National Institute for Health and Care Excellence

Final

Melanoma: assessment and management

[B] Evidence review for the use of sentinel lymph node biopsy in people with melanoma

NICE guideline NG14

Evidence reviews underpinning recommendations 1.4.1 to 1.4.11 and research recommendations in the NICE guideline

July 2022

Final

These evidence reviews were developed by Guideline Updates Team

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1 Sentinel lymph node biopsy

1.1 Review question

RQ 2.1 What is the most accurate method of staging melanoma in people preliminarily assigned:

(a) clinicopathological stage 1A melanoma?

(b) clinicopathological stage 1B to 2C melanoma (including, but not limited to, sentinel lymph node biopsy)?

(c) clinicopathological stage 3 melanoma?

(d) clinicopathological stage 4 melanoma?

1.1.1 Introduction

Sentinel lymph node biopsies (SLNBs) are used during the staging of melanoma to assess the spread of melanoma to local lymph nodes or other parts of the body and to upstage a person found to have sentinel node metastases to clinical stage 3 melanoma, making them eligible for adjuvant therapy.

An update is required in this area due to the recent introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system and the 8th edition of the Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) staging system for melanoma. In particular, the AJCC 8 includes people with a Breslow thickness of 0.8-1.0 mm (along with people with a thickness <0.8 mm if they have ulceration) as having a preliminary stage of 1b. There is uncertainty surrounding whether SLNBs should be offered to people with thin melanomas (melanomas with a Breslow thickness of 1mm or less).

Additionally, there is uncertainty as to the role of imaging prior to a SLNB. It is possible that imaging could be used to accurately identify people with SLN metastases without having to undergo a SLNB, which is invasive and costly.

1.1.2 Summary of the protocols

Table 1 PICO table for predicting positive SLNB in people with thin melanomas

	Predictors of SLNB positivity	Imaging prior to SLNB
Population	People with a diagnosis of a thin melanoma (Breslow thickness ≤1mm) undergoing SLNB	People with a preliminary diagnosis of stage 1-4 melanoma
Intervention (predictors)	The following predictors will be assessed for their relationship with positive SLNB result: • Breslow thickness (0.8-1.0mm versus <0.8mm) • Mitotic rate (≥2 versus <2)	The following predictors will be assessed for their relationship with positive SLNB result: • Ultrasound (US) • CT • PET-CT

	• Ulceration (present versus absent) • Age (<45 versus ≥45) • Clark level (1-3 versus 4-5) • Lymphovascular invasion (present versus absent) • Tumour location (Head, neck or trunk versus extremities or other)	• MRI Any combination of the above imaging methods
Comparator (predicted outcome/reference standard)	• Positive SLNB result	• SLNB
Outcomes	Accuracy for predicting SLNB result will be assessed using: • Risk ratio • Adjusted odds ratio	• Sensitivity/specificity • Likelihood ratios

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.

Primarily, studies reported unadjusted univariate data which were combined in meta-analysis for this review. Some studies reported adjusted odds ratios for the prediction of SLNB positivity. These data were not combined in meta-analysis due to differences between studies in the factors that were controlled for and differences in other baseline characteristics.

For several predictors, it was not possible to dichotomise the data in the same way for all studies. Additionally, prognostic accuracy analyses treating data as continuous was typically not reported.

The methodologies were used to account for differences in the way in which studies dichotomise predictors:

1. Where possible, age was dichotomised into <45 or ≥45 years old. Meta-analysis was conducted on the predictor of age providing that the dichotomy was between 40-50 years old (for example, a study splitting data into <42 versus ≥42 years old would be combined with a study splitting data into <50 versus ≥50 years old; a study comparing <65 to ≥65 years olds was not combined with these other data).
2. The method for classifying mitotic rate has changed over time, such that the previous method allowed for fractional mitosis whereas the current method does not. Additionally, the method for classifying mitotic rate was commonly not reported. For the purposes of this review, studies were combined in meta-analysis regardless of the method used to classify mitotic rate.

3. Where possible, Mitotic rate was dichotomised as ≥2 versus <2. However, typically studies do not report data using this dichotomy. The most common dichotomy reported was ≥1 versus <1. For the purposes of this review, data for mitotic rate was combined regardless of the dichotomy used. A sensitivity analysis was conducted in which only studies comparing ≥2 to <2 are included.
4. Melanomas with a thickness of 0.75mm – 1.04mm were grouped under 0.8-1.0mm when comparing Breslow thickness, in accordance with the 8th edition of the AJCC. Anything <0.75mm was classified as <0.8mm.

1.1.4 Prognostic and diagnostic evidence

1.1.4.1 Included prognostic studies

A systematic literature search was conducted for this review on predicting SLNB positivity in people with melanoma. This returned 6,342 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 5,295 references were excluded, and 49 references were ordered for screening based on their full texts.

Of the 49 references screened as full texts, 37 references met the inclusion criteria specified in the review protocol for this question (appendix A). The clinical evidence study selection is presented as a diagram in appendix C.

1.1.4.2 Included diagnostic studies

A systematic literature search was conducted for this review on the accuracy of imaging for detecting SLNB positivity in people with melanoma. This returned 12,270 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 12, 219 references were excluded, and 51 references were ordered for screening based on their full texts.

Of the 51 references screened as full texts, 22 references met the inclusion criteria specified in the review protocol for this question (appendix A). The clinical evidence study selection is presented as diagrams in D.

1.1.4.3 Excluded studies

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

1.1.5 Summary of studies included in the prognostic evidence

Table 2 Summary of included studies characteristics

Author (year)	Country	Sample size	Predictive factors	SLNB routinely offered for thin melanomas?	+ SLNB	Risk of bias
Andtbacka (2013)	USA	8	Thickness Mitotic rate (≥1/<1) LVI	Unclear	12.5%	Moderate
Bartlett (2014)	USA	781	Thickness Age (≤40/>40) Mitotic rate (≥1/<1) Ulceration LVI Location	Not routinely offered	3.7%	Moderate

Author (year)	Country	Sample size	Predictive factors	SLNB routinely offered for thin melanomas?	+ SLNB	Risk of bias
Cecchi (2007)	Italy	50	Clark level Ulceration Regression Location	Not routinely offered	6.7%	High
Doumas (2010)	Greece	21	Thickness	Unclear	4.8%	Moderate
Durham (2017)	USA	488	*All melanomas were of 0.75-0.99mm thickness* Age (≤45/>45) Mitotic rate (>1/≤1) Ulceration LVI	Routinely offered	6.8%	High
Friedman (2019)	USA	10,108	Thickness Age (<55/≥55) Mitotic rate (≥2/<2) Ulceration Clark level Tumour stage (T1a/1b) LVI Location	Unclear	4.0%	Moderate
Han (2012)	USA	271	Thickness Ulceration Age (<40/≥40) Mitotic rate (≥1/<1) Clark level	Routine for >0.75mm	8.1%	Low (moderate for Breslow thickness analysis)
Han (2013)	Multinational	1250	Thickness Ulceration Mitotic rate (≥1/<1) Clark level LVI	Unclear	5.2%	Moderate
Herbert (2018)	USA	1119	*Multivariate analysis only* Mitotic rate (≥1/<1) Thickness Clark level	unclear	4.3%	Moderate
Isaksson (2018)	Sweden and Australia	1038	Thickness Ulceration Mitotic rate (≥1/0) Age (>/< median) Tumour stage (T1a/1b) Location	Unclear	4.7%	Moderate
Jaber (2011)	USA	38	Thickness	Not routine	5.3%	Moderate
Joyce (2017)	Ireland	65	Breslow Clark level Ulceration Mitotic rate (3+/0-2) Location	If high risk: ulceration, high mitotic rate (1+) or Clark level IV/V.	1.5%	Moderate

Author (year)	Country	Sample size	Predictive factors	SLNB routinely offered for thin melanomas?	+ SLNB	Risk of bias
Kocsis (2020)	Hungary	78	*All patients were pT1b (according to AJCC 7th ed.)* Age (<50/≥50) Ulceration Tumour stage (T1a/1b)* Reclassified to AJCC 8th criteria) Location	Offered to most pT1b patients (all study participants were pT1b)	11.5%	Low
Kunte (2010)	Germany	147	Thickness	If high risk (such as *ulceration or regression of the primary melanoma and Clark level IV or V)*	7.5%	Moderate
Maurichi (2020)	Italy, Greece, UK, Switzerland and Sweden	3402	Thickness Mitotic rate (>1/0-1) Clark level Age (<50/≥50) Ulceration Prognostic tool LVI Location	If high risk according to then-current NCCN guidelines	Cohort 1: 6.6% Cohort 2: 5.3%	Moderate
Maurichi (2014)	Italy, UK and Greece	792	Thickness Ulceration Age (≤50/>50) Mitosis (≥1/<1) Clark level LVI Location	If high-risk: 0.75-1.00 mm, MR 1+, ulceration, LVI, Clark level IV-V, and extensive regression	8.6%	Moderate
Mitteldorf (2014)	Germany	207	Thickness Ulceration Age (<40/>40) Mitosis (≥1/<1) Clark level	If high risk: ulceration, Clark level IV, ≤40, mitosis 1+, regression, and primary nodular or secondary nodular superficial spreading melanoma.	18.4%	Moderate
Mori (2013)	Japan	13	Thickness Mitosis (≥2/0-1) Location	Unclear	7.7%	Moderate
Mozzillo (2013)	Italy	492	Mitosis (≥1/0)	Unclear	5.7%	High
Murali (2012)	Australia	432	Mitosis (≥1/0) Thickness Ulceration Age (≤50/>50) LVI	If considered to have significant risk of metastases (unclear protocol)	6.7%	Moderate
Nahabedian (2003)	USA	24	Thickness Ulceration Age (<45/≥45) Clark level	Unclear	8.3%	Moderate

Author (year)	Country	Sample size	Predictive factors	SLNB routinely offered for thin melanomas?	+ SLNB	Risk of bias
			Location			
Oliveira Filho (2003)	Brazil	77	Mitosis (>5/0-5) Clark level Ulceration	Unclear	7.8%	Moderate
Piazzalunga (2019)	Italy	1196	Mitosis (>1/"absent") Ulceration Thickness Clark level Location	Unclear	6.0%	Moderate
Ranieri (2006)	USA	184	Mitosis (>2/≤2) Ulceration Thickness	Unclear	6.5%	Moderate
Santos (2019)	Brazil	137	Clark Thickness Ulceration Mitosis (present/absent) Location	Indications for SLNB: presence of ulceration, mitosis, thickness more than 0.75mm, regression	7.3%	Moderate
Skochdopole (2020)	USA	4332	Thickness Mitosis rate (≥4/<4) Tumour stage (T1a/1b)	Unclear	5.3%	High (mitotic rate) Moderate (T stage and thickness)
Statius Muller (2001)	The Netherlands	104	Thickness	Routinely performed on ≥0.5mm	13.0%	Low
Stitzenberg (2004)	USA	146	Clark level Ulceration Location	R*outinely performed on* ≥0.75 if no evidence of nodal or distant metastases and on <0.75 mm if one of the following: Clark's level IV or V, ulceration, regression, or patient demand.	4.3%	Low
Tejera-Vaquerizo (2017)	Spain	203	Age (≤65/>65) Mitotic rate (>1/0-1) Tumour stage (T1a/1b) Location	Unclear	6.5%	Moderate
Tejera-Vaquerizo (2019)	Spain Portugal Italy	1090	Miotic rate (≥2/0-1)	Unclear	7.7%	Moderate
Theile (2020)	Australia	240	Thickness Ulceration	Unclear	5.8%	Moderate

Author (year)	Country	Sample size	Predictive factors	SLNB routinely offered for thin melanomas?	+ SLNB	Risk of bias
			Tumour stage (T1a/1b)			
Venna (2013)	USA	484	Thickness Ulceration Miotic rate (≥1/<1) Age (≤43/>43) LVI	All thin melanomas with high-risk histological features	7.0%	Moderate
Vermeeren (2010)	The Netherlands	78	Ulceration Clark level Thickness	Routinely given for most of study period	6.4%	Low (moderate for ulceration)
Watt (2016)	Canada	155	Mitotic rate (≥1/<1)	Unclear	7.7%	Moderate
Wong (2006)	USA	223	Thickness Clark level Miotic rate (≥1/<1) Location	Only given if additional high-risk features are present	3.6%	Moderate
Wright (2008)	USA	631	Thickness Clark level Ulceration Age (≤50/>50) Location	Only given with additional high-risk features	4.9%	Moderate
Yalamanchi (2018)	USA	381	*Multivariate analysis only* Mitosis (Y/N) Ulceration	Unclear	2.0%	Moderate

1.1.6 Summary of studies included in the diagnostic evidence

Table 3 Summary of included studies characteristics

Author (year)	Country	Sample size	Population	Index test	Risk of bias
Arrangoiz (2012)	USA	56	Melanoma >4mm	PET/CT	High
Chai (2012)	USA	325	All melanoma (subgroup by Breslow thickness)	US	Moderate
Cheng (2020)	USA	92	All melanoma	PET/CT	Moderate
Hafner (2004)	Switzerland	100	Melanoma ≥1mm	PET alone US	Moderate
Hinz (2013)	Germany	20	High-risk melanoma (≥2mm or other risk factors such as ulceration)	PET/CT HR-US	Low
Hinz (2011)	Germany	81	All melanomas	US	Moderate
Hocevar (2004)	Slovenia	57	All melanomas	US	Moderate

Author (year)	Country	Sample size	Population	Index test	Risk of bias
Kell (2007)	USA	37	All melanomas	PET/CT	Moderate
Klode (2010)	Germany	61	stage I or II melanoma > 1mm	PET/CT	Moderate
Kunte (2009)	Germany	25	All melanomas	US	low
Maubec (2007)	France	19	Melanomas >4mm	PET/CT	High
Olmedo (2017)	Spain	384	All melanomas	US	Moderate
Riquelme-Mc Loughlin (2019)	Spain	250	Melanoma with >pT2a (Breslow depth >2 mm, regardless of ulceration, or >1 mm with an ulcerated primary tumour)	US	Moderate
Sanki (2009)	Australia	716	All melanomas	US	Moderate
Schaarschmidt (2018)	Germany	52	All melanomas undergoing distant metastases staging	PET/CT PET/MRI	High
Stahlie (2020)	The Netherlands	23	IIB-C	US PET/CT	Moderate
Sibon (2007)	France	131	All melanomas	US	Low
Singh (2008)	Germany	52	AJCC 7th ed. stage I or II Melanoma	PET/CT	Moderate
Thompson (2019)	International	2859	Participants screened for MSLT-II trial	US	Low
Van Rijk (2006)	The Netherlands	107	Stage IV melanoma	US	Moderate
Voit (2014)	Germany	1000	Melanomas >1mm or if less, at least Clark IV/V, ulcerated and/or regressed	US	Low
Wagner (2012)	France	48	Melanomas > 1mm with ulceration or >4mm	PET/CT	High
Wagner (2005)	USA	144	Melanomas >1mm or with locally recurrent/ solitary in-transit recurrent melanoma after a previous excision	PET/CT	Moderate

See appendix D for full evidence tables.

1.1.7 Summary of the prognostic evidence

Table 4 Summary of GRADE tables

Overall risk of bias was very low for all studies. Odds ratios refer to adjusted odds ratios (see GRADE tables in appendix H for further information).

Analysis	No. studies	Sample size	Effect size for presence of + SLNB	excluding high risk of bias studies
Breslow thickness				
Main	27	26,234	RR 1.70 (1.51, 1.92)	N/A
Multivariate analyses	Han (2013)	1,250	OR 2.21 (1.06, 4.61)	N/A
	Mozzillo (2013)	423	OR 1.53 (0.64, 3.67)	N/A
	Herbert (2018)	1,129	OR 4.38 (1.81, 10.58)	N/A
	Piazzalunga (2018)	855	OR 2.02 (1.25,3.26)	N/A
Ulceration				
Main	26	21,551	RR 2.01 (1.69, 2.38)	RR 2.01 (1.69, 2.38)
0.8-1.0mm only	7	1,398	RR 2.10 (1.32, 3.34)	RR 1.95 (1.15, 3.30)
Multivariate analyses	Yalamanchi (2018)	3,183	OR 3.03 (1.55, 5.06)	N/A
	Durham (2017)	488	OR 5.93 (1.81, 19.50)	N/A
	Skochdopole (2020)	2,184	OR 2.04 (1.20, 3.47)	N/A
	Han (2013)	1,250	OR 2.51 (1.25, 5.06)	N/A
	Han (2012)	271	OR 3.09 (0.98, 9.77)	N/A
	Mozzillo (2013)	423	OR 0.47 (0.06, 3.59)	N/A
	Maurichi (2020)	1,635	OR 3.83 (2.56, 5.62)	N/A
	Santos (2017)	137	OR 12.80 (2.77, 59.40)	N/A
	Piazzalunga (2018)	855	OR 2.94 (1.36, 6.31)	N/A
	Skochdopole (2020)	4,332	OR 2.01 (1.39, 2.93)	N/A
	Friedman (2019)	10,108	OR 1.62 (1.22, 2.13)	N/A
Mitotic index				
Main	25	25,129	RR 2.15 (1.57, 2.94)	RR 1.97 (1.41, 2.75)
≥1 vs. <1	13	5,048	RR 1.83 (0.95, 3.54)	RR 1.69 (0.86, 3.35)
≥2 vs. <2	8	15,539	RR 1.73 (1.50, 2.01)	RR 1.71 (1.47, 1.99)
≥3 vs. <3	4	4,542	RR 3.98 (3.08, 5.12)	RR 8.66 (3.31, 22.70)
≥1 vs. <1 0.8-1.0mm only	Andtbacka (2013)	6	RR 0.33 (0.02, 5.97)	N/A
≥2 vs. <2 0.8-1.0mm only	Durham (2017)	488	RR 2.49 [1.14, 5.40]	N/A
≥3 vs. <3 0.8-1.0mm only	Ranieri (2006)	77	RR 5.75 [2.05, 16.14]	N/A
≥4 vs. <3 t1b only	Skochdopole (2020)	2104	RR 3.20 [2.31, 4.44]	N/A
Multivariate analyses (comparing ≥2 vs. <2, see appendix F for other thresholds)	Durham (2017)	488	0.8-1.0mm only: OR 1.79 (0.82, 3.90)	N/A
Age				
Main	16	18,940	RR 1.49 (1.31,1.69)	RR 1.50 (1.32, 1.70)

Analysis	No. studies	Sample size	Effect size for presence of + SLNB	excluding high risk of bias studies
Only studies with cut-off 40-50 years	12	7,592	RR 1.39 (1.17, 1.67)	RR 1.40 (1.17, 1.68)
Only studies with cut-off >50 years	4	10,797	RR 1.59 (1.33, 1.91)	N/A
Multivariate analyses (all 0.8-1.0mm only)	Durham (2017)	488	≤45 vs. >45: OR 2.94 (1.35, 6.67)	N/A
	Yalamanchi (2018)	3,183	<54 vs. 54-70: OR 0.89 (0.52, 1.56)	N/A
	Yalamanchi (2018)	3,183	<54 vs. >70: OR 4.00 (1.75, 11.11)	N/A
Clark				
Main	22	19,651	RR 1.52 (1.34, 1.73)	RR 1.52 (1.34, 1.72)
0.8-1.0mm only	6	1,070	RR 2.12 (1.27, 3.54)	N/A
Multivariate analyses	Han (2013)	1,250	OR 1.80 (1.01, 3.23)	N/A
	Mozzillo (2013)	423	OR 1.92 (0.79, 4.76)	N/A
	Santos (2017)	137	OR 4.11 (0.28, 60.40)	N/A
	Herbert (2018)	1,129	OR 2.86 (1.25 – 6.52)	N/A
	Friedman (2019)	10,108	OR: 1.64 (1.05, 2.56)	N/A
Lymphovascular invasion				
Main	10	16,582	RR 2.24 (1.67, 2.99)	RR 2.30 (1.71, 3.08)
Multivariate analyses	Han (2013)	1,250	Adjusted OR 2.21 (1.06, 4.61)	N/A
	Mozzillo (2013)	423	Adjusted OR 1.53 (0.64, 3.67)	N/A
	Friedman (2019)	10,108	Adjusted OR 2.30 (1.35, 3.95)	N/A
	Maurichi (2020)	1,635	Adjusted OR 2.84 (1.56, 4.58)	N/A
Tumour location				
Main	18	20,171	RR 1.01 (0.89, 1.14)	RR 1.00 (0.89, 1.13)
Multivariate analyses	Mozzillo (2013)	423	Adjusted OR 1.30 (0.56, 3.03)	N/A
Other analyses				
T1b vs. 1a	6	11,732	RR 1.91 (1.52, 2.40)	N/A
Adverse factors (see table 10)	Friedman (2019)	10,108	RR 2.07 [1.65, 2.59]	N/A
Adverse factors (see table 10) Only in T1a	Friedman (2019)	3,014	RR 3.10 [1.70, 5.64]	N/A
Decision aid tool using: ulceration, LVI, regression, age, Breslow thickness and mitotic rate	Maurichi (2020)	1,767	C index: 96.5%	N/A

See appendix H for full GRADE tables.

1.1.8 Summary of the diagnostic evidence

	Study design	No. studies (sample size)	Diagnostic accuracy			Quality
			Sensitivity	Specificity	Likelihood ratios	
PET/CT (per patient)						
Main	Retrospective	3 (150)	0.15 (0.06, 0.30)	0.93 (0.85, 0.97)	LR+ 2.80 (0.89, 8.77)	Low
					LR- 0.90 (0.79, 1.02)	Moderate
PET/CT (per node)						
Main	Retrospective	2 (144)	0.13 (0.04, 0.32)	0.96 (0.90, 0.89)	LR+ 0.73 (0.91, 15.26)	Very low
					LR- 0.96 (0.89, 1.04)	Very low
Excluding high risk of bias studies	Retrospective	1 (59)	0.02 (0.00, 0.32)	0.98 (0.84, 0.99)	LR+ 2.38 (0.04, 115.8)	Low
					LR- 0.98 (0.90, 1.07)	High
t4 melanoma only	Retrospective and prospective	2 (32)	0.23 (0.07, 0.53)	0.89 (0.67, 0.97)	LR+ 1.59 (0.19, 12.87)	Very low
					LR- 0.98 (0.78, 1.23)	Moderate
t4 melanoma only *Excluding high risk of bias studies*	Retrospective	1 (12)	0.31 (0.09, 0.67)	0.91 (0.37, 0.99)	LR+ 3.75 (0.21, 64.56)	Very low
					LR- 0.75 (0.44, 1.26)	Low
t4 melanoma *Studies which included recurrences during follow-up as part of reference standard*	Retrospective and prospective	3 (119)	0.40 (0.27, 0.54)	0.92 (0.80, 0.97)	LR+ 4.68 (1.48, 14.80)	Very low
					LR- 0.81 (0.68, 0.97)	Low
US (per patient)						
Main	Retrospective and prospective	10 (2919)	0.36 (0.22, 0.52)	0.88 (0.81, 0.93)	LR+ 2.78 (2.01, 3.85)	Very low
					LR- 0.73 (0.61, 0.87)	Very low
Studies which included recurrences during follow-up as part of reference standard	Retrospective and prospective	2 (342)	0.59 (0.16, 0.91)	0.97 (0.90, 0.99)	LR+ 24.11 (2.40, 241.58)	Very low
					LR- 0.38 (0.11, 1.26)	Very low
US (per node)						
Main	Retrospective and prospective	3 (4,232)	0.13 (0.04, 0.33)	0.97 (0.97, 0.98)	LR+ 5.21 (2.44, 11.12)	Very low
					LR- 0.86	Very low

	Study design	No. studies (sample size)	Diagnostic accuracy			Quality
			Sensitivity	Specificity	Likelihood ratios	
					(0.74, 1.01)	
PET alone (per patient)						
Main	Prospective	1 (100)	0.09 (0.02, 0.27)	0.99 (0.90, 1.00)	LR+ 13.88 (0.68, 280.17)	Low
					LR- 0.91 (0.80, 1.03)	Moderate
PET alone (per basin)						
Main	Prospective	1 (184)	0.20 (0.11, 0.35)	0.97 (0.92, 0.98)	LR+ 7.37 (2.39, 22.77)	Moderate
					LR- 0.81 (0.69, 0.95)	Moderate
PET-US (per patient)						
Main	Prospective	1 (100)	0.11 (0.03, 0.30)	0.83 (0.73, 0.90)	LR+ 0.71 (0.21, 2.32)	Very low
					LR- 1.05 (0.89, 1.25)	Moderate
PET-MRI (per node)						
Main	Retrospective	1 (82)	0.23 (0.09, 0.48)	0.96 (0.88, 0.99)	LR+ 7.64 (1.52, 38.30)	Very low
					LR- 0.78 (0.60, 1.03)	Very low

See appendix H for full GRADE tables.

1.1.9 Economic evidence

1.1.9.1 Included studies (predictors of SLNB review)

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 7,545 studies. Based on title and abstract screening, 7,526 of the studies could confidently be excluded for this question. Fifteen studies were excluded following the full-text review. There was also a model from NG14 that was included for review. Thus, the review for this question included 5 studies from the existing literature.

1.1.9.2 Included studies (imaging review)

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 7,545 studies. Based on title and abstract screening, 7,526 of the studies could confidently be excluded for this question. Seventeen studies were excluded following the full-text review. Thus, the review for this question includes 2 studies from the existing literature.

1.1.9.3 Excluded studies

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

1.1.10 Summary of included economic evidence

Table wo4 Summary of included economic evidence (predictors of SLNB review)

Study	Applicability	Limitations	Incremental			Uncertainty[1]
			Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
NICE guideline for melanoma: assessment and management (NG14)l (2014) Population: Stage IA-IIC melanomas, tumours >1mm Wide excision and sentinel lymph node biopsy (SNB) vs. Wide excision (WE)	Partially applicable[2]	Minor limitations	£1,816	0.048	£38,149	**Deterministic:** SNB becomes cost effective if the difference in cost between SNB and WE is reduced. All other changes do not result in SNB becoming cost effective. **Probabilistic:** 1000 iterations done, SNB is preferred 43.8% of the time at £20,000/QALY threshold
Hu et al. (2015) Wide excision and sentinel lymph node biopsy (SNB) vs. Wide excision (WE)	Partially applicable[3]	Potentially serious limitations[4]	£2,795	0.19	£14,572	**Deterministic:** SNB is no longer cost effective if more than 23% of nodes are positive or 15% of SNB patients experience regional recurrence. **Probabilistic:** SNB is cost effective in 78-95% of cases when the willingness to pay threshold is between £38,143 - £76,286/QALY
Morton et al. (2009) Wide excision and sentinel lymph node biopsy (SNB) vs. Wide excision (WE) Population: tumours that were 1mm and greater	Partially applicable[5]	Potentially serious limitations[6]	£514	0.44	£1,181	**Deterministic:** Variables that affected cost effectiveness were cost of SNB, cost of delayed complete lymph node dissection and probability of nodal or distant metastases. **Probabilistic:** Not completed

Study	Applicability	Limitations	Incremental			Uncertainty[1]
			Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
Serra-Arbeloa et al. (2016) Wide excision and sentinel lymph node biopsy (SNB) vs. Wide excision (WE)	Partially applicable[7]	Potentially serious limitations[8]	Thin (≤1 mm): £20,767 Intermediate (1-4mm): £3587 Thick (≥4mm): £20,465	Thin: -0.11 Intermediate: 0.03 Thick: -0.03	Thin: WE dominates Intermediate: £149,076 Thick: WE dominates	**Deterministic:** One way and two-way sensitivity analysis was done. No changes altered the preference for WE. **Probabilistic:** Not completed
Wilson et al. (2002) Population: melanomas that were Stage II Treat no one vs. Test and treat appropriately vs. Treat all vs. Test and treat some	Partially applicable[9]	Very serious limitations[10]	Test and treat appropriately: £5720 Treat all: £11,934 Test and treat some: £9,468	Test and treat appropriately: 0.31 Treat all: 0.42 Test and treat some: 0.62	Test and treat appropriately: £18,443 Treat all: Extended dominated Test and treat some: £30,870	**Deterministic:** For test and treat some versus surgery and test and treat appropriately versus test and treat some reducing the cost of relapse to £9,863 increased the ICER to £21,599/QALY and £35,407/QALY respectively. Increasing the cost of relapse to £49,314 reduced the ICERs by £14,301/QALY and £25,742/QALY respectively Sensitivity and specificity of SLNB and the probability of dose changing toxicities were reported to have an insignificant effect on the ICER for both comparisons. **Probabilistic:** Varying across all variables for test and treat some versus surgery the median, 25th and 75th percentiles of the PSA are £19,336, £10,150, and £36,156 per QALY respectively. For test and treat

Study	Applicability	Limitations	Incremental			Uncertainty[1]
			Cost[1] (£)	Effects (QALYs)	ICER[1] (£/QALY)	
						appropriately versus test and treat some the median, 25th and 75th percentiles £29,814, £16,536, and £58,016 per QALY respectively

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 Treatment after sentinel lymph node biopsy included complete lymph node dissection, which is not routinely conducted in current UK clinical practice
3 US healthcare system, utilities obtained from investigator assessment, no discounting used. Treatment after sentinel lymph node biopsy included complete lymph node dissection, which is not routinely conducted in current UK clinical practice.
4 Utilities obtained from investigator assessment, cost obtained from evidence but does not state if it accounts for inflation, financial conflict of interest not stated.
5 Australian healthcare system, discounting at 5%. Treatment after sentinel lymph node biopsy included complete lymph node dissection, which is not routinely conducted in current UK clinical practice.
6 No probabilistic sensitivity analysis done
7 Spanish healthcare system, discounting only done as a sensitivity analysis. Treatment after sentinel lymph node biopsy included complete lymph node dissection, which is not routinely conducted in current UK clinical practice.
8 No probabilistic sensitivity analysis done
9 Treatment for melanoma (interferon that is not currently used in UK practice) also included in modelling, not a UK healthcare perspective
10 Funded by manufacturer, inappropriate time horizon

Table 4 Summary of included economic evidence (imaging review)

Study	Applicability	Limitations	Incremental			Uncertainty[1]
			Cost[1] (£)	Effects	ICER[1] (£/Effect)	
Look Hong (2015) Physical exam with chest radiography (PE/Radiography) vs. Computed Tomography (CT) vs.	Partially applicable[2]	Very serious limitations[3]	CT: £44,077 PE/Radiography: £44,513 PET/CT: £44,646	Probability of accurate diagnosis: CT: 0.90 PE/Radiography: 0.74 PET/CT: 0.94	ICER[4] (£/accurate diagnosis) CT vs PE/Radiography: CT Dominates PET/CT vs CT: £14,226	**Deterministic:** When comparing CT and PE/radiography, CT dominates for all sensitivity analyses except high probability of surgery and high probability of adjuvant therapy. However, these are still below the threshold. When comparing CT and PET/CT, PET/CT is the preferred option for most sensitivity analyses except

Study	Applicability	Limitations	Incremental			Uncertainty[1]
			Cost[1] (£)	Effects	ICER[1] (£/Effect)	
Positron emission tomography and computed tomography (PET/CT)						when the sensitivity of PET/CT is increased **Probabilistic:** From a WTP of £0 to £14,226 CT is the preferred option, £14,226 and above PET/CT is preferred.
Olmedo et al. (2017) All patients received SLNB vs. All patients received a regional lymph node ultrasound, with indeterminate or positive results receiving a core needle biopsy. If biopsy confirmed presence of lymph node metastasis, patient did not undergo SLNB.	Partially applicable[5]	Very serious limitations[6]	£18.39	Probability of identifying lymph node metastasis: 0.15	£123[7]	**Deterministic:** Not completed **Probabilistic:** Not completed

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 Canadian healthcare system, no quality of life outcomes, no discounting due to too short time horizon
3 Time horizon too short, quality of life outcomes not included, financial conflict of interest was not stated, full incremental analysis not conducted

4 ICERs reported were not calculated using a full incremental analysis (i.e., compared to the next best alternative), but absolute costs and effects were reported and therefore ICERs based on a full incremental analysis were calculated by the technical analyst
5 Spanish healthcare system includes non-direct costs, no discounted reported, does not use QALYs.
6 The ICER that was not calculated, incremental average cost effectiveness was calculated, no sensitivity analysis completed, does not report a time horizon
7 Average cost-effectiveness ratio reported, but absolute costs and effects were reported and therefore ICERs based on a full incremental analysis were calculated by the technical analyst

1.1.11 Economic model

No original economic modelling was completed for this review question.

1.1.12 Unit costs

Table 5 Unit costs

Description	Cost	Source
MRI, between 6 and 18 years	£143.21	NHS National Cost Collection
MRI, 5 years and under	£138.45	NHS National Cost Collection
CT (without contrast)	£86.54	NHS National Cost Collection
CE-CT	£109.61	NHS National Cost Collection

1.1.13 Economic evidence statements

Predictors of SLNB review

Five economic studies were included in the evidence. Four of the studies compared sentinel lymph node biopsy and wide excision and wide excision, the other study compared Treat no one, treat everyone, test (with SLNB) and treat some, and test and treat as appropriate. The studies are highly contradictory with a couple of studies showing SLNB to be cost effective and others showing it is not.

Imaging review

Two economic studies were included in the evidence. One study compared a physical exam, CT and PET-CT. The other study compared SLNB with regional ultrasound with positive or indeterminate results receiving a core needle biopsy. Both of the studies were partially applicable and had very serious limitations. One study suggested CT was cost-effective versus PE/Radiography and that PET/CT was cost-effective versus CT. Another study found that SNLB was cost-effective compared with regional lymph node ultrasound with confirmatory core needle biopsy.

1.1.14 The committee's discussion and interpretation of the evidence

1.1.14.1. The outcomes that matter most

This review assessed how well various factors predict SLNB positivity. The committee agreed that adjusted odds ratios are preferable to unadjusted risk ratios as the former have adjusted for important confounders. However, only a few studies reported adjusted odds ratios and pooling of data was not possible. Conversely, many studies provided unadjusted raw data capable of being combined in meta-analysis, therefore both forms of data were important for decision making.

In the context of imaging done to assess sentinel node metastases, the committee agreed that false negative results are particularly important as this result in a person not undergoing a SLNB, potentially missing essential treatment and not benefiting from the therapeutic effect of removing metastatic lymph nodes.

False positives (FP) results may result in a person unnecessarily undergoing a SLNB, which is costly and is an invasive procedure. Alternatively, it may result in the physician electing to not perform a SLNB and incorrectly staging the person. There is also the potential that people with a FP result are wrongly considered for completion lymph node dissection (CLND).

A true positive result would have correctly identified a person with lymphatic spread and would allow accurate re-staging. This person may be spared from having to undergo a SLNB and may be considered for a CLND and/or receive appropriate treatment.

A true negative result would have correctly identified a person without lymphatic spread. This person may not require a SLNB and will have been accurately re-staged.

1.1.14.2 The quality of the evidence

Predictors of SLNB status

Historically, SLNB was not commonly offered to people with thin melanomas. More recently since the introduction of the AJCC 8th edition, SLNB have seen more frequent usage among people with thin melanomas, specifically those with pT1b melanomas.

Most studies included in this review were either conducted before the introduction of the 8th edition of the AJCC, used data from centres which only routinely offered SLNB to people with thin melanomas if they also had additional high-risk features (such as high Clark level, mitoses, ulceration etc.), or they do not specify the circumstances in which SLNB was offered to thin melanomas. Only a few studies used data from centres which routinely offered SLNB to thin melanomas. As all studies contained within this review were retrospective cohort studies, it is very likely that the included participants are disproportionately “high-risk” thin melanomas and are therefore not representative of all thin melanomas. The proportion of participants with positive SLNs varied considerably, from 1.5% to 18.4%, suggesting variance between studies in participant characteristics.

Multivariate analyses, adjusting for various important clinical/histological characteristics which are considered when deciding whether to offer SLNB, were reported by numerous studies. This will account for some of the selection bias but will not be able to fully account for it. Additionally, several studies only controlled for significant predictors from the univariate analysis rather than prespecifying factors to adjust for.

The main analyses for this review used the unadjusted raw data to allow multiple studies to be combined in meta-analysis. The committee noted that the confidence intervals for the meta-analyses were narrow, indicating a high level of precision. The committee agreed that the quality of evidence limited the conclusions which could be drawn but that it was still useful for decision making.

There was variance surrounding how studies reported mitotic index and age data. For the purposes of analysis, these continuous variables had to be dichotomised and the point of dichotomy differed between studies. For mitotic index, most studies compared participants with a mitotic index of ≥1 to those <1 or ≥2 to <2, with the remaining studies selecting an index of 3,4 or 5 as the point of dichotomy. The committee agreed that it was suitable to separate the meta-analysis of mitotic index into three distinct subgroups:

- ≥1 vs. <1
- ≥2 vs. <2
- ≥3 vs. <3, or any dichotomy >3

There was a high degree of inconsistency for the overall analysis of mitotic index (when all three subgroups were combined) and for the subgroup analysis of studies comparing ≥1 to <1 mitosis. The method for determining mitosis has differed over time; older methods allowed

for the possibility of fractional mitoses whereas newer methods do not. Typically, studies did not report their method of scoring mitotic index. It is possible that this contributed to the inconsistency. The analysis comparing ≥1 to <1 mitosis included studies ranging from 2006 to 2018. By contrast, all but one of the studies comparing an index of ≥2 to <2 were from 2017 or later.

The number of reported dichotomies for age was far greater. The committee agreed with the decision to pool all studies but report a subgroup analysis for studies using a cut-off anywhere between 40-50 years of age and for those studies using a cut-off >50 years of age. There was a low level of inconsistency for the overall analysis and the main subgroup analysis (dichotomised between 40-50 years).

Imaging

There are numerous issues with the quality of evidence available for this review question which limit certainty in the evidence and the ability to combine data in meta-analyses.

The reference standards varied between studies. Some studies assessed diagnostic accuracy based solely on the results of the SLNB, which is optimal for the purposes of this review. Other studies used composite reference standards, in which SLN metastases could be diagnosed on the basis of any of the following: SLNB, histology, CLND, FNAB or development of proven metastases during a pre-defined follow-up period (typically up to 6 months). This latter approach is associated with a risk of bias as participants have likely undergone different reference standards which likely differ in their ability to accurately detect SLN metastases. Additionally, it is possible that metastases developed during follow-up, after the imaging was conducted.

In addition to variation in reference standards use, the reported data were either on a per patient or per-node basis. In the former approach, each person who underwent both imaging and SLNB were classified as positive or negative on each test and entered once into the analysis. In the latter approach, each node imaged and biopsied was entered into the analysis, meaning that the same participant could be entered into the analysis multiple times. The committee agreed that the former approach is optimal as it allows an estimation of the actual number of patients correctly classified by imaging.

Most studies were at moderate or high risk of bias. Most studies were retrospective cohort studies and were at risk of selection bias. As the various imaging modalities were not routinely offered at the study centres, it is likely that patients who underwent both imaging and SLNB are not representative of all people with melanoma. This risk is amplified in studies with composite reference standards as the choice of reference standard was likely dependent on clinical characteristics.

1.1.14.3 Discussions about prevalence, pros and cons

Predictors of SLNB status

The committee advised that recommendations in this chapter relate to preliminary staging and should therefore refer to Tumour (T), Nodal (N) and Metastatic (M) categories (in line with the AJCC and UICC) rather than clinical stages.

People who test positive for SLN metastases (clinical stage 3 and over) may be eligible for adjuvant therapy following resection, which has an established clinical- and cost-effectiveness. However, the committee were aware of the high-cost implications of offering SLNB and were cautious to only recommend it for people with a sufficiently high likelihood of positive nodes.

SLNB is an invasive procedure. It has the potential for therapeutic benefit (as well as its prognostic utility) when cancerous lymph nodes are removed. However, there is also the

potential of side effects such as bleeding, pain, allergic reaction, infection and, in rare cases, lymphedema, and a risk of exposing people unnecessarily to an invasive procedure.

The committee also made recommendations to not offer imaging prior to SLNB except in cases of lymph node or distant metastases being suspected. For more information on this, see the chapter on review question 2.1b.

pT1a melanomas

Evidence suggests that overall, melanomas with a Breslow thickness of <0.8mm, or more specifically those with pT1a melanoma, have a very low risk of positivity. The committee agreed that as positive SLNBs are very rare in pT1a melanomas, SLNB should not be offered to this population.

pT1b melanomas between 0.8-1.0mm Breslow thickness

The committee also agreed that a recommendation to consider SLNB for all people with pT1b melanomas would be too costly, place a large strain on practice and may lead to too many people undergoing an invasive procedure unnecessarily.

Evidence suggests that people with a Breslow thickness of 0.8-1.0mm are significantly more likely to have SLNB positivity than those <0.8mm. The committee agreed that in current practice SLNB would very rarely be offered to people with a melanoma <0.8mm in thickness.

However, the group of people with a pT1b melanoma of 0.8-1.0mm Breslow thickness is again too large for everyone to undergo SLNB; as the prevalence of a positive result is still quite small, it would require exposing a large number of people to a costly, invasive procedure to identify a small number of people with a positive result. The committee agreed that a SLNB should only be considered in this group if the person also has “high-risk” features which make SLN positivity more likely.

The committee noted that evidence from the meta-analyses suggests that all predictors evaluated (except for tumour location) are associated with an increase in the risk of positive SLNB. The effect sizes were particularly pronounced for the predictors of ulceration, mitotic index and lymphovascular invasion – both of which had risk ratios above 2. Clark level and age were all also significant predictors of SLNB positivity but with smaller effect sizes.

Ulceration

Evidence from meta-analysis suggests that in people with thin melanomas, ulceration represents a two-fold increase in risk of SLNB positivity compared to those without ulceration, and this effect increased slightly when only including people with a Breslow thickness of 0.8-1.0mm. Evidence from multivariate analyses is consistent with this, with most studies reporting an adjusted odds ratio of at least 2.

The committee were aware of the limitations surrounding the quality of evidence (for all risk factors) and that the findings of multivariate analyses varied. However, they noted that the precision and consistency of the effect estimates for ulceration when looking at the meta-analysis. Additionally, the prevalence of ulceration in thin melanomas is relatively small and will not result in an excessive number of people being referred for SLNB. Based on this they recommended that SLNB be considered if ulceration is present in people with a pT1b melanoma of 0.8-1.0mm Breslow thickness.

Mitotic index

The committee were aware of the issues with the evidence quality for mitotic index analyses, as outlined above. In brief, there was a high level of inconsistency between studies for the overall analysis and the analysis specifically comparing people with ≥1 compared to <1. There has also been variance over time in how mitotic rate has been reported.

The committee advised that that mitotic assessment is complicated in thin melanomas due to the limited amount of tissue available. This can make it difficult to differentiate between people without mitosis and those with 1 mitosis and can lead to people without mitosis being incorrectly classified as having a single mitosis (and vice versa). Using a threshold of ≥2 would limit these classification errors.

The committee noted that the evidence suggests that the risk of SLNB positivity was much higher when using a threshold of at least 3. However, this is based on evidence from just 3 small studies and one large study which has a high risk of bias associated with it.

The committee noted that the predicting accuracy of using a threshold of ≥2 mitoses appears to be smaller than other thresholds. Additionally, there are limited multivariate analyses for the predictive accuracy of a mitotic index of ≥2 and limited data available for subgroup analyses specifically in melanomas with a Breslow thickness of 0.8-1.0mm. As such there is uncertainty in this area. However, the meta-analyses were more precise and consistent than the analysis for a threshold of ≥1, and would be accompanied by fewer practical issues if used as a high-risk criterion. Based on this the committee included a mitotic index of ≥2 as a high-risk feature.

Age

Young age was associated with an increased risk of SLNB positivity in people with thin melanomas however the predictive accuracy was less than other predictors. Specific to people with a Breslow thickness between 0.8 and 1.0mm, a relatively large study (Yalamanchi, 2018; n= 3,183) could not differentiate rates of SLNB positivity between people aged under 54 years and those aged between 54 and 70, after adjusting for confounders, but found a significant difference when comparing those aged under 54 to those aged over 70.

The committee agreed that the risk associated with young age is too small to justify SLNB in the absence of other high-risk features.

Clark level

The committee agreed that the predictive accuracy of a high Clark level (IV or greater) was similar to that of young age. Additionally, the committee advised that Clark level is rarely used in current practice. Based on this the committee did not include high Clark level as a reason to consider SLNB.

LVI

The committee agreed that the presence of lymphovascular invasion was predictive of SLNB positivity and agreed to recommended SLNB be considered if LVI is present in people with a pT1b melanomas of 0.8-1.0mm Breslow thickness.

Tumour location

The committee agreed that tumour location did not appear to be predictive of SLNB positivity but noted that the analysis was limited to a comparison between tumours located on the limbs/extremities and those located elsewhere.

pT1b melanomas <0.8mm Breslow thickness

The committee agreed that SLNB would rarely be conducted for melanomas pT1b melanomas <0.8mm Breslow thickness but did not want to make specific recommendations that SLNB not be offered to these people to allow for its use in certain circumstances (such as the presence of several high-risk factors, such as those outlined above) and to allow for patient preference.

Melanomas >1mm Breslow thickness

The committee felt they could not substantially change recommendations relating to the use of SLNB in people with melanomas >1mm Breslow thickness as the evidence they had reviewed was specific to thin melanomas. They agreed to update this recommendation to again refer to preliminary stages instead of clinical stages.

Imaging

The committee agreed that SLNB is important for staging as it establishes whether cancer has spread to the lymph nodes. It also has potential therapeutic benefit when metastatic lymph nodes are removed.

However, SLNB is nonetheless an invasive procedure, with high costs associated when offered to a large number of people. There is the potential for a sufficiently accurate imaging test to be used to rule-in or rule-out SLN metastases, without the need for performing a SLNB.

The committee agreed that analyses showed that imaging, regardless of modality, has a high specificity, meaning that the risk of false positives is relatively low. However, the committee agreed that using imaging to rule-in metastases without conducting a SLNB would not be a clinically suitable strategy. A SLNB would still need to be performed to ensure accurate staging, due to the residual chance of a false positive result and there may be a desire to remove metastatic SLN's for therapeutic reasons.

The sensitivity of all imaging modalities is very low and as such there will be a high false negative rate. The committee agreed that although US has improved sensitivity compared to other imaging modalities, the best available evidence – combining data from 10 studies on a per-patient basis – suggests a low sensitivity (0.36 [95%CIs 0.22, 0.52]). The committee agreed that based on this evidence there was too high a risk of false negative results for pre-SLNB imaging to have utility.

They recommended that imaging only be conducted after the person has been properly staged, meaning they have either already received a SLNB or have been excluded from undergoing one.

People with melanoma who are pregnant

The committee also discussed the role of SLNB in people who are pregnant. They noted variance in practice and attitudes towards postponing SLNB until after the pregnancy is completed but agreed that it is safe to do so, with no evidence suggesting the contrary. They made recommendations to reflect this but noted that such decisions must be made on a case-by-case basis taking into account the circumstances of the individual.

