analysis show that imaging is not cost effective.
Krug et al. (2010)	Cost utility study Markov Model	Belgium Hospital Healthcare system	Follow-up with suspected pulmonary metastases being examined with whole body computed tomography (WB-CT) Follow-up with suspected pulmonary metastases being examined with fluorine - 18 fluoro - 2 - deoxyglucose (FDG) positron emission tomography (PET) with X - Ray computed tomography (PET-CT)	Patients with resected stage IIC and stage III malignant melanoma. Age, performance status and other demographic data was not reported for this cohort	**Health states:** No suspicion of pulmonary disease, no other evidence of disease, visit for blood and chest X-ray, suspicion of pulmonary metastases, other metastatic disease, PET/CT or conventional strategy, pulmonary metastasectomy, systemic treatment, recurrence free survival, death **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) and confirmed by expert opinion *Effectiveness* – based on the literature (cohort studies) and confirmed by expert opinion	Costs[2]: WB-CT: €4,384 PET-CT: €3,438 Effects: WB-CT: 90.42 LMG (Life Months gained) PET-CT: 90.61 LMG Incremental PET-CT vs WB-CT: Cost: -€946 Effects: 0.1929 LMG ICER: PET-CT Dominates	**Deterministic:** Specificity of PET-CT has the greatest impact on the ICER, but changes in this parameter only varies the value of the ICER by less than 1% **Probabilistic:** 71% of the simulations showed that PET-CT was dominant, 22.6% of the simulations showed that PET-CT was dominated and in 6.4% of the simulations PET-CT was cost effective.	**Source of funding:** not reported. **Limitations identified by authors:** The model only focused on pulmonary recurrences and resectability. The primary clinical data was very heterogeneous and clinical practice varies across hospitals and physicians, so probabilities derived were an average. **Authors conclusions:** PET-CT strategy is cost effective in the diagnostic imaging of patients with

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					Costs – Health Insurance Institution in Belgium *Utilities* – not included **Time horizon:** 10 years **Discount rates:** Costs – 3%, Effects – 1.5%			suspected pulmonary metastasised melanoma

1 Costs in GBP in 2014, costs uprated to GBP in 2020 in summary in main text.
2 Costs in EUR in 2010, costs uprated to GBP in 2020 in summary in main text

Table 107: Economic evidence table

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
De novo model (2021) (BRAF mutant, reduced 2 years)	Cost utility study Markov model	UK Hospital National healthcare system	Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (2 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5) Reduced follow-up (2 years) with positron emission tomography - computed tomography	Patients with Stage III (different recurrence rates were assigned to patients with stage IIIA, IIIB and IIIC) melanoma and had started a course of adjuvant treatment Age: 57 years Male: 64%	**Health states:** disease free, local recurrence – not discovered, local recurrence – patient discovered, local recurrence – imaging discovered, distant recurrence – not discovered, distant recurrence – patient discovered, distant recurrence – imaging discovered, death from melanoma, death from other causes **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) *Effectiveness* – based on the literature (cohort studies) *Costs* – NHS reference costs *Utilities* – from the literature or assumed based on other values included **Time horizon:** 20 years **Discount rates:** 3.5%	Costs: CT (reduced): £126,338 CT: £126,366 PET-CT (reduced): £128,538 PET-CT: £128,698 QALYs: CT (reduced): 8.88965 CT: 8.89157 PET-CT (reduced): 8.93438 PET-CT: 8.93695 Incremental: CT (reduced) vs. CT: £14,548 PET-CT (reduced) vs. CT: £50,744 PET-CT vs. PET-CT (reduced): £62,167	**Deterministic:** For CT vs CT(reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT(reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results was congruent to the deterministic results	**Source of funding:** Built as part of the 2021 update to NG14 **Authors' conclusions:** CT at the standard follow up is the most cost effective follow up option

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			(PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2, annual years 3-5)					
De novo model (2021) (BRAF mutant, reduced 0 years)	Cost utility study Markov model	UK Hospital National healthcare system	Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5)	Patients with Stage III (different recurrence rates were assigned to patients with stage IIIA, IIIB and IIIC) melanoma and had started a course of adjuvant treatment Age: 57 years Male: 64%	**Health states:** disease free, local recurrence – not discovered, local recurrence – patient discovered, local recurrence – imaging discovered, distant recurrence – not discovered, distant recurrence – patient discovered, distant recurrence – imaging discovered, death from melanoma, death from other causes **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) *Effectiveness* – based on the literature (cohort studies) *Costs* – NHS reference costs *Utilities* – from the literature or assumed based on other values included **Time horizon:** 20 years **Discount rates:** 3.5%	Costs: CT (reduced): £126,099 CT: £126,366 PET-CT (reduced): £128,115 PET-CT: £128,698 QALYs: CT (reduced): 8.82752 CT: 8.89157 PET-CT (reduced): 8.87313 PET-CT: 8.93695 Incremental: CT (reduced) vs. CT: £4,169 PET-CT (reduced) vs. CT: CT dominates PET-CT vs. PET-CT (reduced): £51,391:	**Deterministic:** For CT vs CT(reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT(reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results was congruent to the deterministic results	**Source of funding:** Built as part of the 2021 update to NG14 **Authors' conclusions:** CT at the standard follow up is the most cost effective follow up option
De novo model (2021) (BRAF wild type, reduced 2 years)	Cost utility study Markov model	UK Hospital National healthcare system	Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5)	Patients with Stage III (different recurrence rates were assigned to patients with stage IIIA, IIIB and IIIC) melanoma and had started a course of adjuvant treatment Age: 54 years Male: 63%	**Health states:** disease free, local recurrence – not discovered, local recurrence – patient discovered, local recurrence – imaging discovered, distant recurrence – not discovered, distant recurrence – patient discovered, distant recurrence – imaging discovered, death from melanoma, death from other causes **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) *Effectiveness* – based on the literature (cohort studies)	Costs: CT (reduced): £113,360 CT: £113,386 PET-CT (reduced): £115,299 PET-CT: £115,457 QALYs: CT (reduced): 9.35189 CT: 9.35241 PET-CT (reduced): 9.39861 PET-CT: 9.40066	**Deterministic:** For CT vs CT(reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT(reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results was	**Source of funding:** Built as part of the 2021 update to NG14 **Authors' conclusions:** CT at the standard follow up is the most cost effective follow up option

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			Reduced follow-up (0 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, annual years 2-5) Reduced follow-up (0 years) with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, annual years 2-5)		*Costs* – NHS reference costs *Utilities* – from the literature or assumed based on other values included **Time horizon:** 20 years **Discount rates:** 3.5%	Incremental: CT (reduced) vs. CT: £16,785 PET-CT (reduced) vs. CT: £42,332 PET-CT vs. PET-CT (reduced): £76,900	congruent to the deterministic results	
De novo model (2021) (BRAF wild type, reduced 0 years)	Cost utility study Markov model	UK Hospital National healthcare system	Standard follow-up with computed tomography (CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Standard follow-up with positron emission tomography - computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, 6 monthly years 2-3, annual years 4-5) Reduced follow-up (0 years) with computed tomography (CT) (consisting of imaging – 3 monthly years 1, annual years 2-5) Reduced follow-up (0 years) with positron emission tomography -	Patients with Stage III (different recurrence rates were assigned to patients with stage IIIA, IIIB and IIIC) melanoma and had started a course of adjuvant treatment Age: 54 years Male: 63%	**Health states:** disease free, local recurrence – not discovered, local recurrence – patient discovered, local recurrence – imaging discovered, distant recurrence – not discovered, distant recurrence – patient discovered, distant recurrence – imaging discovered, death from melanoma, death from other causes **Data Sources:** *Baseline/natural history* – based on the literature (cohort studies) *Effectiveness* – based on the literature (cohort studies) *Costs* – NHS reference costs *Utilities* – from the literature or assumed based on other values included **Time horizon:** 20 years **Discount rates:** 3.5%	Costs: CT (reduced): £113,031 CT: £113,386 PET-CT (reduced): £114,796 PET-CT: £115,457 QALYs: CT (reduced): 9.29820 CT: 9.35341 PET-CT (reduced): 9.34600 PET-CT: 9.40066 Incremental: CT (reduced) vs. CT: £6,432 PET-CT (reduced) vs. CT: CT dominates PET-CT vs. PET-CT (reduced): £43,830	**Deterministic:** For CT vs CT(reduced) the parameters that affect the results were the percentage of patients that were symptomatic with a reduced imaging follow up. For CT vs. PET-CT and CT vs PET-CT(reduced) the only parameter that affected the results was the sensitivity of CT. **Probabilistic:** The probabilistic results was congruent to the deterministic results	**Source of funding:** Built as part of the 2021 update to NG14 **Authors' conclusions:** CT at the standard follow up is the most cost effective follow up option

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			computed tomography (PET-CT) (consisting of imaging – 3 monthly years 1, annual years 2-5)					

Table 108: Economic evaluation checklist

Study identification **NG14 Model (2014)**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	Model population had not received adjuvant therapy prior to follow-up and therefore the population is not completely indicative patients in current UK clinical practice
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	

Study identification NG14 Model (2014)		
Category	**Rating**	**Comments**
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Partly	Model population had not received adjuvant therapy prior to follow-up and therefore recurrence rates used in the model are higher than would be expected in current UK clinical practice
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Table 109: Economic evaluation checklist

Study identification **Bruno Krug, Ralph Crott, Isabelle Roch, Max Lonneux, Claire Beguin, Jean-François Baurain, Anne-Sophie Pirson & Thierry Vander Borght (2010) Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma, Acta Oncologica, 49:2, 192-200, DOI: 10.3109/02841860903440254**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Partly	Model population had not received adjuvant therapy prior to follow-up and therefore the population is not completely indicative patients in current UK clinical practice
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Belgium healthcare system
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Partly	Life months gained were used instead of QALYs
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Discounting was completed but costs were discounted at 3% and life months gained were discounted at 1.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	No	QALYs not used, life months gained used instead, it is not stated as to why this outcome is preferred
1.8 OVERALL JUDGEMENT	**PARTIALLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	

Study identification **Bruno Krug, Ralph Crott, Isabelle Roch, Max Lonneux, Claire Beguin, Jean-François Baurain, Anne-Sophie Pirson & Thierry Vander Borght (2010) Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma, Acta Oncologica, 49:2, 192-200, DOI: 10.3109/02841860903440254**		
Category	**Rating**	**Comments**
2.4 Are the estimates of baseline outcomes from the best available source?	Unclear	Lack of transparency around the clinical inputs
2.5 Are the estimates of relative intervention effects from the best available source?	Unclear	Lack of transparency around the clinical inputs
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Table 110: Economic evaluation checklist

Study identification ***De novo* model (2021) (BRAF mutant, reduced follow up after 2 years)**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	

Study identification ***De novo* model (2021) (BRAF mutant, reduced follow up after 2 years)**		
Category	**Rating**	**Comments**
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	

Study identification *De novo* model (2021) (BRAF mutant, reduced follow up after 2 years)		
Category	**Rating**	**Comments**
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Some parameters could not be included in the probabilistic sensitivity analysis due to unavailable data
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Table 111: Economic evaluation checklist

Study identification *De novo* model (2021) (BRAF mutant, 0 years of 6 monthly follow up)		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	

Study identification ***De novo* model (2021) (BRAF mutant, 0 years of 6 monthly follow up)**		
Category	**Rating**	**Comments**
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Some parameters could not be included in the probabilistic sensitivity analysis due to unavailable data
2.11 Has no potential financial conflict of interest been declared?	Yes	

Study identification *De novo* model (2021) (BRAF mutant, 0 years of 6 monthly follow up)		
Category	**Rating**	**Comments**
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Table 112: Economic evaluation checklist

Study identification *De novo* model (2021) (BRAF wild type, reduced follow up after 2 years)		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	

Study identification ***De novo* model (2021) (BRAF wild type, reduced follow up after 2 years)**		
Category	**Rating**	**Comments**
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Some parameters could not be included in the probabilistic sensitivity analysis due to unavailable data
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Table 113: Economic evaluation checklist

Study identification ***De novo* model (2021) (BRAF wild type, 0 years of 6 monthly follow up)**		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	

Study identification ***De novo* model (2021) (BRAF wild type, 0 years of 6 monthly follow up)**		
Category	**Rating**	**Comments**
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Some parameters could not be included in the probabilistic sensitivity analysis due to unavailable data
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Appendix I – Health economic model

Review question 6.2 was prioritised for *de novo* economic modelling. The full report can be found 6.2 model write up v5 post QA

Appendix J – Excluded studies

Diagnostic studies

In addition to the studies listed below, the 22 studies included in the evidence review for 2.1b (Imaging to predict SLNB positivity) were screened at full text for this review but were excluded.