1.1.14.4 Cost effectiveness and resource use

Predictors of SLNB status

The committee had not prioritised this review question for *de novo* economic modelling and were therefore only presented with the results of five existing studies, including a model that had been previously developed for NG14. The committee noted that the existing economic evidence was highly contradictory, with the Morton, Hu and Wilson studies supporting the use of SLNB and the NG14 model and the Serra-Arbeloa study showing that SLNB was not cost effective. The studies assessed SLNB in different populations with tumours of varying thickness. Hu did not state a specific tumour thickness, Morton investigated tumours that were 1mm and greater, Wilson investigated melanomas that were Stage II, the NG14 model investigated melanomas that were Stage IA-IIC (direct clinical evidence was for tumours >1mm and adjusted the evidence for thinner tumours) and Serra-Arbeloa investigated all ranges of tumour thickness. However, Serra-Arbeloa was the only study to investigate thin (<1mm) tumours separately, this showed that SLNB was not cost effective when used in

patients with tumours less than 1mm. The committee was particularly concerned with the dramatically different results from Morton, which showed SLNB to be highly cost-effective and the NG14 model, which showed SLNB not to be cost-effective in the same population (patients with tumours ≥1mm in thickness). This is despite the two models being based on the same evidence from the MSLT-1 trial. Information contrasting the modelling approaches for these two studies was therefore also presented to the committee, which included differences in the sensitivity and specificity of SLNB, NG14 was based in the UK and Morton was based in Australia which may mean that there are different costs of treatments and follow-up care as well as the discount rates applied. Morton also had more health states in their model, as different utilities for the diagnosis of distant metastases and distant stable disease were accounted for, whereas the NG14 model just considered distant metastases. However, all five of the existing studies were rated as partly applicable, but the Hu, Morton and Wilson studies were also associated with very serious limitations. The committee noted that four of the studies (Morton, Hu, NG14 model and Serra-Arbeloa) included complete lymph node dissection as the treatment after SLNB, whereas Wilson included tailored interferon treatment after SLNB, both of which are not currently considered part of routine clinical practice in the UK. This is due to the fact that a number of adjuvant treatments (either targeted therapies or immunotherapies) are now available within the UK and the risks associated with complete lymph node dissection are thought to outweigh the benefits in the large majority of eligible patients. The committee therefore felt that it was difficult to reach a conclusion about the cost-effectiveness of SLNB in current clinical practice in the UK from these studies.

The committee wanted to make recommendations about the use of SLNB in patients with tumours of different thickness (e.g., 0.8mm - 1mm and greater than 1mm tumours). For the greater than 1mm group, the committee noted that SLNB is the current standard of care and already routinely offered to such patients. Therefore, a recommendation to consider SLNB in these patients would not result in a substantial resource impact. The committee also felt that a recommendation for SLNB in these patients would ensure inequalities in access to adjuvant therapies across the country are minimised, given a positive SLNB if required before patients become eligible for such treatments. The committee also noted that adjuvant treatment, rather than complete lymph node dissection, is now considered in the majority of patients who have a positive SLNB and is likely to be more effective and may therefore improve the cost-effectiveness of SLNB compared to estimates provided in the NG14 model. For the 0.8mm - 1mm group, the cost-effectiveness of SLNB will depend on the prevalence of SLNB positivity, which is dependent on the population tested within this group and also likely to be lower than in the greater than 1mm group. The committee therefore decided to recommend SLNB for patients with high risk factors, where the probability of SLNB positivity is likely to be larger and therefore the use of SLNB is also more likely to be cost-effective. However, the committee felt that the recommendation to consider SLNB in patients with tumours 0.8mm – 1mm in thickness with at least one high risk factor was likely to only impact a small number of patients and therefore unlikely to be associated with a significant resource impact.

Imaging

The committee did not prioritise this review question for *de novo* economic evidence and therefore they were presented with the results of two existing economic models. The committee noted that the two cost-effectiveness studies evaluated two differing techniques: Look Hong evaluated the cost effectiveness of CT compared with PET/CT and Olmedo evaluated the cost effectiveness of using ultrasound in staging patients. The committee noted that there were very serious limitations in both the studies and felt that they were unsuitable for informing the recommendations on staging.

Look Hong found that PET/CT was the most cost-effective option compared with CT alone. However, the committee felt that a consistent imaging modality throughout the guideline was important as it would mean that all the images could be compared, for staging and all

through follow up. The committee felt that the evidence for CT in follow up was stronger than the evidence for PET/CT in staging therefore, the committee recommended CT in staging rather than PET/CT. The inclusion of brain imaging was not included in the Look Hong study. The committee also noted that if a patient received PET/CT they would have to receive a separate MRI scan of the brain whereas if they received a CT scan then that could be extended to the brain. Therefore, the cost of CT would be lower overall. The committee noted that there was a lot of variation in practice around which patients would receive CT scans especially for the patients with stage IIC melanoma. However, the committee felt that reducing the number of CT scans in the lower stages and potentially increasing the number in the higher stages would not have a large resource impact.

The economic study, Olmedo, found that ultrasound was a cost-effective option for staging patients compared with sentinel lymph node biopsy only. There were very serious limitations with the study, including no sensitivity analyses being done. The committee noted that the sensitivity of ultrasound was low at 46% (specificity was 76%) and would miss a large number of patients with positive regional lymph nodes. Therefore, the committee felt that recommending ultrasound was not clinically appropriate.

1.1.15 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.11. Other evidence supporting these recommendations can be found in the evidence reviews on the follow-up of people who have had melanoma (evidence review F).

1.1.16 References – included studies

1.1.16.1 Prognostic evidence

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Appendices

Appendix A – Review protocols

Review protocol for predicting positive SLNB result in thin melanomas

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Staging melanoma: predicting SLNB positivity in thin melanomas
2.	Review question	RQ 2.1 What is the most accurate method of staging melanoma in people preliminarily assigned: (a) clinicopathological stage 1A melanoma? (b) clinicopathological stage 1B to 2C melanoma (including, but not limited to, sentinel lymph node biopsy)? (c) clinicopathological stage 3 melanoma? (d) clinicopathological stage 4 melanoma?
3.	Objective	To determine which factors are predictive of SLNB positivity in thin melanomas (Breslow thickness ≤1.0mm)
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 for imaging studies only. No date restriction will be used for predictors of SLNB positivity) 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	Stage 1-2C melanoma
6.	Population	People with melanoma and a Breslow thickness of
7.	Intervention/Test	the following prognostic factors will be assessed: Breslow thickness (0.8-1.0mm vs. <0.8mm) Mitotic rate (≥2 vs. <2)

		Ulceration (present vs. absent) Age (≥45 vs. <45) Lymphocyte: neutrophil ratio Clark level (I-II versus III-IV)
8.	Comparator/Reference standard	SLNB positivity
9.	Types of study to be included	Cohort study (prospective or 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 recommendations on the staging of melanoma in view of the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system and the 8th edition of the Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) staging system for melanoma. In particular, the AJCC 8 includes people with a Breslow thickness of 0.8-1.0mm (along with people with a thickness <0.8 mm if they have ulceration) as having a preliminary stage of 1b This guideline will also cover all settings in which NHS care is received or commissioned.
12.	Primary outcomes (critical outcomes)	Prognostics factors will be dichotomised to estimate in increased risk of SLNB positivity.

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 Preliminary melanoma stage. People with a compromised immune system.
18.	Type and method of review	☐
		☒
		☒
		☐
		☐

		☐
		☐
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	26/10/2020
22.	Anticipated completion date	26/11/2020
23.	Stage of review at time of this submission	**Review stage: completed**
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	Staging SLNB Mitotic rate Breslow thickness Ulceration Imaging Melanoma Skin cancer Skin tumour
33.	Details of existing review of same	Update of question 3 in **NICE Guideline NG14 Melanoma: assessment and management**

	topic by same authors	
34.	Current review status	Ongoing
		☐
		☐
		☐
		☐
35..	Additional information	
36.	Details of final publication	**www.nice.org.uk**

Review protocol for imaging to detect SLN metastases

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Staging melanoma: Imaging to detect involved lymph nodes and distant metastases

2.	Review question	RQ 2.1) What is the most accurate method of staging melanoma in people preliminarily assigned: (a) clinicopathological stage 1A melanoma? (b) clinicopathological stage 1B to 2C melanoma (including, but not limited to, sentinel lymph node biopsy)? (c) clinicopathological stage 3 melanoma? (d) clinicopathological stage 4 melanoma?
3.	Objective	Determine the best method of staging people with a preliminary diagnosis of stage 1-4 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 for imaging studies only. No date restriction will be used for predictors of SLNB positivity)

		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	Stage 1-4 melanoma
6.	Population	• People with a preliminary diagnosis of stage 1-4 melanoma
7.	Test	The following imaging modalities will be compared for the detection of involved nodes and distant metastases: • US • CT • PET+CT • MRI

8.	Comparator/Reference standard	• SLNB
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 recommendations on the staging of melanoma in view of the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system and the 8th edition of the Union for International Cancer Control (UICC) Tumour Node Metastasis (TNM) staging system for melanoma. In particular, the AJCC 8 includes people with a Breslow thickness of 0.8-1.0mm (along with people with a thickness <0.8 mm if they have ulceration) as having a preliminary stage of 1b This guideline will also cover all settings in which NHS care is received or commissioned.
12.	Primary outcomes (critical outcomes)	• Sensitivity/specificity • Likelihood ratios
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 • Preliminary melanoma stage. • People with a compromised immune system.
18.	Type and method of review	☒Diagnostic accuracy review
		☒Prognostic accuracy review
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	26/10/2020

22.	Anticipated completion date	26/11/2020
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	• Staging • SLNB • Mitotic rate • Breslow thickness • Ulceration • Imaging • Melanoma • Skin cancer

		• Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 3 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 27th October 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/ (95782)
2 Skin Neoplasms/ (121708)
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (104386)
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. (61895)
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (25092)
6 (hutchinson* adj2 (freckle* or melano*)).tw. (69)
7 dubreuilh*.tw. (73)
8 (maligna* adj2 lentigo*).tw. (1071)
9 LMM.tw. (887)
10 or/1-9 (252664)
11 Sentinel Lymph Node Biopsy/ (11246)
12 (sentinel adj2 node*).tw. (13111)
13 (sentinel adj2 lymphadenectom*).tw. (356)
14 SLNB.tw. (1623)
15 or/11-14 (14975)
16 (breslow adj2 (thick* or depth* or scale* or level* or measur*)).tw. (1573)
17 Mitotic Index/ (5834)
18 ((mitosis or miotic or mitotic) adj2 (activit* or index* or indices or number* or rate* or ratio*)).tw. (16464)
19 ((neutrophil* or lymphocyte*) adj1 ratio*).tw. (5725)
20 NLR.tw. (5020)
21 Skin Ulcer/ (8877)
22 ulcer*.tw. (184391)
23 or/16-22 (215582)
24 exp Ultrasonography/ (440796)
25 (ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (356488)
26 Tomography, X-Ray Computed/ (383251)
27 ((CT or CAT) adj (scan* or imag* or examination* or x ray*)).tw. (112322)
28 (cine adj ct).tw. (154)
29 ((comput* or electron beam) adj3 tomogra*).tw. (258004)
30 tomodensitometr*.tw. (941)
31 Positron Emission Tomography Computed Tomography/ (9816)
32 (PET adj (CT or scan* or imag* or examination*)).tw. (38793)
33 (positron adj2 tomograph*).tw. (49045)
34 or/24-33 (1089140)
35 10 and 15 and 23 (917)
36 10 and 34 (14665)
37 35 or 36 (15520)
38 limit 37 to english language (13256)
39 animals/ not humans/ (4715700)

Database: Medline	
40	38 not 39 (12822)

Table 5 Search strategy for Medline in progress

Database: Medline in Process	
41	limit 40 to (letter or historical article or comment or editorial or news or case reports) (4890)
42	40 not 41 (7932)
43	limit 42 to ed=20141001-20201027 (2461
1	exp Melanoma/ (0)
2	Skin Neoplasms/ (0)
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (11989)
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. (6667)
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (3162)
6	(hutchinson* adj2 (freckle* or melano*)).tw. (1)
7	dubreuilh*.tw. (0)
8	(maligna* adj2 lentigo*).tw. (77)
9	LMM.tw. (176)
10	or/1-9 (19726)
11	Sentinel Lymph Node Biopsy/ (0)
12	(sentinel adj2 node*).tw. (1592)
13	(sentinel adj2 lymphadenectom*).tw. (28)
14	SLNB.tw. (309)
15	or/11-14 (1611)
16	(breslow adj2 (thick* or depth* or scale* or level* or measur*)).tw. (157)
17	Mitotic Index/ (0)
18	((mitosis or miotic or mitotic) adj2 (activit* or index* or indices or number* or rate* or ratio*)).tw. (1167)
19	((neutrophil* or lymphocyte*) adj1 ratio*).tw. (2067)
20	NLR.tw. (1859)
21	Skin Ulcer/ (0)
22	ulcer*.tw. (19031)
23	or/16-22 (22832)
24	exp Ultrasonography/ (0)
25	(ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (55598)
26	Tomography, X-Ray Computed/ (0)
27	((CT or CAT) adj (scan* or imag* or examination* or x ray*)).tw. (17865)
28	(cine adj ct).tw. (9)
29	((comput* or electron beam) adj3 tomogra*).tw. (45447)
30	tomodensitometr*.tw. (60)
31	Positron Emission Tomography Computed Tomography/ (0)
32	(PET adj (CT or scan* or imag* or examination*)).tw. (8428)
33	(positron adj2 tomograph*).tw. (8614)
34	or/24-33 (111107)
35	10 and 15 and 23 (69)
36	10 and 34 (1654)
37	35 or 36 (1717)
38	limit 37 to english language (1702)
39	animals/ not humans/ (1)
40	38 not 39 (1702)
41	limit 40 to (letter or historical article or comment or editorial or news or case reports) (388)

Database: Medline in Process	
42	40 not 41 (1314)
43	limit 42 to dt=20141001-20201027 (981)

Table 6 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)
10	or/1-9 (2857)
11	Sentinel Lymph Node Biopsy/ (0)
12	(sentinel adj2 node*).tw. (293)
13	(sentinel adj2 lymphadenectom*).tw. (5)
14	SLNB.tw. (60)
15	or/11-14 (296)
16	(breslow adj2 (thick* or depth* or scale* or level* or measur*)).tw. (38)
17	Mitotic Index/ (0)
18	((mitosis or miotic or mitotic) adj2 (activit* or index* or indices or number* or rate* or ratio*)).tw. (124)
19	((neutrophil* or lymphocyte*) adj1 ratio*).tw. (409)
20	NLR.tw. (319)
21	Skin Ulcer/ (0)
22	ulcer*.tw. (2518)
23	or/16-22 (3149)
24	exp Ultrasonography/ (0)
25	(ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (7132)
26	Tomography, X-Ray Computed/ (0)
27	((CT or CAT) adj (scan* or imag* or examination* or x ray*)).tw. (2626)
28	(cine adj ct).tw. (1)
29	((comput* or electron beam) adj3 tomogra*).tw. (6022)
30	tomodensitometr*.tw. (2)
31	Positron Emission Tomography Computed Tomography/ (0)
32	(PET adj (CT or scan* or imag* or examination*)).tw. (1694)
33	(positron adj2 tomograph*).tw. (1756)
34	or/24-33 (15580)
35	10 and 15 and 23 (22)
36	10 and 34 (270)
37	35 or 36 (289)
38	limit 37 to english language (287)
39	animals/ not humans/ (0)
40	38 not 39 (287)
41	limit 40 to (letter or historical article or comment or editorial or news or case reports) (7)

Database: Medline Epub	
42	40 not 41 (280)

Table 7 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/ (157154)
2	skin tumor/ or skin cancer/ or epithelium tumor/ (66992)
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (163450)
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. (93147)
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (39663)
6	(hutchinson* adj2 (freckle* or melano*)).tw. (80)
7	dubreuilh*.tw. (73)
8	(maligna* adj2 lentigo*).tw. (1678)
9	LMM.tw. (1511)
10	or/1-9 (331443)
11	sentinel lymph node biopsy/ (16747)
12	(sentinel adj2 node*).tw. (24412)
13	(sentinel adj2 lymphadenectom*).tw. (513)
14	SLNB.tw. (3923)
15	or/11-14 (28812)
16	(breslow adj2 (thick* or depth* or scale* or level* or measur*)).tw. (2899)
17	mitosis index/ or mitosis rate/ (15664)
18	((mitosis or miotic or mitotic) adj2 (activit* or index* or indices or number* or rate* or ratio*)).tw. (22324)
19	neutrophil lymphocyte ratio/ (9818)
20	((neutrophil* or lymphocyte*) adj1 ratio*).tw. (13348)
21	NLR.tw. (11843)
22	skin ulcer/ (18330)
23	ulcer*.tw. (267769)
24	or/16-23 (322530)
25	exp *echography/ (215355)
26	(ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*).tw. (607877)
27	*computer assisted tomography/ or *electron beam tomography/ or x-ray computed tomography/ (184191)
28	((CT or CAT) adj (scan* or imag* or examination* or x ray*)).tw. (229978)
29	(cine adj ct).tw. (220)
30	((comput* or electron beam) adj3 tomogra*).tw. (392693)
31	tomodensitometr*.tw. (1065)
32	positron emission tomography-computed tomography/ (32372)
33	(PET adj (CT or scan* or imag* or examination*)).tw. (99278)
34	(positron adj2 tomograph*).tw. (78585)
35	or/25-34 (1333696)
36	10 and 15 and 24 (1863)
37	10 and 35 (21367)
38	36 or 37 (23064)
39	limit 38 to english language (20646)
40	nonhuman/ not human/ (4720218)

Database: Embase
41 39 not 40 (20040)
42 (conference abstract or conference paper or conference proceeding or "conference review" or letter or editorial).pt. (6485763)
43 41 not 42 (13092)
44 limit 43 to dc=20141001-20201027 (5458)

Table 8 Search strategy for Cochrane Wiley

Database: Cochrane Wiley (CRD/CENTRAL)	
ID	Search Hits
#1	MeSH descriptor: [Melanoma] explode all trees 1795
#2	MeSH descriptor: [Skin Neoplasms] this term only 1552
#3	((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)):ti,ab,kw 5333
#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 3935
#5	(((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*))):ti,ab,kw 676
#6	((hutchinson* NEAR/2 (freckle* or melano*))):ti,ab,kw 9
#7	(dubreuilh*):ti,ab,kw 0
#8	(maligna* NEAR/2 lentigo*) 53
#9	(LMM):ti,ab,kw 113
#10	{or #1-#9} 8391
#11	MeSH descriptor: [Sentinel Lymph Node Biopsy] this term only 271
#12	((sentinel NEAR/2 node*)):ti,ab,kw 1379
#13	((sentinel NEAR/2 lymphadenectom*)):ti,ab,kw 28
#14	(SLNB):ti,ab,kw 204
#15	{or #11-#14} 1405
#16	((breslow NEAR/2 (thick* or depth* or scale* or level* or measur*))):ti,ab,kw 91
#17	MeSH descriptor: [Mitotic Index] this term only 39
#18	(((mitosis or miotic or mitotic) NEAR/2 (activit* or index* or indices or number* or rate* or ratio*))):ti,ab,kw 144
#19	(((neutrophil* or lymphocyte*) NEAR/1 ratio*)):ti,ab,kw 473
#20	(NLR):ti,ab,kw 264
#21	MeSH descriptor: [Skin Ulcer] this term only 198
#22	(ulcer*):ti,ab,kw 26643
#23	{or #16-#22} 27340
#24	MeSH descriptor: [Ultrasonography] explode all trees 13578
#25	((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*)):ti,ab,kw 43578
#26	MeSH descriptor: [Tomography, X-Ray Computed] this term only 4005
#27	(((CT or CAT) NEAR (scan* or imag* or examination* or x ray*))):ti,ab,kw 10513
#28	((cine NEAR ct)):ti,ab,kw 12
#29	(((comput* or electron beam) NEAR/3 tomogra*)):ti,ab,kw 20056
#30	(tomodensitometr*):ti,ab,kw 64
#31	MeSH descriptor: [Positron Emission Tomography Computed Tomography] this term only 96
#32	((PET NEAR (CT or scan* or imag* or examination*))):ti,ab,kw 3823
#33	((positron NEAR/2 tomograph*)):ti,ab,kw 4160

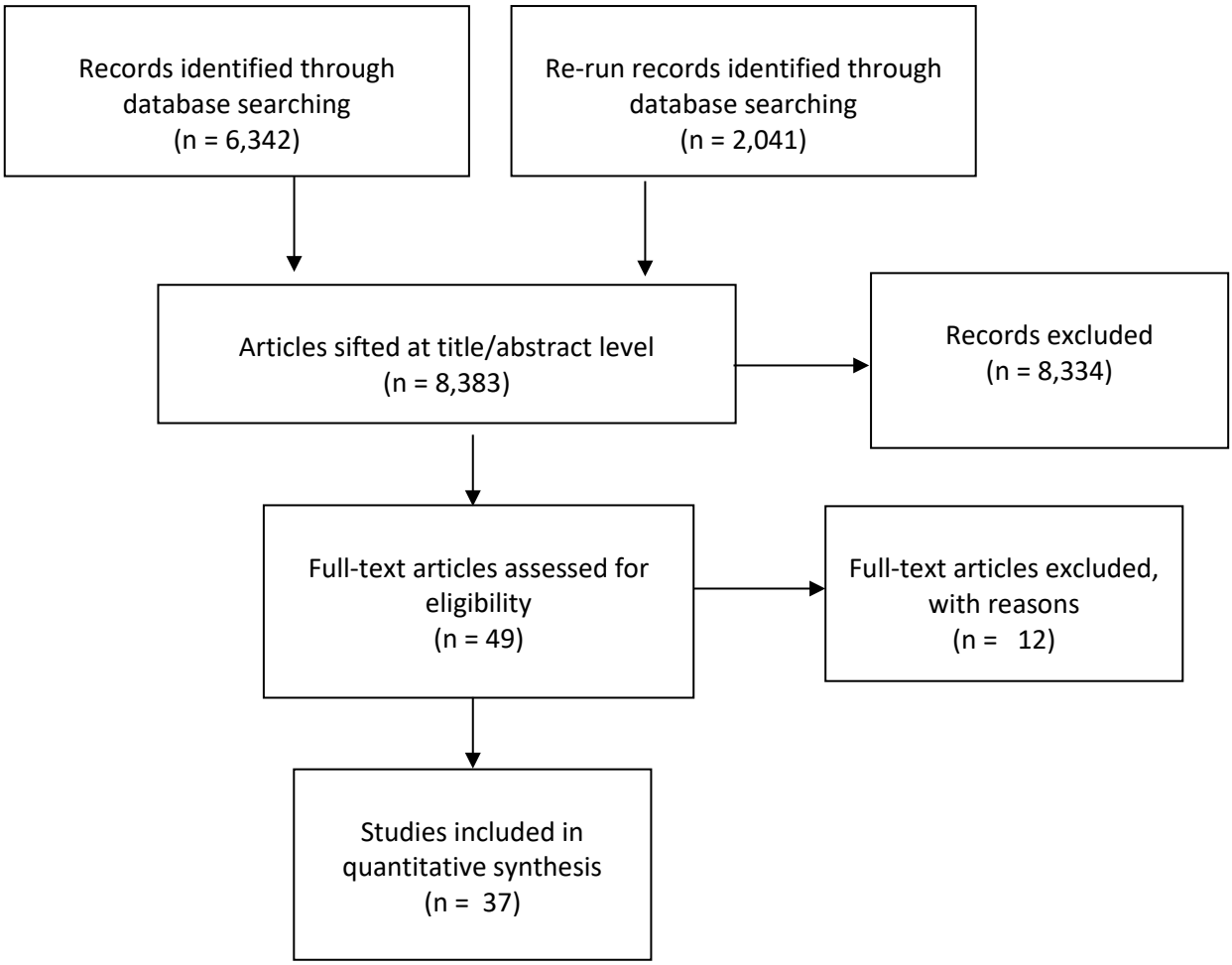
Database: Cochrane Wiley (CRD/CENTRAL)		
#34	{or #24-#33}	73376
#35	#10 AND #15 AND #23	71
#36	#10 AND #34	479
#37	#35 OR #36	548
#38	"conference":pt or (clinicaltrials or trialsearch):so	499881
#39	#37 NOT #38 with Cochrane Library publication date Between Oct 2014 and Nov 2020	133
#40	#37 NOT #38 with Publication Year from 2014 to 2020, in Trials	109

Table 9 Search strategy for CRD (DARE)

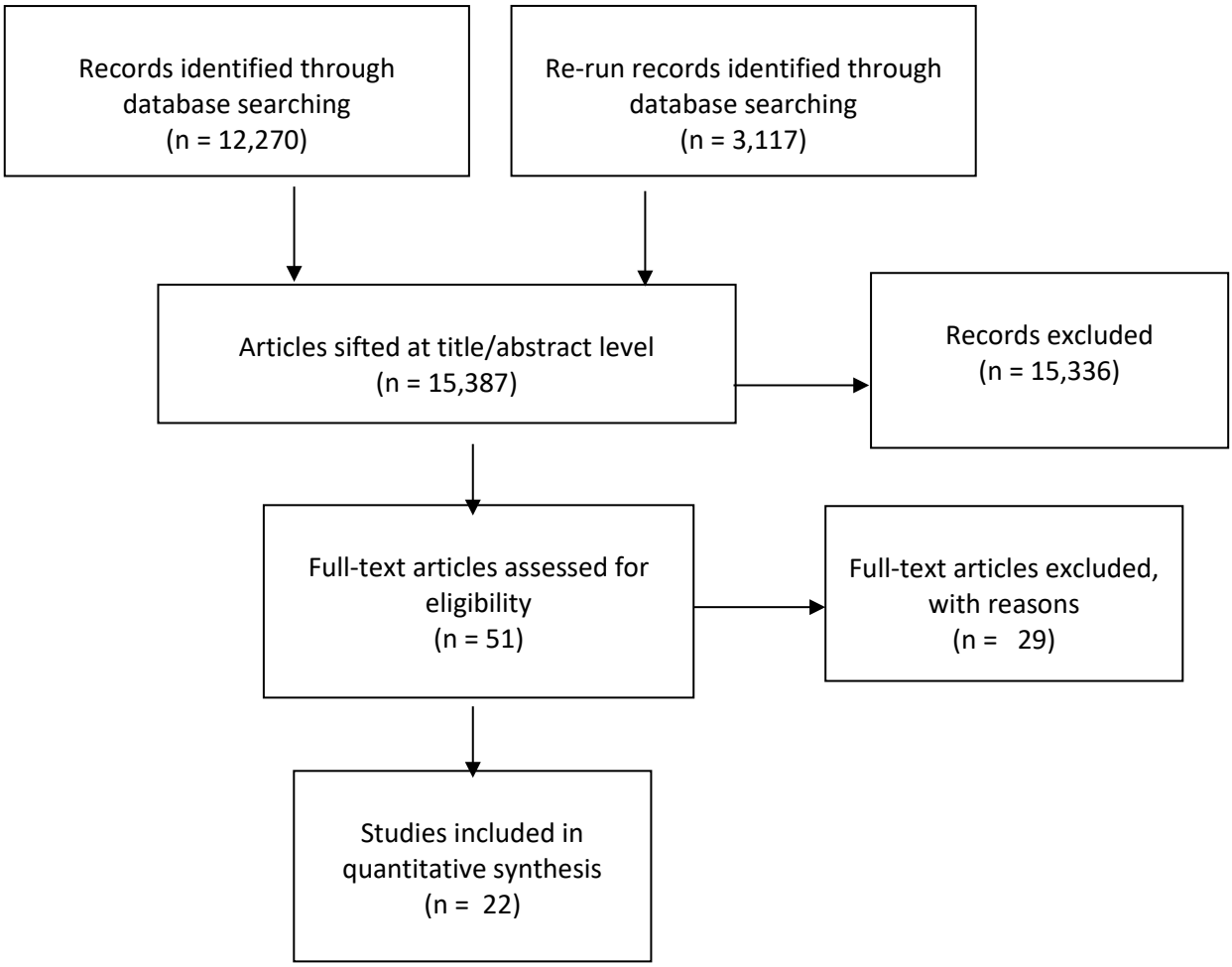
Database: CRD (DARE)		
Search	Hits	
1	MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES	221
2	MeSH DESCRIPTOR Skin Neoplasms	193
3	((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*))	329
4	(((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR1 (adenocarcinoma* or cancer* or carcinoma* 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 Sentinel Lymph Node Biopsy	119
12	((sentinel NEAR2 node*))	149
13	((sentinel NEAR2 lymphadenectom*))	2
14	(SLNB)	13
15	#11 OR #12 OR #13 OR #14	151
16	((breslow NEAR2 (thick* or depth* or scale* or level* or measur*)))	11
17	MeSH DESCRIPTOR Mitotic Index	0
18	(((mitosis or miotic or mitotic) NEAR2 (activit* or index* or indices or number* or rate* or ratio*)))	1
19	(((neutrophil* or lymphocyte*) NEAR1 ratio*))	8
20	(NLR)	3
21	MeSH DESCRIPTOR Skin Ulcer	21
22	(ulcer*)	1550
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	1572
24	MeSH DESCRIPTOR Ultrasonography EXPLODE ALL TREES	1154
25	((ultraso* or sonogra* or echogra* or echoscop* or echosound* or echotomogra*))	2531
26	MeSH DESCRIPTOR Tomography, X-Ray Computed	896
27	(((CT or CAT) NEAR (scan* or imag* or examination* or x ray*)))	490
28	((cine NEAR ct))	0
29	(((comput* or electron beam) NEAR3 tomogra*))	1400
30	(tomodensitometr*)	1
31	MeSH DESCRIPTOR Positron Emission Tomography Computed Tomography	3
32	((PET NEAR (CT or scan* or imag* or examination*)))	356
33	((positron NEAR2 tomograph*))	626
34	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	4357

Database: CRD (DARE)			
35	#10 AND #15 AND #23	3	
36	#10 AND #34	88	
37	#35 OR #36	91	
38	* IN DARE FROM 2014 TO 2020		9540
39	#37 AND #38	8	

Appendix C –Prognostic evidence study selection



Appendix D –Diagnostic accuracy study selection



Appendix E –Prognostic evidence

Andtbacka, 2013

Bibliographic Reference	Andtbacka RH; Donaldson MR; Bowles TL; Bowen GM; Grossmann K; Khong H; Grossman D; Anker C; Florell SR; Bowen A; Duffy KL; Leachman SA; Noyes RD; Sentinel lymph node biopsy for melanoma in pregnant women.; Annals of surgical oncology; 2013; vol. 20 (no. 2)

Study Characteristics

Study design	Retrospective cohort study retrospective review of prospective melanoma database
Study details	Study location USA Study setting HCI and Intermountain Medical Center, Utah Study dates 1997 to 2012. Sources of funding CCSG/share resource support provided financial assistance for manuscript development
Inclusion criteria	Pregnant either during pregnancy or first few weeks afterwards Melanoma Included all clinical stage I/II melanomas (according to AJCC 6-7). However individual patient data were provided and only melanomas of a thickness up to 1.0mm were included Underwent SLNB
Number of participants	8
Outcome(s) of interest	SLNB positivity.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Ulceration - no participants included in the analysis had ulceration Mitotic rate (per mm2) -(<1 versus 1+) Breslow thickness - (<0.75mm versus 0.75mm-1.00mm) Tumour infiltrating lymphocytes (yes versus no) *individual patient data presented for all predictors*
Covariates adjusted for in the multivariable regression modelling	None

Study-level characteristics

	Study (N = 8)
% Female	100
% positive SLNB	12.5
% Breslow Thickness 0.8-1.0mm	75
% High mitotic rate group (see study characteristics for definition)	50
% Positive TIL (see study characteristics for definition)	42.9
% Clark level IV-V	62.5
% Regression	25

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB at study centre. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Potential for confounders that are not adjusted for)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Reason for undergoing SLNB not accounted for. Unclear whether data is representative of all thin melanomas)*
	Directness	Directly applicable

Bartlett, 2014

Bibliographic Reference	Bartlett EK; Gimotty PA; Sinnamon AJ; Wachtel H; Roses RE; Schuchter L; Xu X; Elder DE; Ming M; Elenitsas R; Guerry D; Kelz RR; Czerniecki BJ; Fraker DL; Karakousis GC; Clark level risk stratifies patients with mitogenic thin melanomas for sentinel lymph node biopsy.; Annals of surgical oncology; 2014; vol. 21 (no. 2)

Study Characteristics

Study design	Retrospective cohort study Review of patient database
Study details	Study location USA Study setting Single centre Study dates 1995-2011
Inclusion criteria	Melanoma thin (≤1mm) primary cutaneous melanoma and evaluable data. At authors institution, SLNB is routinely performed for patients with melanoma >1mm in thickness. SLNB in patients with thin melanoma is performed selectively, based on individual patients' melanoma risk factors and comorbidities, discussion of the risks and benefits of the procedure, and patient preferences.
Number of participants and recruitment methods	781
Outcome(s) of interest	SLNB positivity *A false negative SLNB was defined as a regional nodal recurrence in a draining lymph node basin after a negative SLNB. These patients were identified by a query of our pathologic database from 1995-2011 for all nodal recurrences.*

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• thickness: (≤0.75 versus 0.76-1mm)
	• mitoses: (<1 versus 1+)
	  ○ *The method for calculating mitotic rate varied slightly over the study period. Initially, based upon number of mitoses observed divided by the tumor area surveyed, current practice uses hotspot method in which any mitogenic lesion is reported as at least one mitosis (allowing for present (1+) versus absent (0) comparison).*
	• Age (40 years or younger versus 41+ years old)
	  ○ *data available for following age groups: 0-40, 41-65, >65.*
	• Tumour infiltrating lymphocytes (TIL) (present versus absent)

Covariates adjusted for in the multivariable regression modelling	logistic regression model including age, anatomic site, Clark level, thickness, mitoses, TIL, regression and ulceration. However, confidence intervals are not reported therefore multivariate analysis was not used for this review.

Study-level characteristics

	Study (N = 781)
% Female	45

	Study (N = 781)
Median (Range) age *(years)*	51 (14-88)
% T1b disease according to 2009 version	55
% positive SLNB	3.7
% Ulceration	4.5
% Breslow Thickness 0.8-1.0mm	45.3
% High mitotic rate group (see study characteristics for definition)	60.9
% Positive TIL (see study characteristics for definition)	71.9
% Young age (see study characteristics for definition)	26.8
% Clark level IV-V	45.9
% Regression	24.5

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(SNLB was not routine practice for thin melanomas at study centre(s). It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Note. only 698 or 781 participants had eligible mitotic index score on record.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *("The method for calculating mitotic rate varied slightly over the study period. Initially, mitotic rate was calculated based upon number of mitoses observed divided by the tumour area surveyed. This average value led to the possibility of reporting fractional mitoses (mitotic rate between 0-1). Current practice quantifies the number of mitoses in an identified hotspot, which results in any "mitogenic" lesion being reported as having at least one mitosis")*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Multivariate analysis was performed which controlled for various important clinical characteristics)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Only significant predictors were entered into multivariate model, meaning that important confounders were not controlled for.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Change in measurement of mitotic rate over time, not all participants had mitotic rate on record. Thin melanomas were not routinely offered SLNB and study did not adequately control for relevant confounders)*
	Directness	Directly applicable

Cecchi, 2007

Bibliographic Reference	Cecchi R; Buralli L; Innocenti S; De Gaudio C; Sentinel lymph node biopsy in patients with thin melanomas.; The Journal of dermatology; 2007; vol. 34 (no. 8)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Italy Study setting Single hospital Study dates Over a 6 year period Sources of funding not reported
Inclusion criteria	Melanoma thin (1mm or less thickness) stage I–II melanoma Underwent SLNB underwent SLNB contemporarily to a wide excision (if this had not previously been done) with margins of 1 cm of their primary tumor.
Number of participants and recruitment methods	50 (30 relevant to this review)
Outcome(s) of interest	SLNB positivity

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration - present/absent
	  ○ *Only 10 participants have data reported for ulceration*
	• Breslow thickness
	  ○ *both of the 2 positive SLNB patients had a thickness of 0.75-1.00. However data on the number participants with*

	a thicknesses above/below 0.75mm is not presented therefore analysis not possible. • Mitotic rate - not reported • Regression (present vs. absent) o *Only 20 participants have data reported for regression*
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 30)
% Female	44
Mean (range) age *(years)*	57.8 (30-77)
% positive SLNB	6.7
% Ulceration	20 (n=10)
% Clark level IV-V	6.7 (n=30)
% Regression	25 (n=20)

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely performed in participants with thin melanomas at study centre(s). It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	High risk of bias *(Ulceration status data available for only 10/50 participants; only 20/50 participants have data reported for regression; only 30/50 have data reported for Clark level)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(no adjustment for confounders)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High *(No adjustment for confounders and large amount of missing data for prognostic factors of interest to this review.)*
	Directness	Directly applicable

Doumas, 2010

Bibliographic Reference Doumas A; Dionyssopoulos A; Christoforidis T; Papaconstantinou A; Efstratiou I; Iakovou I; Lo-Presti D; Georga S; Nikos V; Karatzas N; Is 0.75 mm Breslow thickness the correct cut-off point for performing sentinel node biopsy in patients with melanoma?; Hellenic journal of nuclear medicine; 2010; vol. 13 (no. 3)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Greece Study setting Single centre
Inclusion criteria	Melanoma of any size (only those up to 1mm included in this study) Underwent SLNB
Number of participants and recruitment methods	64; 21 relevant to this review
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Breslow thickness (0.51-0.75mm versus 0.76 - 1.00mm)
Covariates adjusted for in the multivariable regression modelling	None

Study-level characteristics

	Study (N = 21)
% positive SLNB	4.8
% Breslow Thickness 0.8-1.0mm	52.4

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(no adjustment for confounding variables)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders that were not adjusted for)*
	Directness	Directly applicable *(Note. thinner melanoma cohort only include participants with melanomas 0.51-0.75mm)*

Durham, 2017

Bibliographic Reference	Durham, Alison B; Schwartz, Jennifer L; Lowe, Lori; Zhao, Lili; Johnson, Andrew G; Harms, Kelly L; Bichakjian, Christopher K; Orsini, Amy P; McLean, Scott A; Bradford, Carol R; Cohen, Mark S; Johnson, Timothy M; Sabel, Michael S; Wong, Sandra L; The natural history of thin melanoma and the utility of sentinel lymph node biopsy.; Journal of surgical oncology; 2017; vol. 116 (no. 8); 1185-1192

Study Characteristics

Study design	Retrospective cohort study database search

Study details	Study location USA Study setting Database of Multidisciplinary Melanoma Clinic Study dates January, 2005 to July, 2015
Inclusion criteria	Melanoma of 0.75-0.99mm thickness Underwent WLE Either underwent WLE or WLE + SLNB
Number of participants and recruitment methods	488 (205 WLE alone; 283 WLE + SLNB)
Outcome(s) of interest	Presence of nodal disease determined by SLNB (n=24) or regional nodal basin recurrences developed during follow-up (n=9), either in patients treated with WLE alone or treated with WLE plus had an initially negative SLNB. Only those determined by SLNB were included for the purposes of this review. *SLNB was considered for all patients based on Breslow depth 0.75-0.99 mm.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (45 or under versus >45 years) • Ulceration (present versus absent) • Mitosis (1 or less versus >1) • Lymphatic invasion (Present versus absent) *1.5.1 Defined as angiolymphatic invasion*
Covariates adjusted for in the multivariable regression modelling	Multivariate analysis performed using age, Breslow depth (<0.85 versus 0.85-1.00mm), mitotic rate and ulceration

Study-level characteristics

	Study (N = 488)
% Female	56.1
% positive SLNB	6.8
% Ulceration	3.7
% High mitotic rate group (see study characteristics for definition)	28.7
% Young age (see study characteristics for definition)	20.9
% Regression	25.2
% T1b (AJCC 8th)	74.8

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(SLNB routinely considered for participants meeting inclusion criteria of this study. However, additional factors are noted to increase propensity for receiving SLNB. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Outcome was the presence of nodal disease determined by SLNB or due to regional nodal recurrence during follow-up, in participants having undergone WLE alone. only 283/488 tumours underwent SLNB during study. It was possible to exclude recurrent events from the analysis for this review however for all predictors [except ulceration] the sample sizes had to be taken from the combined cohort [SLNB and WLE alone cohorts])*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Multivariate analysis was conducted which controlled for important confounders.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(data not available for specifically those participants who underwent SLNB)*
Overall risk of bias and directness	Risk of Bias	High *(Not all participants underwent SLNB. The overall sample sizes contains a mixture of participants with underwent SLNB and those who underwent WLE alone. Only positive nodes identified from SLNB were included in the univariate data analysis for this review however the multivariate analysis reported in the paper contains a mixture of both outcomes)*
	Directness	Directly applicable

Friedman, 2019

Bibliographic Reference	Friedman, Chloe; Lyon, Madison; Torphy, Robert J; Thieu, Daniel; Hosokawa, Patrick; Gonzalez, Rene; Lewis, Karl D; Medina, Theresa M; Rioth, Matthew J; Robinson, William A; Kounalakis, Nicole; McCarter, Martin D; Gleisner, Ana L; A nomogram to predict node positivity in patients with thin melanomas helps inform

shared patient decision making.; Journal of surgical oncology; 2019; vol. 120 (no. 7); 1276-1283

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected database
Study details	Study location USA Study setting The National Cancer Database (NCDB) is a joint program of the American College of Surgeons and the American Cancer Society.29 In2012, the NCDB began recording SLNB status. Study dates 2012-2015
Inclusion criteria	Melanoma confirmed diagnosis of thin (0.5-1.0 mm) cutaneous melanoma Underwent SLNB
Exclusion criteria	Known nodal disease metastatic disease Palliative surgery Neoadjuvant chemotherapy and/or radiation Unknown or inconsistent data on key variables
Number of participants and recruitment methods	10,108
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• age (<55 versus 55+) • Breslow thickness (0.50-0.80mm versus 0.80-1.00mm) • Mitotic rate (2+ versus <2) • Regression (Present versus absent) Clark level (1-3 versus 4-5) • Ulceration (present versus absent) • Tumour stage (AJCC 8th ed.) (T1a versus T1b)
Covariates adjusted for in the multivariable regression modelling	“In the subgroup that underwent a SLNB, the association between the different factors and a +SLN was similarly determined. Variables with significant univariate tests at the 0.25 alpha level were initially included in the model to predict a +SLN; those with significant global tests at the 0.05 alpha level, in the multivariable analysis, were retained in the final model, which was used for nomogram development. Age, BT, and MR were modelled using restricted cubic splines, to account for

	nonlinear effects (RCSs).” Model adjusted for age (entered as continuous variable), lymphovascular invasion, Breslow thickness (entered as continuous variable), Mitosis (entered as continuous variable), Clark level (I-II, III or IV-V, entered separately) and ulceration. Results of the multivariate model were used to create a nomogram, however this was not externally validated and did not provide data in an extractable format.

Study-level characteristics

	Study (N = 10,108)
% Female	46.6
Ethnicity	
% White	97.2
% Black	0.3
% Other	2.5
Tumour location	
% head and neck	15.9
% extremities	49.6
% Trunk	34.2
% positive SLNB	4.0
% Ulceration	8.0
% Breslow Thickness 0.8-1.0mm	67.8
% High mitotic rate group (see study characteristics for definition)	31.5
% T1b tumour stage (AJCC 8th)	70.9
% Young age (see study characteristics for definition)	41.2
% Clark level IV-V	54.7
% Regression	18.3

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(potential confounders for undergoing SLNB however multivariate model was conducted which adjusted for all relevant clinical characteristics)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only factors significant at level of 0.25 in univariate analysis were included in the multivariate model.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders. Multivariate model was conducted but the factors controlled for were not prespecified.)*
	Directness	Directly applicable

Han, 2012

Bibliographic Reference	Han D; Yu D; Zhao X; Marzban SS; Messina JL; Gonzalez RJ; Cruse CW; Sarnaik AA; Puleo C; Sondak VK; Zager JS; Sentinel node biopsy is indicated for thin melanomas ≥0.76 mm.; Annals of surgical oncology; 2012; vol. 19 (no. 11)

Study Characteristics

Study design	Retrospective cohort study review of patient data
Study details	Study location USA Study setting patients referred to Moffitt Cancer Center Study dates 2005-2010
Inclusion criteria	Melanoma

	thin melanomas, defined as primary tumor thickness of ≤1 mm Underwent SLNB had a SLNB or patients who did not have a SLNB at the time of primary excision but later developed a nodal recurrence (NR) as first site of recurrence. Only participants who underwent SLNB were included in this study. At Moffitt, SLNB is routinely performed for melanomas ≥0.76 mm and very selectively for thinner lesions based on findings of poor prognostic features (e.g. ulceration, extensive deep biopsy margin involvement, visible residual tumor present). MR ≥1/mm2 was not, absent other factors, considered sufficient to routinely recommend SLNB for melanomas <0.76 mm.
Number of participants and recruitment methods	288; 271 relevant to this review
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.76mm versus 0.76-1.00mm) • Ulceration (absent versus present) • Tumour infiltrating lymphocytes (brisk/non-brisk versus absent) • Mitotic rate per mm2 (<1 versus 1+) • age (<40 versus 40+ years old) • Regression
Covariates adjusted for in the multivariable regression modelling	Multiple logistic regression with the stepwise variable selection technique was adopted to select the most significant risk factors from a set of pre-defined potential risk factors, with the level of entry set at 0.10 and the level of stay set at 0.05.