Study	Reason for exclusion
Abbott RA, Acland KM, Harries M et al. (2011) The role of positron emission tomography with computed tomography in the follow-up of asymptomatic cutaneous malignant melanoma patients with a high risk of disease recurrence. Melanoma research 21(5): 446-449	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Agrawal, Archi, Pantvaidya, Gouri, Murthy, Vedang et al. (2017) Positron Emission Tomography in Mucosal Melanomas of Head and Neck: Results from a South Asian Tertiary Cancer Care Center. World journal of nuclear medicine 16(3): 197-201	- Only included patients with mucosal melanoma
Amaria, Rodabe N, Prieto, Peter A, Tetzlaff, Michael T et al. (2018) Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. The Lancet. Oncology 19(2): 181-193	- Study does not contain a relevant intervention
Annovazzi, Alessio, Vari, Sabrina, Giannarelli, Diana et al. (2020) Comparison of 18F-FDG PET/CT Criteria for the Prediction of Therapy Response and Clinical Outcome in Patients With Metastatic Melanoma Treated With Ipilimumab and PD-1 Inhibitors. Clinical nuclear medicine 45(3): 187-194	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Ayati, N., Sadeghi, R., Kiamanesh, Z. et al. (2020) The value of 18F-FDG PET/CT for predicting or monitoring immunotherapy response in patients with metastatic melanoma: a systematic review and meta-analysis. European Journal of Nuclear Medicine and Molecular Imaging	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Barker, CA, Ahmed, KA, Caudell, JJ et al. (2017) Regional lymph node basin (RLNB) relapse after adjuvant ipilimumab (IPI) anti-CTLA4 immunotherapy in stage III melanoma: a subgroup analysis of a randomized placebo-controlled trial. International journal of radiation oncology biology physics 99(2): S80	- Conference abstract
Beasley GM, Parsons C, Broadwater G et al. (2012) A multicenter prospective evaluation of the clinical utility of F-18 FDG-PET/CT in patients with AJCC stage IIIB or IIIC extremity melanoma. Annals of surgery 256(2): 350-356	- Does not contain any relevant predictors
Berzaczy, D., Fueger, B., Hoeller, C. et al. (2020) Whole-Body [18F]FDG-PET/MRI vs. [18F]FDG-PET/CT in Malignant Melanoma. Molecular Imaging and Biology 22(3): 739-744	- Initial and re-staging groups could not be separated

Study	Reason for exclusion
Bisschop, C, de Heer, E C, Brouwers, A H et al. (2020) Rational use of 18F-FDG PET/CT in patients with advanced cutaneous melanoma: A systematic review. Critical reviews in oncology/hematology 153: 103044	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Blank, Christian U, Rozeman, Elisa A, Fanchi, Lorenzo F et al. (2018) Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. Nature medicine 24(11): 1655-1661	- Conference abstract
Cha, J., Kim, S., Wang, J. et al. (2018) Evaluation of 18F-FDG PET/CT Parameters for Detection of Lymph Node Metastasis in Cutaneous Melanoma. Nuclear Medicine and Molecular Imaging 52(1): 39-45	- Does not separate initial staging data from re-staging data
Chandra, Piyush, Purandare, Nilendu, Shah, Sneha et al. (2017) Diagnostic Accuracy and Impact of Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Preoperative Staging of Cutaneous Malignant Melanoma: Results of a Prospective Study in Indian Population. World journal of nuclear medicine 16(4): 286-292	- Reference standard in study does not match that specified in protocol *SLNB not performed*
Chauvel-Picard, J., Cinotti, E., Huart, E. et al. (2020) The role of ultra-high definition ultrasound in melanoma staging. Annales de Dermatologie et de Venereologie	- Study not reported in English
Davanzo, Jacquelyn M, Binkley, Elaine M, Bena, James F et al. (2019) Risk-stratified systemic surveillance in uveal melanoma. The British journal of ophthalmology 103(12): 1868-1871	- Only included patients with Uveal melanoma
Davies, Michael A, Saiag, Philippe, Robert, Caroline et al. (2017) Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. The Lancet. Oncology 18(7): 863-873	- Not a relevant study design
Deckers, E, Hoekstra-Weebers, J, Damude, S et al. (2018) The melfo-study: a multi-center prospective randomized clinical trial on the effects of a reduced stage-adjusted follow-up schedule on cutaneous melanoma IB-IIC patients: results after 3-years. Annals of surgical oncology 25(1): S40	- Secondary publication of an included study that does not provide any additional relevant information
Deike-Hofmann, K., Dancs, D., Paech, D. et al. (2020) Pre-examinations Improve Automated Metastases Detection on Cranial MRI. Investigative radiology	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Deike-Hofmann, Katerina, Thunemann, Daniel, Breckwoldt, Michael O et al. (2018) Sensitivity of different MRI sequences in	- Study does not contain a relevant outcome or outcome

Study	Reason for exclusion
the early detection of melanoma brain metastases. PloS one 13(3): e0193946	data were not in an extractable format (2x2 data not calculable)
Donina, Simona, Strele, Ieva, Proboka, Guna et al. (2015) Adapted ECHO-7 virus Rigvir immunotherapy (oncolytic virotherapy) prolongs survival in melanoma patients after surgical excision of the tumour in a retrospective study. Melanoma research 25(5): 421-6	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Dummer, Reinhard, Brase, Jan C, Garrett, James et al. (2020) Adjuvant dabrafenib plus trametinib versus placebo in patients with resected, BRAFV600-mutant, stage III melanoma (COMBI-AD): exploratory biomarker analyses from a randomised, phase 3 trial. The Lancet. Oncology 21(3): 358-372	- Secondary publication of an included study that does not provide any additional relevant information
Dummer, Reinhard, Hauschild, Axel, Santinami, Mario et al. (2020) Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. The New England journal of medicine 383(12): 1139-1148	- Secondary publication of an included study that does not provide any additional relevant information
Dummer, Reinhard, Siano, Marco, Hunger, Robert E et al. (2016) The updated Swiss guidelines 2016 for the treatment and follow-up of cutaneous melanoma. Swiss medical weekly 146: w14279	- Secondary publication of an included study that does not provide any additional relevant information
Eggermont, Alexander M M, Blank, Christian U, Mandala, Mario et al. (2019) Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325/KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma. European journal of cancer (Oxford, England: 1990) 116: 148-157	- Secondary publication of an included study that does not provide any additional relevant information
Eggermont, Alexander M M, Blank, Christian U, Mandala, Mario et al. (2018) Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. The New England journal of medicine 378(19): 1789-1801	- Secondary publication of an included study that does not provide any additional relevant information
Eggermont, Alexander M M, Chiarion-Sileni, Vanna, Grob, Jean-Jacques et al. (2016) Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. The New England journal of medicine 375(19): 1845-1855	- Secondary publication of an included study that does not provide any additional relevant information
Eggermont, Alexander M M, Chiarion-Sileni, Vanna, Grob, Jean-Jacques et al. (2019) Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial. European journal of cancer (Oxford, England : 1990) 119: 1-10	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Eggermont, AM, Blank, CU, Mandala, M et al. (2018) Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325- MG/Keynote 054 double-blinded phase III trial. Cancer research 78(13)	- Conference abstract
Eggermont, AM, Chiarion-Sileni, V, Grob, JJ et al. (2014) Ipilimumab versus placebo after complete resection of stage III melanoma: initial efficacy and safety results from the eortc 18071 phase III trial. Journal of clinical oncology 32(18suppl1)	- Conference abstract
Eggermont, AMM, Chiarion-Sileni, V, Grob, J-J et al. (2016) PR Ipilimumab (IPI) vs placebo (PBO) after complete resection of stage III melanoma: final overall survival results from the EORTC 18071 randomized, double-blind, phase 3 trial. Annals of oncology 27	- Conference abstract
Eggermont, AMM, Chiarion-Sileni, V, Jacques Grob, J et al. (2019) Ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial. Journal of clinical oncology 37	- Conference abstract
EUCTR2011-004257-29-IE (2012) A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High-Dose Interferon a-2b for Resected High-Risk Melanoma. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-004257-29-IE	- Clinical trial registry
Garcia, M.A., Lazar, A., Duriseti, S. et al. (2017) Discovery of additional brain metastases on the day of stereotactic radiosurgery: Risk factors and outcomes. Journal of Neurosurgery 126(6): 1756-1763	- Full text paper not available
Garcia, O., Vergara, E., Duarte, C. et al. (2011) Sentinel Node in Cutaneous Malignant Melanoma in the Trunk and Extremities: Experience at the National Cancer Institute, Bogota Colombia, 2000-2007. Revista Colombiana de Cancerologia 15(3): 119-126	- Study not reported in English
Garland-Kledzik, M, Thompson, JF, Cochran, AJ et al. (2020) The utility of ultrasound in the follow-up of patients with melanoma sentinel node metastases undergoing observation: an analysis of MSLT-II. Annals of surgical oncology 27: S32	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Gellen, E, Santha, O, Janka, E et al. (2015) Diagnostic accuracy of (18)F-FDG-PET/CT in early and late stages of high-risk cutaneous malignant melanoma. Journal of the European Academy of Dermatology and Venereology: JEADV 29(10): 1938-44	- Does not contain a relevant population *Unclear whether study population is specific to re-staging or contains a mix of initial staging and re-staging. >10% of*

Study	Reason for exclusion
	participants underwent imaging for reasons other than staging. 2 x 2 data not available for these groups separately.
Gibney, Geoffrey T, Kudchadkar, Ragini R, DeConti, Ronald C et al. (2015) Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma. Clinical cancer research: an official journal of the American Association for Cancer Research 21(4): 712-20	- Does not contain any relevant predictors
Hafstrom, A., Nateghi-Gillberg, B., Nilsson, M.A. et al. (2020) Patients with cutaneous head and neck melanoma, particularly elderly with more advanced primary tumors, seem to benefit from initial CT staging before considering a sentinel lymph node biopsy. Acta Oto-Laryngologica 140(9): 795-802	- diagnostic accuracy data relevant to this review was reported
Hafstrom, Anna, Silfverschiold, Maria, Persson, Simon S et al. (2017) Benefits of initial CT staging before sentinel lymph node biopsy in patients with head and neck cutaneous melanoma. Head & neck 39(11): 2301-2310	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable) *participants underwent CT to look for any metastases. It is not possible to tell whether those with suspicious CT scans were suspected of lymph node metastases or other metastases.*
Hauschild, Axel, Dummer, Reinhard, Schadendorf, Dirk et al. (2018) Longer Follow-Up Confirms Relapse-Free Survival Benefit With Adjuvant Dabrafenib Plus Trametinib in Patients With Resected BRAF V600-Mutant Stage III Melanoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36(35): 3441-3449	- Secondary publication of an included study that does not provide any additional relevant information
Hauswald, Henrik, Habl, Gregor, Krug, David et al. (2013) Whole brain helical Tomotherapy with integrated boost for brain metastases in patients with malignant melanoma-a randomized trial. Radiation oncology (London, England) 8: 234	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Holtkamp, Lodewijka H J, Read, Rebecca L, Emmett, Louise et al. (2017) Futility of imaging to stage melanoma patients with a positive sentinel lymph node. Melanoma research 27(5): 457-462	- Diagnostic accuracy data for those undergoing SLNB not reported
Laurent V, Trausch G, Bruot O et al. (2010) Comparative study of two whole-body imaging techniques in the case of melanoma metastases: advantages of multi-contrast MRI examination including a diffusion-weighted sequence in comparison with PET-CT. European journal of radiology 75(3): 376-383	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)