Study-level characteristics

	Study (N = 271)
% Female	46.8
Median (Range) age *(years)*	55 (12-84)
Tumour location	
% head and neck	16.9
% trunk	37
% extremities	46.1
% positive SLNB	8.1
% Ulceration	6.6
% Breslow Thickness 0.8-1.0mm	87.8
% High mitotic rate group (see study characteristics for definition)	42.2
% Positive TIL (see study characteristics for definition)	69.2

	Study (N = 271)
% Young age (see study characteristics for definition)	15.9
% Clark level IV-V	61.9
% Regression	10.0

Quality Assessment

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(SLNB was routinely preformed in the cohort of patients with a Breslow thickness of 0.76-1.00mm but only performed in thinner melanomas in the presence of poor prognostic features such as ulceration. This will likely bias the results in favour of thinner melanomas for the comparison of Breslow thicknesses. However, most participants had 0.76-1.00mm melanomas and therefore the sample is likely to be representative of thin melanomas, with limited risk of bias for the evaluation of other predictors)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Multivariate modelling was conducted however this is not likely to have accounted for the confounders present in the Breslow thickness group comparison as this issue likely biased the univariate analysis)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low *(Note that for univariate analysis of Breslow thickness this study will be marked down once for risk of bias (moderate risk) due to the potential for confounders being greater for this comparison.)*
	Directness	Directly applicable

Han, 2013

Bibliographic Reference	Han D; Zager JS; Shyr Y; Chen H; Berry LD; Iyengar S; Djulbegovic M; Weber JL; Marzban SS; Sondak VK; Messina JL; Vetto JT; White RL; Pockaj B; Mozzillo N; Charney KJ; Avisar E; Krouse R; Kashani-Sabet M; Leong SP; Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2013; vol. 31 (no. 35)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Multinational (unclear which countries participated during time of data collection) Study setting review of sentinel lymph node working group database (international collaboration containing data from 30 institutions) Study dates 1994 - 2012
Inclusion criteria	Melanoma thin melanoma up to 1mm thickness Underwent SLNB
Number of participants and recruitment methods	1250
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.75mm versus 0.75-1.00mm) • Ulceration (present versus absent) • Mitotic rate per mm2 (<1 versus 1+) • Tumour infiltrating lymphocytes (brisk/non-brisk versus absent) • Clark level (1-3 versus 4-5) • Regression (present versus absent)
Covariates adjusted for in the multivariable regression modelling	2 Multiple logistic regression models: 1) adjusted for Breslow thickness (in 1mm increments), Clark level 4+, ulceration, absence of regression, mitotic rate per mm2 1+ 2) adjusted for Breslow thickness (75mm+), Clark level 4+, ulceration, absence of regression, mitotic rate per mm2 1+

Study-level characteristics

	Study (N = 1250)
% Female	47.4
Median (Range) age *(years)*	54.3 (12.5-90)
% positive SLNB	5.2

	Study (N = 1250)
% Ulceration	8.9
% Breslow Thickness 0.8-1.0mm	71.3
% High mitotic rate group (see study characteristics for definition)	50.2
% Positive TIL (see study characteristics for definition)	73.7
% Clark level IV-V	50.8
% Regression	22.6

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for giving SLNB and likely different between the different institutions providing data to the Sentinel lymph node working group. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Low of missing data for all prognostic variables except for mitotic rate and TILS. >20% of participants did not have available data for mitotic rate and TILs)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(multivariate model adjusted for various relevant clinical characteristics including Breslow thickness, ulceration, Clark level, regression and mitotic rate.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Study contained data from 30 different institutions. Although the study adjusted for several important clinical characteristics, this is unlikely to account for the propensity for receiving a SLNB and the protocol for giving SLNBs will differ between institutions. Data on mitotic rate and TILs was missing for a large number of participants.)*

Section	Question	Answer
	Directness	Directly applicable

Herbert, 2018

Bibliographic Reference	Herbert, Garth; Karakousis, Giorgos C; Bartlett, Edmund K; Zaheer, Salman; Graham, Danielle; Czerniecki, Brian J; Fraker, Douglas L; Ariyan, Charlotte; Coit, Daniel G; Brady, Mary S; Transected thin melanoma: Implications for sentinel lymph node staging.; Journal of surgical oncology; 2018; vol. 117 (no. 4); 567-571

Study Characteristics

Study design	Retrospective cohort study Review of prospectively maintained database
Study details	Study location USA Study setting Two centres: Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Pennsylvania (UPenn). Study dates between January 1995 and June 2014
Inclusion criteria	Melanoma Thin melanoma Underwent SLNB
Exclusion criteria	Found to have deeper (than 1mm) melanoma during excision
Number of participants and recruitment methods	1129
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Mitotic rate (1+ versus 0) *determined using the "hot spot" technique* Breslow depth (>0.75mm versus 0.75mm or less) Clark level (4 versus 2-3)
Covariates adjusted for in the multivariable regression modelling	The three prognostic factors outline above were entered into multivariate model along with Positive deep margin.

Study-level characteristics

	Study (N = 1129)
% Female	46.4
Mean age (SD)	52.2 (15.1)
Clark level	
II	6.8
III	33.7
IV	59.6
Mitotic rate *(per mm2)*	
None	34.1
1+	65.9
% positive SLNB	4.3

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for offering SLNB at study centres. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear protocol for offering SLNB)*
	Directness	Directly applicable

Isaksson, 2018

Bibliographic Reference	Isaksson, Karolin; Nielsen, Kari; Mikiver, Rasmus; Nieweg, Omgo E; Scolyer, Richard A; Thompson, John F; Ingvar, Christian; Sentinel lymph node biopsy in patients with thin melanomas: Frequency and predictors of metastasis based on analysis of two large international cohorts.; Journal of surgical oncology; 2018; vol. 118 (no. 4); 599-605

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected database
Study details	Study location Sweden and Australia Study setting information from two large melanoma registries: the Swedish national, population-based Melanoma Register (SMR) and the database of Melanoma Institute Australia (MIA), a single high-volume unit. Patients diagnosed with invasive melanoma in Sweden are registered in the SMR via the Information Network for Cancer Care (INCA) portal; the SMR coverage of the Swedish population data is nearly total (98% to 99%). At MIA all melanoma patients who present for management are asked to provide consent to have their management and follow-up details recorded in the MIA database, and the vast majority (>98%) agree to this request. Study dates 2009-2016
Inclusion criteria	Melanoma thin cutaneous melanomas (≥0.5 to ≤1.0 mm) Underwent SLNB
Number of participants and recruitment methods	1038
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (Median age or younger versus > median age)* ○ **median age 59 for Sweden cohort, 52 for Australia cohort* • Breslow thickness (<0.8mm versus 0.8-1.0mm) • Mitotic rate (1+ versus 0) • Ulceration (present versus absent) • Tumour stage (AJCC 8th ed.) (T1a versus T1b)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 1038)
% Female	51.3

	Study (N = 1038)
% positive SLNB	4.7
% Ulceration	15.6
% Breslow Thickness 0.8-1.0mm	75.5
% High mitotic rate group (see study characteristics for definition)	73.3
% Young age group (see study characteristics for definition)	51.7
% Tumour stage T1b (AJCC 8th)	80.3

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(No protocol for offering SLNB at study centres. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(no adjustment for confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders and not adjusted for)*
	Directness	Directly applicable

Jaber, 2011

Bibliographic Reference	Jaber JJ; Clark JI; Muzaffar K; Ruggiero FP; Feustel PJ; Frett MJ; Zender CA; Evolving treatment strategies in thin cutaneous head and neck melanoma: 1 institution's experience.; Head & neck; 2011; vol. 33 (no. 1)

Study Characteristics

Study design	Retrospective cohort study review of medical records
Study details	Study location USA Study setting Single medical centre, Illinois Study dates 2002-2008
Inclusion criteria	underwent surgical treatment Malignant melanoma of the head or neck 1 mm of less thickness No prior head or neck cancer no evidence of lymph node metastases no clinical or radiographic evidence of regional lymph node metastasis at initial presentation minimum follow-up of 6 months Underwent wide local excision and SLNB
Number of participants and recruitment methods	49 (38 relevant to this review)
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration: no participants had ulceration • Breslow thickness: less than 0.75mm versus 0.75mm • Mitotic rate: data not in extractable format • Clark level (1-3 versus 4-5)
Covariates adjusted for in the multivariable regression modelling	None

Study-level characteristics

	Study (N = 38)
% Female	39
% white ethnicity	100
Mean (range) age *(years)*	55 (37-79)
Mean (range) Breslow thickness *(mm)*	0.7 (0.3-1.0)

	Study (N = 38)
Mean (range) mitotic rate *(per mm2)*	1.4 (0-7)
% positive SLNB	5.3
% Ulceration	0
% Breslow Thickness 0.8-1.0mm	47.4
% Clark level IV-V	31.6

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(SLNB was not standard practice for all thin melanomas, reason for undergoing SLNB not accounted for. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(however note that data not extractable for mitotic rate as outcome as raw data not available and participants were not grouped into <1 versus 1+ per mm2.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(potential confounders not adjusted for.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Reason for undergoing SLNB was not adjusted for)*
	Directness	Directly applicable

Joyce, 2017

Bibliographic Reference	Joyce, K M; McInerney, N M; Piggott, R P; Martin, F; Jones, D M; Hussey, A J; Kerin, M J; Kelly, J L; Regan, P J; Analysis of sentinel node positivity in primary

cutaneous melanoma: an 8-year single institution experience.; Irish journal of medical science; 2017; vol. 186 (no. 4); 847-853

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Ireland Study setting Single hospital Study dates between January 2005 and December 2012.
Inclusion criteria	Melanoma Study included participants with melanoma of any thickness, only thin melanomas were included in this review (up to 1mm) Underwent SLNB underwent surgical treatment underwent definitive treatment (wide local excision) of their lesions who were without evidence of metastatic disease at the time of initial diagnosis.
Number of participants and recruitment methods	318; 65 relevant to this review
Outcome(s) of interest	SLNB positivity *SLNB was offered to patients with melanoma more than 1.00 mm in thickness and to patients with thin melanomas (<1.00 mm) and g*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Breslow thickness (<0.75mm versus 0.75-1.0mm) Mitotic rate (3+ versus 0-2) Clark level (1-3 versus 4-5) Ulceration (present versus absent)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 65)
% Female	53.8
Mean age	55.2
Tumour location	

	Study (N = 65)
head and neck	15.4
extremities	50.7
Trunk	33.8
% positive SLNB	1.5
% Ulceration	4.9
% Breslow Thickness 0.8-1.0mm	58.5
% High mitotic rate group (see study characteristics for definition)	8.9
% Clark level IV-V	33.8

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely given for thin melanomas at study centres unless patient also has additional risk factors. Sample is not likely to be representative of all thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(13.8% missing data for mitotic rate and Clark level)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No adjustment for confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders without adjustment. Moderate level of missing data for several predictive factors.)*
	Directness	Directly applicable

Kocsis, 2020

Bibliographic Reference	Kocsis, A.; Karsko, L.; Kurgyis, Z.; Besenyi, Z.; Pavics, L.; Dosa-Racz, E.; Kis, E.; Baltas, E.; Ocsai, H.; Varga, E.; Bende, B.; Varga, A.; Mohos, G.; Korom, I.; Varga, J.; Kemeny, L.; Nemeth, I.B.; Olah, J.; Is it Necessary to Perform Sentinel Lymph Node Biopsy in Thin Melanoma? A Retrospective Single Center Analysis; Pathology and Oncology Research; 2020; vol. 26 (no. 3); 1861-1868

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Hungary Study setting Single centre (The Department of Dermatology and Allergology, University of Szeged, is a regional centre for the management of cutaneous malignancies) Study dates between January 2011 and December 2014
Inclusion criteria	Melanoma pT1b according to AJCC 7th ed. Underwent SLNB Underwent WLE and SLNB
Number of participants and recruitment methods	78
Outcome(s) of interest	SLNB positivity *SLNB was offered to most eligible patients with pT1b (AJCC 7th ed.) melanomas as part of their surgical management in the absence of clinically evident nodal disease, or known distant metastases. SLNB was not advised if any sign of dissemination was detected in the case of high biological age, severe comorbidities or pregnancy.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• AJCC 8th ed. stage (pT1a vs. b) • ulceration (present v. absent) • age (<50 versus 50+) • Regression (Present versus absent)
Covariates adjusted for in the multivariable regression modelling	Multivariate logistic regression model of the clinicopathologic parameters: age, gender, mitosis, regression, Breslow, Clark

Study-level characteristics

	Study (N = 78)
% Female	56.4
Mean age (SD)	48.5
Tumour location	
% head and neck	5.1
% extremities	43.6
% Trunk	48.7
Other	2.6
Reclassified stage (AJCC 8th ed.)	
%pT1a	47.4
pT1b	52.6
% positive SLNB	11.5
% Ulceration	10.3
% Young age (see study characteristics for definition)	50
% Regression	37.2

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(SLNB offered to most pT1b patients)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(SLNB routinely offered to participants meeting inclusion criteria for study (pT1b) according to AJCC 7th edition). Additionally, multivariate analyiss was conducted including various important clinical characteristics.)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
	Directness	Directly applicable

Kunte, 2010

Bibliographic Reference	Kunte C; Geimer T; Baumert J; Konz B; Volkenandt M; Flaig M; Ruzicka T; Berking C; Schmid-Wendtner MH; Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma.; Melanoma research; 2010; vol. 20 (no. 4)

Study Characteristics

Study design	Prospective cohort study
Study details	Study location Germany Study setting Department of Dermatology and Allergology, University of Munich Study dates September 1996 and November 2007
Number of participants and recruitment methods	854: 147 had thin melanomas and were relevant to this review
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Breslow thickness (<0.75mm versus 0.75 - 1.00mm)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 147)
% positive SLNB	7.5
% Breslow Thickness 0.8-1.0mm	63.9

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(SLNB was not routinely performed for thin melanomas. author notes that most participants undergoing SLNB at study centre presented with cutaneous melanoma with a tumour thickness >1mm or with other risk factors, such as ulceration or regression of the primary melanoma and Clark level IV or V. Those participants with thin melanomas therefore had additional clinical features which warranted SLNB and are not representative of all thin melanomas)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(no adjustment for confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Confounders that are not adjusted for)*
	Directness	Directly applicable

Maurichi, 2020

Bibliographic Reference	Maurichi, A.; Miceli, R.; Eriksson, H.; Newton-Bishop, J.; Nsengimana, J.; Chan, M.; Hayes, A.J.; Heelan, K.; Adams, D.; Patuzzo, R.; Barretta, F.; Gallino, G.; Harwood, C.; Bergamaschi, D.; Bennett, D.; Lasithiotakis, K.; Ghiorzo, P.; Dalmasso, B.; Manganoni, A.; Consoli, F.; Mattavelli, I.; Barbieri, C.; Leva, A.; Cortinovis, U.; Espeli, V.; Mangas, C.; Quaglino, P.; Ribero, S.; Broganelli, P.; Pellacani, G.;

Longo, C.; Del Forno, C.; Borgognoni, L.; Sestini, S.; Pimpinelli, N.; Fortunato, S.; Chiarugi, A.; Nardini, P.; Morittu, E.; Florita, A.; Cossa, M.; Valeri, B.; Milione, M.; Pruneri, G.; Zoras, O.; Anichini, A.; Mortarini, R.; Santinami, M.; Factors affecting sentinel node metastasis in thin (T1) cutaneous melanomas: Development and external validation of a predictive nomogram; Journal of Clinical Oncology; 2020; vol. 38 (no. 14); 1591-1601

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Development cohort: Italy Validation cohort: Italy, Greece, UK, Switzerland, Sweden Study setting Validation cohort: Single centreDevelopment cohort: Regional Cancer Center, (Stockholm, Sweden; n = 672, 15.9%); University of Leeds,Queen Mary University of London, or Royal Marsden NationalHealth Service Trust (London, United Kingdom; n =623; 14.7%); Istituto Oncologico Svizzera Italiana (Bellinzona,Switzerland; n = 16, 0.4%); University Hospital ofHeraklion (Heraklion, Greece; n = 346, 8.2%); and UniversityHospitals of Brescia, Florence, Genoa, Modena,Pavia, Reggio Emilia, or Turin (Italy; n = 2,570; 60.8%). Study dates 2001 - 2018 Sources of funding Supported in part by Grants No. C588/A19167, C8216/A6129, andC588/A10721 from Cancer Research UK and by Grant No. CA83115from the US National Institutes of Health.
Inclusion criteria	Melanoma T1 melanoma (up to 1mm thickness) Underwent SLNB >18 years old
Number of participants and recruitment methods	Development cohort: 1635 Validation cohort: 1767
Outcome(s) of interest	SLNB positivity *Patients at study centres underwent SLNB because they were considered at high risk of occult nodal metastasis according to then-current [NCCN] guidelines. Criteria for SLNB did not change over the study period in either the development or validation cohort, and SNB was performed after discussing benefits and harms with the patient and obtaining informed consent.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (<50 versus 50+) • Breslow thickness (<0.8mm versus 0.8-1.0mm) • Mitotic rate (>1 versus 1 or less) • Ulceration (present versus absent) • Clark level (1-3 versus 4+) • Regression (Present versus absent)

	• Tumour invading lymphocytes (Brisk/nonbrisk versus absent) • Prognostic risk tool ○ developed using the development cohort and tested on the validation cohort. The tool contains the below factors: Mitotic rate, ulceration, lymphovascular invasion, regression, age at diagnosis and Breslow thickness.
Covariates adjusted for in the multivariable regression modelling	Methodology of nomogram development: "Briefly, a random forest procedure was applied to select development cohort variables for inclusion in a multiple binary logistic model to estimate the probability of SN positivity; the nomogram was elaborated from this model. Nomogram performance was assessed in the development cohort by a calibration plot as indicator of internal calibration, the Hosmer-Lemeshow test to evaluate goodness of fit, and Harrell's C statistic as a measure of discriminative ability. Nomogram performance was assessed in the validation cohort using the same methods as the development cohort, overall and in each country. The 16 patients from Bellinzona (Italian-speaking Switzerland) were grouped with Italian patients. Decision curve analyses were then applied to the development cohort to assess nomogram performance in comparison with other methods of selecting patients for SNB. The analyses were performed with SAS (version 9.2) and R software.

Study-level characteristics

	Development cohort N=1635 Validation cohort N =1767
% Female	
Development cohort	47.6
Validation cohort	48.2
Median (Range) age	
Development cohort	51 (18-80)
Validation cohort	53 (18-81)

	Development cohort N=1635 Validation cohort N =1767
Tumour location	
Head and neck	
Development cohort	18.6
Validation cohort	14.1
Extremities	
Development cohort	35.5
Validation cohort	38.7
Trunk	
Development cohort	45.9
Validation cohort	47.2
% positive SLNB	
Development cohort	6.6
Validation cohort	5.3
% Ulceration	
Development cohort	5.4
Validation cohort	4.5
% Breslow Thickness 0.8-1.0mm	
Development cohort	68.7
Validation cohort	75.1
% High mitotic rate group (see study characteristics for definition)	
Development cohort	23.9
Validation cohort	21.8

	Development cohort N=1635 Validation cohort N =1767
% Positive TIL (see study characteristics for definition)	
Development cohort	67.6
Validation cohort	72.6
% Young age (see study characteristics for definition)	
Development cohort	48.7
Validation cohort	47.4
% Clark level IV-V	
Development cohort	57.8
Validation cohort	52.1
% Regression	
Development cohort	26.4
Validation cohort	21.0

Quality assessment for main analysis

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias (SLNB was offered to those considered at high risk of occult nodal metastasis according to then-current NCCN guidelines. Participants are not representative of all thin melanomas)
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias

Section	Question	Answer
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Potential for confounders as SLNB was not routinely given to thin melanomas in the study centres. Development cohort underwent multivariate modelling which adjusted for various relevant clinical characteristics.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(to produce the nomogram, a random forest procedure was applied to select development cohort variables for inclusion in a multiple binary logistic model to estimate the probability of SN positivity. However, adjusted odds ratios for individual predictors is not provided. Additionally, raw data was taken from the validation cohort to investigate individual risk factors for the purpose of this review. This cohort did not undergo similar statistical tests)*
Overall risk of bias and directness	Risk of Bias	Moderate *(potential for confounders not adequately adjusted for)*
	Directness	Directly applicable

Maurichi, 2014

Bibliographic Reference	Maurichi, Andrea; Miceli, Rosalba; Camerini, Tiziana; Mariani, Luigi; Patuzzo, Roberto; Ruggeri, Roberta; Gallino, Gianfranco; Tolomio, Elena; Tragni, Gabrina; Valeri, Barbara; Anichini, Andrea; Mortarini, Roberta; Moglia, Daniele; Pellacani, Giovanni; Bassoli, Sara; Longo, Caterina; Quaglino, Pietro; Pimpinelli, Nicola; Borgognoni, Lorenzo; Bergamaschi, Daniele; Harwood, Catherine; Zoras, Odysseas; Santinami, Mario; Prediction of survival in patients with thin melanoma: results from a multi-institution study.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2014; vol. 32 (no. 23); 2479-85

Study Characteristics

Study design	Retrospective cohort study review of prospectively maintained databases
Study details	Study location Italy, UK and Greece Study setting 6 european centres Study dates 1996 through 2004
Inclusion criteria	Melanoma Breslow thicness 1mm or less. Underwent SLNB

Number of participants and recruitment methods	2,243, 792 underwent SLNB and were included in this review
Outcome(s) of interest	SLNB positivity *Treatment consisted of diagnostic excision with 1-to 2-mm margins followed by wider excision to achieve histologically confirmed 1-cm margins in healthy tissue. SNB was offered to high-risk patients, for which criteria were Breslow thickness 0.75 to 1.00 mm, MR one or more mitoses per square millimetre, presence of ulceration, presence of LVI, Clark level IV or V, and extensive regression. The benefits and risks of SNB were discussed with patients.* *Some patients asked for and received SNB, although the risk of occult nodal metastasis was low.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (50 or younger versus >50) • Ulceration (present versus absent) • Breslow thickness (<0.76mm versus 0.76-1.00mm) • Tumour infiltrating lymphocytes (present vs. absent) • Mitosis per mm2 (<1 versus 1+) • Clark level (2-3 versus 4) • Regression (Present versus absent)
Covariates adjusted for in the multivariable regression modelling	Multivariate analysis deemed not possible due to few positive SLNs

Study-level characteristics

	Study (N = 794)
% Female	52.1
Tumour location	
head and neck	19.5
extremities	39.9
Trunk	40.6
% positive SLNB	8.6
% Ulceration	53.0
% Breslow Thickness 0.8-1.0mm	58.2
% High mitotic rate group (see study characteristics for definition)	55.4

	Study (N = 794)
% Positive TIL (see study characteristics for definition)	55.5
% Young age (see study characteristics for definition)	68.4
% Clark level IV-V	53.4
% Regression	44.1

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely given to thin melanomas at study site unless additional clinical characteristics are present. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No adjustment for confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders and no adjustments made.)*
	Directness	Directly applicable *(Note. mitosis analysis marked down once for directness as study compared 1+ to <1 instead of 2+ to <2.)*

Mitteldorf, 2014

Bibliographic Reference	Mitteldorf C; Bertsch HP; Jung K; Thoms KM; Schön MP; Tronnier M; Kretschmer L; Sentinel node biopsy improves prognostic stratification in patients with thin

(pT1) melanomas and an additional risk factor.; Annals of surgical oncology; 2014; vol. 21 (no. 7)

Study Characteristics

Study design	Retrospective cohort study review of patient data
Study details	Study location Germany Study setting Department of Dermatology of the University of Gottingen Study dates November 1997 to July 2013
Inclusion criteria	Melanoma Thin melanoma (up to 1mm) Underwent SLNB
Number of participants and recruitment methods	207
Outcome(s) of interest	SLNB positivity *the indication for SLNB in thin melanoma requires at least one of the following additional risk factors: ulceration, Clark level IV, age 40 years or younger, mitosis C1, regression, and primary nodular or secondary nodular superficial spreading melanoma. All included participants had at least one of these additional features.*

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration (present versus absent)
	  ○ *defined as a complete defect of the epidermis, including the basement membrane.*
	• Age (<40 versus >40)
	• Breslow thickness (<0.76mm versus 0.76 - 1.00mm)
	• Mitotic rate (<1 versus 1+)
	  ○ *Unclear method of determining mitosis*
	• Clark level (4 versus 2-3)

Covariates adjusted for in the multivariable regression modelling	Age, Clark level, regression and mitoses were included in a multivariate regression model. Confidence intervals for multivariate analysis were not reported and therefore was not included in this review.

Study-level characteristics

	Study (N = 207)
% Female	51.7
% positive SLNB	18.4

	Study (N = 207)
% Ulceration	4.0
% Breslow Thickness 0.8-1.0mm	79.7
% High mitotic rate group (see study characteristics for definition)	58.4
% Young age (see study characteristics for definition)	27.1
% Clark level IV-V	43.3
% Regression	38.4

Quality assessment (for individual risk factors)

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(The study centre offered SLNB to people with thin melanomas with the presence of at least one clinical additional clinical factor indicative of poor prognosis, see study characteristics for more detail. It is unlikely that participants included in this study are representative of all people with thin melanoma.)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Multivariate model was conducted which contained several clinical factors which contributed to propensity for receiving SLNB. However, this is not likely to capture all confounding variables and Breslow thickness was not contained within this model.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounding variables not adequately adjusted for in multivariate analyses.)*
	Directness	Directly applicable

Quality assessment (for nomogram)

Section		Answer
Participant selection		Low risk of bias *(Nomogram was validated on a separate cohort of participants which was recruited from a larger number of centres than the development cohort)*
Predictors		Low risk of bias
Outcome		Low risk of bias
Sample size and participant flow		Low risk of bias
Analysis		Moderate risk of bias *(C-statistic given without confidence intervals)*
Overall risk of bias and directness	Risk of Bias	Moderate risk of bias
	Direcness	Directly applicable

Mori, 2013

Bibliographic Reference	Mori M; Sugiura M; Kono M; Matsumoto T; Sawada M; Yokota K; Yasue S; Shibata S; Sakakibara A; Nakamura S; Tomita Y; Akiyama M; Clinicopathologic analysis of 66 Japanese thin melanomas with metastasis of sentinel or regional lymph node.; Journal of cutaneous pathology; 2013; vol. 40 (no. 12)

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected database
Study details	Study location Japan Study setting Single hospital dermatology department Study dates 1998-2008
Inclusion criteria	Melanoma

	Clarks level 2-4 data relevant to this review was only available for participants in the Clarks level 2-4 cohort
Number of participants and recruitment methods	66: 13 underwent SLNB and were relevant to this review
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Breslow thickness (<0.75mm versus 0.75-1.00mm) Mitotic rate per mm2 (0 versus 1+) Tumour infiltrating lymphocytes (TIL) (none/slight versus intensely/non-intensely infiltrated)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 13)
% Female	58
Mean age (SD)	61
% positive SLNB	7.7
% Breslow Thickness 0.8-1.0mm	23.1
% High mitotic rate group (see study characteristics for definition)	7.7
% Positive TIL (see study characteristics for definition)	76.9
% Clark level IV-V	50.8
% Regression	22.6

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely performed for thin melanomas. Likely that those participants undergoing SLNB are not representative of all thin melanomas. It is unlikely that*

Section	Question	Answer
		participants included in this study are representative of all people with thin melanoma)
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No adjustment for confounders (such as factors making a SLNB more likely to be conducted))*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(data on prognostic factors of interest are only reported for the Clark 2-4 cohort)*
Overall risk of bias and directness	Risk of Bias	Moderate *(No adjustment for confounders and data only available for Clark level 2-4 cohort)*
	Directness	Directly applicable

Mozzillo, 2013

Bibliographic Reference	Mozzillo N; Pennacchioli E; Gandini S; Caracò C; Crispo A; Botti G; Lastoria S; Barberis M; Verrecchia F; Testori A; Sentinel node biopsy in thin and thick melanoma.; Annals of surgical oncology; 2013; vol. 20 (no. 8)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Italy Study setting 2 centres (Milan and Naples) Study dates 1998-2011
Inclusion criteria	Melanoma diagnosed with either a thin (<1 mm) or thick (4 mm+) melanoma (only thin melanomas extracted for this review). Underwent SLNB

Number of participants and recruitment methods	492; 423 relevant to this review
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Mitotic rate per mm2 (0 versus 1+) *Event data for mitotic rate was back calculated. Number of participants with 1+ reported and 9% had a positive SLNB. Number of participants with 0 not reported. It is noted that 4 participants had a positive SLNB and that this represented 2% of participants with a mitotic rate of 0 therefore a sample size of 200 is assumed.* *adjusted odds ratio also provided*
Covariates adjusted for in the multivariable regression modelling	multivariate model adjusted for age and sex

Study-level characteristics

	Study (N = 423)
% Female	58
Tumour location	
% Head and neck	4
% Extremities	46
% Trunk	50
Clark level	
% II	23
% III	53
% IV	19
% positive SLNB	5.7
% High mitotic rate group (see study characteristics for definition)	52.7

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(unclear protocol for offering SLNBs for thin melanomas at the centres involved in the study. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(Unclear level of missing data for key prognostic variables)*
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Event data not available for several prognostic factors (only multivariate data). It was possible to calculate mitotic rate event data but has the assumption that there was no missing data.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Multivariate model adjusted for age and sex however this does not capture all cofounding variables (such as clinical characteristics which make a person with a thin melanoma more likely to undergo SLNB).)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High *(Limited data reporting of event data. Unclear level of missing data. Multivariate model will be marked as moderate risk of bias).*
	Directness	Directly applicable

Murali, 2012

Bibliographic Reference	Murali R; Haydu LE; Quinn MJ; Saw RP; Shannon K; Spillane AJ; Stretch JR; Thompson JF; Scolyer RA; Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma.; Annals of surgery; 2012; vol. 255 (no. 1)

Study Characteristics

Study design	Retrospective cohort study review of patient database
Study details	Study location Australia Study setting Melanoma Institute Australia

	Study dates 1992 - 2009
Inclusion criteria	Melanoma diagnosed with a single thin primary cutaneous melanoma (1mm or less) Underwent SLNB author notes that at the centre in which the study is conducted SLNB is routinely offered (to patients with melanoma more than 1.00 mm in thickness and to patients with thin melanomas (≤1.00 mm) if they are considered at significant risk of metastasis, criteria for which include primary melanoma characteristics such as presence of ulceration, high mitotic rate (MR), or Clark level IV or V invasion. Other factors that contributed to recommendations regarding SLNB in selected cases included patient age, tumor location, and patient comorbidities.)
Number of participants and recruitment methods	432
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.76mm versus 0.76 to 1.00mm) ○ *data also available for the following cohorts: 0.50mm or less, 0.51-0.75mm, 0.76-0.90mm, 0.91-1.00mm* • Age (50 years or less versus >50 years old) • Mitosis (absent versus present) • Ulceration (absent versus present)

Study-level characteristics

	Study (N = 432)
% Female	47.7
Median (Range) age *(years)*	49.5 (14.4 – 85)
% positive SLNB	6.7
% Ulceration	5.6
% Breslow Thickness 0.8-1.0mm	73.1
% High mitotic rate group (see study characteristics for definition)	67.0
% Young age (see study characteristics for definition)	52.8
% Clark level IV-V	41.9

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(SLNB was only routinely offer to patients with thin melanomas*

Section	Question	Answer
		(≤1.00 mm) if they are considered at significant risk of metastasis, criteria for which include primary melanoma characteristics such as presence of ulceration, high mitotic rate (MR), or Clark level IV or V invasion, or if other factors contributed to recommendations regarding SLNB in selected cases such as patient age, tumour location, and patient comorbidities. It is unlikely that participants included in this study are representative of all people with thin melanoma)
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(confounding variables (such as presence of factors contributing to likelihood of being referred for SLNB) not adjusted for.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders, not adjusted for)*
	Directness	Directly applicable

Nahabedian, 2003

Bibliographic Reference	Nahabedian MY; Tufaro AP; Manson PN; Sentinel lymph node biopsy for the T1 (thin) melanoma: is it necessary?; Annals of plastic surgery; 2003; vol. 50 (no. 6)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Johns Hopkins Study dates

	June 1997 to November 2000
Inclusion criteria	Melanoma Stage 1 and T1 melanoma Clark level 3-4
Number of participants and recruitment methods	24
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness: (<0.75mm versus 0.75-1.00mm) • Ulceration (present versus absent) • Age (<45 years versus 45 years+) • Clark level (1-3 versus 4-5) • Regression (present versus absent) *individual data presented therefore alternative cut offs possible.*
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N =)
% Female	45.8
Mean (range) age *(years)*	47.6 (23-88)
% positive SLNB	8.3
% Ulceration	4.2
% Breslow Thickness 0.8-1.0mm	45.8
% Young age (see study characteristics for definition)	45.8
% Clark level IV-V	33.3
% Regression	8.3

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB and only Clark level 3-*

Section	Question	Answer
		4 included. It is unlikely that participants included in this study are representative of all people with thin melanoma)
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No adjustment for confounders (such as clinical factors which make person more likely to undergo SLNB). However sample size is small and raw data is available for each participant including data on some important clinical variables (such as Clark level, ulceration, age and regression.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear protocol for undergoing SLNB and only Clark level 3-4 included.)*
	Directness	Directly applicable

Oliveira Filho, 2003

Bibliographic Reference Oliveira Filho RS; Ferreira LM; Biasi LJ; Enokihara MM; Paiva GR; Wagner J; Vertical growth phase and positive sentinel node in thin melanoma.; Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas; 2003; vol. 36 (no. 3)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location Brazil Study setting Single centre Study dates June 1997 and January 2002,
Inclusion criteria	Melanoma clinically localized cutaneous melanoma up to 1mm in depth

	Underwent SLNB
Number of participants and recruitment methods	77
Outcome(s) of interest	SLNB positivity *defined by paper as sentinel node micrometastases*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Clark level (III versus IV) • Mitotic rate (>5 versus less than 5 or less) • Ulceration (absent versus present) • Regression (present versus absent)
Covariates adjusted for in the multivariable regression modelling	None

Study-level characteristics

	Study (N =)
% Female	55.8
Tumour location	
% Head and neck	18.2
% Extremities	35.1
% Trunk	46.8
% positive SLNB	7.8
% Ulceration	22.1
% High mitotic rate group (see study characteristics for definition)	29.8
% Clark level IV-V	51.9
% Regression	19.5

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for offering SLNB at study hospital. It is likely that higher risk patients are overrepresented. It is*

Section	Question	Answer
		unlikely that participants included in this study are representative of all people with thin melanoma)
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No adjustments for confounding variables)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(potential for confounders which were not adjusted for)*
	Directness	Directly applicable *(Note: Indirectly applicable for mitotic rate analysis as the comparison is between those with a rate of 5+ per mm2 compared to those with 5 or less, representing a much more severe cohort than analysis conducted in this review)*

Piazzalunga, 2019

Bibliographic Reference Piazzalunga, Dario; Ceresoli, Marco; Allievi, Niccolo; Ribero, Simone; Quaglino, Pietro; Di Lorenzo, Sara; Corradino, Bartolo; Campana, Luca Giovanni; Mocellin, Simone; Rossi, Carlo Riccardo; IMI (Italian Melanoma, Intergroup); Can sentinel node biopsy be safely omitted in thin melanoma? Risk factor analysis of 1272 multicenter prospective cases.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2019; vol. 45 (no. 5); 820-824

Study Characteristics

Study design	Retrospective cohort study retrospective analysis of prospectively collected data
Study details	Study location Italy Study setting 4 centres Study dates

	1998 - 2017
Inclusion criteria	Melanoma Thin melanoma Underwent SLNB
Number of participants and recruitment methods	1196
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Clark level (1-3 versus 4-5) • Breslow thickness (<0.75mm versus >0.75mm) • Ulceration (present versus absent) • Mitosis (>1 versus absent)
Covariates adjusted for in the multivariable regression modelling	Significant predictors in univariate model were entered into multivariate model (Breslow thickness (categorical and continuous) and ulceration

Study-level characteristics

	Study (N =)
% Female	51.7
Mean age (SD)	50.9 (14.5)
Tumour site	
% Head and neck	4.3
% Extremities	44.2
% Trunk	51.5
% positive SLNB	6.0
% Ulceration	4.0
% Breslow Thickness 0.8-1.0mm	42.8
% High mitotic rate group (see study characteristics for definition)	67.0
% Clark level IV-V	19.2

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for offering SLNB and the 4 study centres. Study took place between 1998 and 2017, covering 4 editions of the AJCC (5th-8th editions) meaning that the participants contained in this study will likely represent very different cohorts both over time and compared to all people with thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Unclear categorisation of mitotic rate (likely that absent refers to a rate of 1 or less))*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Multivariate model conducted but only included ulceration and Breslow thickness)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Moderate risk of bias *(Only significant predictors were entered into multivariate model)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear protocol for giving SLNB with study taking place over 19 years. Multivariate model not adequately conducted.)*
	Directness	Directly applicable

Ranieri, 2006

Bibliographic Reference Ranieri JM; Wagner JD; Wenck S; Johnson CS; Coleman JJ; The prognostic importance of sentinel lymph node biopsy in thin melanoma.; Annals of surgical oncology; 2006; vol. 13 (no. 7)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Review of Indiana University Interdisciplinary Melanoma Program computerized database Study dates

	1994-2003
Inclusion criteria	Melanoma clinically localized melanoma (1 mm or less) Underwent SLNB
Number of participants and recruitment methods	184
Outcome(s) of interest	SLNB positivity

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.75 versus 0.75-1.00mm)
	• Ulceration (present versus absent)
	  ○ *data also available for participants with 0.75-1.00mm melanomas*
	• Mitotic rate per mm2 (>2 versus 2 or less)
	  ○ *data also available for participants with 0.75-1.00mm melanomas*
	• Clark level (2-3 versus 4)
	  ○ *data also available for participants with 0.75-1.00mm melanomas*
	• Regression (Present versus absent)

Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 184)
% positive SLNB	6.5
% Ulceration	5.1
% Breslow Thickness 0.8-1.0mm	53.3
% High mitotic rate group (see study characteristics for definition)	10.4
% Clark level IV-V	36.3
% Regression	17.1

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB at study centre. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Note high risk for mitotic rate (>20% of participants with missing data) and moderate risk for ulceration (10-20% of missing data for this outcome))*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Did not adjust for confounders however data were available for predicting specifically in the cohort of patients with 0.75mm-1.00mm thick melanomas.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders that were not adjusted for. Attrition bias for ulceration and mitotic rate predictors.)*
	Directness	Directly applicable *(Note. Indirectly applicable for mitotic rate analysis as study only provided data on mitotic rate of 2 or less per mm2 and over 2 per mm2.)*

Santos, 2019

Bibliographic Reference Santos, Fernando De Marco Dos; Silva, Felipe Correa da; Pedron, Julia; Furian, Roque Domingos; Fortes, Cristina; Bonamigo, Renan Rangel; Association between tumor-infiltrating lymphocytes and sentinel lymph node positivity in thin melanoma.; Anais brasileiros de dermatologia; 2019; vol. 94 (no. 1); 47-51

Study Characteristics

Study design	Retrospective cohort study Cross sectional study
Study details	Study location Brazil Study setting data registered between 2003 and 2015

	Study dates data registered between 2003 and 2015 Sources of funding none
Inclusion criteria	Melanoma Cases with invasive lesions ≤1mm, with no clinical lymph node involvement Underwent SLNB
Number of participants and recruitment methods	137
Outcome(s) of interest	SLNB positivity *The following factors were listed as indications for SLNB: presence of ulceration, mitosis, thickness more than 0.75mm, regression*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Clark index (1-2 versus 3-5) • Breslow thickness (<0.76m versus 0.76-1.00mm) • Tumour infiltrating lymphocytes (negative/few versus moderate/marked) • Ulceration (absent versus present) • Mitosis (present versus absent) • Regression (Present versus absent)
Covariates adjusted for in the multivariable regression modelling	Sex, Clark, Regression, Ulceration and TIL entered into multivariate regression

Study-level characteristics

	Study (N = 137)
% Female	56.2
Mean age (SD)	53
Tumour location *(%)*	
% Head and neck	8.8
% Extremities	37.2
% Trunk	48.9
% Other	5.1
% positive SLNB	7.3

	Study (N = 137)
% Ulceration	1.5
% Breslow Thickness 0.8-1.0mm	40.9
% High mitotic rate group (see study characteristics for definition)	80.3
% Positive TIL (see study characteristics for definition)	64.2
% Clark level IV-V	24.8
% Regression	57.7

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely given to people with thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Circumstances under which SLNB would be offered to patients with thin melanomas are given. Multivariate analysis was conducted including several of these factors however some important clinical variables were not included (Breslow thickness, mitosis).)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders not fully adjusted for.)*
	Directness	Directly applicable *(Note. Mitotic analysis will be marked down once for*

Section	Question	Answer
		directness as this study only looked at present versus absent (unclear definition and not matching protocol).)

Skochdopole, 2020

Bibliographic Reference	Skochdopole, A.J.; Kutlu, O.C.; Engelhardt, K.E.; Abbott, A.M.; Camp, E.R.; High Mitotic Rate Predicts Sentinel Lymph Node Involvement in Thin Melanomas; Journal of Surgical Research; 2020; vol. 256; 198-205

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting the SEER database, a cancer registry designed to represent the U S population through targeted sampling. The SEER program is an epidemiologic surveillance system sponsored by the National Cancer Institute. The registry represents approximately 25% of the U S population from a variety of sociodemographic and geographic regions meant to purposively sample cases to create a nationally representative database. Study dates 2010-2013 Sources of funding no funding
Inclusion criteria	Melanoma thin melanoma Underwent SLNB
Number of participants and recruitment methods	4332
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow depth (<0.75mm versus 0.75-1.0mm) • Mitotic rate (4+ versus <4) • Tumour stage (AJCC 8th) (T1a versus T1b)
Covariates adjusted for in the multivariable regression modelling	Multivariable binary logistic regression analyses were performed correcting for age, sex, race, MR, ulceration, location of the tumor (trunk, upper, and lower extremity), and tumor depth to identify the factors affecting nodal positivity and the impact of MR. This was performed separately for the entire

	cohort, for tumor depth <0.75mm and 0.75-1.00mm, and for SLN negative and SLN positive groups. A cut-off of 0.75mmwas selected for this study to reflect the most recent AJCC staging guidelines. In the eighth edition, T1b melanoma is defined as ranging in depth from 0.8mm to 1.0 mm; specified thickness is rounded to the nearest one-tenth of a millimetre (e.g., 0.75 mm rounds to 0.8 mm).

Study-level characteristics

	Study (N = 4332)
% Female	48.2
Median age (range)	55.6 (18-85)
Tumour location	
% Extremities	60.5
% Trunk	39.5
Ethnicity	
% White	98.0
% Black	0.3
% Other	1.7
% positive SLNB	5.3
% Breslow Thickness 0.8-1.0mm	50.4
% High mitotic rate group (see study characteristics for definition)	10.4
% Tumour stage 1b (AJCC 8th)	48.6

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB at study centre(s). People with head and neck tumours were excluded.)*
Study Attrition	Study Attrition Summary	Low risk of bias

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	High risk of bias *(Study provided an exploratory analysis of how mitotic rate affects SLNB positivity, cut off points for which data are provided represent optimal predictive value and were not pre-specified.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(adjusted for various important confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	High (Potential for confounders. Mitotic rate dichotomy was not prespecified and data used for this review represents the optimal cut-off points from the data used in the present study. Other predictors and multivariate analyses will be marked as moderate risk of bias)
	Directness	Directly applicable

Statius Muller, 2001

Bibliographic Reference	Statius Muller MG; van Leeuwen PA; van Diest PJ; Vuylsteke RJ; Pijpers R; Meijer S; No indication for performing sentinel node biopsy in melanoma patients with a Breslow thickness of less than 0.9 mm.; Melanoma research; 2001; vol. 11 (no. 3)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location The Netherlands Study setting Single medical centre, Amsterdam Study dates August 1993 and September 1999 Sources of funding none reported
Inclusion criteria	Melanoma proven clinical stage I (AJCC stages I and II) cutaneous melanoma with a Breslow thickness exceeding 0.5 mm

Number of participants and recruitment methods	349: 104 with thin melanomas and relevant to this review
Outcome(s) of interest	SLNB positivity *In all patients the triple technique was used, consisting of preoperative visualization of the lymph channels from the initial site of the melanoma towards the SN by (dynamic) LS, intraoperative visualization of those particular lymph channels and nodes with blue dye, and a gamma probe to measure accumulated radioactivity in radiolabelled lymph nodes.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Breslow thickness (0.50 - 0.89mm versus 0.90-1.00mm)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 104)
% positive SLNB	13.0
% Breslow Thickness 0.8-1.0mm	53.7

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	Low risk of bias *(SLNB was routinely performed on participants with a thickness over 0.5mm referred to institution.)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No adjustment for confounding variables. It is possible that the reason for referral represented a confounding factor however as SLNB were routinely performed on melanomas*

Section	Question	Answer
		with a thickness of 0.50mm at the centre in which the study was conducted, this is not likely to be a major cause for concern.)
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
	Directness	Directly applicable

Stitzenberg, 2004

Bibliographic Reference	Stitzenberg KB; Groben PA; Stern SL; Thomas NE; Hensing TA; Sansbury LB; Ollila DW; Indications for lymphatic mapping and sentinel lymphadenectomy in patients with thin melanoma (Breslow thickness < or =1.0 mm).; Annals of surgical oncology; 2004; vol. 11 (no. 10)

tudy Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting Single centre Study dates January 1998 – January 2004
Inclusion criteria	Melanoma Thin melanomas up to 1mm Underwent SLNB
Number of participants and recruitment methods	146
Outcome(s) of interest	SLNB *all patients* *with a primary melanoma of Breslow thickness 0.75 or greater* *mm and no evidence of nodal or distant metastases on* *clinical examination were offered SLNB at study centre. <0.75 mm were* *offered LM/SL only if one of the* *following criteria was met: Clark's level IV or V, ulceration,* *regression, or patient demand.*

Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Clarks level (1-3 versus 4-5) Ulceration (present versus absent)
Covariates adjusted for in the multivariable regression modelling	All univariate factors were entered into a multivariate model (gender, primary site, Clark level, regression, race, ulceration. None were significant predictors in either model.

Study-level characteristics

	Study (N = 146)
% Female	39.8
Ethnicity	
% White	92.8
% Black	1.7
% Asian	0.6
% Other	4.9
Tumour location	
% Head and neck	21.2
% Extremities	41.8
% Trunk	35
Other	2
% positive SLNB	4.3
% Ulceration	2.9
% Clark level IV-V	23.4

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	Moderate risk of bias *(0.75mm-1.00mm cohort were routinely offered SLNB at study centre. Those <0.75mm were offered SLNB if additional factors were present. It is unlikely that participants included in this study are representative of all people with thin melanoma)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Multivariate model was conducted which controlled for various clinical factors which influenced decision to offer SLNB to people with <0.75mm melanomas)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Low
	Directness	Directly applicable

Subramanaian, 2021

Bibliographic Reference Subramanian, S., Han, G., Olson, N., Leong, S. P., Kashani-Sabet, M., White, R. L., ... & Han, D. (2021). Regression is significantly associated with outcomes for patients with melanoma. *Surgery*

Study Characteristics

Study design	Retrospective cohort study review of data from the Sentinel Lymph Node Working Group database
Study details	Study location USA Study dates 1993-2018
Inclusion criteria	Melanoma known regression status and known SLN status from 1993 to 2018 ≥18 years old
Number of participants and	4,790

recruitment methods	
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (continuous) • Breslow thickness (continuous) • Ulceration
Covariates adjusted for in the multivariable regression modelling	• Age • Sex • Breslow thickness • Ulceration • Primary site • Microsatellites • LVI • Regression

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB at the study centres. Risk factors are likely to be comorbid. Participant characteristics are not presented for those patients with thin melanomas)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Adjusted for numerous important clinical confounders however only significant predictors after adjustment were reported.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(limited reporting of results and study characteristics relevant to this review.)*

Section	Question	Answer
	Directness	Directly applicable

Tejera-Vaquerizo, 2017

Bibliographic Reference	Tejera-Vaquerizo, A; Perez-Cabello, G; Marinez-Leborans, L; Gallego, E; Oliver-Martinez, V; Martin-Cuevas, P; Arias-Santiago, S; Aneiros-Fernandez, J; Herrera-Acosta, E; Traves, V; Herrera-Ceballos, E; Nagore, E; Is mitotic rate still useful in the management of patients with thin melanoma?.; Journal of the European Academy of Dermatology and Venereology : JEADV; 2017; vol. 31 (no. 12); 2025-2029

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected database
Study details	Study location Spain Study setting 4 Spanish hospitals Study dates 2000-2014 IVO database between January 1, 2000 and December 31, 2014, in the HVV database between October 1, 2001 and December 31, 2014, in the HVN database between January 1, 2012 and December 31, 2014, or in the HGUV database between January 1, 2006 and December 31, 2014.
Inclusion criteria	Melanoma patients with a single cutaneous melanoma with a thickness of ≤1 mm Underwent SLNB Entered prospectively into database
Exclusion criteria	unknown mitotic rate
Number of participants and recruitment methods	203
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (>65 versus 65 or younger) • Tumour stage (AJCC 8th ed.) T1a versus T1b • Mitotic rate (1+ versus 0) • Regression (Present versus absent)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 203)
% Female	57.6
% positive SLNB	6.5
% High mitotic rate group (see study characteristics for definition)	28.6
% Young age (see study characteristics for definition)	75.2
% Regression	30.8

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for offering SLNB. Study period was over 14 years and the protocol for giving SLNB likely changed over this time. Participants without mitotic rate on record were excluded from the study. Other studies show that mitotic rate is often not recorded and therefore many participants which could provide data on other variables are likely to have been missed. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(No adjustment for confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of confounding variables and no multivariate model conducted to account for these.)*
	Directness	Directly applicable

Tejera-Vaquerizo, 2019

Bibliographic Reference	Tejera-Vaquerizo, Antonio; Ribero, Simone; Puig, Susana; Boada, Aram; Paradela, Sabela; Moreno-Ramirez, David; Canueto, Javier; de Unamuno, Blanca; Brinca, Ana; Descalzo-Gallego, Miguel A; Osella-Abate, Simona; Cassoni, Paola; Carrera, Cristina; Vidal-Sicart, Sergi; Bennassar, Antoni; Rull, Ramon; Alos, Llucia; Requena, Celia; Bolumar, Isidro; Traves, Victor; Pla, Angel; Fernandez-Orland, A; Jaka, Ane; Fernandez-Figueres, Maria T; Hilari, Josep M; Gimenez-Xavier, Pol; Vieira, Ricardo; Botella-Estrada, Rafael; Roman-Curto, Concepcion; Ferrandiz, Lara; Iglesias-Pena, Nicolas; Ferrandiz, Carlos; Malvehy, Josep; Quaglino, Pietro; Nagore, Eduardo; SENTIMEL, group; Survival analysis and sentinel lymph node status in thin cutaneous melanoma: A multicenter observational study.; Cancer medicine; 2019; vol. 8 (no. 9); 4235-4244

Study Characteristics

Study design	Retrospective cohort study review of prospectively collected database
Study details	Study location Spain, Portugal and Italy Study setting 9 hospitals (7 in Spain, 1 in Portugal and 1 in Italy) Study dates Patients registered in any of the databases January 1, 1998 up to December 31, 2016
Inclusion criteria	Melanoma solitary localized melanoma, without evidence of metastasis at diagnosis with a thickness of 1 mm or less >18 years old Entered prospectively into database
Number of participants and recruitment methods	1090
Outcome(s) of interest	SLNB positivity *notes that participants only began undergoing SLNB due to being at risk of regional lymphatic metastases in 1998. Therefore prior cases were excluded.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Mitotic rate (0/1 versus 2+) ○ *evaluated using the hot spot method, which consists of identifying the area of the dermis with the highest number of mitotic figures and counting the mitoses in adjacent fields until an area of 1 mm2 is reached. reported as 0, 1, 2 or >2.* • Clark level (2-3 versus 4-5) • Ulceration (present versus absent) • Breslow thickness (<0.8mm versus 0.8-1.0mm) *Note. Event data only available for mitotic rate. Odds ratios provided for other variables but total number of participants in each comparison group is not reported.*

Covariates adjusted for in the multivariable regression modelling	adjusted for all study variables (age, sex, tumour location, Breslow thickness, ulceration, mitotic rate, regression, Clark level, histologic subtype, lymphovascular invasion) however odds ratio data only given for significant variables (mitotic rate).

Study-level characteristics

	Study (N = 480)
% positive SLNB	7.7
% High mitotic rate group (see study characteristics for definition)	30.8

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for offering SLNB. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	High risk of bias *(Only 713/1090 participants had mitotic rate data available)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(Potential for confounders however multivariate model adjusted for numerous important clinical characteristics.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Low risk of bias for mitotic rate however note that data for other predictors was not extractable due to limited reporting)*
Overall risk of bias and directness	Risk of Bias	Moderate *(High attrition rate. Potential for confounders however this was likely adequately adjusted for in multivariate model. Limited reporting for most predictive variables.)*
	Directness	Directly applicable

Theile, 2020

Bibliographic Reference	Theile, H.; Moore, J.; Dunn, N.; Cossio, D.; Forristal, C.E.; Green, A.C.; Smithers, B.M.; Regional nodal metastasis and 5-year survival in patients with thin melanoma in Queensland: a population-based study; ANZ journal of surgery; 2020; vol. 90 (no. 4); 503-507

Study Characteristics

Study design	Retrospective cohort study Database review
Study details	Study location Australia Study setting histology reports from the Queensland Cancer Register and Queensland Hospital Admitted Patient Data Collection, matched to the patient's management across all hospitals in Queensland. Study dates 1 January 2001 to 31 December 2015
Inclusion criteria	Melanoma Thin melanoma Underwent SLNB
Number of participants and recruitment methods	240
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.8 versus 0.8-1.0mm) • Ulceration (present versus absent) • T stage AJCC 8th ed. (T1a versus T1b)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 240)
% positive SLNB	5.8
% Ulceration	10.4
% Breslow thickness (0.8-1.0mm)	65.8
% Tumour stage 1b (AJCC 8th)	69.2

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB. Study conducted over long period (2001-2015) meaning that the indication for offering SLNB will have differed over time and are unlikely to be representative of all people with thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No adjustment for confounders. However, data used in study were reclassified according to AJCC (8th ed.) tumour stage, with breakdown by breslow thickness. This will likely allow for a comparison of participants with more homogenous clinical characteristics)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(potential for confounders not controlled for.)*
	Directness	Directly applicable

Venna, 2013

Bibliographic Reference	Venna SS; Thummala S; Nosrati M; Leong SP; Miller JR; Sagebiel RW; Kashani-Sabet M; Analysis of sentinel lymph node positivity in patients with thin primary melanoma.; Journal of the American Academy of Dermatology; 2013; vol. 68 (no. 4)

Study Characteristics

Study design	Retrospective cohort study
Study details	Study location USA Study setting single centre

	Study dates 1994-2007 Sources of funding none
Inclusion criteria	Melanoma thin melanomas (defined as #1.0 mm) and high-risk histologic features Underwent SLNB Thin melanomas with high risk histological features were routinely offered SLNB in additoin to standard re-excision of the primary site
Number of participants and recruitment methods	484
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness: <0.8mm versus 0.8mm+ • Ulceration: Absent versus present • Mitotic rate per mm2: <1 versus 1+ per • age: 43 years or younger versus 44 years+ • Lymphovascular invasion: Study reported “vascular involvement” defined as “presence of vascular involvement defined as vascular invasion with tumor cells within blood or lymphatic vessels; or uncertain vascular invasion, with melanoma cells immediately adjacent to the endothelium.”
Covariates adjusted for in the multivariable regression modelling	Univariate model included: TILs, age, Breslow thickness, tumour location, Clark level, tumour vascularity, mitotic rate, vascular involvement, sex and ulceration. However, confidence intervals were not reported and therefore these data were not extracted for this review. Significant predictors were entered into a multivariate model (TILs, age, location and thickness)

Study-level characteristics

	Study (N = 484)
% Female	45
Mean age (SD)	52.2
Tumour location	
% head and neck	19.6
% lower extremity	16.7
% upper extremity	19.8

	Study (N = 484)
% trunk	43.8
% positive SLNB	7.0
% Ulceration	14.2
% Breslow Thickness 0.8-1.0mm	63.4
% High mitotic rate group (see study characteristics for definition)	72.7
% Positive TIL (see study characteristics for definition)	24.3
% Young age (see study characteristics for definition)	28.3
% Clark level IV-V	40.5

Quality assessment

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(People with thin melanomas and high risk histologic features were routinely offered SLNB. It is unclear how representative this cohort is of all people with thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias *(note that there is a high risk of bias for the following prognostic factors due to limited data available: Mitotic rate, ulceration and TILs)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Low risk of bias *(high risk histological features likely represent confounding factors however various histological features (Breslow depth, Clark level, ulceration, MR, tumor vascularity, vascular involvement, and TILs) were entered into univariate analysis, with significant predictors of SLNB being entered into a multivariate model.)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(SLNB routinely given to high histological risk patients with thin melanomas. As various histological factors were controlled for in regression analysis and therefore multivariate analysis will not be marked down for risk of bias)*
	Directness	Directly applicable *(However, note that for the meta-analysis, data on Breslow thickness from this study will be marked down once for indirectness as use of the AJCC8 would mean that 0.75mm melanomas are grouped into the 0.8mm+ category (due to rounding) but this study (seemingly) only included 0.80mm+ in this group.)*

Vermeeren, 2010

Bibliographic Reference Vermeeren L; Van der Ent F; Sastrowijoto P; Hulsewé K; Sentinel lymph node biopsy in patients with thin melanoma: occurrence of nodal metastases and its prognostic value.; European journal of dermatology : EJD; 2010; vol. 20 (no. 1)

Study Characteristics

Study design	Retrospective cohort study review of prospective database
Study details	Study location The Netherlands Study setting Single hospital Study dates January 1994 - August 2007
Inclusion criteria	Melanoma thin melanoma Underwent SLNB within study dates
Exclusion criteria	In situ or non-cutaneous melanoma
Number of participants and recruitment methods	78
Outcome(s) of interest	SLNB positivity

	until 2004, SLNB was offered regardless of melanoma thickness. After 2004 SLNB was offered for all patients with a thickness of >0.75mm
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Ulceration (present versus absent) ○ *unclear number of participants without ulceration, for this review it is assumed there was no missing data* • Clark level (2-3 versus 4+) • Breslow thickness (<0.75 mm versus 0.75-1.00mm)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 78)
% Female	59
Mean (range) age *(years)*	47 (25-86)
Tumour location	
% head and neck	12
% extremities	56
% Trunk	32
% positive SLNB	6.4
% Ulceration	6.4
% Breslow Thickness 0.8-1.0mm	50
% Clark level IV-V	37.2

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	Low risk of bias *(SLNB routinely given to all thin melanomas for most of study period and to all melanomas of 0.75-1.00mm thickness for entire study period. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Unclear attrition bias for ulceration as level of missing data cannot be established)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(no adjustment for confounders however as SLNB is routinely given for most of the study period, this is not expected to have a large impact.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias *(Note. High risk for ulceration. Data presented as number of participants with positive SLNB and ulceration, and number of participants with ulceration. However, it is unclear how many participants were without ulceration (unclear level of missing data for this factor))*
Overall risk of bias and directness	Risk of Bias	Low *(Note. Moderate risk of bias for ulceration analysis due to uncertainty surrounding attrition bias.)*
	Directness	Directly applicable

Wat, 2016

Bibliographic Reference	Wat, H., Senthilselvan, A., & Salopek, T. G. (2016). A retrospective, multicenter analysis of the predictive value of mitotic rate for sentinel lymph node (SLN) positivity in thin melanomas. *Journal of the American Academy of Dermatology*, *74*(1), 94-101.

Study Characteristics

Study design	Retrospective cohort study retrospective review of regional database
Study details	Study location Canada Study setting province of Alberta, Canada Study dates between January 2007 and December 2013 Sources of funding none
Inclusion criteria	Melanoma Included all melanomas, only those of a thickness up to 1.0mm were included in this review. Underwent SLNB

Number of participants	990; 155 relevant to this review
Outcome(s) of interest	SLNB positivity.
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Mitotic rate (per mm2) -(<1 versus 1+)
Covariates adjusted for in the multivariable regression modelling	None specific to thin melanomas

Study-level characteristics

	Study (N = 155)
% positive SLNB	7.7
% High mitotic rate group (see study characteristics for definition)	64.5

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB at study centre. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(Potential for confounders that are not adjusted for)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Reason for undergoing SLNB not accounted for.*

Section	Question	Answer
		Unclear whether data is representative of all thin melanomas)
	Directness	Directly applicable

Wong, 2006

Bibliographic Reference	Wong SL; Brady MS; Busam KJ; Coit DG; Results of sentinel lymph node biopsy in patients with thin melanoma.; Annals of surgical oncology; 2006; vol. 13 (no. 3)

Study Characteristics

Study design	Retrospective cohort study Review of prospectively collected database
Study details	Study location USA Study setting Memorial Sloan-Kettering Cancer Center Study dates May 1991 to October 2004 Sources of funding none reported
Inclusion criteria	Melanoma Thin melanoma Underwent SLNB
Number of participants and recruitment methods	223
Outcome(s) of interest	SLNB positivity *SLN biopsy is not performed routinely for all patients with thin melanoma. Most patients in the study population were selected for the procedure because of high-risk clinicopathologic features of the primary tumor, usually a Clark level of IV or higher, ulceration, or both.*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Breslow thickness (<0.75mm versus 0.75-1.00) • Clark level (2-3 versus 4-5) ○ *Data available for 0.75-1.00mm thick melanomas specifically* • Mitotic rate (1+ versus <1) • Tumour infiltrating lymphocytes (brisk/minimal versus none) • Regression (Present versus absent)

Covariates adjusted for in the multivariable regression modelling	None

Study-level characteristics

	Study (N = 223)
% Female	48
median age *(years)*	54
Tumour site	
% head and neck	13
% extremity	44
% Trunk	43
Median Breslow thickness *(mm)*	0.9
% positive SLNB	3.6
% Ulceration	9.3
% Breslow Thickness 0.8-1.0mm	67.3
% High mitotic rate group (see study characteristics for definition)	72.7
% Positive TIL (see study characteristics for definition)	51.8
% Clark level IV-V	68.2
% Regression	54.6

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Was not protocol for thin melanomas to undergo SLNB routinely. Presence of additional risk factor was needed. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Note. High risk of bias for mitotic rate and TIL prognostic factors (>20% participants with missing data) and moderate risk for ulceration (10-20% missing data).)*

Section	Question	Answer
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	Moderate risk of bias *(No adjustment for potential confounders however univariate analysis done for most clinical characteristics identified as being necessary when offering SLNB)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders not controlled for and attrition bias for several prognostic factors)*
	Directness	Directly applicable

Wright, 2008

Bibliographic Reference	Wright BE; Scheri RP; Ye X; Faries MB; Turner RR; Essner R; Morton DL; Importance of sentinel lymph node biopsy in patients with thin melanoma.; Archives of surgery (Chicago, Ill. : 1960); 2008; vol. 143 (no. 9)

Study Characteristics

Study design	Retrospective cohort study Review of prospectively maintained database
Study details	Study location USA Study setting Single tertiary cancer center Study dates
Inclusion criteria	Melanoma Thin primary cutaneous melanoma Underwent SLNB since standardization of the technique in 1991
Number of participants and recruitment methods	631

Outcome(s) of interest	SLNB positivity *"Those with thin primary lesions are offered SLNB on a more select basis. These patients are not selected for SLNB according to a specific protocol or institutional criteria, however. Rather, the options and rationale for SLNB are discussed individually between each patient and their respective dedicated melanoma surgeon.* *A large number of factors contribute to specific recommendations regarding SLNB, including patient age, tumor location and depth, presence or absence of ulceration, and other variables thought to affect nodal status. Also of great importance are the patient's concerns regarding nodal status and desire to undergo SLNB despite a relatively low risk of occult nodal metastasis."*
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	• Age (50 or younger versus >50) • Clarks level (2-3 versus 4-5) Ulceration (yes versus no) • Breslow thickness (<0.76m versus 0.76-1.00)
Covariates adjusted for in the multivariable regression modelling	none

Study-level characteristics

	Study (N = 631)
% Female	46
% positive SLNB	4.9
% Ulceration	6.8
% Breslow Thickness 0.8-1.0mm	41.0
% Young age (see study characteristics for definition)	46.4
% Clark level IV-V	19.5

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(SLNB not routinely given for thin melanomas at study centre. Various reasons are noted for a person with a thin melanoma being offered SLNB and it is likely that patients are not representative of all thin melanomas. It is unlikely that participants included in this study are representative of all people with thin melanoma)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias
Outcome Measurement	Outcome Measurement Summary	Low risk of bias
Study Confounding	Study Confounding Summary	High risk of bias *(various potential factors are noted to influence decision to offer SLNB to thin melanomas and these are not adjusted for.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Potential for confounders not controlled for)*
	Directness	Directly applicable

Yalamanchi, 2018

Bibliographic Reference Yalamanchi, Pratyusha; Brant, Jason A; Chen, Jinbo; Newman, Jason G; Clinicopathologic Factors Predictive of Occult Lymph Node Involvement in Cutaneous Head and Neck Melanoma.; Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery; 2018; vol. 158 (no. 3); 489-496

Study Characteristics

Study design	Retrospective cohort study Review of prospectively collected database
Study details	Study location USA Study setting National Cancer Database (NCDB).At the time of this study "the NCDB is a nationwide, facility-based, comprehensive oncology data set that uses the third edition of the International Classification of Diseases for Oncology (ICD-O-3) for topography(primary site) and morphology (histology) definitions and stages according to the American Joint Committee on Cancer (AJCC) manual for staging of cancer. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein." Study dates 2004 and 2012
Inclusion criteria	Melanoma Head and neck melanoma; only those with a Breslow thickness of 0.75-1.00mm were included in this review

	Underwent SLNB
Number of participants and recruitment methods	3183
Outcome(s) of interest	SLNB positivity
Prognostic factors or risk factor(s) or sign(s)/symptom(s)	Mitosis (present v absent) Ulceration (present v absent)
Covariates adjusted for in the multivariable regression modelling	Multivariate model adjusted for age (<54, 54-70 or >70 years), sex, histology (MM, superficial spreading melanoma, lentigo maligna melanoma or other), primary site, mitosis (present or absent), ulceration and vertical growth phase

Study-level characteristics

	Study (N = 3183)
% Female	27.7
Race	
% White	98.2
% Black	0.1
% Other	1.7
% positive SLNB	2.0

Quality assessment

Section	**Question**	**Answer**
Study participation	Summary Study participation	High risk of bias *(Unclear protocol for undergoing SLNB. It is unlikely that participants included in this study are representative of all people with thin melanoma)*
Study Attrition	Study Attrition Summary	Low risk of bias
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	High risk of bias *(Subsequent studies (Friedman 2019) using the NCDB note that SLNB status was only routinely entered from 2012. It is unclear whether there are specific reasons why a participant has a SLNB status prior to 2012.)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Potential for confounders. Multivariate model adjusted for several important clinical characteristics.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	Low risk of bias
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear protocol for undergoing SLNB and possibility for bias recording of SLNB status. Multivariate model did not include sufficient adjustment for confounders.)*
	Directness	Partially applicable *(Note. Only included people with head and neck cancer. Mitotic rate analysis will be marked down once for indirectness due to only comparing present mitoses versus absent,)*

Appendix F -Diagnostic evidence

Arrangoiz, 2012

Bibliographic Reference	Arrangoiz R; Papavasiliou P; Stransky CA; Yu JQ; Tianyu L; Sigurdson ER; Berger AC; Farma JM; Preoperative FDG-PET/CT Is an Important Tool in the Management of Patients with Thick (T4) Melanoma.; Dermatology research and practice; 2012; vol. 2012

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • USA Setting • Two referral centres Study dates • January 2003 - January 2009
Inclusion criteria	• Melanoma • Breslow thickness >4mm • No clinical evidence of locoregional or distant metastatic disease • Underwent PET/CT during staging work-up
Number of participants	56
Index test(s)	PET-CT Procedure • all patients were asked to fast for at least 4 hours before the study. After measurement of blood glucose level and confirming it is below 200, the patient was given an I.V. injection of approximately 15mCi of 18F-FDG as standard dose. After a delay of 1 to 2 hours, the patient voided, and the PET/CT scan was performed on a GE Discovery LS PET/CT Scanner or a Siemens Biograph 16 PET/CT Scanner from the vertex of the head down to feet for all patients to cover the entire skin surface. The CT images were acquired in helical mode during normal breathing and were used for registration with the PET images and for applying attenuation correction. • For Discovery LS (from 2003 to 10/2010), the CT scan acquisition parameters were 140 kVp, 90mA, 0.8 s per rotation, slice thickness of 5 mm, 0.75 pitch, and interval of 4.25 mm. The field of view for PET

	and CT images was 50 cm diameter.The PET scans were acquired for 6 or 7 minutes per bed position in 2D mode with a single-slice overlap and were reconstructed using ordered subsets expectation maximization (OSEM) algorithm with 28 subsets and 2 iterations using manufacturer-supplied software. The PET system has a 2-dimensional transaxial resolution of 4.7mmfull width half maximum (FWHM) at 1 cm radius and 5.2mm at 10 cm radius. • For Siemens Biograph (from 10/2010 to present), the CT scan was acquired using CareDose4D with the following acquisition parameters: 130 kVp, reference mAs of 100, 0.6s per rotation, 5mm slice thickness, pitch of 1.0, and 70 cm diameter field of view. The PET scan was acquired for 2 to 3 minutes per bed position in 3D mode with 16-slice overlap and was reconstructed using TrueX algorithm with 21 subsets and 2 iterations, with 63 cm diameter field of view using manufacturer-supplied software. The PET system has a 2- dimensional transaxial resolution of 4.4mm FWHM at 1 cm radius and 4.6mm at 10 cm radius. • The PET reconstruction included corrections for random and scatter. Attenuation correction was applied based on the low-dose CT to reduce radiation exposure to the patients. All images were corrected for body weight, dose administered, and radioactive decay and displayed on an eNTEGRA or Xeleris workstation for GE scanner or multimodality workplace for Siemens scanner with an initial standardized uptake value (SUV) gray scale of 0 (white) to 5 (black). Interpretation • The PET scans were reviewed to determine the length of the abnormality with an SUV of 2.5 as cutoff value to delineate the tumor extent. The maximum SUV within the tumor volume was also determined by manufacturer build-in computer algorithm. • The SUV values are comparable between the two scanners with cross-calibration performed by manufacturer trained field engineers and our in-house medical physicist. • There are many studies displayed and reviewed in both systems during the transition period from GE to Siemens scanner. • A true positive PET/CT for regional disease and metastatic disease was defined by the presence of malignant disease in the final pathology specimen and during the workup of metastatic disease (ultrasound-guided or CT-guided biopsies of the metastatic foci).
Reference standard (s)	Detection of metastases at final pathological workup • 48 participants underwent SLNB however 2x2 data is only provided for the overall cohort which could have had regional disease determined by histology following SLNB or CLND.

Study-level characteristics

	Study (N = 56)
Female	57%
Mean age (range)	67 (26-89) years
Median (range) tumour thickness *(mm)*	6 (4.1 to 40)
Ulceration %	67%
Tumour location	
head and neck	21%
Trunk	29%
extremities	50%
Satellitosis	25%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Retrospective study; unclear protocol for giving both PET-CT and SLNB at study centre.)*
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 *(likely unblinded)*
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?	For Pre-SLNB: High *(No mention of blinding and limited detail on how SLNB was performed. Decision to give SLNB was dependent on results of PET-CT scan, with 6 participants no longer receiving SLNB due to findings on the PET-CT stan.)* For detection of regional/distant metastases: Unclear *(Unclear protocol for determining final disease status*

Section	Question	Answer
		during follow-up. Very limited information on how reference standard was performed.)
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 *(For detection of regional/distant metastases: Participants likely received different reference standards. Unclear timing of the different tests and when the final pathological workup was completed. SLNB: Final status could have been the result of histology following SLNB or CLND, or follow-up. Reference standards and tests given depended on results of other tests. 6 participants did not receive SLNB due to findings of PET/CT scan.)*
Overall risk of bias and directness	Risk of Bias	High *(Risk of bias due to selection of participants and the flow, timing and conduct of the reference standard.)*
	Directness	Directly applicable

Chai, 2012

Bibliographic Reference Chai CY; Zager JS; Szabunio MM; Marzban SS; Chau A; Rossi RM; Sondak VK; Preoperative ultrasound is not useful for identifying nodal metastasis in melanoma patients undergoing sentinel node biopsy: preoperative ultrasound in clinically node-negative melanoma.; Annals of surgical oncology; 2012; vol. 19 (no. 4)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • US Setting • Single centre Study dates

	• June 2005 and September 2009 Sources of funding • nr
Inclusion criteria	• Melanoma diagnosis • No clinical evidence of locoregional or distant metastatic disease • Confirmed diagnosis of primary cutaneous melanoma without palpable lymphandenopathy in regional nodal basins. • Ultrasound performed prior to scheduled lymphoscintigraphy and SLNB.
Number of participants	325
Index test(s)	US Procedure • The preoperative ultrasound was performed using high resolution linear 9 and 12 MHz transducers either immediately or several days prior to lymphoscintigraphy. No absolute criteria were used for evaluating nodes ultrasonographically, but in general suspicious lymph nodes appeared round in shape, had partial or complete absence of the fatty hilum and/or diffuse or eccentric thickening of the cortex. The loss of central perfusion or presence of peripheral perfusion was not included in the morphologic criteria. The size of the lymph node by itself was not considered an indication of abnormality. For correlation with SLNB results, readings of "benign" or "no nodes visualized" were considered negative, and readings called "abnormal," "suspicious" or "indeterminate recommending a short-term follow up" were scored as positive. In cases of an abnormal ultrasound performed prior to the day of surgery, patients were offered an ultrasound-guided FNA and, if positive, proceeded directly to therapeutic lymphadenectomy without SLNB; patients with a negative FNA underwent SLNB. • The nodal ultrasound was ordered according to the primary melanoma site and was at the discretion of the attending surgeon, but was intended to encompass all basins potentially draining the primary site. Patients with extremity melanomas underwent ultrasound of the ipsilateral groin or axilla. Generally, patients with melanoma on the hand or forearm also had an epitrochlear ultrasound, while patients with melanoma on the lower leg, from toe to calf, had a popliteal ultrasound. Head and neck melanomas underwent, at minimum, ipsilateral neck, partoid and supraclavicular ultrasound. For melanomas on the trunk, Sappey's line was used as a rough guide: melanomas at or above the beltline included axillary ultrasound, and those at or below

	included groin ultrasound. Lesions in close proximity to the midline had bilateral ultrasounds performed.
Reference standard (s)	SLNB Procedure • SLNB was offered to medically fit patients with melanoma depth ≥0.76 mm without palpable lymphadenopathy or <0.76 mm with high-risk features such as ulceration, high mitotic rate or a positive deep margin. Lymphoscintigraphy was performed the morning of surgery by injecting radiolabeled colloid (either 99mTc-sulfur colloid or 99mTc-tilmanocept) at the primary tumor site. In the operating room, 1 to 2 mL of isosulfan blue dye was injected intradermally. Sentinel lymph nodes were identified based on blue color, radioactivity above background and at least 10% of the hottest node, or palpable abnormality. All sentinel nodes were serially sectioned and evaluated by hematoxylin-eosin and immunohistochemical staining. Interpretation • All lymph nodes with proven tumor deposits, regardless of size, were considered positive.
Subgroup analyses	Breslow thickness • ≤1 mm • 1.01 - 2 mm • 2.01 - 4 mm • >4 mm

Study-level characteristics

	Study (N = 325)
Female	41.8%
Nominal	41.8
Median (range) age	58 (18 – 86) years
Tumour location	
head and neck	10.5%
Trunk	39.7%
Upper extremity	31.1%
Lower extremity	18.8%

	Study (N = 325)
Breslow thickness (mm) *(%)* Median 1.78 (range 0.42 to 14.4)	
≤1.00	17.2%
1.01 - 2.00	41.8%
2.01 - 4.00	27.1%
>4.00	13.5%
Unknown	0.3%
Clark's level *(%)*	
Level III	7.4%
Level IV	84.6%
Level V	6.2%
Unknown	1.8%
Ulceration *(%)*	
Absent	65.3%
Present	29.8%
Unknown	4.9%

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 *(Note: In cases of an abnormal ultrasound performed prior to the day of surgery, patients were offered an ultrasound-guided FNA and, if positive, proceeded directly to therapeutic lymphadenectomy without SLNB; patients with a negative FNA underwent SLNB.)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low *(No absolute criteria were used for evaluating nodes ultrasonographically, but in general suspicious lymph nodes appeared round in shape, had partial*

Section	Question	Answer
		or complete absence of the fatty hilum and/or diffuse or eccentric thickening of the cortex.) 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?	Low *(SLNB procedures were described)* 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?	Unclear *(Ultrasound was performed either immediately or several days prior to SLNB but exact timing was not reported.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding; unclear timing between index test and reference standard)*
	Directness	Directly applicable

Cheng, 2020

Bibliographic Reference	Cheng, D.; McNicoll, C.F.; Kirgan, D.; Jones, M.S.; Rivera, M.R.; Doyle, G.M.; De Guzman, M.D.; Baynosa, J.; St Hill, C.R.; The role of FDG-PET-CT is limited in initial staging of nodal metastasis for thin cutaneous melanoma; American Journal of Surgery; 2020

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • US

	Setting • Single centre Study dates • 2005 to 2015 Sources of funding • This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Inclusion criteria	• Melanoma *Cutaneous malignant melanoma, identified by ICD-9-CM codes*
Number of participants	92
Length of follow-up	Follow-up, median, IQR (days) 425 (38.5, 811.5)
Index test(s)	PET-CT All radiographic studies were fluorodeoxyglucose (FDG) PET-CT. A positive PET-CT result was defined as significant uptake, read as concerning for metastases, in the relevant nodal basin for the corresponding primary melanoma site.
Reference standard (s)	SLNB Positive lymph nodes were defined as any microscopic or macroscopic disease on pathologic analysis of the corresponding regional nodal basin on SLNB or CLND.

Study-level characteristics

	Study (N = 92)
Female	33%
Age: Mean (SD)	59.7 (16.1) years
Breslow thickness (mm): mean (SD)	4.75 (5)
Ulceration	41%

Quality assessment

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?	Unclear *(Melanoma stages not reported)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Limited information on how the index test was performed)*
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 *(Limited information on how the reference standard was performed)*
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 *(Timing between index test and reference standard was not reported)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Study is retrospective; limited information about index test and reference standard)*
	Directness	Directly applicable

Hafner, 2004

Bibliographic Reference	Hafner J; Schmid MH; Kempf W; Burg G; Künzi W; Meuli-Simmen C; Neff P; Meyer V; Mihic D; Garzoli E; Jungius KP; Seifert B; Dummer R; Steinert H; Baseline staging in cutaneous malignant melanoma.; The British journal of dermatology; 2004; vol. 150 (no. 4)

Study Characteristics

Study type	Prospective cohort study
Study details	Study location

	• Switzerland Setting • Single centre Study dates • August 1999 to March 2002
Inclusion criteria	• Melanoma • Breslow thickness 1mm or more
Exclusion criteria	• locally recurrent cutaneous MM within the former excisional scar implying no primary MM • other metastatic tumour • age >80 years • Pregnancy • comorbidities resulting in a raised risk of anaesthesia • disabling disease
Number of participants	100
Index test(s)	PET alone whole-body PET scans after a 6-h fast. Fifty minutes after intravenous injection of 350 MBq of 2-fluorine-18-fluoro-deoxy-D-glucose (FDG) an ECAT 951R scanner in septa-extended two-dimensional mode (Siemens/CTI, Knoxville, TN, U.S.A.) acquired coronal, sagittal, and transaxial sections US Abdominal US: of liver, spleen, iliac and retroperitoneal lymph nodes, kidneys and pancreas. Lymph node US: of the regional lymph nodes of the groins, axillae and neck was performed together with the abdominal US. Timing (General) Participants were to undergo the following staging procedures within 4 weeks after primary excision: physical examination, chest X-ray, US of the abdomen and the regional lymph nodes, and whole body PET.
Reference standard (s)	SLNB Interpretation • Practical pathology work-up of the SN was based on the recommendations of the European Organization for Research and the Treatment of Cancer (EORTC) melanoma cooperative group, pathology subgroup. There were four different diagnoses based on the recommendations of the International Union against Cancer: (i) no

	tumour, (ii) isolated tumour cells, (iii) micrometastasis (< 2 mm), and (iv) metastasis (> 2 mm). Procedure • A wash out phase of 48 h after the FDG-PET scan was maintained before starting the lymph node scintigraphy. Lymphatic mapping to identify the draining lymph node basins was performed in the afternoon before surgery. A total dose of 100 MBq Tc99-labelled nanocolloids were injected intracutaneously in four quadrants 5 mm around the excision site of the primary melanoma. Biplanar images were created 2 h later, and the sentinel node was marked in two planes using a waterproof pen.

Study-level characteristics

	Study (N = 100)
Female	45%
Median (Range) age *(years)*	55.5 (18 to 79)
Median (range) Breslow thickness *(mm)*	2.25 (1 to 17)
Tumour location *(%)*	
head and neck	16%
Trunk	35%
extremities	49%
>1 draining basin *(%)*	5%

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Study was prospectively conducted. However, there are several exclusion criteria which may pose a risk of bias (age >80, pregnancy, comorbidities posing a risk of anesthesia).)*
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?	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?	Unclear *(Patients were "recommended" to undergo index tests within 4 weeks of diagnosis however actual timing is unclear.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding and timing of index tests)*
	Directness	Directly applicable

Hinz, 2013

Bibliographic Reference	Hinz T; Voth H; Ahmadzadehfar H; Hoeller T; Wenzel J; Bieber T; Schmid-Wendtner MH; Role of high-resolution ultrasound and PET/CT imaging for preoperative characterization of sentinel lymph nodes in cutaneous melanoma.; Ultrasound in medicine & biology; 2013; vol. 39 (no. 1)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Germany Setting • Single centre Study dates • January 2009 to January 2011 Sources of funding

	• supported by a grant from the German Cancer Aid (Program for the Development of Interdisciplinary Oncology Centers of Excellence in Germany), Bonn, Germany.
Inclusion criteria	• High-risk melanoma 1.5.2 *including subject with a higher tumor thickness (2.0 mm or larger) or further risk factors like ulceration or regression.* • Breslow thickness 1mm or more • Underwent PET/CT and high-resolution US 1.5.3 *HRUS was performed in all participants undergoing SLNB. PET/CT was only performed in those deemed sufficiently high risk.*
Number of participants	20
Index test(s)	PET-CT Procedure • A dual modality PET/CT system (Biograph; Siemens Medical Solutions Inc., Erlangen, Germany) was used and the images were interpreted in routine clinical fashion especially for exclusion or detection of visceral metastases, deep soft-tissue metastases, LN metastases or a second occult malignancy in the melanoma patients. high-resolution US Procedure • A real-time scanner (Nemio SSA-550A;Toshiba DiagnosticUltrasound System,Neuss, Germany) with a 6.0–11.0 MHz linear transducer was employed for investigation of all relevant regional LN basins depending of the localization of the primary melanoma. General information Timing • HRUS was applied in all 20 patients before performing FDG-PET/CT. Interpretation • Assessment of LNs was performed according to the criteria of Solbiati et al. (1988), Vassalo et al. (1992) and Voit et al. (2010) with the categories ‘‘reactive lymph node’’ (oval structure with hyperechoic center and hypoechoic margin), ‘‘metastatic lymph node’’ (round structure with axial to longitudinal diameter ratio ,2/Solbiato-Vassallo-Index, displacement of hilus, or homogenous hypoechoic morphology) and ‘suspicious lymph node’’ (LN with irregular extension of the hypoechoic margin, so-called ‘‘hump structure’’).

	• If HRUS revealed a suspicious LN, the consistency of this LN with the SLN was confirmed by a second ultrasound examination performed after lymphoscintigraphic marking.
Reference standard (s)	SLNB When SLNB was offered • If the patients show clear-cut clinical signs for metastases like a visible enlargement of lymph nodes or palpable nodes they had been excluded from SLNB procedure and directly referred to CLND if ultrasound examinations supported the presumptive diagnosis of lymph node metastases. Additionally, for patients with ‘‘classic’’sonomorphologic criteria for lymph node metastases like rounding of the normal ovoid shape (so called ‘‘balloonshape’’), loss of normal hilar echos as well as homogenous echo-poor morphology, no SLNB but a CLND was planned after exclusion of further distant metastases. Procedure • After formalin fixation the SLNs were bisected longitudinallythrough the hilus, cut into 2 mm sections and totally embedded in paraffin blocks. Five slides were prepared from each paraffin block (H&E, Giemsa, S-100, HMB 45 and Melan A staining) and analyzed by two experienced dermatopathologists (J.W., T.B.), respectively. The metastatic deposit of the SLNs was documented concerning location within the LN and size. According to Carlson et al. (2003) positive SLNs were subdivided histopathologically in macrometastasis (.2 mm), micrometastasis (#2 mm), a cluster of cells (10–30 grouped cells) in the subcapsular space or interfollicular zone, or isolated melanoma cells (1 to#20 individual cells) in subcapsular sinuses. With the support of immunohistochemical staining nodal metastases could be detected at a microscopic level consisting of aggregates of only a few cells. In summary, the diagnosis of a micrometastasis was pointed out if 1 or more melanoma cells could be detected in the SLN (Spanknebel et al. 2005). Additionally, the distance of the most centripetally advanced tumor cells from the margin of the lymph node capsule was measured under light microscopy (Starz et al. 2001).

Study-level characteristics

	Study (N = 20)
% Female	55.5%
Nominal	55.5
Tumour location	
head and neck	0%

	Study (N = 20)
Trunk	50%
extremities	50%
Breslow thickness *(mm)*	
1mm or less	0%
1.01-2.00	15%
2.01-4.00	45%
>4.00	40%
% ulcerated	35%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Seems to be the case that all participants with high-risk melanoma undergoing SLNB will have received PET/CT.)*
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?	Low

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low *(However, note that blinding is not reported)*
	Directness	Directly applicable

Hinz, 2011

Bibliographic Reference	Hinz T; Wilsmann-Theis D; Buchner A; Wenzel J; Wendtner CM; Bieber T; Reinhard G; Baumert J; Schmid-Wendtner MH; High-resolution ultrasound combined with power Doppler sonography can reduce the number of sentinel lymph node biopsies in cutaneous melanoma.; Dermatology (Basel, Switzerland); 2011; vol. 222 (no. 2)

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Germany Setting • Single centre Study dates • October 2007 and February 2009 Sources of funding • The study was supported by a grant from the German Cancer Aid (Program for the Development of Interdisciplinary Oncology Centers of Excellence in Germany), Bonn, Germany.
Inclusion criteria	• Melanoma • Dissection of SLNs was indicated
Exclusion criteria	Any clear-cut sonographical signs for lymph node metastases
Number of participants	81
Index test(s)	US

	Procedure • Preceding SLNB, high-resolution ultrasound combined with power Doppler sonography (PDS) sonography of regional lymph nodes (LN) basins was performed twice, before and after lymphoscintigraphy of the patients by dermatologists with special skills in lymph node sonography certificated by the German Society of Ultrasound in Medicine. A real time scanner (Nemio SSA-550A; Toshiba Diagnostic Ultrasound System, Neuss, Germany) with a 6.0- to 11.0-MHz linear transducer was used, according to the depth of the explored LN. At the first ultrasound examination, all 'candidate' lymph node areas predicted by the location of the primary melanoma were examined. Longitudinal and cross-sections were used for the documentation of number, size, and morphological structure of all lymph nodes. • After the lymphoscintigraphy, a second ultrasound examination was done before SLNB. At this time point especially the anatomic region marked by lymphoscintigraphy was documented and reevaluated critically. During the first and second ultrasound examination a PDS examination for visualization of the lymph node vessels of suspicious structures and, if possible, of vascularization patterns was additionally performed . Special care was taken to identify intralesional color signals that were considered to be indicative for the vascular supply of suspicious lesions. Interpretation • The criteria for lymph node suspicious for metastases according to Vassallo et al. (1992) and Solbiati et al. (1988) were: a round rather than overall oval morphology (axial to longitudinal diameter ratio <2/Solbiato-Vassallo Index); absence, attenuation, or displacement of the hilus; nodular hypoechoic focus within the lymph node; asymmetrical irregular extension of the lymph node margin. In contrast, the criteria for reactive lymph nodes were symmetrical and oval structures with hyperechoic centers and hypoechoic margins. If no LN could be detected within areas marked during the lymphoscintigraphy, a benign lymph node was assumed, because 'unaffected' lymph nodes often cannot be separated from surrounding tissue because their acoustic impedance is identical. The criteria for a reactive lymph node were hilar or longitudinal vessels or branching of longitudinal vessels. Lymph node metastases were assumed in case of accessory peripheral vessels or a displacement of intranodal vessels or asymmetric avascular areas or aberrant course of central vessels. Especially peripheral perfusion has recently been shown to be an early sign of metastatic involvement. • Results of the first and second ultrasound examinations were documented separately. If one of both (high-resolution B-mode ultrasound or PDS) or both (high resolution B-mode ultrasound and PDS) types of examination revealed hints for malignancy according to the above-mentioned criteria, LNs were assumed to be highly

	suspicious for malignancy in the final sonographic classification. Contrast-enhanced ultrasound was not performed in the current investigation.
Reference standard (s)	SLNB • The SLNB was performed using standard procedures. After formalin fixation of the SLNs, they were bisected longitudinally through the hilus, cut into 2-mm sections and totally embedded in paraffin blocks. From each paraffin block, five slides were prepared (HE, Giemsa, S-100, HMB 45, and Melan A staining) and analyzed by two experienced dermatopathologists (J.W. and T.B.). The metastatic deposit was documented for each SLN concerning location within the LN and size. Positive SLN specimens were subdivided histopathologically according to Carlson et al. (2003). The size of the metastatic deposit was defined as macrometastasis (>2 mm), micrometastasis (≤2 mm), a cluster of cells (10–30 grouped cells) in the subcapsular space or interfollicular zone, or isolated melanoma cells (1 to ≤20 individual cells) in subcapsular sinuses. The distance of the most centripetally advanced tumor cells from the margin of the lymph node capsule was measured under light microscopy (2001).