Study	Reason for exclusion
Long, GV, Hauschild, A, Santinami, M et al. (2018) Updated relapse-free survival (RFS) and biomarker analysis in the COMBI-AD trial of adjuvant dabrafenib 1 trametinib (D 1 T) in patients (PTS) with resected BRAF V600-mutant stage III melanoma. Annals of oncology 29: viii734-viii735	- Conference abstract
Ludwig V, Komori T, Kolb D et al. (2002) Cerebral lesions incidentally detected on 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography images of patients evaluated for body malignancies. Molecular imaging and biology 4(5): 359-362	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Memari, Niloofar, Hayen, Andrew, Bell, Katy J L et al. (2015) How Often Do Patients with Localized Melanoma Attend Follow-Up at a Specialist Center?. Annals of surgical oncology 22suppl3: 1164-71	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Momtaz, P, Harding, JJ, Merghoub, T et al. (2017) Adjuvant dabrafenib (dab) in patients (pts) with surgically resected stage IIIC BRAFV600E/K mutated melanoma (mel). Pigment cell & melanoma research 30(1): 122-123	- Conference abstract
Morton RL; Craig JC; Thompson JF (2009) The role of surveillance chest X-rays in the follow-up of high-risk melanoma patients. Annals of surgical oncology 16(3): 571-577	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Murchie P, Nicolson MC, Hannaford PC et al. (2010) Patient satisfaction with GP-led melanoma follow-up: a randomised controlled trial. British journal of cancer 102(10): 1447-1455	- Study does not contain a relevant intervention
Namikawa, K, Tsutsumida, A, Mizutani, T et al. (2017) Randomized phase III trial of adjuvant therapy with locoregional interferon beta versus surgery alone in stage II/III cutaneous melanoma: japan Clinical Oncology Group Study (JCOG1309, J-FERON). Japanese journal of clinical oncology 47(7): 664-667	- Does not contain any relevant predictors
NCT01018004 (2009) Comparing Follow-Up Schedules in Patients With Newly Diagnosed Stage IB or Stage II Melanoma. https://clinicaltrials.gov/show/NCT01018004	- Clinical trial registry
NCT01682083 (2012) Dabrafenib With Trametinib in the Adjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma (COMBI-AD). https://clinicaltrials.gov/show/NCT01682083	- Clinical trial registry
Ogata, Dai, Uematsu, Takayoshi, Yoshikawa, Shusuke et al. (2014) Accuracy of real-time ultrasound elastography in the differential diagnosis of lymph nodes in cutaneous malignant	- Reference standard in study does not match that specified in protocol

Study	Reason for exclusion
melanoma (CMM): a pilot study. International journal of clinical oncology 19(4): 716-21	*No mention of SLNB being performed*
Oldan, J.D., Glaubiger, S.A., Khandani, A.H. et al. (2020) Detectable size of melanoma metastases to brain on PET/CT. Annals of Nuclear Medicine 34(8): 545-548	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Olthof, S.-C., Forschner, A., Martus, P. et al. (2020) Influence of 18F-FDG PET/CT on clinical management and outcome in patients with advanced melanoma not primarily selected for surgery based on a linked evidence approach. European Journal of Nuclear Medicine and Molecular Imaging 47(10): 2313-2321	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Ortega-Candil, A, Rodriguez-Rey, C, Cano-Carrizal, R et al. (2016) Breslow thickness and (18)F-FDG PET-CT result in initial staging of cutaneous melanoma: Can a cut-off point be established?. Revista espanola de medicina nuclear e imagen molecular 35(2): 96-101	- Study not reported in English
Otero, J.C.R., Dagatti, M.S., Bussy, R.F. et al. (2019) Sentinel lymph node biopsy in patients with thick primary cutaneous melanoma. World Journal of Oncology 10(2): 112-117	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Ozdemir, S.; McCook, B.; Klassen, C. (2020) Whole-body versus routine skull base to mid-thigh 18F-fluorodeoxyglucose positron emission tomography/ computed tomography in patients with malignant melanoma. Journal of Clinical Imaging Science 10(1): 47	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Podlipnik, S, Moreno-Ramirez, D, Carrera, C et al. (2019) Cost-effectiveness analysis of imaging strategy for an intensive follow-up of patients with American Joint Committee on Cancer stage IIB, IIC and III malignant melanoma. The British journal of dermatology 180(5): 1190-1197	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Prabhakaran, Sangeetha, Fulp, William J, Gonzalez, Ricardo J et al. (2016) Resection of Gastrointestinal Metastases in Stage IV Melanoma: Correlation with Outcomes. The American surgeon 82(11): 1109-1116	- Only included patients with GI metastases
Rabbie, R., Ferguson, P., Wong, K. et al. (2020) The mutational landscape of melanoma brain metastases presenting as the first visceral site of recurrence. British Journal of Cancer	-Cannot separate melanoma cohort out from the overall cohort
Radzhabova ZA, Barchuk AS, Kostromina EV et al. (2009) [The detection of early regional metastases in patients with skin melanoma by dopplerography]. Vestnik khirurgii imeni I. I. Grekova 168(1): 50-53	- Study not reported in English

The follow up of people with melanoma

Study	Reason for exclusion
Revel A, Revel C, Dolivet G, Gillet N, Didot N, Meneroux B EA (2010) Is 18FDG PET-CT useful for detecting occult nodal metastases in patients with cutaneous head and neck melanoma, in addition to sentinel lymph node biopsy? [La TEP-TDM au 18FDG a-t-elle un interet dans la stadification ganglionnaire des melanomes malins cutanes cervicofaciaux beneficiant de la technique du ganglion sentinelle? A propos de 22 cas]. Medecine Nucleaire	- Study not reported in English
Rinne D, Baum RP, Hör G et al. (1998) Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. Cancer 82(9): 1664-1671	- Stages of participants is not reported
Rozeman, EA, Sikorska, K, Van De Wiel, BA et al. (2018) 30 months relapse-free survival, overall survival, and long-term toxicity update of (neo)adjuvant ipilimumab (ipi) 1 nivolumab (nivo) in macroscopic stage III melanoma (OPACIN trial). Annals of oncology 29: x43	- Conference abstract
Rozeman, Elisa A, Menzies, Alexander M, van Akkooi, Alexander C J et al. (2019) Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. The Lancet. Oncology 20(7): 948-960	- Does not contain any relevant predictors
Sachpekidis, Christos, Anwar, Hoda, Winkler, Julia et al. (2018) The role of interim 18F-FDG PET/CT in prediction of response to ipilimumab treatment in metastatic melanoma. European journal of nuclear medicine and molecular imaging 45(8): 1289-1296	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Schadendorf, D, Hassel, JC, Fluck, M et al. (2019) Adjuvant immunotherapy with nivolumab (NIVO) alone or in combination with ipilimumab (IPI) versus placebo in stage IV melanoma patients with no evidence of disease (NED): a randomized, double-blind phase II trial (IMMUNED). Annals of oncology 30: v903-v904	- Conference abstract - Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Schadendorf, D, Larkin, J, Chiarion-Sileni, V et al. (2016) Efficacy and quality of life outcomes in patients with advanced melanoma (MEL) who discontinued treatment with nivolumab (NIVO) plus ipilimumab (IPI) due to toxicity in a phase 3 trial (CheckMate 067). Melanoma research 26: e4	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Schadendorf, Dirk, Hauschild, Axel, Santinami, Mario et al. (2019) Patient-reported outcomes in patients with resected, high-risk melanoma with BRAFV600E or BRAFV600K mutations treated with adjuvant dabrafenib plus trametinib	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)

Study	Reason for exclusion
(COMBI-AD): a randomised, placebo-controlled, phase 3 trial. The Lancet. Oncology 20(5): 701-710	
Schmittel, A, Proebstle, T, Engenhart-Cabillic, R et al. (2003) Brain metastases following interleukin-2 plus interferon-alpha-2a therapy: a follow-up study in 94 stage IV melanoma patients. European journal of cancer 39(4): 476-480	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Schwarz, D.; Bendszus, M.; Breckwoldt, M.O. (2020) Clinical Value of Susceptibility Weighted Imaging of Brain Metastases. Frontiers in Neurology 11: 55	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Sheldon, James A, Yap, Kelvin K, Taubman, Kim L et al. (2018) Prevalence of non 18 F-fluorodeoxyglucose-avid incidental findings of clinical significance on whole body positron emission tomography/computed tomography: A review of 500 consecutive cases. Journal of medical imaging and radiation oncology 62(2): 194-202	- Study does not contain a reference standard
Souza, Luiza Boava; Peres, Gabriel; Schmitt, Juliano Vilaverde (2020) Imaging tests in cutaneous malignant melanoma staging: a retrospective cohort. Anais brasileiros de dermatologia 95(1): 106-108	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Twycross, S H; Burger, H; Holness, J (2019) The utility of PET-CT in the staging and management of advanced and recurrent malignant melanoma. South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie 57(3): 44-49	- Study does not contain a reference standard
Voit, Christiane A, Oude Ophuis, Charlotte M C, Ulrich, Jens et al. (2016) Ultrasound of the sentinel node in melanoma patients: echo-free island is a discriminatory morphologic feature for node positivity. Melanoma research 26(3): 267-71	- Secondary publication of an included study
Webb, Heather R; Latifi, Hamid R; Griffeth, Landis K (2018) Utility of whole-body (head-to-toe) PET/CT in the evaluation of melanoma and sarcoma patients. Nuclear medicine communications 39(1): 68-73	- Study does not contain a relevant outcome or outcome data were not in an extractable format (2x2 data not calculable)
Weber, J, Del Vecchio, M, Mandala, M et al. (2020) Adjuvant nivolumab (NIVO) vs ipilimumab (IPI) in resected stage III/IV melanoma: 4-y recurrence-free and overall survival (OS) results from CheckMate 238. Annals of oncology 31: S731-S732	- Conference abstract
Weber, JS, Mandala, M, Del Vecchio, M et al. (2018) Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: updated results from a phase III trial (CheckMate 238). Journal of clinical oncology 36(15)	- Conference abstract

Study	Reason for exclusion
Weber, JS, Mandala, M, Del Vecchio, M et al. (2018) Adjuvant therapy with nivolumab versus ipilimumab after complete resection of stage III/IV melanoma: updated results from a phase 3 trial (CheckMate 238). British journal of cancer. Conference: 2018 national cancer research institute cancer conference, NCRI 2018. United kingdom 119(1): 41-42	- Conference abstract