Study-level characteristics

	Study (N = 81)
% Female	40.7
Age	
<40 years	23.4%
41-50 years	20.9%
51–60 years	17.2%
61–70 years	27.1%
>70 years	11.1%
Tumour location *(%)*	
Head	2.4%
Trunk	44.4%
Upper extremity	17.2%
Lower extremity	28.3%

	Study (N = 81)
Acral	7.4%
Tumor thickness *(%)*	
0.75–1.00 mm	24.6%
1.01–1.50 mm	29.6%
1.51–2.00 mm	14.8%
2.01–4.00 mm	22.2%
>4.00 mm	8.6%
Clark's level *(%)*	
Level II	1.4%
Level III	32%
Level IV	58%
Level V	8.6%
Ulceration *(%)*	17.3%

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)*
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?	Unclear *(Ultrasound was performed*

Section	Question	Answer
		before SLNB but exact timing was not reported.)
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding; unclear timing between index test and reference standard.)*
	Directness	Directly applicable

Hocevar, 2004

Bibliographic Reference Hocevar M; Bracko M; Pogacnik A; Vidergar-Kralj B; Besic N; Zgajnar J; Music MM; The role of preoperative ultrasonography in reducing the number of sentinel lymph node procedures in melanoma.; Melanoma research; 2004; vol. 14 (no. 6)

Study Characteristics

Study type	Retrospective cohort study - *Unclear; assumed to be retrospective*.
Study details	Study location • Slovenia Setting • Single centre Study dates • June 2002 to August 2003
Inclusion criteria	• Metastatic melanoma • underwent preoperative US examination of the regional lymph nodes
Number of participants	57
Index test(s)	US • All US examinations were carried out by an oncologically dedicated radiologist, using a linear array transducer, small parts probe of 12 and 15 MHz (Power Vision 8000, Toshiba Corporation, Ottawara, Japan). US results were categorized as benign or malignant. The US features considered as malignant were a rounded appearance of the lymph node

	(changed long to short diameter), loss of the hilar echogenic reflex and deformed radial nodal vascularity.
Reference standard (s)	SLNB Interpretation • The cytological diagnoses were compared with the histological diagnosis, either of the SLNs or of the lymph nodes from complete regional lymphadenectomy, and the sensitivity, specificity and positive (PPV) and negative (NPV) predictive values were calculated. Procedure • Dynamic and static lymphoscintigraphy were performed on the morning of surgery, 2–6 h before the operation, with a total dose of 40–60 MBq of 99mTc nanocolloid (Nanocoll, Nycomed Amersham, Sorin, Italy) in a total volume of 0.4 ml of normal saline injected intradermally at four spots around the biopsy site or primary MM. The position of SLN was marked on the skin with indelible ink. SLN biopsy was conducted under general anaesthesia, 2– 6 h after lymphoscintigraphy. Shortly before surgery, 0.5– 1 ml of Patent Blue (Blue Patente V, Laboratorie Guerbet, Aulnaysous-Bois, France) was injected intradermally at the same spots as the 99mTc nanocolloid. Surgical dissection was guided by a hand-held gamma probe (Navigator GPS System, Norwalk, CT, USA) and by a blue-stained afferent lymphatic channel. The identified SLN was excised and measured for ex vivo radioactivity. Additional hot nodes were removed until the ratio of the background radioactivity to the hottest ex vivo SLN was less than 10%

Study-level characteristics

	Study (N = 57)
Female	63.2%
Tumour location Of primary tumour	
head and neck	25%
extremities	42%
Trunk	33%
Breslow thickness (mm)	

	Study (N = 57)
<1	4%
1.01-2	40%
2.01-4	35%
>4	21%
Ulcerated	37%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Unclear study design. Unclear when a person would undergo both SLNB and US.)*
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 *(limited information on how the US test was conducted.)*
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 whether test was interpreted blind to index test results)*
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 SLNB relative to US. Also note that three participants' results were based on histology following LND. All other participants received SLNB.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear study design, blinding and timing of SLNB relative to US. Limited detail on conduct of US.)*
	Directness	Directly applicable

Kell, 2007

Bibliographic Reference	Kell MR; Ridge JA; Joseph N; Sigurdson ER; PET CT imaging in patients undergoing sentinel node biopsy for melanoma.; European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology; 2007; vol. 33 (no. 7)

Study Characteristics

Study type	Retrospective cohort study review of prospectively collected database
Study details	Study location • USA Setting • Philadelphia Study dates • Over a 12 month period
Inclusion criteria	• PET/CT during staging work-up • Melanoma
Number of participants	37
Length of follow-up	n/a
Index test(s)	PET-CT • PET/CT was performed on patients prior to surgical intervention. Combined PET/CT imaging was performed using standard protocols. Briefly, intravenous 2-[18F]fluoro-2-deoxy-D-glucose (18FDG) was administered and after a 2 h delay, a PET/CT scan was performed from the skull base to the feet without contrast. Combined PET/CT images were evaluated quantitatively for areas of abnormally increased 18FDG uptake relative to surrounding normal tissues and areas of increased physiologic uptake.
Reference standard (s)	SLNB

	• institutional policy to offer SLNB to patients with malignant melanoma greater then 0.75 mm who do not have evidence of either systemic or regional metastasis

Study-level characteristics

	Study (N = 37)
Mean age (SD)	61.4 years
mean Breslow thickness *(mm)*	2.4

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study was retrospective. Based on patient demographics provided, of all those people with melanoma who underwent SLNB during the study period, less than half underwent PET-CT scan and these patients were significantly more likely to have a positive SLNB and had thicker melanomas)*
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 *(limited detail on how PET-CT result was established)*
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?	Low
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 *(Limited detail on the timing of index test relative to reference standard)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Likely suffered from selection bias and there was limited detail on how and when index test was conducted.)*
	Directness	Directly applicable

Klode, 2010

Bibliographic Reference	Klode J; Dissemond J; Grabbe S; Hillen U; Poeppel T; Boeing C; Sentinel lymph node excision and PET-CT in the initial stage of malignant melanoma: a retrospective analysis of 61 patients with malignant melanoma in American Joint Committee on Cancer stages I and II.; Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]; 2010; vol. 36 (no. 4)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Germany Setting • single centre Study dates • January 2004 to December 2006
Inclusion criteria	• PET/CT during staging work-up • Melanoma • stage I or II with a Breslow thickness over 1.0mm
Number of participants	61
Index test(s)	PET-CT Procedure • The PET-CT examination was performed in fasting patients approximately 1 hour after administration of approximately 340MBq of fluorine-18 fluorodeoxyglucose on a Siemens biograph duo PET-CT

	scanner (Siemens, Erlangen). Blood sugar level was checked before the scan, and the patients then drank 1,500 mL of a negative oral contrast agent. The CT was acquired in the craniocaudal direction after approximately 140 mL of iodine-containing contrast agent was administered. Images taken ranged from cranial base to midfemur. Additional views were obtained depending on melanoma localization. Interpretation • Each hypermetabolic tumor focus of a lymph node detected using PET-CT was considered a positive result if the histopathologic survey confirmed a metastasis. • All hypermetabolic tumors not showing any metastases during histopathologic evaluation were considered false-positive results. • Inconspicuous PET-CT findings without histologic metastasis were considered negative results. • A result was considered as false negative if the PET-CT findings were inconspicuous and the histopathologic survey detected a metastasis in the SLN.
Reference standard (s)	SLNB When SLNB was offered • offered to all patients with malignant melanoma in AJCC stages I and II, indicating a tumor thickness greater than 1.0 mm. Procedure • A dermatopathologist performed the microscopic review. A tumor focus of less than 2.0 mm was defined as micrometastasis and of 2.0 mm or more was defined as macrometastasis

Study-level characteristics

	Study (N = 61)
% Female	41%
Age range	31 - 82
White ethnicity *(%)*	100%
nodular malignant melanoma	44.3%
superficially spreading malignant melanoma	32.8%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(PET-CT was offered according to the guidelines of the DDG. Only roughly half of those people undergoing SLNB during the study period received PET-CT. It is not clear how much these two groups differed.)*
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?	Low
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.)*
	Directness	Directly applicable

Kunte, 2009

Bibliographic Reference	Kunte C; Schuh T; Eberle JY; Baumert J; Konz B; Volkenandt M; Ruzicka T; Schmid-Wendtner MH; The use of high-resolution ultrasonography for preoperative detection of metastases in sentinel lymph nodes of patients with cutaneous melanoma.; Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al.]; 2009; vol. 35 (no. 11)

Study Characteristics

Study type	Prospective cohort study

Study details	Study location • Germany Setting • Single centre Study dates • December 2002 to March 2003
Inclusion criteria	Melanoma
Number of participants	25
Index test(s)	US • During the 24 h preceding SLNB, high-resolution B-Mode US of regional LN basins was performed twice, before and after lymphoscintigraphy of the patients by two experienced dermatologists. Interpretation • Lesions suspicious for metastases were identified using the following criteria: a round rather than overall oval morphology (axial to longitudinal diameter ratio o2) (Figure 1A), representing the Solbiato-Vassallo-Index; absence, attenuation, or displacement of the hilus; nodular hypoechoic focus within the LN; and asymmetrical irregular extension of the LN margin (Figure 1B).16–19 Reactive or postinflammatory LNs were assumed when symmetrical, oval structures with hyperechoic centers and hypoechoic margins could be found using US examination. • If no LN structure could be detected sonographically in the areas marked after lymphoscintigraphy, a benign LN was assumed, because normal ‘‘unaffected’’ LNs often cannot be separated from surrounding tissue because their acoustic impedance is identical.21 After lymphoscintigraphy, a second US examination was performed before SLNB was done. At this US examination, the anatomic region of the scintigraphically marked SLN, verified using gamma-probe measurement performed immediately before US, was reevaluated and documented.
Reference standard (s)	SLNB When was SLNB offered

	• Centre seems to have an enhanced protocol for offering SLNB: cutaneous melanomas 1.0 mm thickness or more or with other risk factors such as ulceration or regression of primary melanoma and Clark Level IV and V. Procedure • SLNB was performed using standard procedures. Interpretation • LNs with histologically proven tumor deposits were considered metastatic except when fewer than four isolated tumor cells were present. The metastatic deposit was documented for each SLN concerning location within the LN and size (micrometastasis and macrometastasis).

Study-level characteristics

	Study (N = 25)
% Female	40
Mean (range) number of SLNs removed	1.4 (1-3)

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Study was prospectively conducted and it is assumed that all patients undergoing SLNB during the study period were offered US. It is assumed that the centre used the enhanced screening protocol outlined by the author when deciding whether to offer SLNB.)*
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 *(''standard US device'' (high-resolution B-mode US) was used, without additional US functions such as color-coded Doppler sonography or FNAC. Unclear how lymph nodes were selected for evaluation.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or	Low

Section	Question	Answer
	interpretation differ from the review question?	
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?	Low
Overall risk of bias and directness	Risk of Bias	Low *(However note that blinding is unclear.)*
	Directness	Directly applicable

Maubec, 2007

Bibliographic Reference Maubec E; Lumbroso J; Masson F; Suciu V; Kolb F; Mamelle G; Cavalcanti A; Boitier F; Spatz A; Aupérin A; Leboulleux S; Avril MF; F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm.; Melanoma research; 2007; vol. 17 (no. 3)

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • France Setting • Single centre Study dates • Between January 2004 and June 2005
Inclusion criteria	• Melanoma • >4mm Breslow thickness

	• Underwent chest radiograph, abdominal ultrasonograph and an FDG-PET scan
Exclusion criteria	• distant metastasis already identified
Number of participants	25, 19 included in final analysis
Index test(s)	PET-CT Interpretation • In the analysis of the results, an uptake site was considered as positive if it was suspected of being malignant or was not clearly explained by a benign etiology. Abnormal PET scan findings were correlated to pathology when the patient underwent a surgical procedure, and thereafter, were correlated to the course of the disease, the follow-up including repeated clinical examinations and conventional imaging. Timing • Unclear, author notes: "it was decided that the surgical excision should not be delayed for the realization of this imaging technique". Procedure • All imaging and data acquisitions were performed on an integrated PET/CT Biograph LSO system (Siemens Medical Solutions, Erlangen, Germany). PET/computed tomography (CT) scanning was performed after an intravenous injection of 5 MBq/kg 18FDG, followed by a 60–120-min uptake phase. All patients had fasted for 6 h and the blood glucose level was normal in all cases. During the image acquisition, patients maintained their arms above their head and no specific breathing instructions were given. The PET elements of the system are based on a full-ring tomograph (ECAT ACCEL, CPS Innovation, Knoxville, Tennessee, USA). Emission data were acquired for 4 min at each bed position from the top of the head to the mid-thigh and included, if necessary, the lower limbs. The three-dimensional mode was used for PET image acquisition. PET data were reconstructed on a 128 128 matrix, using an iterative algorithm (FORE and AWOSEM) with two iterations, eight subsets, and a 5-mm full-width half maximum (FWHM) Gaussian postfilter. Reconstruction data were acquired with a single slice spiral CT (Somatom Emotion, Siemens Medical Solutions) without intravenous contrast agent. CT parameters were set to 80 mA and 110 kV, slice thickness of 5 mm, and pitch 1.5. CT data were reconstructed using filtered back projection with a smooth filter on a 512 512 matrix. Standardized uptake values (SUVs) were estimated for abnormal uptake sites to obtain quantitative informations about the FDG uptake.

Reference standard (s)	SLNB Interpretation • Sentinel nodes were processed according to the technique described by the EORTC melanoma group: fixed in formaldehyde, cut in half through the hilum and its longest dimension and embedded in paraffin. Five serial step sections of 4 mm each were cut from each face of the lymph node, and staining with H&E, S100, HMB-45, and Melan A was performed. Procedure • a preoperative lymphoscintigraphy was performed using a g camera. Four intradermal injections of 99m Tc (Nanocis, US Bio International Schering, Gif-sur-Yvette, France) were injected around the primary melanoma tumor or site in case of prior limited excision. Dynamic images of 1 min per frame were acquired until the first node was visualized (the SN). Delayed images of the SN basin were acquired at 1 h. The lymph nodes were marked on the skin. All SNBs were performed under general anesthesia within 1–18 h from the time of lymphoscintigraphy. Sentinel nodes were identified by detecting the residual radioactivity using a hand-held g probe (Europrobe, Euromedical Instruments, Le Chesnay, France). The node(s) were then excised. Following excision, the probe was used to detect any evidence of remaining radioactivity, before closure of the surgical wound. Other • Additional imaging procedures were prescribed according to medical history and/or doubtful results in the initial work-up.

Study-level characteristics

	Study (N = 25)
% Female	40%
Mean age (SD)	60 (14-87)
Tumour location	
head and neck	36%
Trunk	32%
extremities	32%
Pathological type	

	Study (N = 25)
nodular	56%
superficial spreading melanoma	20%
Lentigo MM	8%
Other	16%
Mean (range) Breslow thickness *(mm)* of primary lesion	6.6 (4.8 to 12.5)
Tumour stage	
IIB	40%
IIC	16%
IIIA	16%
IIIB	24%
IIIC	4%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(6 participants were excluded from final analysis due primarily to entering a different treatment pathway based on workup and not receiving SLNB as a result)*
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 if those tests conducted after SLNB were blinded.)*
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.)*

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?	High *(PET/CT scan could be after SLNB, with it being performed up to 4 months after SLNB in some patients. Additionally, the author notes that additional tests were used depending on medical history and/or doubtful results in the initial work-up, allowing for variation between participants. It is noted that "The initial staging work-up consisted of a chest radiograph and pelvic and abdominal ultrasonography for 11 patients. Among these patients, four patients had an additional brain CT, and 14 patients had a CT of the pelvis, abdomen, and chest and for brain evaluation, a CT or MRI.")*
Overall risk of bias and directness	Risk of Bias	High *(Unclear blinding and potential for selection bias and bias due to flow and timing of tests.)*
	Directness	Directly applicable

Olmedo, 2017

Bibliographic Reference	Olmedo, D; Brotons-Segui, M; Del Toro, C; Gonzalez, M; Requena, C; Traves, V; Pla, A; Bolumar, I; Moreno-Ramirez, D; Nagore, E; Use of Lymph Node Ultrasound Prior to Sentinel Lymph Node Biopsy in 384 Patients with Melanoma: A Cost-Effectiveness Analysis.; Actas dermo-sifiliograficas; 2017; vol. 108 (no. 10); 931-938

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Spain Setting • Single centre Study dates

	• January 2004 and December 2015 Sources of funding • nr
Inclusion criteria	Underwent lymph node ultrasound before SLNB as part of their staging
Exclusion criteria	Lymph node metastasis had been detected during the physical examination Mucosal, uveal, and unknown primary melanomas, as well as those with insufficient information on the result of the lymph node biopsy, UGB, or SLNB
Number of participants	384
Index test(s)	US • Patients with primary cutaneous melanoma who fulfilled the criteria for SLNB were systematically evaluated beforehand as part of the staging study using B-flow and Doppler lymph node ultrasound. Ultrasound was performed by 2 experienced radiologists (CD and MG). Lymph nodes were classified as benign, indeterminate, or suspicious for melanoma according to standard criteria. The ultrasound examination covered all possible drainage territories depending on the site. In the case of indeterminate or suspicious findings, an ultrasound-guided core-needle biopsy (Tru-cut) was performed.
Reference standard (s)	SLNB • Histopathology of the biopsies performed included hematoxylin-eosin study and immunohistochemistry (S100 and melan-A). In patients whose histology work-up revealed melanoma cells, therapeutic lymph node dissection of the affected lymphatic basin was performed directly. The remaining patients underwent SLNB, followed by therapeutic lymph node dissection if melanoma cells were present.
Additional comments	

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study is retrospective; characteristic of participants was not reported)*

Section	Question	Answer
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?	Unclear *(Ultrasound was performed before SLNB but exact timing was not reported.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding; unclear timing between index test and reference standard.)*
	Directness	Directly applicable

Riquelme-Mc Loughlin, 2019

Bibliographic Reference Riquelme-Mc Loughlin, Constanza; Podlipnik, Sebastian; Bosch-Amate, Xavier; Riera-Monroig, Jose; Barreiro, Alicia; Espinosa, Natalia; Moreno-Ramirez, David; Giavedoni, Priscila; Vilana, Ramon; Sanchez, Marcelo; Vidal-Sicart, Sergi; Carrera, Cristina; Malvehy, Josep; Puig, Susana; Diagnostic accuracy of imaging studies for initial staging of T2b to T4b melanoma patients: A cross-sectional study.; Journal of the American Academy of Dermatology; 2019; vol. 81 (no. 6); 1330-1338

Study Characteristics

Study type	Cross-sectional study
Study details	Study location • Spain Setting

	• Single centre Study dates • January 2011 to April 2017 Sources of funding • The study in the Melanoma Unit, Hospital Clinic, Barcelona, was partly supported by grants from Fondo de Investigaciones Sanitarias PI 12/00840, PI 15/00956, and PI 15/00716 Spain; by the Centro de Investigacion Biomedica en Red de Enfermedades Raras of the Instituto de Salud Carlos III, Spain, cofunded by ‘‘Fondo Europeo de Desarrollo Regional (FEDER), Union Europea, Una manera de hacer Europa’’; by the Agency for Management of University and Research Grants (AGAUR) 2014_SGR_603 and 2017_SGR_1134 of the Catalan Government, Spain; by a grant from ‘‘Fundacio La Marato de TV3, 201331-30,’’ Catalonia, Spain; by the European Commission under the 6th Framework Programme, Contract No. LSHC-CT-2006-018702 (GenoMEL); by Centres de Recerca de Catalunya (CERCA) Programme/Generalitat de Catalunya; by a research grant from ‘‘Fundacion Cientıfica de la Asociacion Espaňola Contra el Cancer’’ GCB15152978SOEN, Spain; and by a grant from the European Academy of Dermatology and Venereology (EADV) (PPRC-2017/19).
Inclusion criteria	Melanoma with >pT2a (Breslow depth >2 mm, regardless of ulceration, or >1 mm with an ulcerated primary tumor) without clinical evidence of metastasis after a complete physical examination
Exclusion criteria	• Palpable lymph nodes or clinically evident metastasis before the imaging studies were performed • Breslow T1 and T2a
Number of participants	308 participants but only 250 underwent ultrasound
Index test(s)	US • Ultrasound imaging was performed before lymphoscintigraphy and sentinel lymph node biopsy. The regional lymph node areas that were explored according to protocol were the ipsilateral axillary group for upper limb melanoma, ipsilateral inguinal group for lower limb melanoma, bilateral neck and supraclavicular groups for head and neck melanoma, and bilateral axillary and inguinal groups for trunk melanoma.
Reference standard (s)	Composite

	• Fine-needle aspiration biopsy, Tru-Cut, open biopsy, SLNB or clinical follow-up
Additional comments	Diagnostic accuracy measures for CT and PET-CT were calculated excluding lymph node metastases and only considering distant metastases. Lymph node ultrasound imaging was performed in 250 participants but 58 ultrasound studies were missing

Study-level characteristics

	Study (N = 308)
% Female	44.5%
Mean age (range)	63 (49-74)
Tumour location *(%)*	
Trunk	39.3%
head and neck	19.2%
Lower extremity	16.2%
Upper extremity	11%
Acral	10.4%
Mucosa	3.9%
Breslow thickness (mm)	4.8%
Ulceration *(%)*	65.6%
AJCC staging *(%)* 2009 AJCC classification	
T2b-T3a	30.8%
T3b-T4a	38%
T4b	31.2%

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Only imaging studies performed within the first 4 months after the primary*

Section	Question	Answer
		melanoma diagnosis were included in the statistical analysis)
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 *(Limited information about 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 *(Ultrasound imaging was performed before reference standards but there was no information about timing between them)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Limited information about reference standard; unclear blinding)*
	Directness	Directly applicable

Sanki, 2009

Bibliographic Reference	Sanki A; Uren RF; Moncrieff M; Tran KL; Scolyer RA; Lin HY; Thompson JF; Targeted high-resolution ultrasound is not an effective substitute for sentinel lymph node biopsy in patients with primary cutaneous melanoma.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2009; vol. 27 (no. 33)

Study Characteristics

Study type	Retrospective cohort study

Study details	Study location • Australia Setting • Participants in the MSLT-I and MSLT-II trials. Study dates • January 2001 - August 2005 Sources of funding • none
Inclusion criteria	• Melanoma • Underwent US
Index test(s)	US Interpretation • US reports of SLN were classified as normal, suspicious or highly probable for metastatic disease (based on the wording of original report). Suspicious or highly probably were classified as positives for this study. Findings suggestive (suspicious or highly probably features) of metastatic disease included an increased vascular signature, rounding of the normal ovoid shape of the node such that the length-to-width ratio of the node was less than 2, loss of the normal hilar echoes and their replacement with low-level internal echoes, and the presence of focal low-level subcapsular space echoes or an asymmetric widening of the subcapsular space. Timing • performed immediately after LS. Procedure • Done using an ATL Ultramark-9 HDI diagnostics US system and linear array L10-5 transducer at a frequency of 5-10 MHz. After 2004 this switched to using a Toshiba Aplio US system with a PLT-1204AT high-resolution, small parts probe at 10-14 MHz.

Reference standard (s)	SLNB When SLNB was offered • SLNB at study centre was recommended to people without clinically detectable metastases and with a Breslow thickness >1mm. It was also recommended for those under 1mm with adverse histological features such as Clark level IV, ulceration etc. Interpretation • Status ultimately determined by histopathologic exam. DUring study period, 12 patients with negative SLNB had metastases confirmed using reverse transcriptase PCR. This was not included in the analysis. Histological exam of SLN alone was used as reference standard. Timing • WLE performed within 24h after LS and US were conducted. Procedure • Each SLN was excised once its blue staining and high radioactivity had identified it.

Study-level characteristics

	Study (N = 716)
Mean (range) Breslow thickness *(mm)*	2 (0.2 to 16)

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Unclear study design. Unclear which patients would have been given both US and SLNB.)*
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?	Unclear *(Limited detail on procedure and 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?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear study design and blinding.)*
	Directness	Directly applicable

Schaarschmidt, 2018

Bibliographic Reference Schaarschmidt, Benedikt Michael; Grueneisen, Johannes; Stebner, Vanessa; Klode, Joachim; Stoffels, Ingo; Umutlu, Lale; Schadendorf, Dirk; Heusch, Philipp; Antoch, Gerald; Poppel, Thorsten Dirk; Can integrated 18F-FDG PET/MR replace sentinel lymph node resection in malignant melanoma?.; European journal of nuclear medicine and molecular imaging; 2018; vol. 45 (no. 12); 2093-2102

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Germany Setting • Single centre Study dates • January 2012 until December 2015 Sources of funding • nr
Inclusion criteria	• Melanoma

	All melanoma patients that underwent a clinically indicated PET/CT and subsequent PET/MR after the injection of a single 18F-FDG dose for distant metastases staging prior to SPECT/CT and consecutive SLNB
Number of participants	52
Index test(s)	PET-CT Procedure • PET/CT scans were performed 60 min after the injection of a weight-adapted activity of 260 ± 50 MBq 18F-FDG. Blood glucose levels were below 150 mg/dL in all patients. Wholebody examinations were performed either in full-dose or low dose technique on a Biograph mCT (Siemens Healthineers, Erlangen, Germany). Full-dose PET/CT scans were performed after the injection an iodine-based contrast agent (100 mL Ultravist, Bayer Vital GmbH Deutschland, Radiology, Leverkusen). To reduce radiation exposure, vendor-specific dose reduction techniques were used (Full dose: CareKV: preset 120 kV and CareDose 4D: preset 210 mAs; Low-dose: CareKV: preset 120 kV and CareDose 4D: preset 40 mAs). PET data were acquired for 2 min per bed position and reconstructed using a 3D attenuation-weighted ordered subsets expectation maximization (OSEM) algorithm with three iterations and 21 subsets and a 4 mm postreconstruction Gaussian filter in a 256 × 256 matrix. Portal venous images were used for attenuation correction. Interpretation • Image analysis was performed on a dedicated OsiriX Workstation (OsiriX MD 8.0.2, Pixmeo SARL, Bernex, Switzerland). One radiologists with 4 (BS) and one nuclear medicine physician with 6 (TP) years of experience in integrated PET/MR reading analyzed PET/CT, PET/MR and PET/MR including DWI in separate sessions to avoid recognition bias. All images were analyzed side by side with the fused SPECT/CT images performed after lymphoscintigraphy to correctly identify the sentinel lymph node on the PET/MR or PET/CT image. Then, the probability of malignancy for each lymph node was determined on a 5-point Likert scale ranging from 1 (definitely not malignant) to 5 (definitely malignant) according to the following imaging criteria: • In PET/CT evaluation, an increased tracer uptake in comparison to the background and to adjacent lymph nodes was considered as a sign of malignancy. Morphology was not analyzed in PET/CT to avoid a potential bias caused by the fact that PET/CT scans in low-dose technique for mere attenuation correction and contrast enhanced, high quality full-dose PET/CT scans were included. PET-MRI

	Procedure • Subsequently to PET/CT, PET/MR imaging was performed 186 ± 48 min after tracer injection on a Biograph mMR (Siemens Healthineers, Erlangen, Germany). For signal reception, a 16-channel radiofrequency head and neck coil, up to four 6-channel radiofrequency surface body coils and a 24-channel radiofrequency spine coil were used. The following MR sequences were acquired: ○ A transverse T1 3D volume interpolated breath-hold examination (VIBE) sequence in Dixon technique for attenuation correction (TR 3.6 ms, TE1 1.23 ms, TE2 2.46 ms, flip angle 10°, slice thickness 3.12 mm, field of view (FOV) 500 × 500 mm2, matrix size 96 × 96, PAT mode: GRAPPA, PAT factor: 2) ○ A transverse T1 fast low-angle shot (FLASH) sequence prior to contrast agent administration (TR 1510 ms, TE 2.15 ms, slice thickness 5.0 mm, FOV 450 × 366 mm2, matrix size 320 × 256, PAT mode: GRAPPA, PAT factor: 2) ○ A transverse T2 half-Fourier acquired single shot turbo spin echo (HASTE) sequence (TR 1500 ms, TE 117 ms, slice thickness 5.0 mm, FOV 450 × 366 mm2, matrix size 320 × 259, PAT mode: GRAPPA, PAT factor: 2) ○ A coronal T2 turbo inversion recovery magnitude (TIRM) sequence (TR 3190 ms, TE 55 ms, TI 220 ms, slice thickness 5.0 mm, FOV 450 × 338mm2, matrix size 384 × 288, PAT mode: GRAPPA, PAT factor: 2) ○ A transverse DWI sequence (b0, b500, b1000, TR 9900 ms, TE 82 ms, TI 220 ms, slice thickness 5.0 mm, FOV 420 × 315 mm2, matrix size 160 × 120, two averages, PAT mode: GRAPPA, PAT factor: 2) ○ A transverse, fat suppressed T1 VIBE sequence prior to injection of a weight-adapted dose of a gadolinium-based contrast agent (TR 4.08 ms, TE 1.49 ms, flip angle 9°, slice thickness 3.5 mm, FOV 400 × 300 mm2, matrix size 512 × 307, PAT mode: GRAPPA, PAT factor: 2) • PET data were acquired for 4 min per bed position in list mode and reconstructed using a 3D attenuation weighted ordered subsets expectation maximization (OSEM) algorithm with three iterations and 21 subsets and a 4 mm postreconstruction Gaussian filter in a 256 × 256 matrix. For attenuation correction, we used a vendor-provided solution based on a four class tissue segmentation that was derived from a 3D Dixon-VIBE sequence. Interpretation • In PET/MR evaluation, morphological criteria and increased tracer uptake were suspicious for metastases. Suspicious morphological criteria were: a) central necrosis, b) loss of a fatty hilus sign, c) round shape, d) focally increased cortical thickness and e) irregular external contour. At least two suspicious morphological criteria or an increased tracer uptake in comparison to the background and to adjacent lymph nodes were considered as signs of malignancy. • In PET/MR including DWI evaluation, the aforementioned criteria complemented by restricted diffusion were suspicious for metastases. At least two suspicious morphological criteria, an increased tracer uptake in comparison to the background and to adjacent lymph nodes or an increased signal of the lymph node in b1000 images accompanied by reduced ADC-values in comparison to adjacent muscular tissue were considered as signs of malignancy.
Reference standard (s)	SLNB SLNB is performed as a standard procedure at the Department of Dermatology, University Hospital Essen, Germany according to the guidelines of the Deutsche Dermatologische Gesellschaft (DDG, German Association of

	Dermatology). The procedure was applied in melanoma patients in AJCC stages I and II (tumor depth of ≥1.0 mm). Subsequent SLNB was performed either under tumescent local anesthesia (LA) or general anesthesia (GA). Preparation and subsequent excision of all marked lymph nodes was carried out via an incision over the location measuring maximum radio-isotype activity by a mobile manual scintillation measuring probe (C-Trak, Care Wise Medical Products Corporation) or by preoperative marking on the skin according to information obtained from SPECT/CT. Surgery was terminated when no further radioactive foci could be traced in the surgical field. The surgical technique was identical in both cohorts. Dyes such as patent blue were not used because of potential allergic reactions and the risk of a permanent tattoo. The histopathological reports after sentinel lymph node dissection served as a reference standard. Apart from the lymph node status (lymph node metastasis: yes/no), the size of the metastatic tissue in the lymph node was noted.
Additional comments	In a second reading session, discrepant findings between both readers were resolved. Additionally, SUVmax and SUVpeak were automatically assessed by the software after drawing a spherical volume of interest (VOI) encompassing the whole lymph node on the morphological images, which was then copied to the attenuation corrected the PET image. ADCmean and ADCmin were evaluated by drawing a region of interest around the lymph node on the b0-image of DWI, which was then copied to the ADC-map. Short axis diameter was determined on the CT images in PET/CT examinations and on the unenhanced T1 FLASH images in PET/MR examinations.

Study-level characteristics

	Study (N = 52)
% Female	57.6%
Mean age (SD)	50.5 (16)
Tumour location *(%)*	
head and neck	7.7%
Upper arm	7.7%
Lower arm	5.8%
Torso	46.1%
Upper thigh	15.4%
Lower thigh	11.5%
Foot	5.8%

	Study (N = 52)
Clark's level *(%)*	
Level II	3.8%
Level III	17.3%
Level IV	19.2%
Level V	1.9%
Not further classified	57.8%
Ulcerations *(%)*	28.8%
Tumour thickness (mm): Mean (SD) Range: 0.8mm to 10mm	2.28 (1.97)

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study is retrospective; only included patients who underwent SPECT/CT after lymphoscintigraphy (this allowed a more reliable correlation of the sentinel lymph node than planar lymphoscintigraphy alone))*
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

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Index tests were performed before reference standard but specific timing was not reported.)*
Overall risk of bias and directness	Risk of Bias	High *(Retrospective study; potential for selection bias; unclear blinding; unclear timing between index tests and reference standard)*
	Directness	Partially applicable *(Staging not reported at baseline)*

Sibon, 2007

Bibliographic Reference	Sibon C; Chagnon S; Tchakérian A; Bafounta ML; Longvert C; Clerici T; Zimmermann U; Saiag P; The contribution of high-resolution ultrasonography in preoperatively detecting sentinel-node metastases in melanoma patients.; Melanoma research; 2007; vol. 17 (no. 4)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • France Setting • Single centre Study dates • January 1999 - May 2005
Inclusion criteria	• Melanoma • Underwent US
Number of participants	146; 131 underwent US before SLNB and were included in study.
Index test(s)	US When US was offered • Since September 1995, study centre prospectively added hrUS of the resected tumor scar, lymphatic drainage area(s) and regional LN zones to the routine initial and follow-up examinations performed in our

	department for all new stage I–III melanoma patients. However, pre-SLNB hrUS was not systematically performed due to difficulties in scheduling timing of events. Only those undergoing US pre-SLNB were included in the study. Timing • During the 24 h preceding SNB and before the lymphoscintigraphy (see below), hrUS was performed by experienced radiologists. Procedure • A Power Vision 6000 (Toshiba Medical France SA, Puteaux, France) was used, with a 6–12-MHz linear transducer set between 7.5 and 12 MHz according to the depth of the LN being explored. When the interpretation of images was doubtful, a consensus was reached with the main investigating radiologist. Regional lymphatic basins predicted by the location of the melanoma were examined. A longitudinally configured LN with an echogenic hilum was considered reactive. A circular/oval hypoechoic LN with a Solbiati index < 1.5 and no hyperechoic hilum constituted the major criteria defining metastatic involvement. Interpretation • Minor criteria for LN metastasis were a nodular hypoechoic focus within an LN with an irregular LN margin. Stringent criteria were the presence of all three major criteria. Nonstringent criteria of LN metastasis were the presence of one or two major criteria and/or one or two minor criteria.
Reference standard (s)	SLNB When SLNB was offered • In January 1999, the study centre introduced SLNB into routine practice for patients with no clinically detectable LN metastasis and a Breslow index Z 1 mm or, when the Breslow index was < 1 mm, with regression/ ulceration Interpretation • performed without knowledge of the hrUS results. All LN with histologically proven tumor deposits, regardless of their size, were considered metastatic, except when fewer than five isolated tumor cells were present. The metastatic deposit size was measured under light microscopy in each histological section and the largest one was retained to define its diameter. When two or more SNs were invaded, the largest metastasis was retained for the measurement.

	Procedure • The afternoon before SNB, lymphoscintigraphy was performed using 99mTc-labeled colloidal rhenium sulfur (Nannocis, Schering CIS Bio International, Saclay, France). The skin site corresponding to the hottest emission point was marked. On the day of surgery, 15 min before skin incision, patent blue dye (patent blue V sodium 2.5%, Guerbet, Roissy, France) was intradermally injected around the melanoma excision scar. A hand-held g camera (Navigator GPS, Mallinckrodt, Tycs International Ltd, Carlsbad, California, USA) was used to measure background and SN radioactivity preoperatively. The SN was identified as a hot and/or blue-dyed LN.

Study-level characteristics

	Study (N = 131)
% Female	46.6%
Mean age (SD)	56 (17 to 92)
Tumour location	
head and neck	14%
Trunk	32%
extremities	54%
Mean Breslow thickness *(mm)*	
<1mm	51%
1.01-2.00mm	27%
2.01-4.00mm	12%
>4mm	1%
% ulcerated	10%
histological type	
superficial spreading melanoma	50%
nodular	27%
Other	23%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(hrUS was routinely given to all people undergoing SLNB. Although the author states that not all participants undergoing SLNB received US prior to surgery, only 131/146 participants receiving SLNB during the study period underwent pre-SLNB US. Only these participants were included in the analysis)*
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 *(Study allowed for the classification of regional metastases using stringent or nonstringent criteria and provided diagnostic accuracy data for both.)*
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?	Low *(blinded to hrUS result)*
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 *(US conducted in 24hr prior to SLNB)*
Overall risk of bias and directness	Risk of Bias	Low
	Directness	Directly applicable

Singh, 2008

Bibliographic Reference	Singh B; Ezziddin S; Palmedo H; Reinhardt M; Strunk H; Tüting T; Biersack HJ; Ahmadzadehfar H; Preoperative 18F-FDG-PET/CT imaging and sentinel node

biopsy in the detection of regional lymph node metastases in malignant melanoma.; Melanoma research; 2008; vol. 18 (no. 5)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • Germany Setting • Single centre Study dates • unclear
Inclusion criteria	• PET/CT during staging work-up • performed prior to SLNB • Melanoma • All participants had AJCC 7th ed. stage I or II
Exclusion criteria	• previous sentinel or complete lymphadenectomy • histologically unproven primary melanoma • Stage III/IV
Number of participants	52
Index test(s)	PET-CT Interpretation • Two experienced observers assessed 18F-FDG PET/CT fusion imaging independently. The PET readers were blinded to the results of LS. The definite decision for classifying a focus in PET as pathologic was on the basis of only the visual evaluation. Any focal uptake more than background was counted as suspect only if it was not a false-positive focus (physiologic accumulation or brown fat tissue) in fusion imaging. Thus, such false-positive foci have not been included in our statistics. A focus of increased 18F-FDG activity (activity greater than background) in the lymphatic basin by preoperative PET scanning was considered as true positive, when the corresponding lesions were involved histopathologically and, if not, the lesions were designated as false positive. For concordant PET and histological negative findings, the PET results were described as true negative. Conversely, in discordant, PET negative and histopathological positive findings, the PET results were considered as false negative.

Timing

- day before SLNB

procedure

- All imaging studies were performed with a dual-modality PET/CT system (Biograph; Siemens Medical Solutions Inc., Hoffman Estates, Illinois, USA). The Biograph scanner consists of a combination of a dual-detector helical CT and a high-resolution PET scanner with a 15.8- cm axial field of view and an in-plane spatial resolution of 4.6 mm. PET imaging started 101 ± 21 min after intravenous injection of 370 ± 40 MBq FDG through an anterior cubital vein. Blood glucose measured before FDG injection was 5.55 ± 1.11 mmol/l. PET acquisition was performed in three parts, from the base of the skull to the apex of the lungs in two bed positions at 5 min per bed position with the arms down, from the shoulders to upper thighs in five to seven bed positions at 5 min per bed position with the arms up, and finally in patients with melanoma of the leg from the proximal femora to the tip of the toes in six beds at 3 min per bed position. CT imaging was performed within 1 min before PET imaging with the patient in precisely the same position. The acquisition parameters for dual-detector helical CT were 130 kV, 40 mAs, 0.8 s per CT rotation, 5-mm slice thickness, and pitch 1.5. One liter of an iodinated oral contrast agent (Peritrast-oral-GI; Ko¨hler Chemie GmbH, Alsbach, Germany) was applied within 1 h before CT imaging for better delineation of intestinal structures. An intravenous infusion of contrast medium (120 ml of Ultravist-300) was given at a dose rate of 2.5 ml/s for 50 s.
- Immediately after the infusion of contrast media, the whole-body CT data were acquired. A limited breathhold technique was used for CT and shallow breathing for PET imaging to avoid motion-induced artifacts in the area of the diaphragm. Briefly, patients were asked to breathe quietly throughout the PET scan, but to hold their breath for about 10 s when the CT tube approached the lower mediastinum until it passed the liver [22]. Total acquisition time varied between 40 and 50 min and up to 70 min, when a patient with melanoma of the leg was scanned down to the toes. Before starting the PET data acquisition, the net radioactivity (full syringe–empty syringe) administered and the time of injection were recorded to measure the standard uptake value. PET images were iteratively reconstructed with attenuation correction on the basis of a rescaling of the CT image as described elsewhere [23]. All patients provided written informed consent after the nature of the imaging studies was fully explained. The anatomical and functional images were first displayed individually, as transversal, coronal, and sagittal slices and then by image fusion (ESOFT version 3.0.7.32, Siemens, Germany) of the corresponding CT and PET slices and interpreted by the same team of radiologists and nuclear physicians.

Reference standard (s)	SLNB Interpretation • Conducted non-blind, Histological examination of the excised lymph nodes (SLN and non-SLN) was performed by using conventional hematoxylin and eosin staining. In case of negative findings in the hematoxylin and eosin staining, the specimens were subjected to immunohistochemical staining (S 100, HMB 45). Timing • Preoperative lymphoscintigraphy performed on all patients the day before surgery Procedure • A hand-held gamma probe (Navigator, USSC, Norwalk, Connecticut, USA) was used to precisely locate the skin projection of the sentinel node, using the skin mark as a guide. The skin incision was made directly over this point and the sentinel node was removed using the gamma probe to guide dissection. In some patients, two or more sentinel nodes were identified in different basins; all of them were excised. After excision of the SLNs, the lymphatic basin was rechecked for radioactivity.

Study-level characteristics

	Study (N = 52)
% Female	30.8%
Mean age (SD)	55 (13)
Mean (range) Breslow thickness *(mm)*	2.87 (1 to 12)
tumour thickness *(mm)*	
1.00-2.00mm	53.8%
2.01-4.00mm	23.1%
>4mm	23.1%
Tumour location	
head and neck	25%
Trunk	31%
extremities	44%

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(Unclear study design. Unclear whether all participants undergoing SLNB also received PET/CT scans.)*
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 *(Conducted blind to LS results)*
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 *(unblinded to PET/CT results)*
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 PET-CT scan however LS and SLNB were done within 24h.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear study design and SLNB interpretation was non-blind to results of PET/CT scan.)*
	Directness	Directly applicable

Stahlie, 2021

Bibliographic Reference	Stahlie, E. H. A., van der Hiel, B., Bruining, A., van de Wiel, B., Schrage, Y. M., Wouters, M. W. J. M., ... & van Akkooi, A. C. J. (2021). The value of lymph node ultrasound and whole body 18F-FDG PET/CT in stage IIB/C melanoma patients prior to SLNB. *European Journal of Surgical Oncology*, *47*(5), 1157-1162

Study Characteristics

Study type	Prospective cohort study
Study details	Study location

	• The Netherlands Setting • Single centre Study dates • between April 2019 and January 2020 Sources of funding • none
Inclusion criteria	• Melanoma stage IIB-C • patients with a primary melanoma with a Breslow thickness >2 mm with ulceration and with a Breslow thickness >4 mm without ulceration. • Planned for WLE and SLNB • Underwent US and PET/CT
Exclusion criteria	• Patients with palpable nodal metastases or symptomatic distant metastases detected by S100B prior to LSG and SLNB.
Index test(s)	• US US examinations were performed using the Philips EPIQ 7 Ultrasound (Bothell, Washington, USA). Lymph nodes that presented with a loss of fatty hilum, cortical nodules, a short axis diameter of >1 cm, a convex aspect and/or blurred margins were considered suspicious. In case of suspicious lymph nodes, US-guided FNAC was performed. Images were assessed and FNAC was performed by experienced radiologists. US images were considered to be true positive (TP) when suspicious lesions were proven metastases by FNAC and false positive (FP) when FNAC failed to prove metastases. US images were considered to be true negative (TN) when US was negative and SLNB failed to detect SN metastases. US images were considered false negative (FN) when US was negative but SLNB did detect SN metastases or when US failed to detect metastases but 18F-FDG PET/ CT did detect cytologically or proven metastases. • PET/CT Whole body 18F-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 (Cleveland, USA). Abnormal FDG accumulation was evaluated according to location, size and intensity. Images were assessed by experienced nuclear medicine physicians and the treating surgeon, who took the clinical setting into account. 18F-FDG PET/CT images were considered to be TP when suspicious lesions were proven

	metastases by FNAC of histological biopsy and FP when these failed to prove metastases. 18F-FDG PET/CT was considered to be TN when 18F-FDG PET/CT was negative and the SLNB failed to detect SN metastases. 18F-FDG PET/CT images were considered FN when 18F-FDG PET/CT was negative but the SLNB did detect SN metastases or when 18F-FDG PET/CT failed to detect metastases but US did detect FNAC-proven metastases
Reference standard (s)	SLNB When SLNB was offered Patients who had no metastases detected by the preoperative 18F-FDG PET/CT or US, proceeded to undergo LSG and SLNB. SNpositive patients (microscopic disease) entered, depending on their tumor burden, follow-up guided by US or started 1-year adjuvant systemic therapy. SN-negative patients entered standard follow-up, consisting of appointments with the nurse practitioner and dermatologist: 3-monthly the first year and 6-monthly the following 2-5 years. Patients with metastases (macroscopic disease) detected by preoperative 18F-FDG PET/CT or US, confirmed by cytology, did not undergo LSG or SLNB. Patients with regional lymph node metastases underwent lymph node dissection (LND) followed by adjuvant therapy.

Study-level characteristics

	Study (N = 23)
Female	30%
Median (range) age, years	74 (37-85)
Stage	
IIB	52%
IIC	48%
Location	
Extremities	57%
Trunk	44%
Head/neck	0%
Microsatellites	13%

	Study (N = 23)

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low *(Prospective study. However, note that as only those patients who underwent both US and PET/CT pre-operatively were included, there is a chance of selection bias).*
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 *(People with positive findings on pre-operative imaging did not undergo SLNB.)*
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 *(Different reference standard depending on findings of pre-operative imaging.)*
	Directness	Directly applicable

Thompson, 2019

Bibliographic Reference	Thompson, J.F.; Haydu, L.E.; Uren, R.F.; Andtbacka, R.H.; Zager, J.S.; Beitsch, P.D.; Agnese, D.M.; Mozzillo, N.; Testori, A.; Bowles, T.L.; Hoekstra, H.J.; Kelley,

M.C.; Sussman, J.; Schneebaum, S.; Smithers, B.M.; McKinnon, G.; Hsueh, E.; Jacobs, L.; Schultz, E.; Reintgen, D.; Kane, J.M.; Friedman, E.B.; Wang, H.; Van Kreuningen, L.; Schiller, V.; Elashoff, D.A.; Elashoff, R.; Cochran, A.J.; Stern, S.; Faries, M.B.; Preoperative Ultrasound Assessment of Regional Lymph Nodes in Melanoma Patients Does not Provide Reliable Nodal Staging: Results from a Large Multicenter Trial; Annals of surgery; 2019

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • USA, Canada, Australia, Finland, Germany, Italy, Israel, The Netherlands, Spain, Sweden, Switzerland and UK. Setting • 63 institutions Study dates • December 20, 2004, to May 6, 2013
Inclusion criteria	• Took part in MSLT-II trial *underwent screening for inclusion in the MSLT-II trial, which required US.*
Number of participants	3526 enrolled in MSLT-II; 2877 eligible for pre-op US study; 2859 (3302 basins) patients underwent SLNB of the same node for which US was performed.
Index test(s)	US Timing • In some centers, general US assessment of the entire node basin was performed before the LSG, while in other centers it was performed after the LSG, when the location of SNs was known, allowing focused US examination of them if the result of the LSG was known to the ultrasonographer. Procedure • All participants in the MSLT-II trial underwent preoperative US and lymphoscintigram. The US guidelines stated that an abnormal node was characterized by the detection of either 1 or 2 of the following: (1) length:depth ratio <2; (2) a hypoechoic center; (3) inability to identify a nodal hilar vessel; (4) a focal rounded area of low-level echoes with increased vascularity in that area. US data for each center were collected prospectively, and were correlated with the findings from

	subsequent histologic examination of the SN(s) removed from each patient. Patients in whom no SN was identified (n ¼ 12) were excluded. Patients in whom the preoperative US was of a basin other than the SN basin subsequently demonstrated by lymphoscintigraphy were also excluded (n ¼ 5). Of 3437 possible SN basins, 25 had no SN identified and 110 basins assessed by US were non-SN basins, resulting in 3302 eligible basin evaluations (see Fig. 1). Patients with SNs found to be positive only by RT-PCR were considered pathologically negative for this study.
Reference standard (s)	SLNB At all centers, the SN histopathology was assessed using standard hematoxylin and eosin (H&E) stained sections, and with immunohistochemistry (including S100, Mart-1, and HMB45), as previously described.14,15 Central pathology review of all SNs that had been reported by the contributing centers to contain metastatic disease was performed by one of the authors (AJC).