Economic Studies

Table 114 Excluded Economic Studies

Study reference	Reason for exclusion
Adams E, Asua J, Conde Olasagasti J, Erlichman M, Flynn K, Hurtado-Saracho I (1999) Positron emission tomography: experience with PET and synthesis of the evidence (INAHTA Joint Project). Boston: U. S. Department of Veterans Affairs (VATAP): 41	- Systematic review
(2014) Positron Emission Tomography (PET) for metastatic melanoma. Lansdale, PA: HAYES, Inc	- Bibliographic record only, no cost effectiveness data
Positron emission tomography (PET) review: colorectal, melanoma and ovarian cancer. Medical Services Advisory Committee (MSAC)	-Bibliographic record only, no cost effectiveness data
Barbieri, M.; Richardson, G.; Paisley, S. (2018) The cost-effectiveness of follow-up strategies after cancer treatment: A systematic literature review. British Medical Bulletin 126(1): 85-100	- Systematic review
Basseres N, Grob J J, Richard M A, Thirion X, Zarour H, Noe C, Collet-Vilette A M, Lota I, Bonerandi J J (1995) Cost-effectiveness of surveillance of stage I melanoma: a retrospective appraisal based on a 10-year experience in a dermatology department in France. Dermatology 191(3): 199-203	- Does not use current health economic methods, does not use national cost data or QALYs, no incremental analysis completed
Bastiaannet E, Uyl-De Groot CA, Brouwers AH, van der Jagt EJ, Hoekstra OS, Oyen W, Verzijlbergen F, van Ooijen B, Thompson JF, Hoekstra HJ (2012) Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. Annals of Surgery 255(4): 771-776	- No QoL data included, costs reported separately to outcomes and too short time horizon
Department of Science and Technology - Brazilian Health Technology Assessment General, Coordination (2005) 18-FDG positron emission tomography for melanoma. Brasilia: Department of Science and Technology - Brazilian Health Technology Assessment General Coordination (DECIT-CGATS)	- Model not available, Published in Portuguese
Dieng M, Khanna N, Nguyen MTH, *et al* (2020) Cost-effectiveness analysis of PET/CT surveillance imaging to detect systemic recurrence in resected stage III melanoma: study protocol *BMJ Open* 2020;**10:**e037857. doi: 10.1136/bmjopen-2020-037857	- Study protocol

Study reference	Reason for exclusion
Antonio Eleuteri, Alda Cunha Rola, Helen Kalirai, et al (2021) Cost-utility analysis of a decade of liver screening for metastases using the Liverpool Uveal Melanoma Prognosticator Online (LUMPO), Computers in Biology and Medicine, Volume 130, doi.org/10.1016/j.compbiomed.2021.104221.	- Non economic evaluation, No ICER and no explanation of how cost were obtained
Facey K, Bradbury I, Laking G, Payne E (2007) Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers. Health Technology Assessment 11(44): 1-288	- Bibliographic record only, no cost effectiveness data
Francken, A.B., Hoekstra-Weebers, J.E.H.M., Deckers, E. et al. (2020) ASO Author Reflections: Stage-Adjusted Reduced Follow-Up of Melanoma Patients is Justified and Cost Effective, Until Biomarkers to Predict Prognosis Have Been Identified. Annals of Surgical Oncology 27(5): 1418-1419	- Authors reflections
Hayward, Nicholas K.; Johansson, Peter A.; Walpole, Sebastian et al. (2021) Microsimulation Model for Evaluating the Cost-Effectiveness of Surveillance in BAP1 Pathogenic Variant Carriers. JCO clinical cancer informatics 5: 143-154	- Different decision problem
Hengge U R, Wallerand A, Stutzki A, Kockel N (2007) Cost-effectiveness of reduced follow-up in malignant melanoma. Journal of the German Society of Dermatology 5(10): 898-907	- ICER not calculated and not possible to calculate from the available data
Hofmann U, Szedlak M, Rittgen W, Jung E G, Schadendorf D (2002) Primary staging and follow-up in melanoma patients: monocenter evaluation of methods, costs and patient survival. British Journal of Cancer 87(2): 151-157	- No QoL outcomes, not clear how the outcomes were obtained and an ICER cannot be obtained
Institute for Clinical Systems, Improvement (2001) PET scans for solitary pulmonary nodules, non-small cell lung cancer, recurrent colorectal cancer, lymphoma, and recurrent melanoma. Bloomington MN: Institute for Clinical Systems Improvement (ICSI)	- Bibliographic record only, no cost effectiveness data
Kelly, J (2013) Does the addition of positron emission tomography/computed tomography (PET/CT) to the routine investigation and assessment of patients with melanoma yield clinical and economic benefits?. Glasgow: Healthcare Improvement Scotland	- Bibliographic record only, no cost effectiveness data
Medical Services Advisory, Committee (2000) Positron emission tomography. Canberra: Medical Services Advisory Committee (MSAC): 124isb064273514x	- Bibliographic record only, no cost effectiveness data
Medical Services Advisory, Committee (2001) Positron emission tomography [Part 2(i)]. Canberra: Medical Services Advisory Committee (MSAC): 126isb0642820112	- Bibliographic record only, no cost effectiveness data
Medical Services Advisory, Committee (2001) Positron emission tomography [Part 2(ii)]. Canberra: Medical Services Advisory Committee (MSAC): 169	- Bibliographic record only, no cost effectiveness data
Medical Services Advisory, Committee (2008) Positron emission tomography (PET) review: colorectal, melanoma and ovarian cancer. Canberra: Medical Services Advisory Committee (MSAC)	- Bibliographic record only, no cost effectiveness data
Meregaglia, M. and Cairns, J. (2015) Economic evaluations of follow-up strategies for cancer survivors: A systematic review and quality appraisal of the literature. Expert Review of Pharmacoeconomics and Outcomes Research 15(6): 913-929	- Systematic review
Mooney MM, Mettlin C, Michalek AM, Petrelli NJ, Kraybill WG. Life-long screening of patients with intermediate-thickness cutaneous melanoma for asymptomatic pulmonary	- Intervention is X-ray which is no longer used in current UK practice