Study-level characteristics

	Study (N = 2,859)
Mean Breslow Thickness of primary tumour *(mm)*	2.24

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?	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

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Unclear timing of tests relative to each other. Additionally, LSG could be performed prior to or after the US. Diagnostic accuracy data is provided separately for these US performed pre and post-LSG however this is only provided for the overall cohort and not the subgroups.)*
Overall risk of bias and directness	Risk of Bias	Low *(However, note unclear blinding and timing of reference standard.)*
	Directness	Directly applicable

van Rijk, 2006

Bibliographic Reference van Rijk MC; Teertstra HJ; Peterse JL; Nieweg OE; Olmos RA; Hoefnagel CA; Kroon BB; Ultrasonography and fine-needle aspiration cytology in the preoperative evaluation of melanoma patients eligible for sentinel node biopsy.; Annals of surgical oncology; 2006; vol. 13 (no. 11)

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • The Netherlands Setting • Single centre Study dates • November 2000 and December 2004 Sources of funding • nr
Inclusion criteria	• Melanoma • Clinically localised cutaneous melanoma • Breslow thickness 1mm or more • Clark's level • At least level IV

Number of participants	107
Index test(s)	US • Ultrasonography was performed one or several days prior to lymphatic mapping. A 7.5-MHz transducer (Siemens Elegra, Erlangen, Germany) or a Kretz Voluson 730 expert (GE Medical Systems, Zipf, Austria) with a 6–12 MHz transducer was used. • Criteria to classify a lymph node as suspicious were a length–depth ratio of less than two, conversion of a fatty hilum to a hypoechoic hilum, substantial cortical asymmetry or a focal area of low-level echoes in the subcapsular sinus of the node. Based on a study by Van den Brekel et al. (1998) lymph nodes in the neck at levels 1, 3 and 4 were also classified as suspicious when the diameter exceeded 5 mm. Fine-needle aspiration of suspicious lymph nodes was performed with a 21-gauge (0.8-mm) or 22-gauge (0.7-mm) needle. The aspirated material was air dried, methanol fixated and stained according to the May-Grunwald-Giemsa method. Patients with tumour positive FNAC were scheduled for formal dissection of the involved basin and wide local (re-)excision of the primary tumour. Patients without tumour cells in their aspirate were scheduled for sentinel node biopsy and wide local (re-)excision.
Reference standard (s)	SLNB • Lymphatic mapping was performed with the aid of 99mTc-nanocolloid (Nanocoll, General Electric Health Care, Eindhoven, The Netherlands), lymphoscintigraphic images (ADAC Vertex, Milpitas, CA, USA), patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) and a gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany). The procedure has been described in detail previously. A hot spot on the lymphoscintigraphic image was considered to be a sentinel node if an afferent lymphatic channel was visualised, if the hot spot was the first one seen in a sequential pattern or if the hot spot was the only one depicted. An afferent blue lymphatic vessel coming directly from the tumour site also defined a node as the sentinel node. • All sentinel nodes were formalin fixated, bisected, paraffin embedded and cut at a minimum of six levels at 50- to 150-lm intervals. Pathological evaluation included both hematoxylin-eosin and immunohistochemical staining (S-100 and HMB-45). Metastases were classified as either >2 mm in diameter or ≤2 mm, as 2 mm is the current spatial resolution of ultrasonography according to Rossi et al. (2003). Patients with tumour cells in the sentinel node were offered dissection of the involved basin. After April 2002, patients with a small

	solitary subcapsular deposit did not undergo node dissection in accordance with the guidelines proposed by Starz et al. (2001).

Study-level characteristics

	Study (N = 107)
% Female	47%
Mean age (SD)	Mean 50 (range 15 to 82)
Tumour location *(%)* Primary	
head and neck	6%
Trunk	40%
Arm	22%
leg	32%
Breslow thickness (mm)	Median 2.0 (range 0.6 to 12.5)
Clark's level *(%)*	
Level II	1%
Level III	35%
Level IV	51%
Level V	8%
Undeterminable	5%
Ulceration *(%)*	30%

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?	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?	Unclear *(Ultrasonography was performed one or several days prior to SLNB but specific timing was not reported.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear blinding; unclear timing between index test and reference standard.)*
	Directness	Directly applicable

Voit, 2014

Bibliographic Reference	Voit, C. A., Gooskens, S. L., Siegel, P., Schaefer, G., Schoengen, A., Röwert, J., ... & Eggermont, A. M. (2014). Ultrasound-guided fine needle aspiration cytology as an addendum to sentinel lymph node biopsy can perfect the staging strategy in melanoma patients. *European Journal of Cancer*, *50*(13), 2280-2288

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • Germany Setting • Single centre Study dates • July 2001 – November 2010

Inclusion criteria	• Histopathologically proven primary malignant melanoma (at least 1.00 mm Breslow thickness, or if less, at least Clark IV/V, ulcerated and/or regressed) • Planned for a sentinel node procedure
Number of participants	1000
Length of follow-up	Mean and median follow-up was 56 and 53 months, respectively (range 1 to 132 months)
Index test(s)	US • In the timeslot between lymphoscintigraphy and surgery, patients were examined by ultrasound (US) in B-mode and Power Doppler. All US examinations were performed using the high-end device MyLab 70 (ESAOTE, Genova, Italy) equipped with three transducers (1–18 MHz) (B-mode, 30 pictures per second, colour Doppler, Power Mode). The lymph node was measured, the pattern was described and it was classified as benign [b], suspicious [s] or malignant [m] by an expert ultrasonographist (C.V.). During the course of the study, two additional and less extensively trained ultrasonographists were integrated into the team. An ultrasound was considered suspicious, when Peripheral perfusion (PP) was present or if the central echo was wandering towards the rim. US was considered malignant if there was a total loss of central echoes (LCE) or if the lymph node was enlarged and balloon shaped (BS). If none of these morphological criteria were present, the lymph node was considered benign.
Reference standard (s)	SLNB • Lymph nodes were fixed for 24 h in buffered formalin. After fixation they were cut in half through the hilum and its longest dimension and embedded in paraffin. In rare cases, exceptionally large nodes were sectioned parallel to the first cut in order to fit in the blocks. Five serial step sections of 4 lm each were cut from each face of the lymph node, and staining with H&E, S100 and HMB-45 was performed. Microanatomic location of the metastases and SN tumour burden were assessed according to the Dewar and Rotterdam criteria, respectively.

Study-level characteristics

	Study (N = 1000)
Mean age (SD)	59 years (range 15 to 94)
mean Breslow thickness *(mm)*	Mean 2.58 (range 0.2 to 44)

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 (Note: If US depicted a suspicious or malignant SN, FNAC was performed for verification of the lesion. If a clearly malignant ultrasound pattern could not be verified by FNAC, patients proceeded to undergo a SLNB. In the early phase of the study, all patients with positive FNAC proceeded to undergo a SN nonetheless (n = 47). During the course of the study, a change in hospital policy allowed the surgeon to proceed to an immediate CLND after a positive FNAC. The decision to change a planned SN to a CLND was always based on a positive cytology. If the US did not show any suspicious nodes or if cytology is negative, the patients proceed to undergo the scheduled SN.)
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?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low (Note: Final histology of the SN or LND was considered as the golden standard.)
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear *(Limited detail on the timing of index test relative to reference standard)*
Overall risk of bias and directness	Risk of Bias	Moderate (variation in reference standard used. Unclear timing)
	Directness	Directly applicable

Wagner, 2012

Bibliographic Reference	Wagner T; Chevreau C; Meyer N; Mourey L; Courbon F; Zerdoud S; Routine FDG PET-CT in patients with a high-risk localized melanoma has a high predictive positive value for nodal disease and high negative predictive value for the presence of distant metastases.; Journal of the European Academy of Dermatology and Venereology : JEADV; 2012; vol. 26 (no. 11)

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location • France Setting • Single centre
Inclusion criteria	• PET/CT during staging work-up • underwent FDG PET-CT for initial staging. All participants did not present any clinical or paraclinical signs of nodal involvement or distant metastases at the time they were referred for PET-CT. • Melanoma • presented with either an ulcerated melanoma with a BT > 1 mm or with a BT > 4 mm
Number of participants	48
Index test(s)	PET-CT Image interpretation • Images were interpreted by at least one experienced nuclear medicine specialist, aware of all the clinical findings. For the assessment of regional nodal disease, PET findings were considered positive if there was abnormally increased FDG uptake in a lymph node in the drainage territory of the melanoma, and negative otherwise. The gold standard for nodal status was pathological examination. For the assessment of distant metastasis, PET findings were classified as positive (FDG uptake indicative of distant metastasis), negative (absence of FDG uptake indicative of distant metastasis) or non-conclusive (FDG uptake not typically indicative of distant metastasis, but it could not be ruled out). The diagnosis of metastasis was considered as confirmed on the data of conventional imaging and clinical follow-up, and/or histological examination of a biopsy of the lesion whenever feasible. Initial PET evaluations were considered as true negative, true positive,

	false negative or false positive depending on the presence or absence of detectable metastatic disease within 6 months after the PET scan. Details of procedure • Patients were asked to recline in a horizontal position for 60–90 min after injection, and were advised to remain rested, to refrain from speaking, and to minimize swallowing so as to avoid local, unspecific FDG uptake due to muscular activation. Acquisitions of the whole body were performed using a PET-CT camera (Discovery ST; General Electric Healthcare, Waukesha, WI, USA) Acquisitions were performed in two-dimensional mode, 5 min/bed position. Two-D sinograms were reconstructed in 256*256 matrix size, with a field of view of 50 cm and corrected for attenuation, random and scatter. Data were reconstructed using an iterative OSEM (Ordered Subset Expectation Maximization) algorithm (3 iterations; 10 subsets; loop filter with a FWHM 5.0 mm; postfilter with a FWHM of 3.5 mm). CT imaging was performed for attenuation correction and anatomical correlation with a 200 mA tube current, 140 kV tube voltage, a helical pitch of 0.75:1 and a reconstructed slice thickness of 3.75 mm for an interval between slices of 3.27 mm. Images were interpreted on a Xeleris workstation (General Electric Healthcare, Waukesha, WI, USA).
Reference standard (s)	SLNB For detection of regional metastases. Limited detail on how the procedure was conducted. Composite For detection of any metastases: using data from conventional imaging and clinical follow-up, and/or histological examination of a biopsy of the lesion whenever feasible.

Study-level characteristics

	Study (N = 48)
Mean (SD) Breslow Thickness *(mm)*	7.6 (4.5)
% with ulceration and Breslow thickness 1-4mm	39.6%
% Breslow thickness >4mm without ulceration	20.8%
% Breslow thickness >4mm with ulceration	39.6%
Tumour stage *(according to the AJCC 7th ed.)*	
IIA	16.7%
IIB	39.6%

	Study (N = 48)
IIIC	39.6%
Unclear but >4mm Breslow thickness	4.2%

Risk of bias

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Study is retrospective. It is unclear whether PET-CT was routinely given to people undergoing a SLNB or whether it was reserved for specific cases. Most participants in this cohort were ulcerated and had a high proportion of people with thick melanomas. Additionally, the protocol for offering SLNB at the study centre is 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 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 *(Limited information regarding how SLNB was conducted, whether it was conducted blind and whether)*
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, it is noted that two patients positive for regional metastases on PET/CT scan did not undergo SLNB and instead had metastases confirmed using LND. A potential false positive PET/CT result underwent additional analysis in which the surgeon dissected iliac internal nodes*

Section	Question	Answer
		and pathologic analysis confirmed that the hot node on PET harboured metastatic deposits.)
Overall risk of bias and directness	Risk of Bias	High *(Potential for selection bias and it is unclear how and when the SLNB was conducted. Some participants received additional exploration of lymph nodes depending on pattern of results.)*
	Directness	Directly applicable

Wagner, 2005

Bibliographic Reference Wagner, JD; Schauwecker, D; Davidson, D; Logan, T; Coleman III, JJ; Hutchins, G; Love, C; Wenck, S; Daggy, J; Inefficacy of F-18 fluorodeoxy-D-glucose-positron emission tomography scans for initial evaluation in early-stage cutaneous melanoma; Cancer; 2005; vol. 104 (no. 3); 570-579

Study Characteristics

Study type	Prospective cohort study
Study details	Study location • USA Setting • Single centre
Inclusion criteria	• Melanoma 1.5.4 *biopsy-proven* • primary cutaneous melanoma • Breslow thickness 1mm or more or with locally recurrent/ solitary in-transit recurrent melanoma after a previous excision • at least 18 years of age
Exclusion criteria	• age >80 years • comorbidities resulting in a raised risk of anaesthesia • ocular or mucosal melanomas • clinical evidence of regional lymph node basin metastases or distant metastatic (M1) disease • palpable lymphadenopathy • Infection • inflammation in the regional node basin(s) • previous wide excision of > 4 cm diameter • lymph node dissections • Skin grafts

	• tissue transfers or flaps that altered the lymphatic drainage pattern from the primary tumour site • pregnant or breast-feeding females • previous malignancy 1.5.5 (except in situ lesions, Stage I basal and squamous cell skin malignancies, and patients without evidence of disease > 5 years after treatment) • allergy to isosulfan blue dye or fluorodeoxyglucose
Number of participants	150; 144 included in analysis
Index test(s)	PET-CT Interpretation • PET data were reconstructed initially by filtered back projection technique (FBP) to permit rapid scan interpretations. PET scan findings believed to be suspicious for possible distant metastatic disease were investigated further with conventional imaging modalities, and if indicated, biopsy. Subjects with PET scan findings suspicious for possible distant metastases that could not be confirmed with conventional imaging studies underwent SLNB. These patients were followed clinically to identify the site(s) of initial disease recurrence and underwent follow-up targeted conventional imaging 3–6 months after surgery to reevaluate PET scan findings suspicious for distant metastatic disease. • PET scan images for research interpretation purposes were derived from an ordered subset expectation maximization (OSEM) data reconstruction algorithm, when possible. Knowing only the location of the primary melanoma tumor, a single nuclear medicine specialist experienced in FDG-PET scan imaging for melanoma performed the PET scan interpretations in a blinded fashion using a receiver operator curve (ROC). The researcher interpreted OSEM reconstruction images (or best FBP reconstruction images) and assigned each lymph node basin at risk for occult disease a reading of definitely positive, probably positive, uncertain, probably negative, or definitely negative. • When applicable, standardized uptake values (SUV) were calculated to obtain quantitative informa-tion on the FDG uptake. Strong focal hypermetabolic lesions (SUV 2.5) were considered malignant. In the majority of cases, the definite decision for classifying a focus as a metastasis was based on the visual evaluation, with appropriate consideration to location, symmetry, and uptake pattern. The research interpretation also evaluated possible foci of distant metastases using the original data set. Blinded ROC readings were reported for non-lymph node areas of increased FDG uptake determined to be suspicious for possible distant metastases. Procedure • After confirmation of eligibility, subjects underwent preoperative whole-body FDG-PET scans. Scans were performed with an ECAT

	951/31R PET scanner (Siemens, South Iselin, NJ). Patients fasted 6 hours before scanning was performed. Two imaging protocols were used during the study. During the initial portion of the research study (Patients 1–24), whole body attenuation-corrected scans were performed. • For melanomas of the upper extremities, head, neck, or trunk, a transmission scan including the cervical, axillary, and ilioinguinal lymph node basins was obtained for attenuation correction purposes. The lower extremities below the inguinal lymph node basin were studied without attenuation correction. A venous catheter was placed in the arm of the patient (opposite the location of the melanoma, if located on the upper extremity). Thirty minutes before imaging, the subject was injected with approximately 10 mCi of FDG. Scans were initiated 30 minutes after FDG injection and data acquisition continued for 60 minutes with scan duration of 5 minutes at each bed position. Subjects with primary lesions of the trunk or lower extremity had a triple lumen bladder catheter placed for continuous saline flushing during the scan. • During the latter portion of the study (Patients 25–150), a high sensitivity scanning protocol for the regional lymph node basin(s) was employed. The protocol was similar, but scanning began 60 minutes after the injection of FDG. Multiple bed position emission images were obtained over the lymph node basin(s) of interest with scan duration of 10 minutes at each position. Depending on the location of the cutaneous melanoma tumor, the following lymph node basins were imaged: for melanomas of the face and scalp, bilateral parotids, cervical, and suboccipital basins; for melanomas of the neck, bilateral cervical basins; for melanomas of the shoulder and upper chest (above the level of the nipples), bilateral axillary and cervical basins; for melanomas of the upper extremity, ipsilateral axillary (including the epitrochlear region if below the elbow); for melanomas of the trunk, at or below the nipples, bilateral axillary and bilateral inguinal • basins; and for melanomas of the lower extremity, ipsilateral inguinal and pelvic basins (including the popliteal region if below the knee). Immediately after a 5-minute per bed position transmission study, the dose of FDG was injected. Sixty minutes after the FDG injection, emission scans were performed over the same regions of the body for 10 minutes at each bed position. Finally, a whole-body study was performed (without attenuation correction) as a screen for distant metastatic disease.
Reference standard (s)	Composite interpretation • The gold standard for comparison of lymph node metastases was sentinel lymph node histology and clinical follow-up. Blinded PET scan interpretations for each lymph node basin defined to be at risk by lymphoscintigraphy were compared with the histologic analysis of SLNB tissue specimens from the same basin and also with clinical examination performed 6 months after the biopsy was performed. Each biopsy specimen of the lymph node basin was considered an independent observation. For lymph node metastases, blinded readings

of definitely or probably positive were counted as positive. Sensitivity, specificity, and positive and negative predictive value for PET scan detection of occult regional lymph node metastases were estimated along with the corresponding exact 95% confidence intervals (CI).

Procedure

- Preoperative dynamic lymphoscintigraphy was performed to identify the basin(s) at risk for lymph node disease. Lymphoscintigraphy was performed on the same day as SLNB. In the current study, 1–2 mCi of unfiltered technetium 99M-sulfur colloid was injected intradermally in 2–4 divided doses at the tumor site 2–4 hours before surgery. Scintigraphic imaging with a large field of view gamma camera was performed.
- Imaging continued, depending on the location of the melanoma site, for 2.5 hours for sites of potentially equivocal lymphatic drainage. The initial lymph node(s) in each basin to accumulate radiotracer, and any additional lymph nodes with a visualized lymphatic channel from the site of injection, were marked on the skin.
- After the induction of anesthesia, 0.5–2.0 mL of Lymphazurin Blue (Zenith Parenterals, Rosemont, IL) was injected intradermally around the site of the cutaneous tumor just before skin preparation.
- All lymph node basins identified by lymphoscinitgraphy wereexplored through incisions directed by the use of a hand-held gamma probe (C-Track, Care Wise Medical Products, Morgan Hill, CA). All blue lymph nodes were removed as sentinel lymph nodes. Ex vivo sentinel lymph node to residual lymph node basin radioactivity ratio was calculated. If necessary, additional radioactive lymph nodes were removed until the scintigraphic ratio of the most radioactive sentinel lymph node to residual basin was 10:1. If frozen section or permanent section analysis of sentinel lymph nodes demonstrated evidence of metastatic melanoma, complete regional lymphadenectomy was performed on the involved lymph node basin(s).

- Pathologic analysis was performed without knowledge of FDG-PET scan findings. Suspicious sentinel lymph nodes were sometimes submitted for intraoperative frozen section analysis. Nonsuspicious and frozen section- negative sentinel lymph nodes were fixed in formalin and submitted for 1-mm step sections of theentire lymph node(s). These sections were analyzed with hematoxylin and eosin (H&E) stains. Sentinel lymph nodes negative for metastases by this analysis were recut for additional sections and stained with S-100 and/or HMB-45 immunoassays.
- Nonsentinel lymph nodes and completion lymphadenectomy specimens were analyzed in routine fashion after formalin fixation, with one to three sections from the central region of the lymph node(s) reserved for H&E staining.

Study-level characteristics

	Study (N = 144)
% Female	49%
Mean age (SD) mean range	54 (24-79)
Tumur location	
Axial	68%
extremities	32%
Mean (range) Breslow thickness *(mm)*	2.81 (1 to 14)

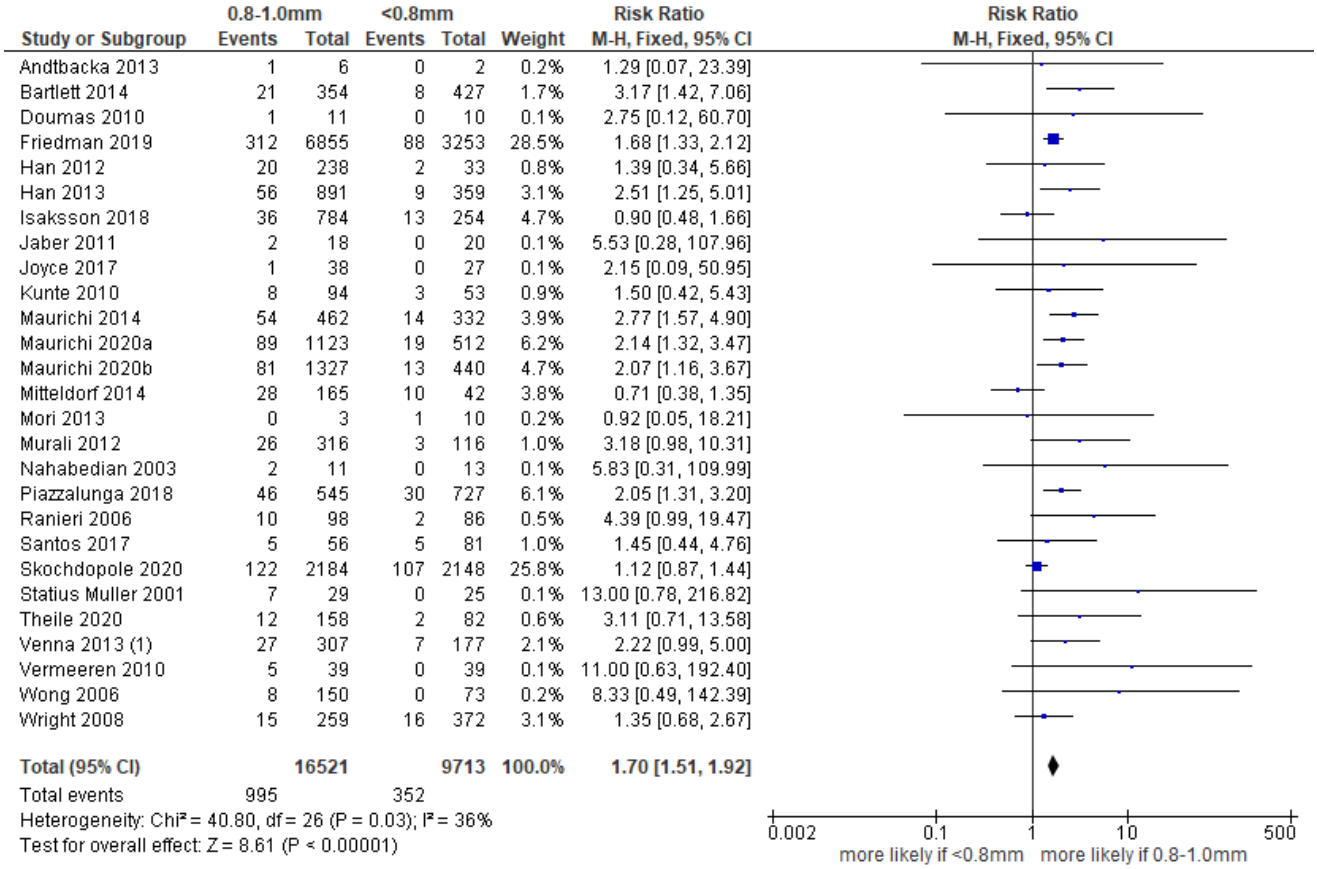
Risk of bias

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?	Low *(conducted blind)*
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 *(Lack of clarity as to the role of follow-up as part of the reference standard. It is unclear whether the time of clinical exam differed between participants and how many lymph node*

Section	Question	Answer
		metastases were determined at follow-up rather than SLNB.)
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear role of follow-up as part of reference standard.)*
	Directness	Directly applicable

Appendix G - Forest plots

Figure 1: Breslow thickness (0.8-1.0mm compared to <0.8mm) as a predictor of SLNB positivity



Footnotes
(1) Compared 0.80-1.00mm (according to AJCC 7th ed.)

Figure 2: Ulceration as a predictor of SLNB positivity

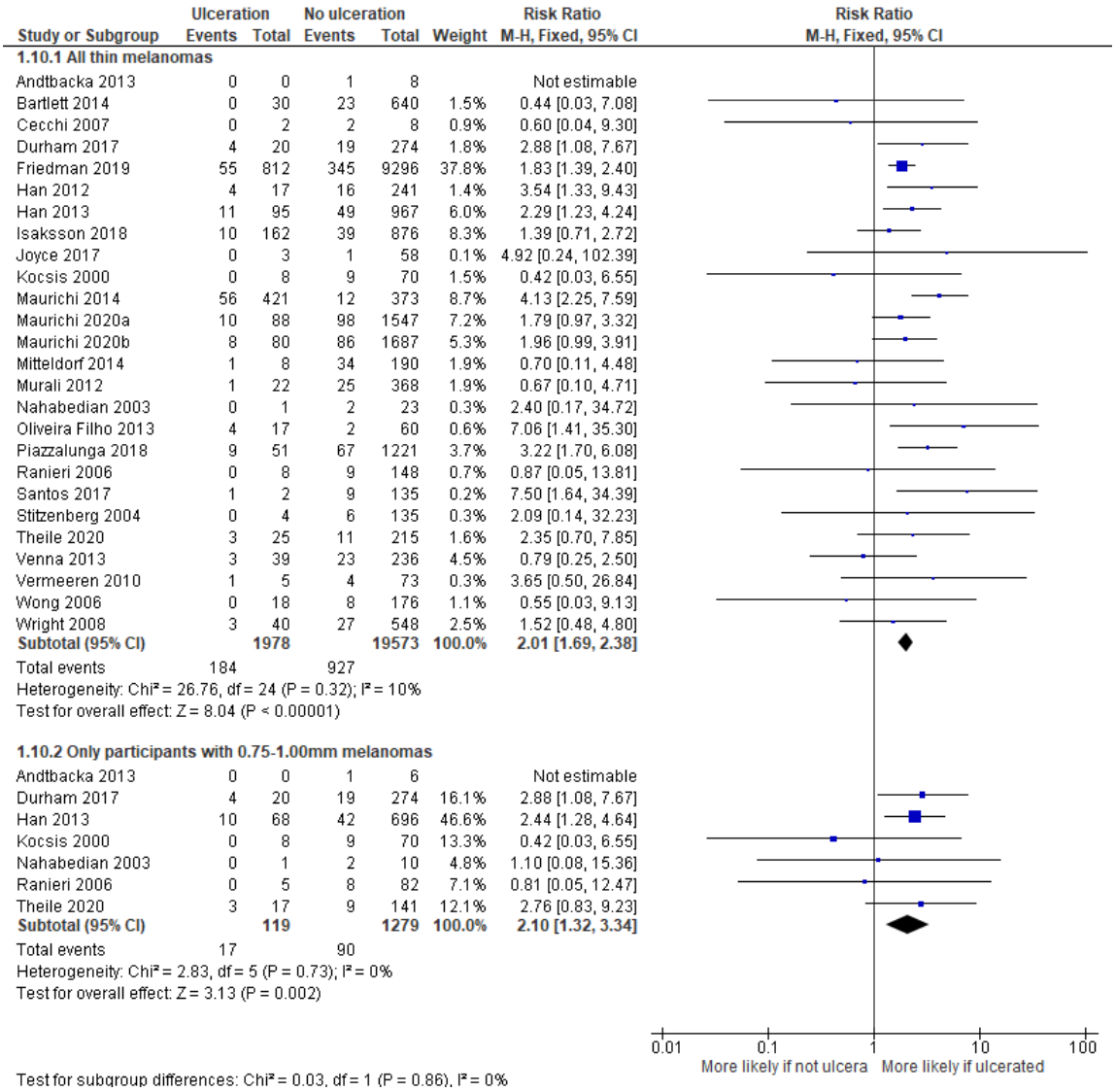


Figure 3: Ulceration as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

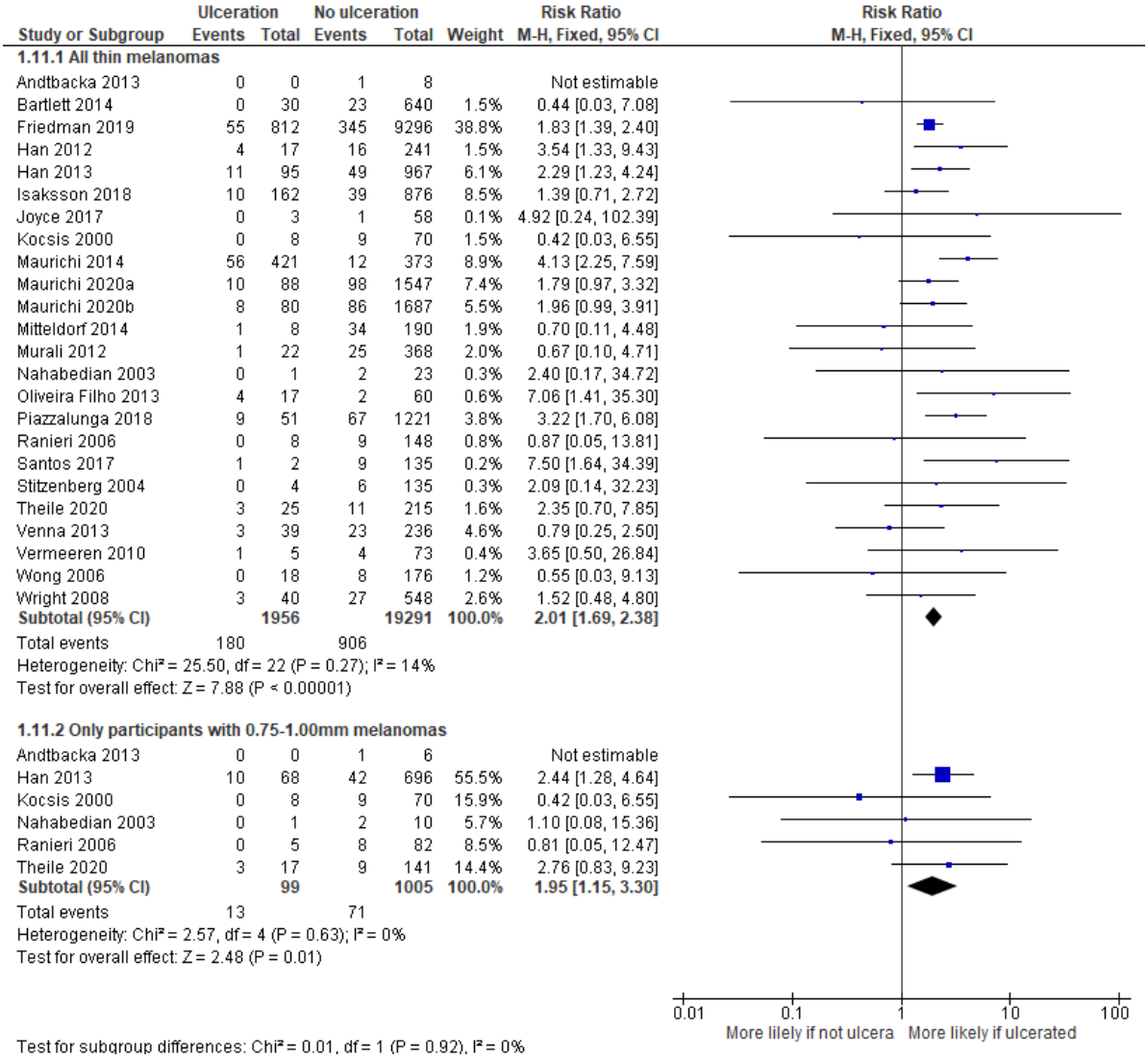
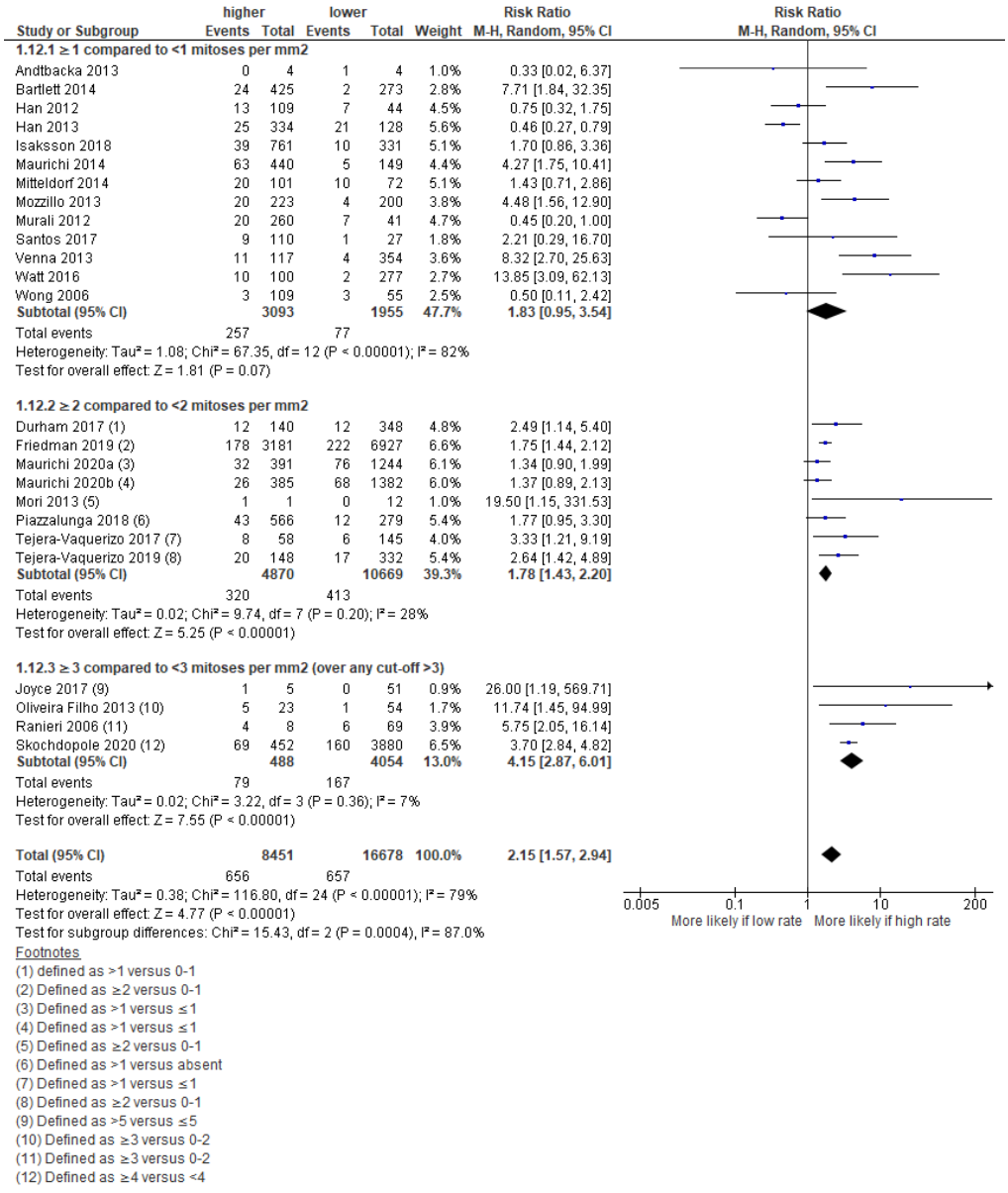
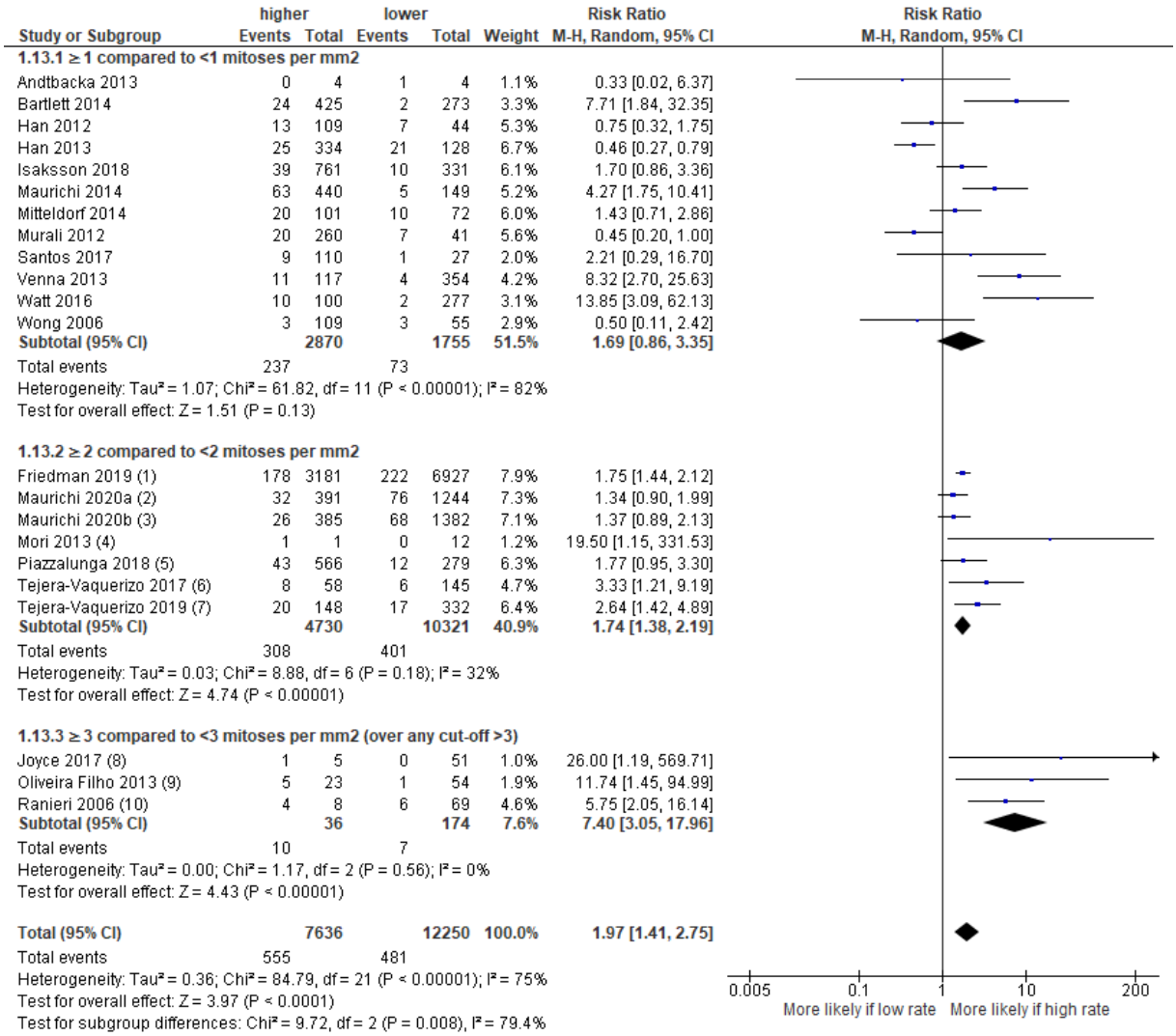


Figure 4: Mitotic index (high versus low rate per mm^2) as a predictor of SLNB positivity



Footnotes
(1) defined as >1 versus 0-1
(2) Defined as ≥2 versus 0-1
(3) Defined as >1 versus ≤1
(4) Defined as >1 versus ≤1
(5) Defined as ≥2 versus 0-1
(6) Defined as >1 versus absent
(7) Defined as >1 versus ≤1
(8) Defined as ≥2 versus 0-1
(9) Defined as >5 versus ≤5
(10) Defined as ≥3 versus 0-2
(11) Defined as ≥3 versus 0-2
(12) Defined as ≥4 versus <4

Figure 5: Mitotic index (high versus low rate per mm^2) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)



Footnotes
(1) Defined as ≥2 versus 0-1
(2) Defined as >1 versus ≤1
(3) Defined as >1 versus ≤1
(4) Defined as ≥2 versus 0-1
(5) Defined as >1 versus absent
(6) Defined as >1 versus ≤1
(7) Defined as ≥2 versus 0-1
(8) Defined as >5 versus ≤5
(9) Defined as ≥3 versus 0-2
(10) Defined as ≥3 versus 0-2

Figure 6: Subgroup analysis: Mitotic index (≥1 versus <1 per mm^2) as a predictor of SLNB positivity

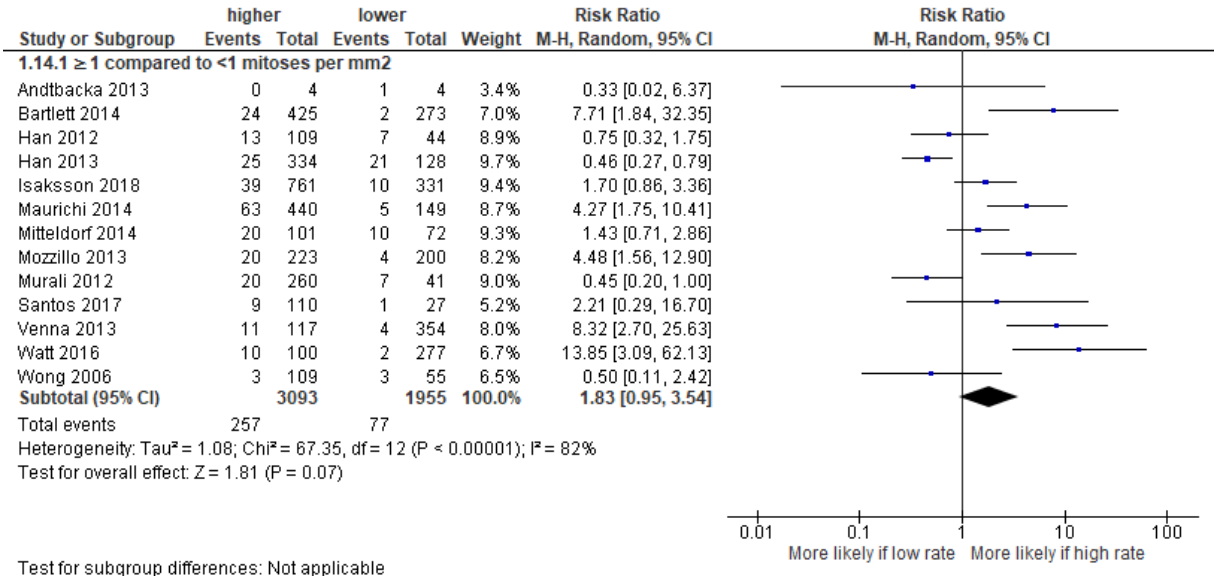
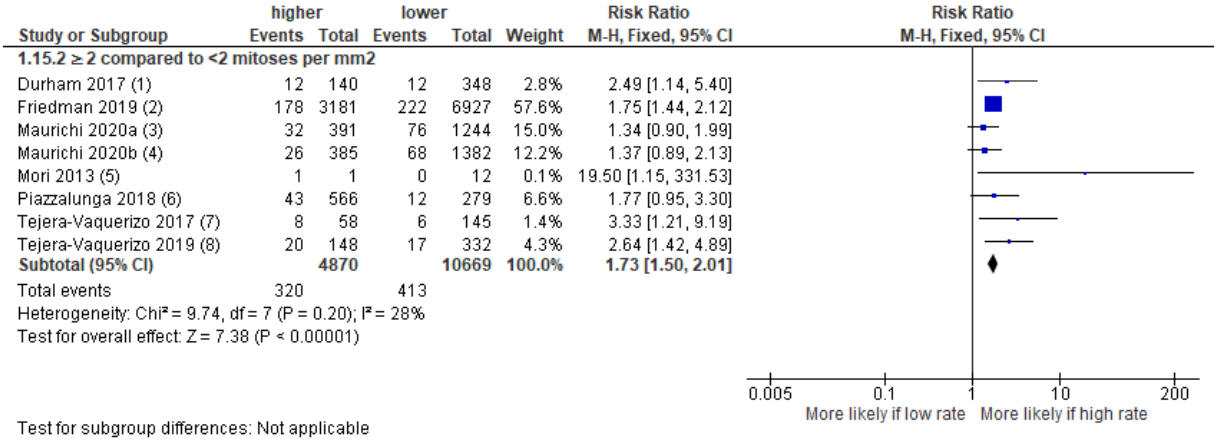


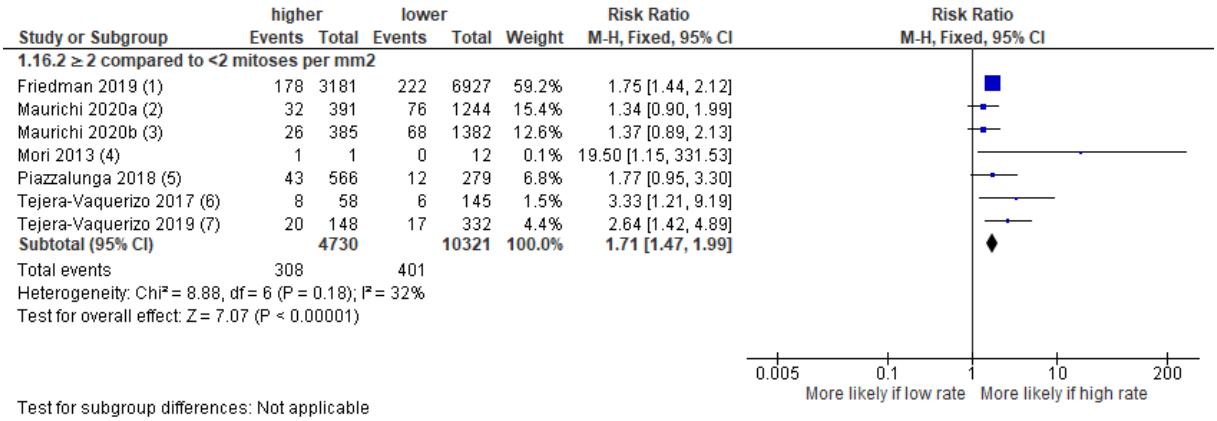
Figure 7: Subgroup analysis: Mitotic index (≥2 versus <2 per mm^2) as a predictor of SLNB positivity



Footnotes

(1) defined as >1 versus 0-1
(2) Defined as ≥2 versus 0-1
(3) Defined as >1 versus ≤1
(4) Defined as >1 versus ≤1
(5) Defined as ≥2 versus 0-1
(6) Defined as >1 versus absent
(7) Defined as >1 versus ≤1
(8) Defined as ≥2 versus 0-1

Figure 8: Subgroup analysis: Mitotic index (≥2 versus <2 per mm^2) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

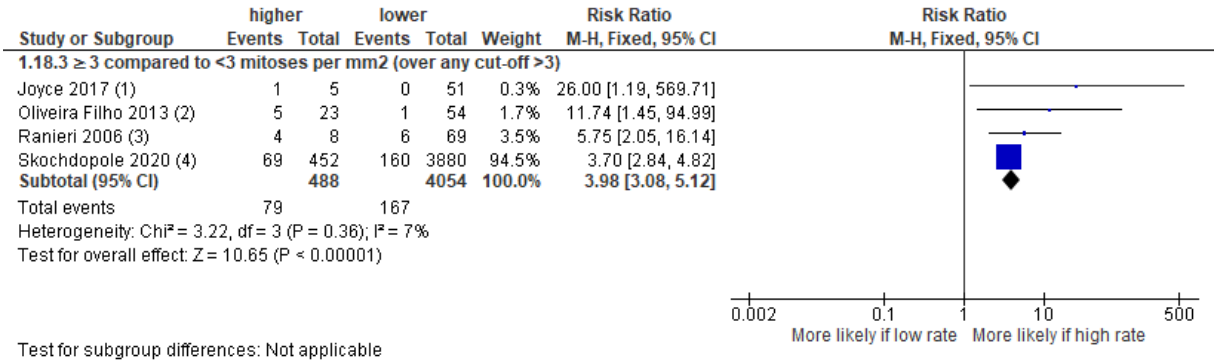


Test for subgroup differences: Not applicable

Footnotes

(1) Defined as ≥2 versus 0-1
(2) Defined as >1 versus ≤1
(3) Defined as >1 versus ≤1
(4) Defined as ≥2 versus 0-1
(5) Defined as >1 versus absent
(6) Defined as >1 versus ≤1
(7) Defined as ≥2 versus 0-1

Figure 9: Subgroup analysis: Mitotic index (≥3 versus <3 per mm^2) as a predictor of SLNB positivity

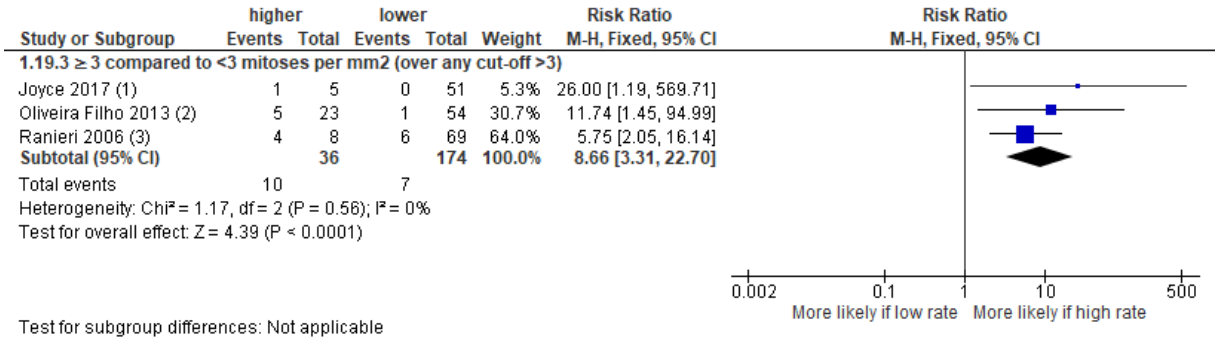


Test for subgroup differences: Not applicable

Footnotes

(1) Defined as >5 versus ≤5
(2) Defined as ≥3 versus 0-2
(3) Defined as ≥3 versus 0-2
(4) Defined as ≥4 versus <4

Figure 10: Subgroup analysis: Mitotic index (≥3 versus <3 per mm^2) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

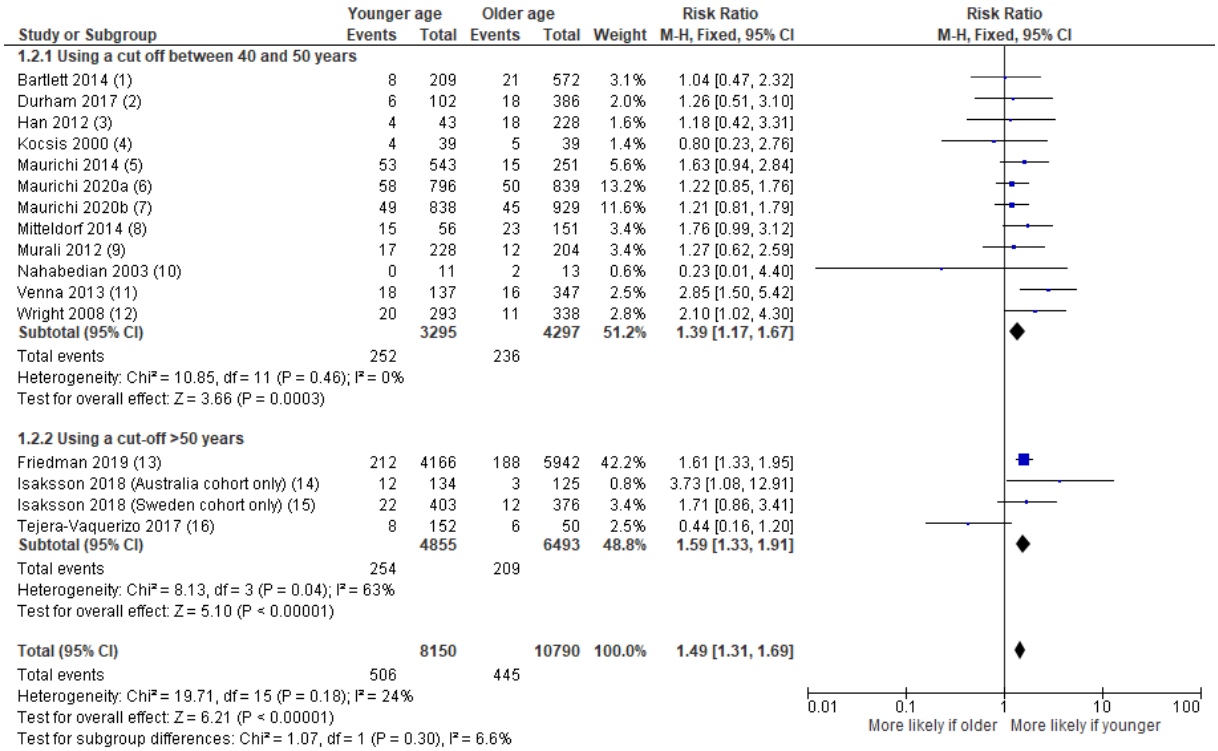


Test for subgroup differences: Not applicable

Footnotes

(1) Defined as >5 versus ≤5
(2) Defined as ≥3 versus 0-2
(3) Defined as ≥3 versus 0-2

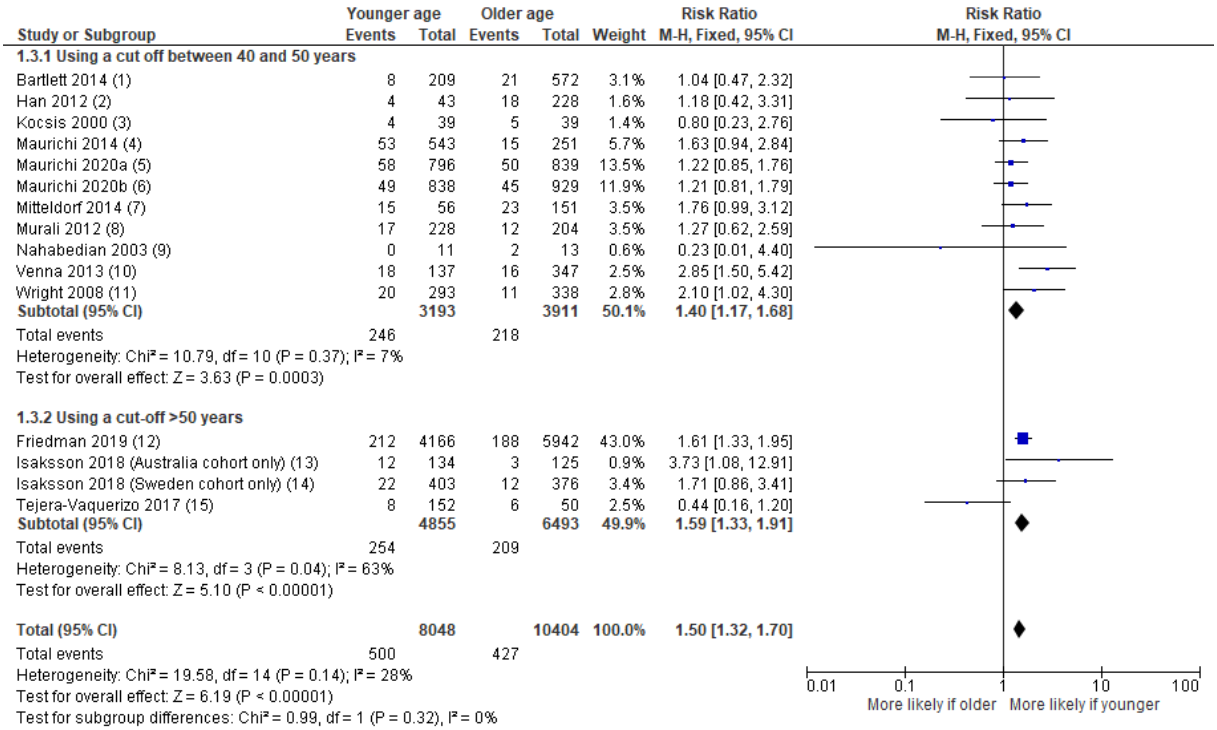
Figure 11: Age (younger versus older age) as a predictor of SLNB positivity



Footnotes

(1) <41 versus ≥41 years
(2) ≤45 versus >45
(3) <40 versus ≥40 years
(4) <50 versus ≥50
(5) ≤50 versus >50
(6) <50 versus ≥50
(7) <50 versus ≥50
(8) <40 versus >40
(9) <50 versus ≥50
(10) <45 versus ≥45
(11) ≤43 versus >43
(12) ≤50 versus >50
(13) <55 versus ≥55
(14) ≤52 versus >52
(15) ≤59 versus >59
(16) ≤65 versus >65

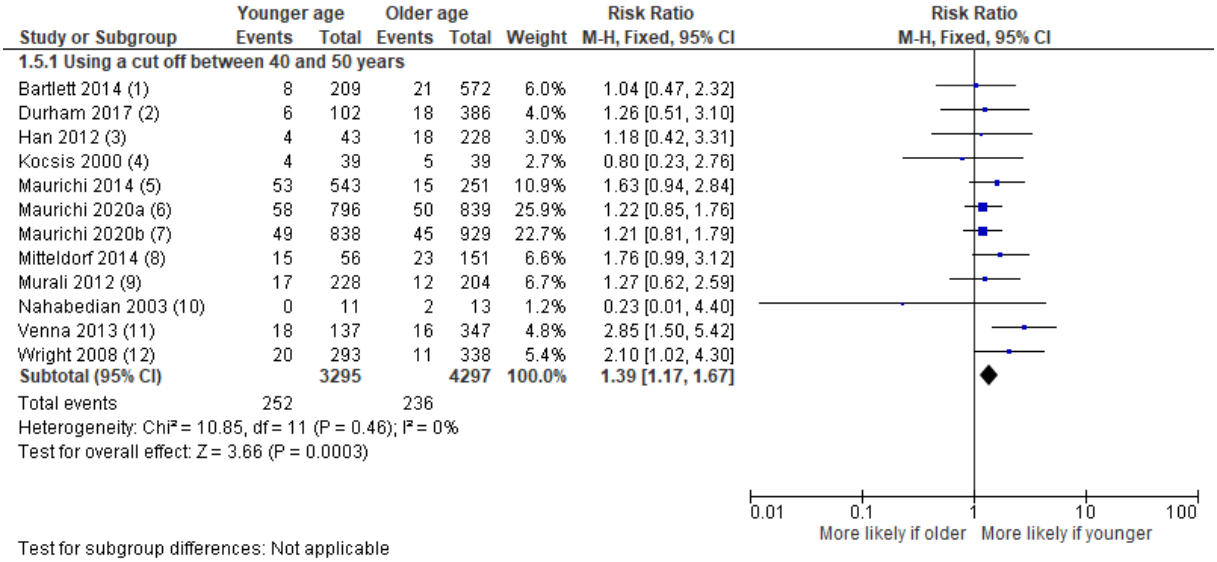
Figure 12: Age (younger versus older age) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)



Footnotes

(1) <41 versus ≥41 years
(2) <40 versus ≥40 years
(3) <50 versus ≥50
(4) ≤50 versus >50
(5) <50 versus ≥50
(6) <50 versus ≥50
(7) <40 versus >40
(8) <50 versus ≥50
(9) <45 versus ≥45
(10) ≤43 versus >43
(11) ≤50 versus >50
(12) <55 versus ≥55
(13) ≤52 versus >52
(14) ≤59 versus >59
(15) ≤65 versus >65

Figure 13: Subgroup analysis: Age (younger versus older age) as a predictor of SLNB positivity, dichotomised between 40 and 50 years of age

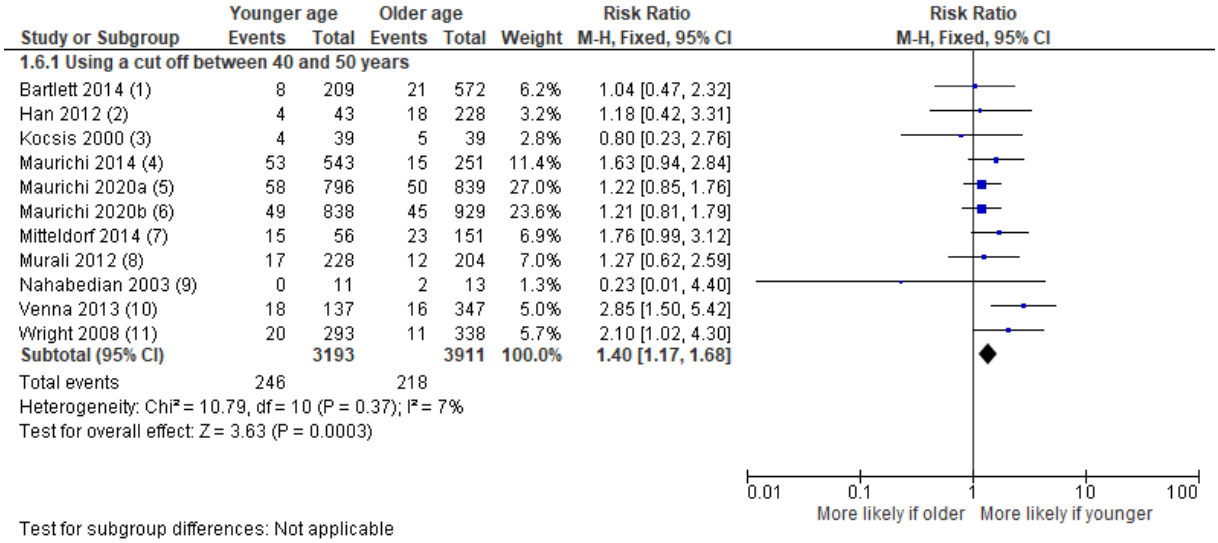


Test for subgroup differences: Not applicable

Footnotes

(1) <41 versus ≥41 years
(2) ≤45 versus >45
(3) <40 versus ≥40 years
(4) <50 versus ≥50
(5) ≤50 versus >50
(6) <50 versus ≥50
(7) <50 versus ≥50
(8) <40 versus >40
(9) <50 versus ≥50
(10) <45 versus ≥45
(11) ≤43 versus >43
(12) ≤50 versus >50

Figure 14: Subgroup analysis: Age (younger versus older age) as a predictor of SLNB positivity, dichotomised between 40 and 50 years of age (sensitivity analysis excluding high risk of bias studies)



Study or Subgroup	Younger age Events	Younger age Total	Older age Events	Older age Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Using a cut off between 40 and 50 years						
Bartlett 2014 (1)	8	209	21	572	6.2%	1.04 [0.47, 2.32]
Han 2012 (2)	4	43	18	228	3.2%	1.18 [0.42, 3.31]
Kocsis 2000 (3)	4	39	5	39	2.8%	0.80 [0.23, 2.76]
Maurichi 2014 (4)	53	543	15	251	11.4%	1.63 [0.94, 2.84]
Maurichi 2020a (5)	58	796	50	839	27.0%	1.22 [0.85, 1.76]
Maurichi 2020b (6)	49	838	45	929	23.6%	1.21 [0.81, 1.79]
Mitteldorf 2014 (7)	15	56	23	151	6.9%	1.76 [0.99, 3.12]
Murali 2012 (8)	17	228	12	204	7.0%	1.27 [0.62, 2.59]
Nahabedian 2003 (9)	0	11	2	13	1.3%	0.23 [0.01, 4.40]
Venna 2013 (10)	18	137	16	347	5.0%	2.85 [1.50, 5.42]
Wright 2008 (11)	20	293	11	338	5.7%	2.10 [1.02, 4.30]
Subtotal (95% CI)		**3193**		**3911**	**100.0%**	**1.40 [1.17, 1.68]**
Total events	246		218			

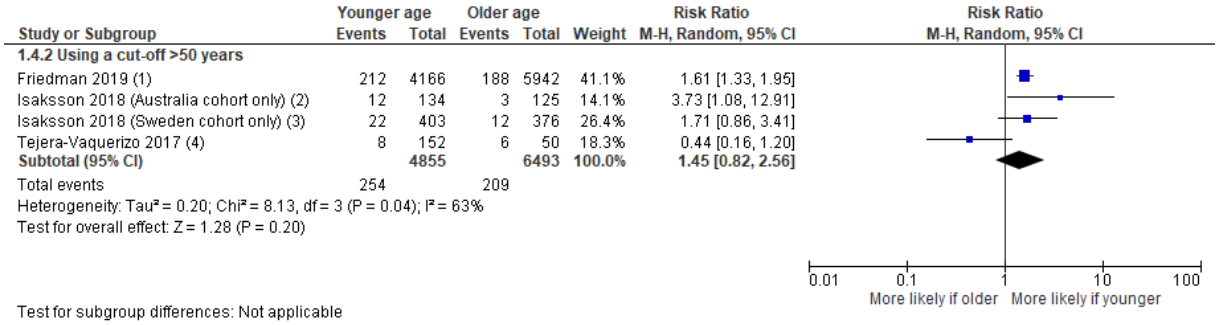
Heterogeneity: Chi² = 10.79, df = 10 (P = 0.37); I² = 7%
Test for overall effect: Z = 3.63 (P = 0.0003)

Test for subgroup differences: Not applicable

Footnotes

(1) <41 versus ≥41 years
(2) <40 versus ≥40 years
(3) <50 versus ≥50
(4) ≤50 versus >50
(5) <50 versus ≥50
(6) <50 versus ≥50
(7) <40 versus >40
(8) <50 versus ≥50
(9) <45 versus ≥45
(10) ≤43 versus >43
(11) ≤50 versus >50

Figure 15: Subgroup analysis: Age (younger versus older age) as a predictor of SLNB positivity, dichotomised over 50 years of age



Study or Subgroup	Younger age Events	Younger age Total	Older age Events	Older age Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.2 Using a cut-off >50 years						
Friedman 2019 (1)	212	4166	188	5942	41.1%	1.61 [1.33, 1.95]
Isaksson 2018 (Australia cohort only) (2)	12	134	3	125	14.1%	3.73 [1.08, 12.91]
Isaksson 2018 (Sweden cohort only) (3)	22	403	12	376	26.4%	1.71 [0.86, 3.41]
Tejera-Vaquerizo 2017 (4)	8	152	6	50	18.3%	0.44 [0.16, 1.20]
Subtotal (95% CI)		**4855**		**6493**	**100.0%**	**1.45 [0.82, 2.56]**
Total events	254		209			

Heterogeneity: Tau² = 0.20; Chi² = 8.13, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable

Footnotes

(1) <55 versus ≥55
(2) ≤52 versus >52
(3) ≤59 versus >59
(4) ≤65 versus >65

Figure 16: Clark level (IV-V compared to I-III) as a predictor of SLNB positivity

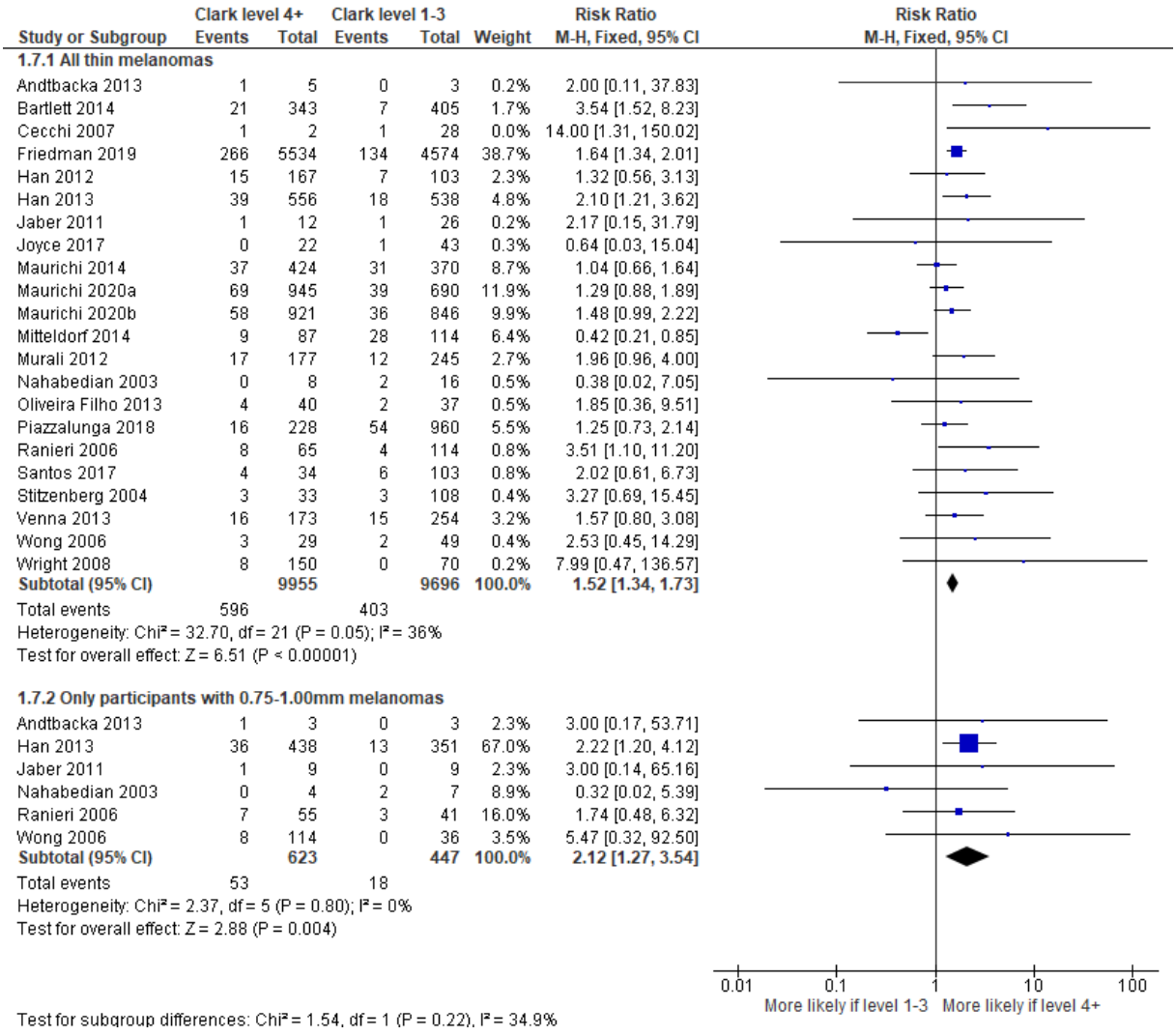


Figure 17: Clark level (IV-V compared to I-III) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

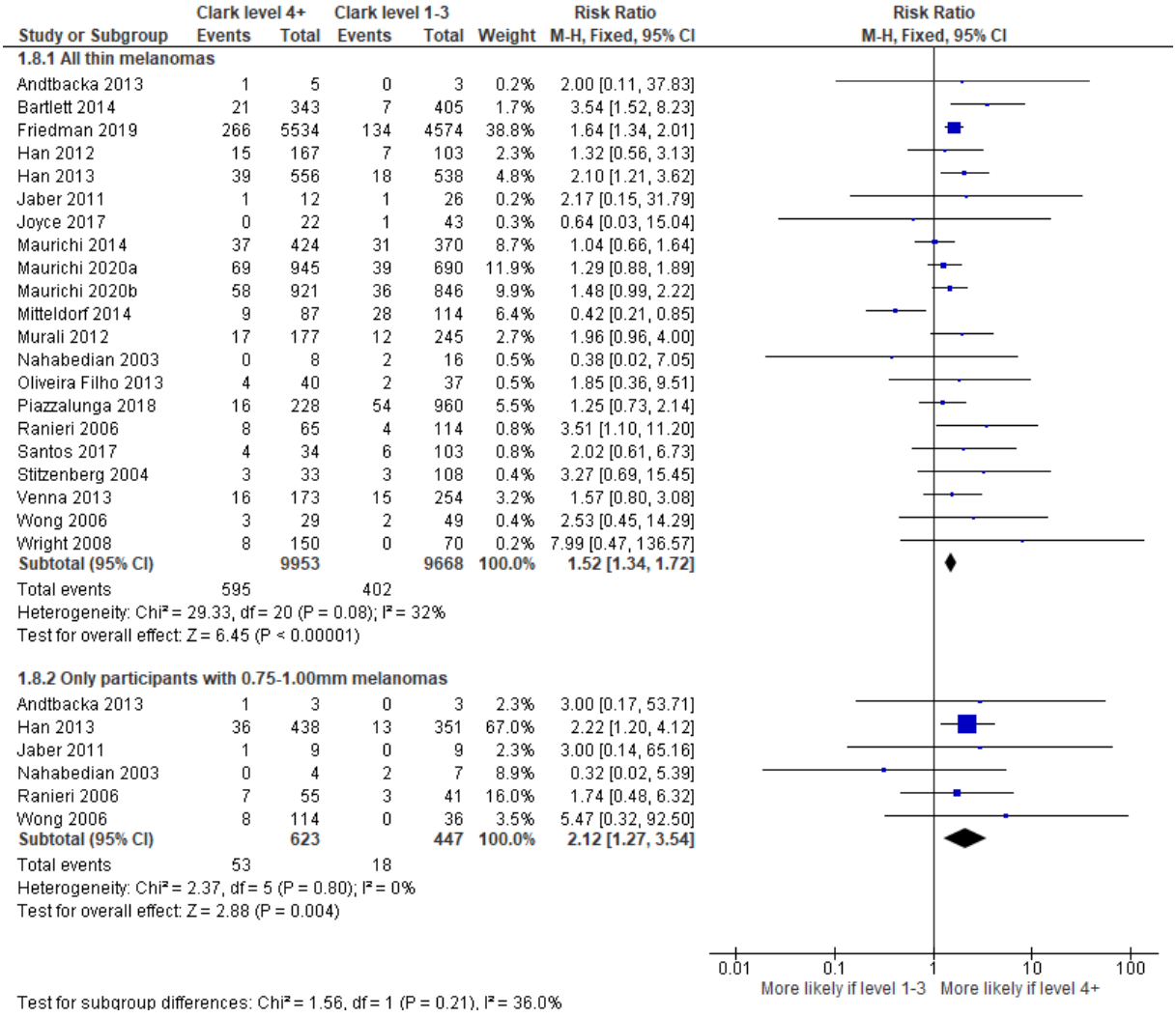


Figure 18: AJCC 8th edition tumour stage (T1b compared to T1a) as a predictor of SLNB positivity

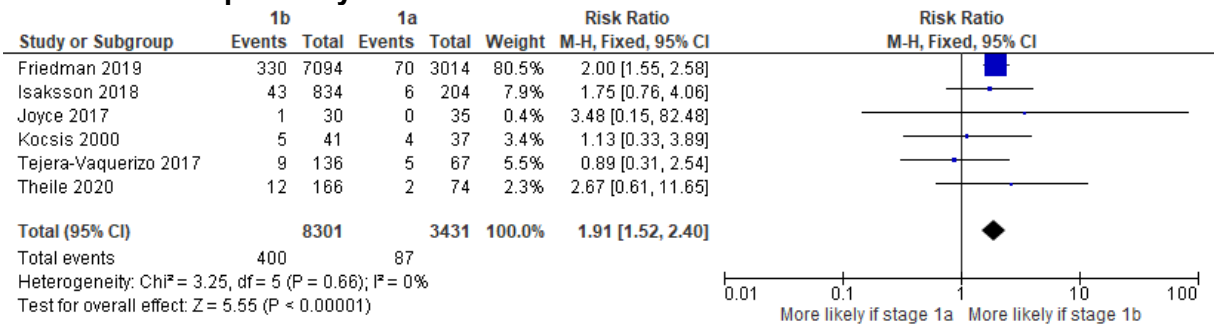


Figure 19: Lymphovascular invasion as a predictor of SLNB positivity

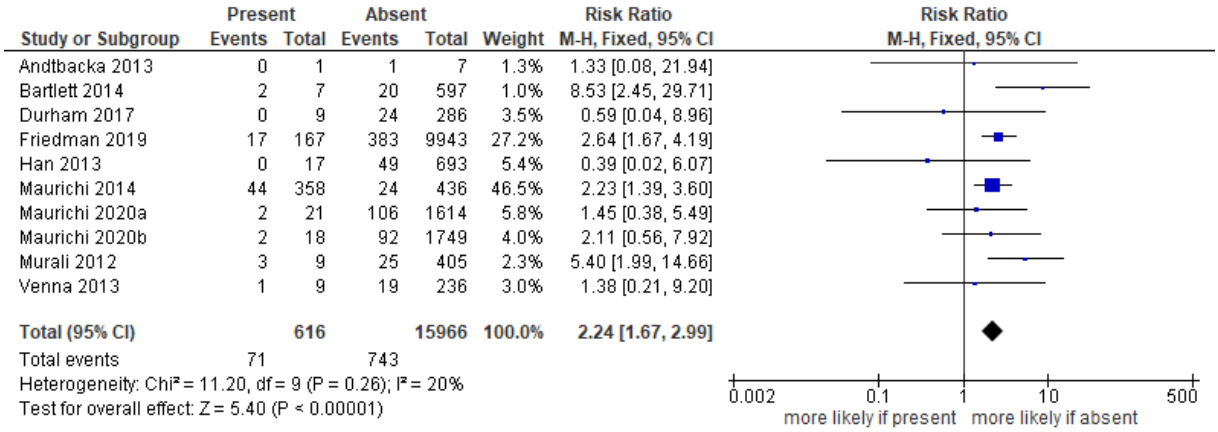


Figure 20: Lymphovascular invasion as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

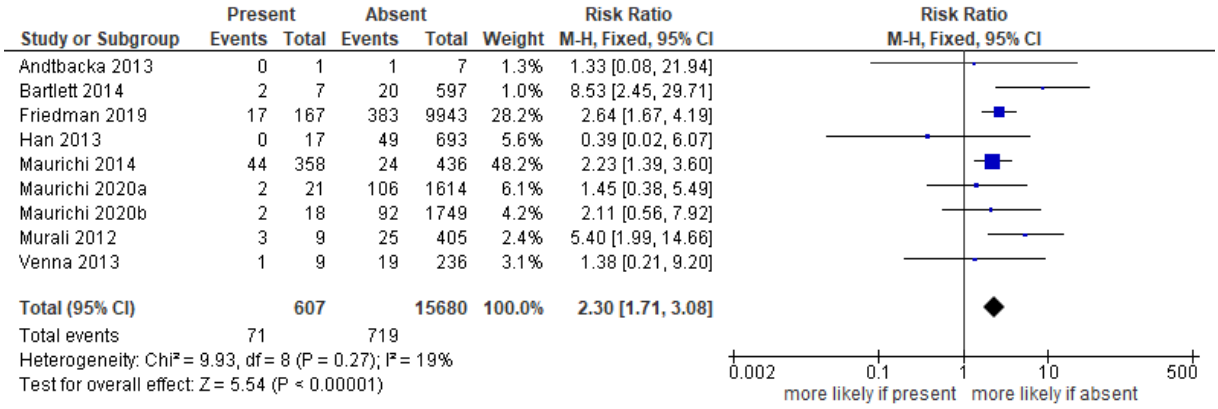


Figure 21: Tumour location (head, neck or trunk compared to extremities or other location) as a predictor of SLNB positivity

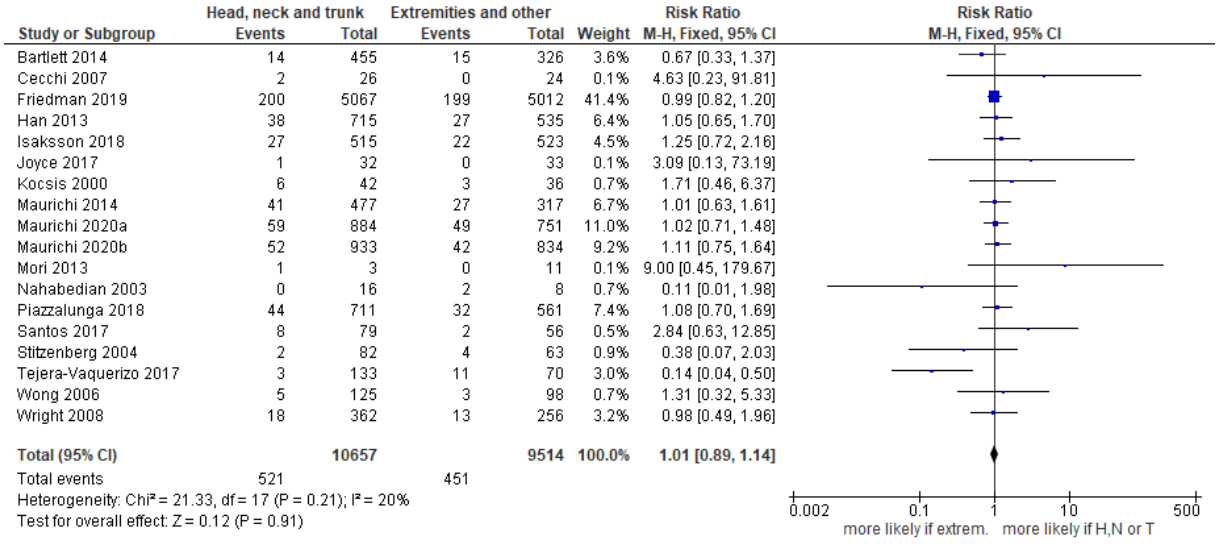


Figure 22: Tumour location (head, neck or trunk compared to extremities or other location) as a predictor of SLNB positivity (sensitivity analysis excluding high risk of bias studies)

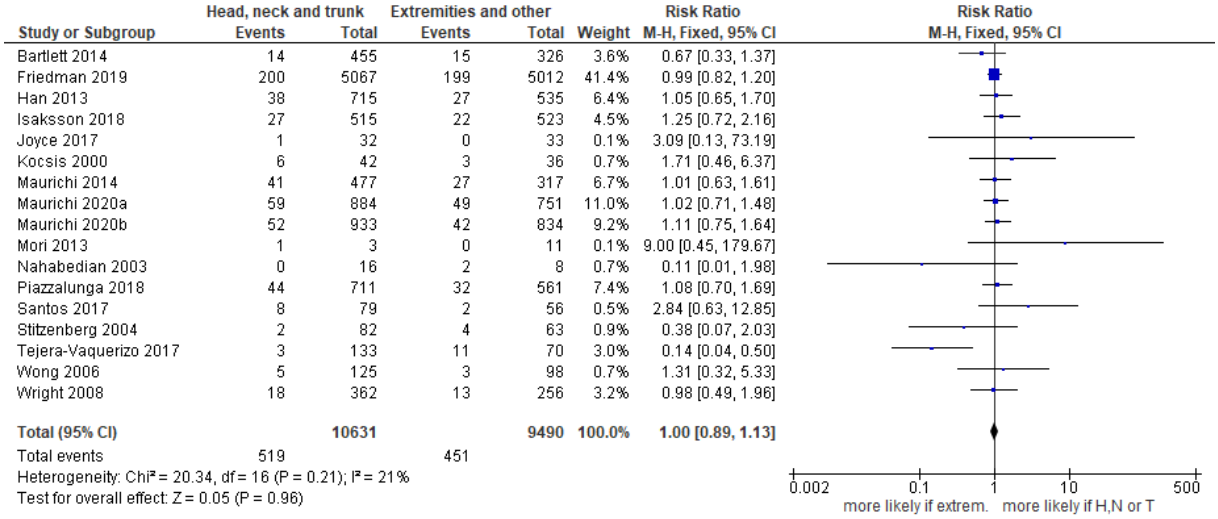
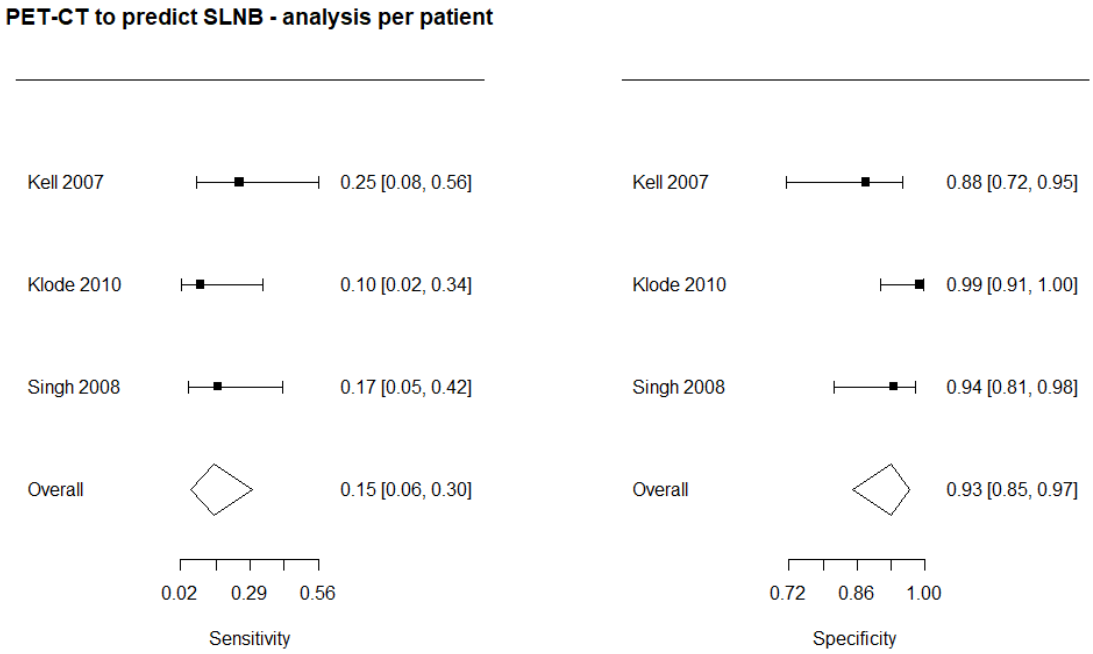
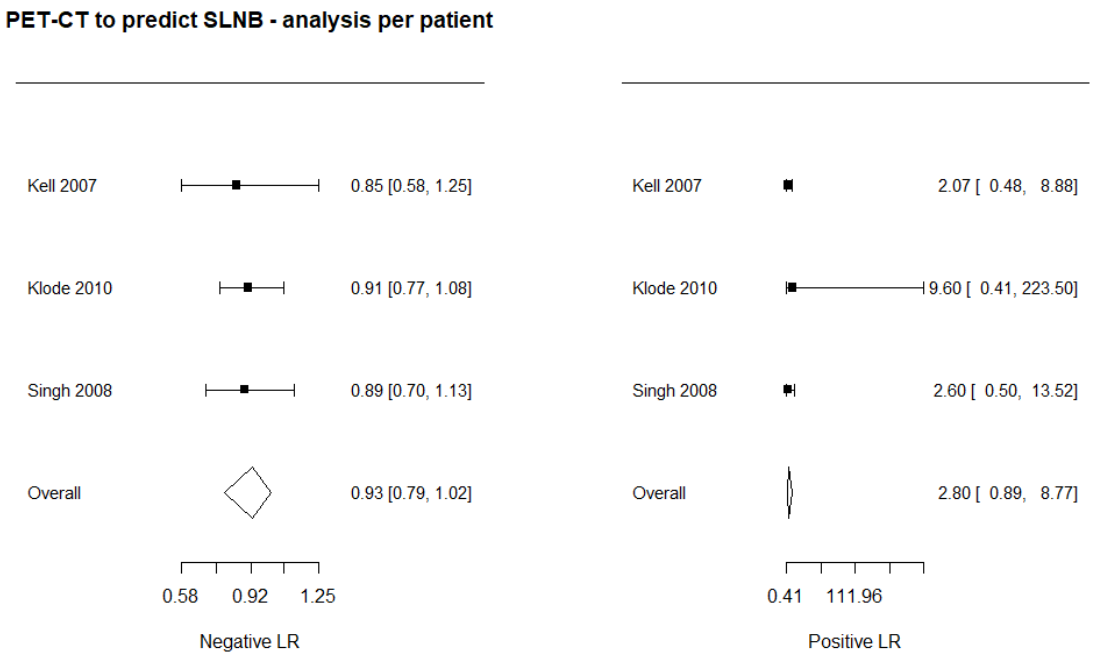


Figure 23: Sensitivity and specificity for PET-CT to predict SLNB (per patient analysis)



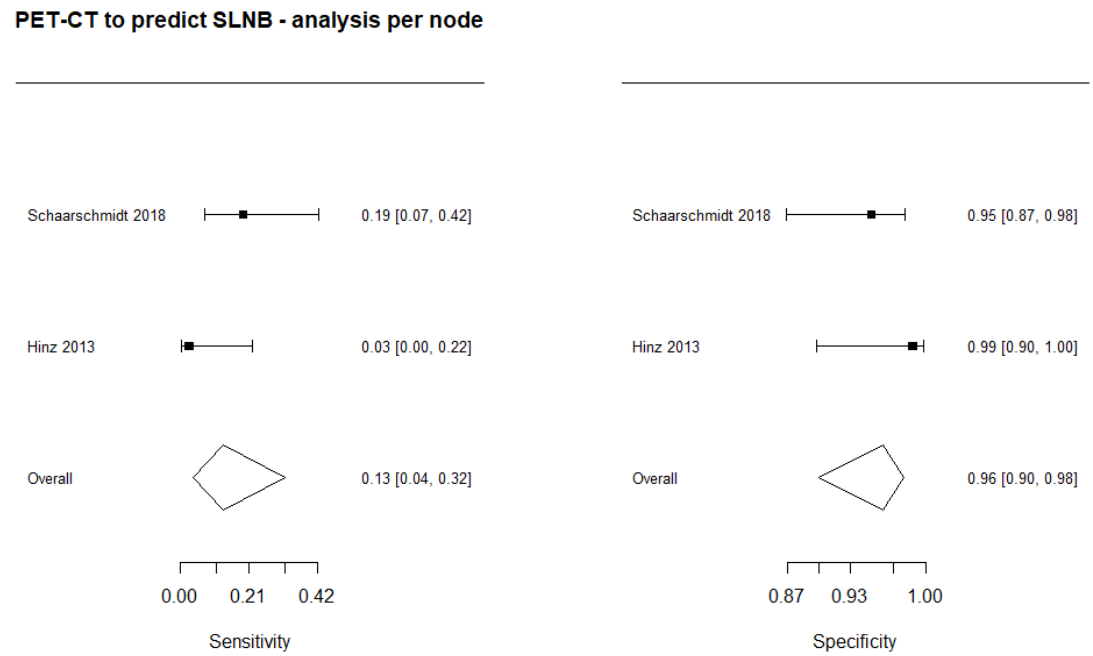
I^2 (sensitivity) = 0.0% (FE model), I^2 (specificity) = 24.7% (FE model)

Figure 24: Likelihood ratios for PET-CT to predict SLNB (per patient analysis)



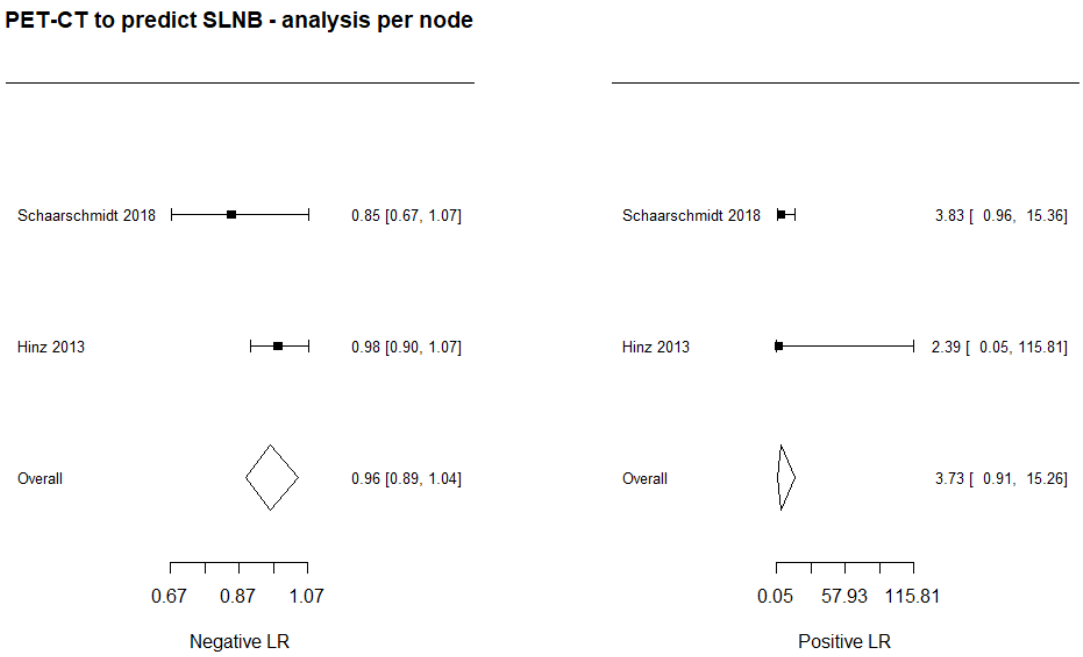
I^2 (negative LR) = 0.0% (FE model), I^2 (positive LR) = 0.0% (FE model)

Figure 25: Sensitivity and specificity for PET-CT to predict SLNB (per node analysis)



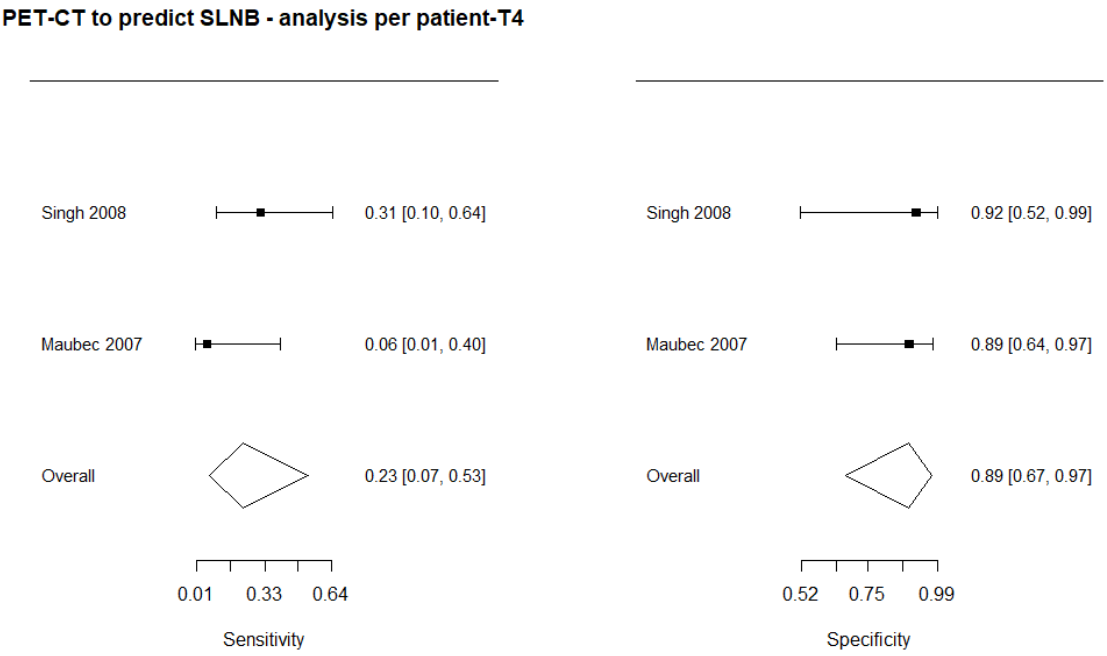
I^2 (sensitivity) = 37.4% (FE model), I^2 (specificity) = 0.0% (FE model)