Study reference	Reason for exclusion
recurrences: a cost-effectiveness analysis. Cancer. 1997 Sep 15;80(6):1052-64. doi: 10.1002/(sici)1097-0142(19970915)80:6<1052::aid-cncr7>3.0.co;2-b.	
Morland, B (2003) Positron emission tomography (PET) - diagnostic and clinical use. Oslo: The Norwegian Knowledge Centre for the Health Services (NOKC)	- Bibliographic record only, no cost effectiveness data
Mundy L, Merlin T, Hodgkinson B, Braunack-Mayer A, Hiller J E (2004) Combined CT and PET scanner. Adelaide: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC)	- Bibliographic record only, no cost effectiveness data
NHS Quality Improvement, Scotland (2002) Positron emission tomography (PET) imaging in cancer management; HTA Advice 2: Positron emission tomography (PET) imaging in cancer management; Understanding HTBS Advice; Use of PET imaging for cancer in Scotland. Amendment to full report published July 2005. Glasgow: NHS Quality Improvement Scotland (NHS QIS)	- Bibliographic record only, no cost effectiveness data
Podlipnik, S, Moreno-Ramirez, D, Carrera, C et al. (2019) Cost-effectiveness analysis of imaging strategy for an intensive follow-up of patients with American Joint Committee on Cancer stage IIB, IIC and III malignant melanoma. The British journal of dermatology 180(5): 1190-1197	- Cannot replicate the analysis using the same reference standard. Not possible to calculate accurate ICER from available information.
Robays J, Stordeur S, Hulstaert F, Baurain J-F, Brochez L, Caplanusi T, Claes K, Legius E, Rottey S, Schrijvers D, t'Kint de Roodenbeke D, Ullman U, Van Maerken T, Poppe B (2015) Oncogenetic testing, diagnosis and follow-up in Birt-Hogg-DubÃ© syndrome, familial atypical multiple mole melanoma syndrome and neurofibromatosis 1 and 2. Brussels: Belgian Health Care Knowledge Centre (KCE)	- Different decision problem, not a cost effectiveness study
Valk P E, Pounds T R, Tesar R D, Hopkins D M, Haseman M K (1996) Cost-effectiveness of PET imaging in clinical oncology. Nuclear Medicine and Biology 23(6): 737-743	- Intervention not appropriate, compares PET to CT where in current practice only PET/CT is available
Wilson L S, Reyes C M, Lu C, Lu M, Yen C (2002) Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma. Melanoma Research 12(6): 607-617	- Different decision problem, analysing the treatment of melanoma

Appendix K – Research recommendations – full details

1.1 Follow-up strategies

Research recommendation 1 (follow-up strategies)

1. What is the effectiveness of high versus low intensity surveillance with cross sectional and/or ultrasound surveillance for the follow-up of stage IIB-IIIC melanoma?

Why this is important

There is much uncertainty surrounding the utility of follow-up of people with melanoma using cross sectional imaging. In particular, it is unclear how frequently this should be done to maximise recurrence detection whilst minimising overexposure to imaging. There is additional uncertainty surrounding its use in people with stage IIB-C disease who, despite have poor long-term prognosis, have typically not received cross sectional imaging. A study comparing high versus low intensity CT imaging for the follow-up of people with IIB-IIIC melanoma would help identify the best approach. Additionally, there is a lack of uncertainty surrounding the use of ultrasound during follow-up. Ultrasound is understood to be more sensitive for the detection of lymph node metastases. However, it is unknown whether routine surveillance with ultrasound in addition to modern surveillance schedules requiring frequent cross sectional imaging results in the earlier detection of lymph node metastases or improves outcomes such as mortality, distant progression, and quality of life.

Finally, the exact role of brain imaging in people with melanoma needs further clarification. In particular, MRI is known to be more sensitive at detecting brain metastases than CT however it is not clear whether in practice this would lead to metastases being detected significantly earlier, or whether earlier detection impacts upon mortality. This could be assessed by stratifying the brain imaging element of follow-up to MRI or CT.

Rationale for research recommendation 1

Importance to 'patients' or the population	There is very limited good quality evidence comparing different frequencies of imaging follow-up for people with melanoma. Additionally, there is a lack of data separating out the utility of ultrasound imaging for the detection of lymph node metastases and the use of cross-sectional imaging, and how these two interact when used in modern surveillance strategies.
Relevance to NICE guidance	NICE currently recommends the use of CT and US imaging during follow-up. These were made primarily by consensus with very limited evidence to guide recommendations. The committee were particularly uncertain surrounding the use of US, optimal frequency of CT and the benefit of US in people already receiving frequent CT surveillance.
Relevance to the NHS	Identifying the optimal combination and frequency of imaging will help to maximise the use of NHS resources.
National priorities	High
Current evidence base	No studies specific to stages IIB-III

Equality considerations	People for whom physical examination is less effective (such as people with obesity) should be given special consideration.

Modified PICO table

Population	People with a diagnosis of stage IIB-III melanoma
Intervention	Cross-sectional imaging: • Frequent cross-sectional imaging (as defined by study author) Ultrasound imaging: • Frequent ultrasound imaging (as defined by study author) Brain imaging: • MRI
Comparator	Cross-sectional imaging: • Less frequent cross-sectional imaging (as defined by study author) • No cross-sectional imaging Ultrasound imaging: • Less frequent ultrasound imaging (as defined by study author) • No ultrasound imaging Brain imaging: • CT
Outcome	• All-cause mortality • Time to recurrence • All recurrences • Distant progression • Quality of life • Adverse events
Study design	• RCT • Prospective cohort study
Timeframe	Long-term
Additional information	None

1.2 Survivorship

Research recommendation 2 (patient experiences)

What are the experiences of people who have had melanoma with regards to survivorship and their disease journey?

Why this is important

There is a lack of understanding with regards to the views of people with melanoma on important areas of diagnosis, treatment and follow-up. This information is vital to making recommendations which take into account the needs and desires of the people they affect.

Rationale for research recommendation

The follow up of people with melanoma

Importance to ‘patients’ or the population	This qualitative research will help to guide future recommendations in a manner which will improve convenience and quality of life for people with melanoma.
Relevance to NICE guidance	Current NICE guidance relied on the experiences of a small number of committee members (lay members) and very limited quality of life evidence to help inform recommendations with patient experiences. This qualitative research will offer insight into these experiences to help guide future recommendations.
Relevance to the NHS	Knowledge
National priorities	Moderate
Current evidence base	
Equality considerations	None known

Modified SPIDER table

Sample	People with a diagnosis of melanoma
Phenomenon of Interest	The experiences of people who have had melanoma with regards to survivorship and their disease journey
Design	Qualitative including focus groups, unstructured and semi-structured interview-based studies, mixed methods studies.
Evaluation	Evidence should relate to the experiences of people with a diagnosis of melanoma