Figure 26: Likelihood ratios for PET-CT to predict SLNB (per node analysis)



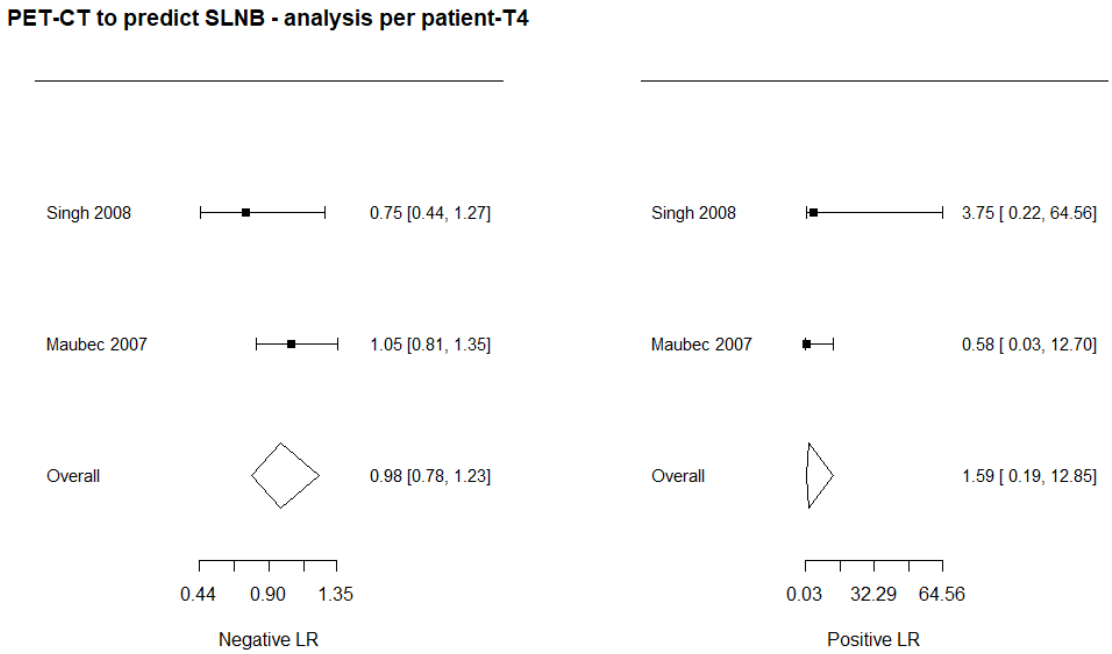
I^2 (negative LR) = 13.8% (FE model), I^2 (positive LR) = 0.0% (FE model)

Figure 27: Sensitivity and specificity for PET-CT to predict SLNB in patients with T4 (per patient analysis)



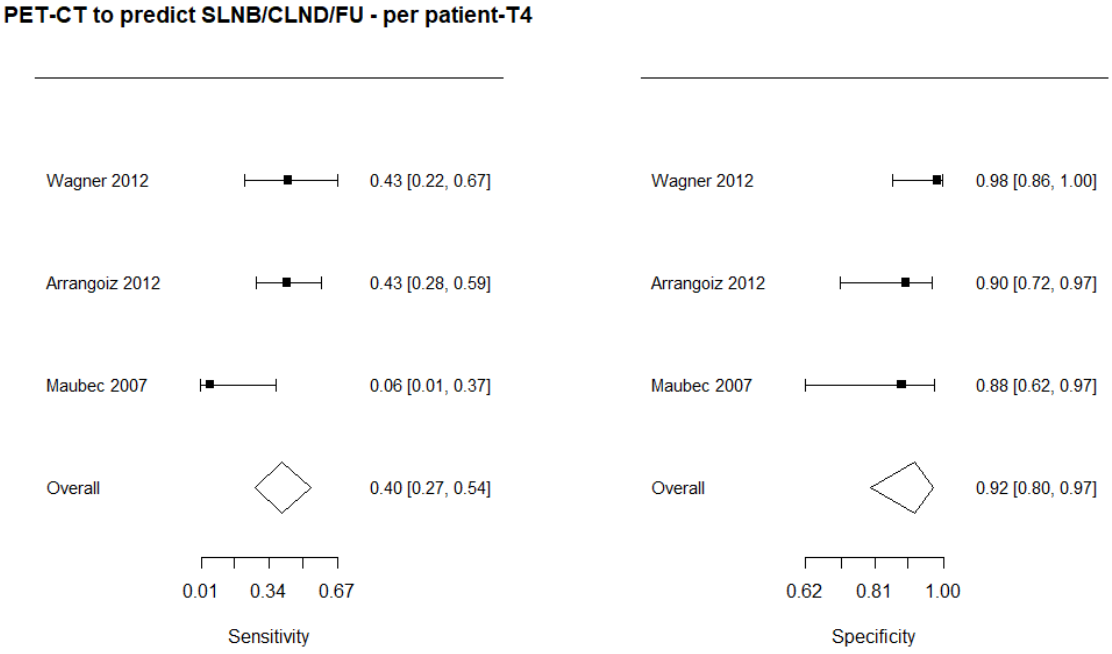
I^2 (sensitivity) = 26.3% (FE model), I^2 (specificity) = 0.0% (FE model)

Figure 28: Likelihood ratios for PET-CT to predict SLNB in patients with T4 (per patient analysis)



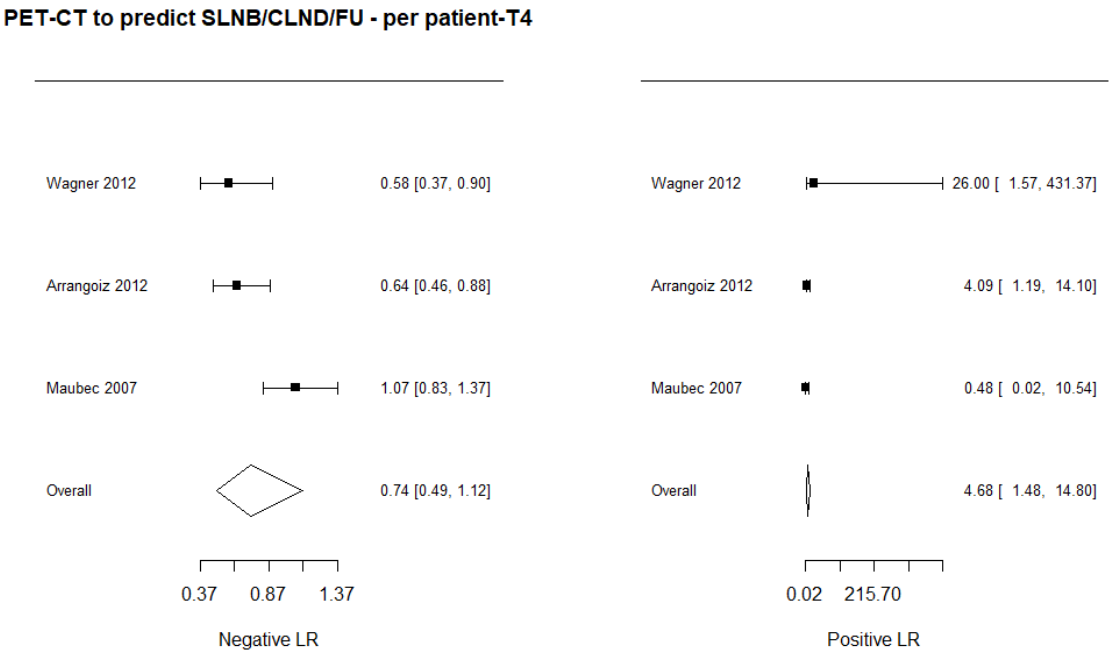
I^2 (negative LR) = 21.5% (FE model), I^2 (positive LR) = 0.0% (FE model)

Figure 29: Sensitivity and specificity for PET-CT to predict SLNB/CLND/clinical follow-up in patients with T4 (per patient analysis)



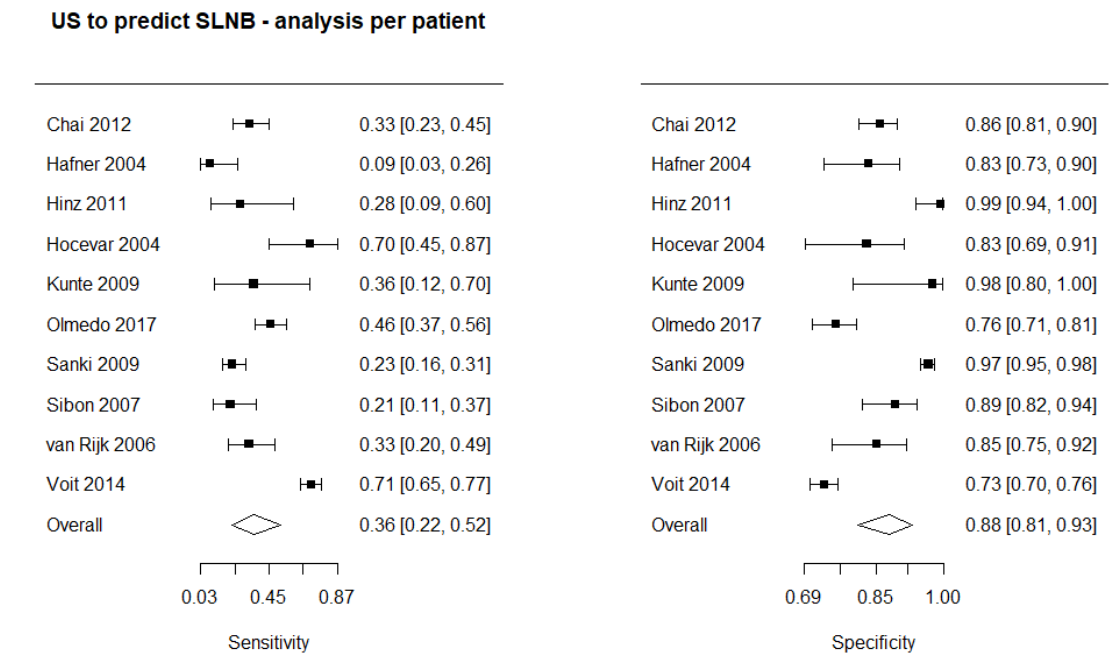
I^2 (sensitivity) = 31.8% (FE model), I^2 (specificity) = 0.0% (FE model)

Figure 30: Likelihood ratios for PET-CT to predict SLNB/CLND/clinical follow-up in patients with T4 (per patient analysis)



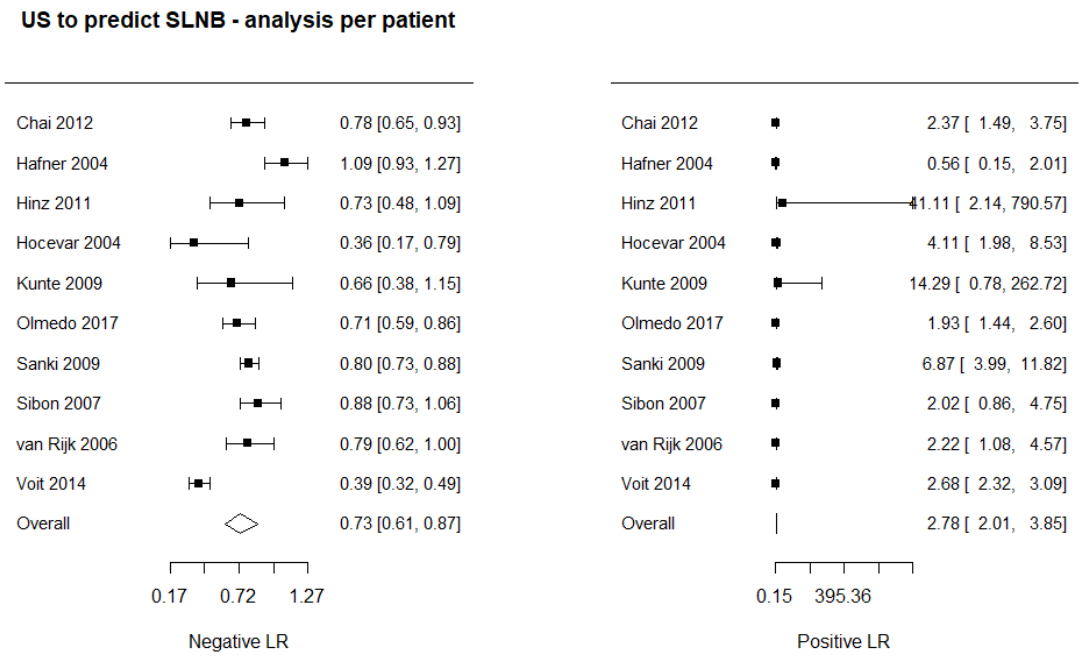
I^2 (negative LR) = 78.3% (RE model), I^2 (positive LR) = 43.2% (FE model)

Figure 31: Sensitivity and specificity for US to predict SLNB (per patient analysis)



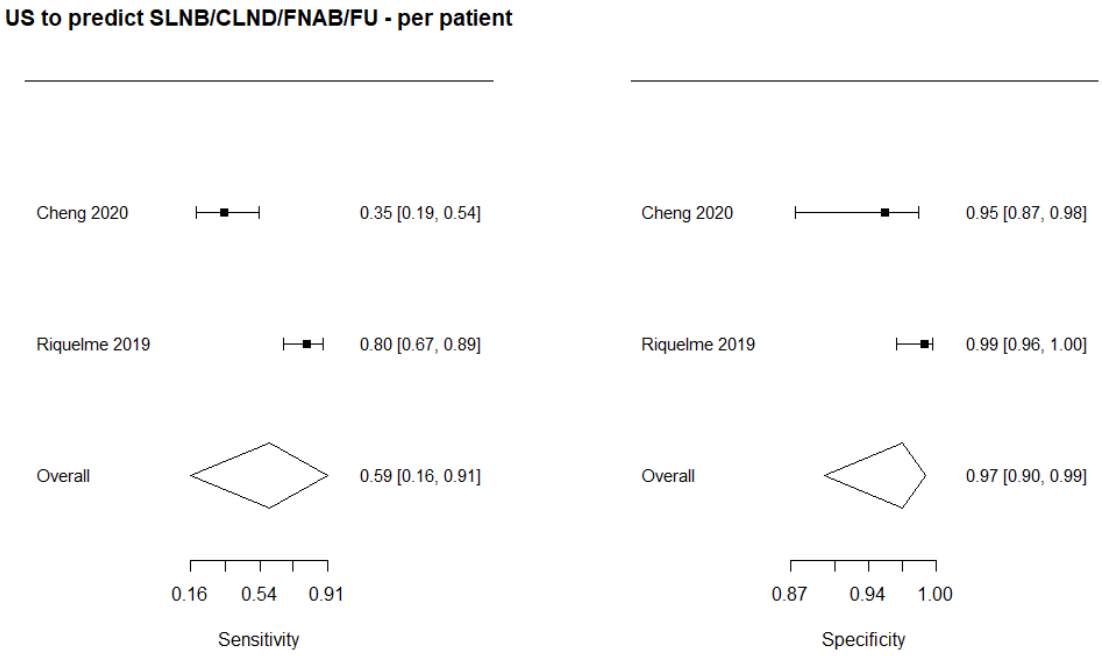
I^2 (sensitivity) = 91.3% (RE model), I^2 (specificity) = 92.6% (RE model)

Figure 32: Likelihood ratios for US to predict SLNB (per patient analysis)



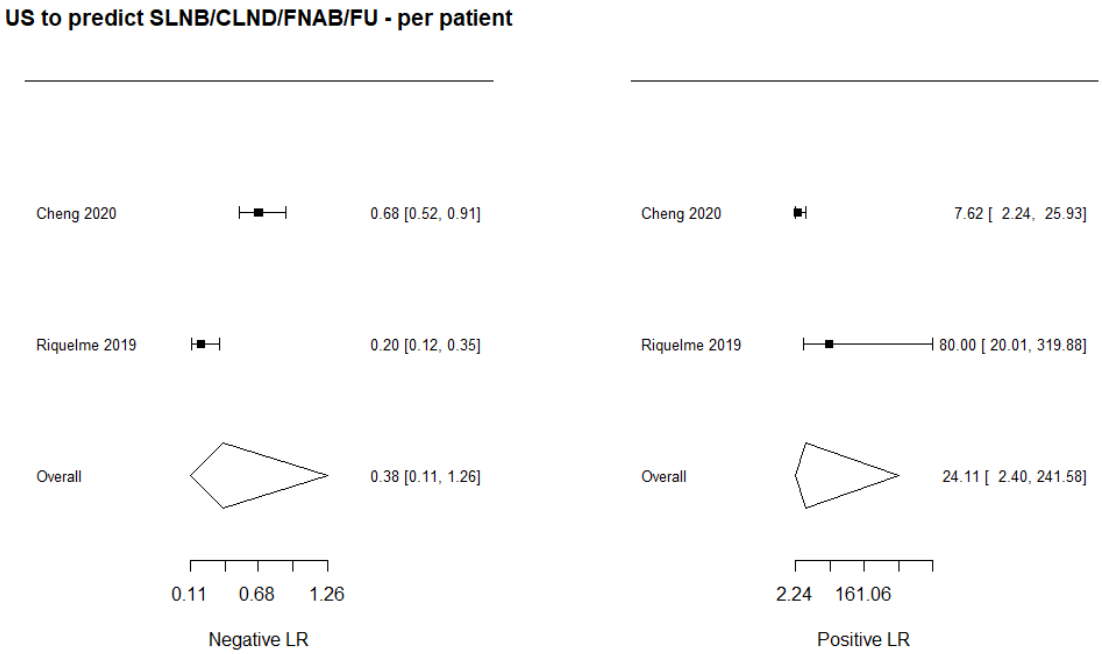
I^2 (negative LR) = 68.7% (RE model), I^2 (positive LR) = 86.4% (RE model)

Figure 33: Sensitivity and specificity for US to predict SLNB/CLND/FNAB/clinical follow-up (per patient analysis)



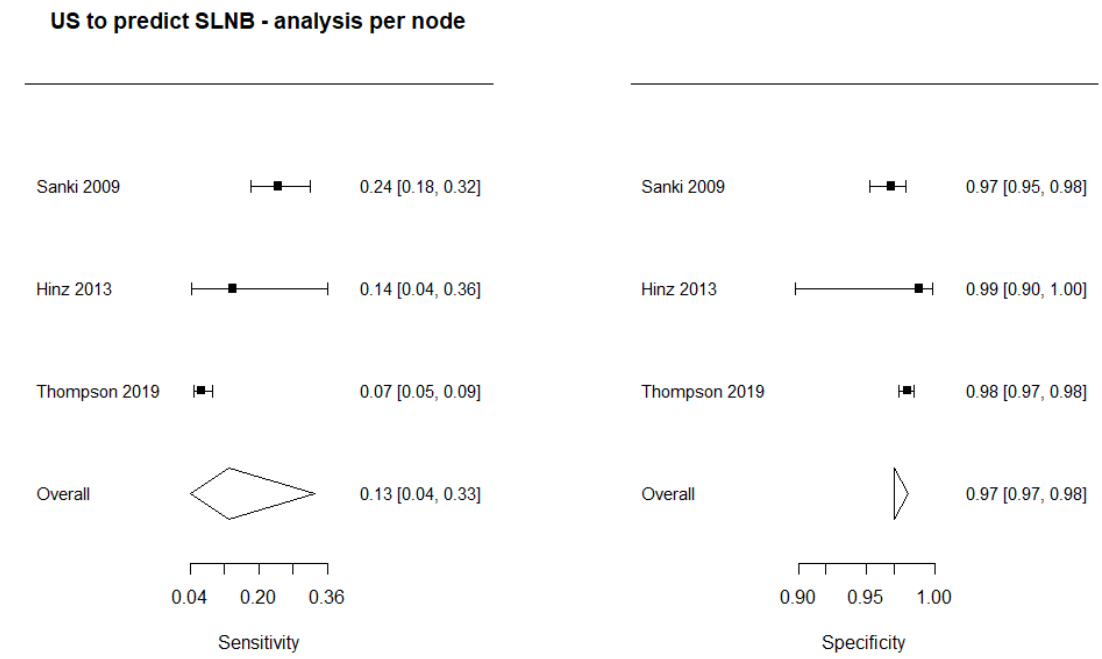
I^2 (sensitivity) = 92.8% (RE model), I^2 (specificity) = 64.5% (RE model)

Figure 34: Likelihood ratios for US to predict SLNB/CLND/FNAB/clinical follow-up (per patient analysis)



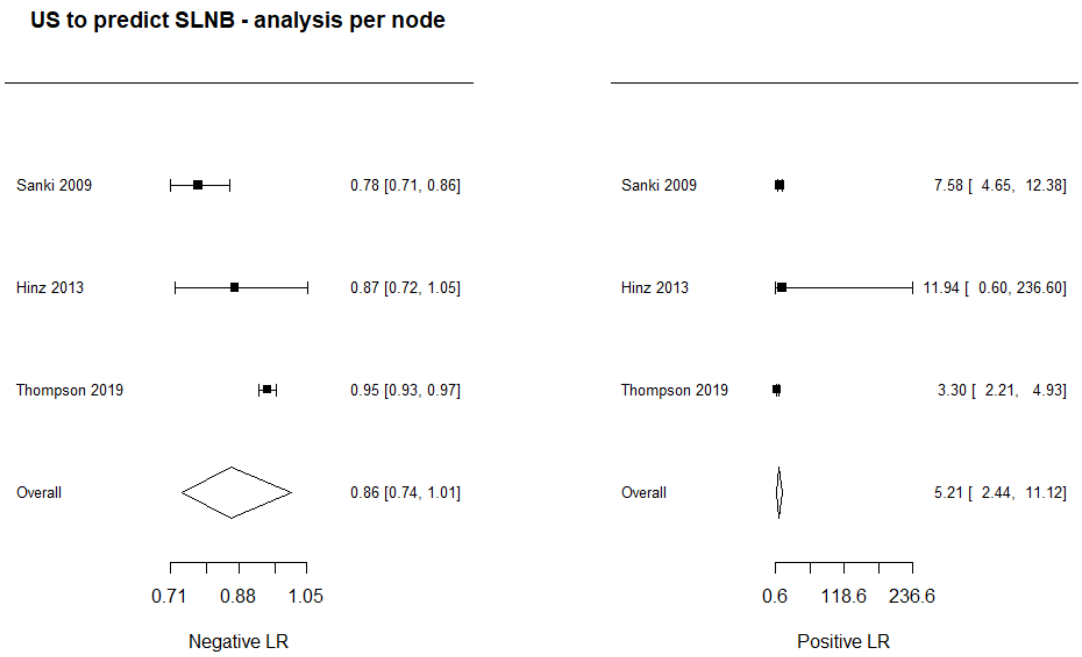
I^2 (negative LR) = 93.2% (RE model), I^2 (positive LR) = 83.9% (RE model)

Figure 35: Sensitivity and specificity for US to predict SLNB (per node analysis)



I^2 (sensitivity) = 94.2% (RE model), I^2 (specificity) = 44.6% (FE model)

Figure 36: Likelihood ratios for US to predict SLNB (per node analysis)



I^2 (negative LR) = 88.2% (RE model), I^2 (positive LR) = 72.1% (RE model)

Appendix H – GRADE tables

Predictors of SLNB positivity

Breslow thickness to predict SLNB positivity

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			0.8-1.0mm	<0.8mm					
Main analysis: Breslow thickness of 0.8-1.0mm compared to <0.8mm (Figure 1**)**									
27	26,234	RR 1.70 (1.51, 1.92)	995/16521 (6.0%)	352/9713 (3.6%)	Serious[1]	Not serious	Serious[2]	Not serious	Very low
Multivariate analyses									
Han (2013)	1,250	Adjusted[3] OR 2.21 (1.06, 4.61)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[5]	Very low
Mozzillo (2013)	423	Adjusted[6] OR 1.53 (0.64, 3.67)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[7]	Very low
Herbert (2018)	1,129	Adjusted[8] OR 4.38 (1.81 – 10.58)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Piazzalunga (2018)	855	Adjusted[9] OR 2.02 (1.25,3.26)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Subramanaian (2021)	1,552	Adjusted[10] OR 9.85 (2.42, 40.05) *Entered as continuous variable*	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low

1. >33% of studies were at moderate or high risk of bias.
2. I^2 >33%.
3. Model adjusted for Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1).
4. Study was at moderate risk of bias.
5. 95% CIs cross one line of the MID (0.8, 1.25).

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			0.8-1.0mm	<0.8mm					

6. Model adjusted for age and sex.
7. 95% CIs cross both lines of the MID (0.8, 1.25).
8. Model adjusted for Clark level (4 vs. 1-3), mitotic (1+ v. 0), Breslow thickness (0.75-1.00mm vs. <0.75mm) and positive deep margin.
9. Model adjusted for Breslow thickness (entered separately as a continuous and dichotomous variable) and ulceration.
10. Model adjusted for age, Breslow thickness and ulceration.

Ulceration to predict SLNB positivity

No. studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			ulcerated	Not ulcerated					
Main analysis: Ulceration compared to no ulceration (Figure 2**)**									
26	21,551	RR 2.01 (1.69, 2.38)	184/1978 (9.3%)	927/19573 (4.7%)	Serious[1]	Not serious	Not serious	Not serious	Very low
*Sensitivity analysis (excluding high risk of bias studies): Ulceration compared to no ulceration (*Figure 3*)*									
24	21,247	RR 2.01 (1.69, 2.38)	180/1956 (9.2%)	906/19291 (4.7%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis only in participants with 0.8-1.0mm melanomas: Ulceration compared to no ulceration (Figure 2**)**									
7	1,398	RR 2.10 (1.32, 3.34)	17/119 (14.3%)	90/1279 (7.0%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Sensitivity analysis (excluding high risk of bias studies) only in participants with 0.8-1.0mm melanomas: Ulceration compared to no ulceration (Figure 3)									
6	1,104	RR 1.95 (1.15, 3.30)	13/99 (13.1%)	71/1005 (6.4%)	Serious[1]	Not serious	Not serious	Serious[2]	Very low
Multivariate analyses: in 0.8-1.0mm melanomas									
Yalamanchi (2018)	3,183	Adjusted[13] OR 3.03 (1.55, 5.06)	N/A	N/A	Serious[4]	Serious[14]	Not serious	Not serious	Very low

No. studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			ulcerated	Not ulcerated					
Durham (2017)	488	Adjusted[8] OR 5.93 (1.81, 19.50)	N/A	N/A	Very serious[9]	Not serious	N/A	Not serious	Very low
Skochdopole	2,184	Adjusted[11] OR 2.04 (1.20, 3.47)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Very low
Multivariate analyses: In all melanomas ≤1.0mm									
Han (2013)	1,250	Adjusted[3] OR 2.51 (1.25, 5.06)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Han (2012)	271	Adjusted[4] OR 3.09 (0.98, 9.77)	N/A	N/A	Not serious	Not serious	N/A	Serious[2]	Very low
Mozzillo (2013)	423	Adjusted[5] OR 0.47 (0.06, 3.59)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[6]	Very low
Santos (2017)	137	Adjusted[7] OR 12.80 (2.77, 59.40)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Piazzalunga (2018)	855	Adjusted[10] OR 2.94 (1.36, 6.31)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Skochdopole (2020)	4,332	Adjusted[11] OR 2.01 (1.39, 2.93)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Friedman (2019)	10,108	Adjusted[12] OR 1.62 (1.22, 2.13)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Very low
Maurichi (2020)	1,635	Adjusted[13] OR 3.83 (2.56, 5.62)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Subramanaian (2021)	1,552	Adjusted[15] OR 2.37 (1.28, 4.37)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low

1. >33% of studies were at moderate or high risk of bias
2. 95% CIs cross one line of the prespecified MIDs (0.8, 1.25)

No. studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			ulcerated	Not ulcerated					

3. Model adjusted for Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1).
4. Stepwise logistic regression model inputting age group, Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1), tumour infiltrating lymphocytes, deep biopsy margin, T stage and vertical growth phase. Odds ratios were only reported for mitotic rate and ulceration (all other predictors are noted as being non-significant).
5. Model adjusted for age and sex
6. 95% CIs cross both lines of the prespecified MIDs (0.8, 1.25)
7. Model adjusted for sex, Clark (1/2 vs. 4/5), Tumour infiltrating lymphocytes, ulceration and regression.
8. Model adjusted for age (>45 vs. 45 or younger), Breslow depth (<0.85 versus 0.85-1.00mm), mitotic rate (>1 versus 1 or less) and ulceration.
9. Study at high risk of bias.
10. Model adjusted for Breslow thickness (entered separately as a continuous and dichotomous variable) and ulceration.
11. Model adjusted for age, sex, race, MR, ulceration, location of the tumour (trunk, upper, and lower extremity), and tumour depth.
12. Model adjusted for age (entered as continuous variable), lymphovascular invasion, Breslow thickness (entered as continuous variable), Mitosis (entered as continuous variable), Clark level (I-II, III or IV-V, entered separately) and ulceration.
13. Model adjusted for age (<54, 54-70 or >70 years), sex, histology (MM, superficial spreading melanoma, lentigo maligna melanoma or other), primary site, mitosis (present or absent), ulceration and vertical growth phase.
14. Study was only partially applicable to the review question
15. Model adjusted for age, Breslow thickness and ulceration.

Mitotic rate to predict SLNB positivity

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			High rate	Low rate					
Main analysis: High versus low rate of mitosis (see Figure 4 **for more detail on how data were dichotomised into high/low)**									
25	25,129	RR 2.15 (1.57, 2.94)	656/8451 (7.8%)	657/16678 (3.9%)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			High rate	Low rate					
Sensitivity analysis (excluding high risk of bias studies): High versus low rate of mitosis (see Figure 5 *for more detail on how data were dichotomised into high/low)*									
22	19,886	RR 1.97 (1.41, 2.75)	555/7636 (7.3%)	481/12250 (3.9%)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
Subgroup analysis: Mitotic index ≥1 compared to <1 per mm^2 (Figure 6**)**									
13	5,048	RR 1.83 (0.95, 3.54)	257/3093 (8.3%)	77/1955 (3.9%)	Serious[1]	Not serious	Very serious[2]	Serious[3]	Very low
Sensitivity analysis (excluding high risk of bias studies): Mitotic index ≥1 compared to <1 per mm^2 **(**Figure 5*)*									
12	4,625	RR 1.69 (0.86, 3.35)	237/2870 (8.3%)	73/1755 (4.2%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis: Mitotic index ≥2 compared to <2 per mm^2 (Figure 7**)**									
8	15,539	RR 1.73 (1.50, 2.01)	320/4870 (6.6%)	413/10669 (3.9%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Sensitivity analysis (excluding high risk of bias studies): Mitotic index ≥2 compared to <2 per mm^2 **(**Figure 8**)**									
7	15,051	RR 1.71 (1.47, 1.99)	308/4730 (6.5%)	401/10321 (3.9%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis: Mitotic index ≥3 compared to <3 per mm^2 (or any value >3 as the cut-off, see Figure 9 **for further detail)**									
4	4,542	RR 3.98 (3.08, 5.12)	79/488 (16.2%)	167/4054 (4.1%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Sensitivity analysis (excluding high risk of bias studies): Mitotic index ≥3 compared to <3 per mm^2 (or any value >3 as the cut-off, see Figure 10 *for further detail)*									
3	210	RR 8.66 (3.31, 22.70)	10/36 (27.8%)	7/174 (4.0%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis only in participants with 0.8-1.0mm melanomas: Mitotic index ≥1 compared to 0 per mm^2									
Andtback a (2013)	6	RR 0.33 (0.02, 5.97)	0/3 (0%)	1/3 (33.3%)	Serious[4]	Not serious	N/A	Very serious[6]	Very low

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			High rate	Low rate					
Subgroup analysis only in participants with 0.8-1.0mm melanomas: Mitotic index >1 compared to 0-1 per mm²									
Durham (2017)	488	RR 2.49 [1.14, 5.40]	12/140 (8.6%)	12/348 (3.4%)	Very serious[5]	Not serious	N/A	Serious[3]	Very low
Subgroup analysis only in participants with 0.8-1.0mm melanomas: Mitotic index ≥3 compared to <3 per mm²									
Ranieri (2006)	77	RR 5.75 [2.05, 16.14]	4/8 (50%)	6/69 (8.7%)	Serious[4]	Not serious	N/A	Not serious	Very low
Subgroup analysis only in participants with tumour stage 1b (according to AJCC 8th edition): Mitotic index ≥4 compared to <4 per mm²									
Skochdopole (2020)[17]	2104	RR 3.20 [2.31, 4.44]	47/284 (16.5%)	94/1820 (5.2%)	Very serious[5]	Not serious	N/A	Not serious	Very low
Multivariate analyses: In 0.8-1.0mm melanomas (≥1 compared <1 unless stated otherwise)									
Durham (2017)[11]	488	Adjusted[10] OR 1.79 (0.82, 3.90)	N/A	N/A	Very serious[5]	Not serious	N/A	Serious[3]	Very low
Skochdopole (2020)[17]	2,184	Adjusted[14] OR 1.20 (1.11, 1.29)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Very low
Yalamanchi (2018)	3,183	Adjusted[15] OR 3.03 (1.55, 5.06)	N/A	N/A	Serious[4]	Serious[16]	Not serious	Not serious	Very low
Multivariate analyses: In all melanomas ≤1.0mm (≥1 compared <1 unless stated otherwise)									
Han (2013)	1,250	Adjusted[7] OR 1.01 (0.56, 1.83)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[6]	Very low
Han (2012)	271	Adjusted[8] OR 2.45 (1.14, 5.25)	N/A	N/A	Not serious	Not serious	N/A	Serious[3]	Very low
Mozzillo (2013)	423	Adjusted[9] OR 6.44 (2.17, 19.15)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Herbert (2018)	1,129	Adjusted[12] OR 1.66 (0.75 – 3.67)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[6]	Very low

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			High rate	Low rate					
Tejera-Vaquerizo (2019)	1,090	Adjusted[13] ORs: 1 vs 0: 1.30 (0.60-2.90)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[6]	Very low
		2 vs. 0: 2.10 (0.90, 4.95)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[6]	Very low
		>2 vs. 0: 2.90 (1.22, 7.00)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Very low
Skochdopole (2020)[17]	4,332	Adjusted[14] OR 1.24 (1.18, 1.31)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[3]	Very low

1. >33% of studies were at moderate or high risk of bias
2. I^2 >66.6%
3. 95% CIs cross one line of the prespecified MIDs (0.8, 1.25)
4. Study at moderate risk of bias
5. Study at high risk of bias
6. 95% CIs cross both lines of the prespecified MIDs (0.8, 1.25)
7. Model adjusted for Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1).
8. Stepwise logistic regression model inputting age group, Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1), tumour infiltrating lymphocytes, deep biopsy margin, T stage and vertical growth phase. Odds ratios were only reported for mitotic rate and ulceration (all other predictors are noted as being non-significant).
9. Model adjusted for age and sex.
10. Model adjusted for age (>45 vs. 45 or younger), Breslow depth (<0.85 versus 0.85-1.00mm), mitotic rate (>1 versus 1 or less) and ulceration
11. Study compared mitotic rate of ≥2 to 0-1.
12. Model adjusted for Clark level (4 vs. 1-3), mitotic (1+ v. 0), Breslow thickness (0.75-1.00mm vs. <0.75mm) and positive deep margin
13. Model adjusted for age, sex, anatomic location, Breslow thickness (<0.75 versus 0.75-1.00mm), ulceration, mitotic rate, histologic subtype, Clark level, lymphovascular invasion, and regression. Only mitotic rate reported (all versus 0 mitoses): 1 mitosis OR 1.3 (0.6-2.9), 2 mitosis OR 2.1 (0.9-4.95), >2 OR 2.9 (1.22-7)
14. Model adjusted for age, sex, race, MR, ulceration, location of the tumour (trunk, upper, and lower extremity), and tumour depth.
15. Model adjusted for age (<54, 54-70 or >70 years), sex, histology (MM, superficial spreading melanoma, lentigo maligna melanoma or other), primary site, mitosis (present or absent), ulceration and vertical growth phase.
16. Study was only partially applicable to the review question.

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			High rate	Low rate					
17. Study compared mitotic rate of ≥4 to <4.									

Age to predict SLNB positivity

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Younger	Older					
Main analysis: younger versus older age (see Figure 11 **for more detail how data were dichotomised into young/old)**									
16	18,940	RR 1.49 (1.31,1.69)	506/8150 (6.2%)	445/10790 (4.1%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Sensitivity analysis (excluding high risk of bias studies): High versus low rate of mitosis (see Figure 12 *for more detail on how data were dichotomised into high/low)*									
15	18,452	RR 1.50 (1.32, 1.70)	500/8048 (6.2%)	427/10404 (4.1%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis: younger versus older age (dichotomised at any point between 40 and 50 years of age, see Figure 13**)**									
12	7,592	RR 1.39 (1.17, 1.67)	252/3295 (7.6%)	236/4297 (5.5%)	Serious[1]	Not serious	Not serious	Serious[2]	Very low
Sensitivity analysis (excluding high risk of bias studies): younger versus older age (dichotomised at any point between 40 and 50 years of age, see Figure 14*)*									
11	7,104	RR 1.40 (1.17, 1.68)	246/3193 (7.7%)	218/3911 (5.6%)	Serious[1]	Not serious	Not serious	Serious[2]	Very low
Subgroup analysis: younger versus older age (dichotomised at any point over 50 years of age, see Figure 15**)**									
4	10,797	RR 1.59 (1.33, 1.91)	254/4855 (5.2%)	209/6493 (3.2%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Multivariate analyses: In 0.8-1.0mm melanomas									
Durham (2017)[3]	488	Adjusted[4] OR 2.94 (1.35, 6.67)	N/A	N/A	Very serious[5]	Not serious	N/A	Not serious	Very low

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Younger	Older					
Yalamanchi (2018)	3,183	*<54 vs. 54-70 years old:* Adjusted[15] OR 0.89 (0.52, 1.56)	N/A	N/A	Serious[6]	Serious[7]	Not serious	Very serious[8]	Very low
		<54 vs. >70 years old: Adjusted[15] OR 4.00 (1.75, 11.11)	N/A	N/A	Serious[6]	Serious[7]	Not serious	Not serious	Very low
Multivariate analyses: all melanomas ≤1.0mm									
Subramanaian (2021)	1,552	Adjusted[10] OR 0.97 (0.95, 0.98)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low

1. >33% of studies were at moderate or high risk of bias.
2. 95% CIs cross one line of the MID (0.80, 1.25).
3. Study compared ≤45 to >45 years of age.
4. Model adjusted for age (>45 vs. ≤45 years) , Breslow depth (<0.85 versus 0.85-1.00mm), mitotic rate (>1 versus 1 or less) and ulceration. Age OR 0.34 (0.15, 0.74), mitosis OR 1.79 (0.82, 3.90) ulceration OR 5.93 (1.81, 19.50).
5. Study at high risk of bias.
6. Model adjusted for age (<54, 54-70 or >70 years), sex, histology (MM, superficial spreading melanoma, lentigo maligna melanoma or other), primary site, mitosis (present or absent), ulceration and vertical growth phase.
7. Study was only partially applicable to the review question.
8. 95% CIs cross both lines of the MID (0.80, 1.25).
9. Model adjusted for age, Breslow thickness and ulceration.

Clark level to predict SLNB positivity

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Level IV-V	Level I-III					
Main analysis: Clark level IV-V versus I-III (Figure 16**)**									

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Level IV-V	Level I-III					
22	19,651	RR 1.52 (1.34, 1.73)	596/9955 (6.0%)	403/9696 (4.2%)	Serious[1]	Not serious	Serious[2]	Not serious	Very low
Sensitivity analysis (excluding high risk of bias studies): Clark level IV-V versus I-III (see Figure 17*)*									
21	19,621	RR 1.52 (1.34, 1.72)	595/9953 (6.0%)	402/9668 (4.2%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Subgroup analysis only in participants with 0.8-1.0mm melanomas: Clark level IV-V versus I-III (Figure 16**)**									
6	1,070	RR 2.12 (1.27, 3.54)	53/623 (8.5%)	18/447 (4.0%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Multivariate analyses: In all melanomas ≤1.0mm)									
Han (2013)	1,250	Adjusted[3] OR 1.80 (1.01, 3.23)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[5]	Very low
Mozzillo (2013)	423	Adjusted[6] OR 1.92 (0.79, 4.76)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[7]	Very low
Santos (2017)	137	Adjusted[8] OR 4.11 (0.28, 60.40)	N/A	N/A	Serious[4]	Not serious	N/A	Very serious[7]	Very low
Herbert (2018)	1,129	Adjusted[9] OR 2.86 (1.25 – 6.52)	N/A	N/A	Serious[4]	Not serious	N/A	Not serious	Very low
Friedman (2019)	10,108	Adjusted[10] OR: 1.64 (1.05, 2.56)	N/A	N/A	Serious[4]	Not serious	N/A	Serious[5]	Very low

1. >33% of studies were at moderate or high risk of bias.
2. I^2 >33%
3. Model adjusted for Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1).
4. Study at moderate risk of bias
5. 95% CIs cross one line of the MID (0.8, 1.25)
6. Model adjusted for age and sex
7. 95% CIs cross both lines of the MID (0.8, 1.25)

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Level IV-V	Level I-III					

8. Model adjusted for sex, Clark (1/2 vs. 4/5), Tumour infiltrating lymphocytes, ulceration and regression. Clark level 4-5 was compared specifically to 1-2, excluding level 3.
9. Model adjusted for Clark level (4 vs. 1-3), mitotic (1+ v. 0), Breslow thickness (0.75-1.00mm vs. <0.75mm) and positive deep margin.
10. Model adjusted for age (entered as continuous variable), lymphovascular invasion, Breslow thickness (entered as continuous variable), Mitosis (entered as continuous variable), Clark level (I-II, III or IV-V, entered separately) and ulceration. Analysis of Clark level was taken for 4-5 versus 1-2, excluding level 3.

Tumour pathological staging to predict SLNB positivity

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Stage 1b	Stage 1a					
Main analysis: pT1b versus pT1a (Figure 18**)**									
6	11,732	RR 1.91 (1.52, 2.40)	400/8301 (4.8%)	87/3431 (2.5%)	Serious[1]	Not serious	Not serious	Not serious	Very low

1. Study is at moderate risk of bias

Multiple predictors to predict SLNB positivity

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			With	Without					
Main analysis: At least one of Mitosis 2+ per mm^2, lymphovascular invasion or age <55 years compared to those without any of the listed features									

Author (year)	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			With	Without					
Friedman (2019)	10,108	RR 2.07 [1.65, 2.59]	303/6082 (5.0%)	97/4026 (2.4%)	Serious[1]	Not serious	N/A	Not serious	Very low
Subgroup analysis in people with stage t1a melanoma: At least one of Mitosis 2+ per mm^2, lymphovascular invasion or age <55 years compared to those without any of the listed features									
Friedman (2019)	3,014	RR 3.10 [1.70, 5.64]	57/1750 (3.3%)	13/1264 (1.0%)	Serious[1]	Not serious	N/A	Not serious	Very low
Nomogram 1 (ulceration, lymphovascular invasion, regression, age, and Breslow thickness and mitotic rate)									
Maurichi (2020)	1,767	C index: 96.5%	NA	NA	Serious[1]	Not serious	N/A	Very serious[2]	Very low

1. Study is at moderate risk of bias
2. Confidence intervals not reported

Lymphovascular invasion to predict SLNB positivity

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Present	Absent					
Main analysis: Present versus absent (Figure 19**)**									
10	16,582	RR 2.24 (1.67, 2.99)	71/616 (11.5%)	743/15966 (4.7%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Sensitivity analysis excluding high risk of bias studies: Present versus absent **(**Figure 20**)**									
9	16,187	RR 2.30 (1.71, 3.08)	71/607 (11.7%)	719/15680 (4.6%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Multivariate analyses									

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Present	Absent					
Han (2013)	1,250	Adjusted[4] OR 2.21 (1.06, 4.61)	N/A	N/A	Serious[8]	Not serious	N/A	Serious[2]	Very low
Mozzillo (2013)	423	Adjusted[5] OR 1.53 (0.64, 3.67)	N/A	N/A	Serious[8]	Not serious	N/A	Very serious[3]	Very low
Friedman (2019)	10,108	Adjusted[6] OR 2.30 (1.35, 3.95)	N/A	N/A	Serious[8]	Not serious	N/A	Not serious	Very low
Maurichi (2020)	1,635	Adjusted[7] OR 2.84 (1.56, 4.58)	N/A	N/A	Serious[8]	Not serious	N/A	Not serious	Very 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. 95% CIs cross both lines of the MID (0.8, 1.25)
4. Model adjusted for Clark level (IV+ vs. I-III), Breslow thickness (≥0.75mm vs. <0.75mm), ulceration, regression, mitotic rate (≥1 vs. <1).
5. Model adjusted for age and sex.
6. Model adjusted for age (entered as continuous variable), lymphovascular invasion, Breslow thickness (entered as continuous variable), Mitosis (entered as continuous variable), Clark level (I-II, III or IV-V, entered separately) and ulceration
7. Model adjusted for Breslow thickness, ulceration, mitotic rate, lymphovascular invasion, Regression and age.
8. Study is at moderate risk of bias

Tumour location to predict SLNB positivity

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Head, neck, torso	Extremities, other					
Main analysis: Primary tumour location of head, neck or trunk compared to extremities or other location (Figure 21**)**									
18	20,171	RR 1.01 (0.89, 1.14)	521/10657	451/9514	Serious[1]	Not serious	Not serious	Not serious	Very low

No. Studies	Sample size	Effect size	No. + SLNBs (%)		Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
			Head, neck, torso	Extremities, other					
			(4.9%)	(4.7%)					
Sensitivity analysis (excluding high risk of bias studies): Primary tumour location of head, neck or trunk compared to extremities or other location (Figure 22)									
17	20,121	RR 1.00 (0.89, 1.13)	519/10631 (4.9%)	451/9490 (4.8%)	Serious[1]	Not serious	Not serious	Not serious	Very low
Multivariate analyses									
Mozzillo (2013)	423	Adjusted[2] OR 1.30 (0.56, 3.03)	N/A	N/A	Serious[3]	Not serious	N/A	Very serious[4]	Very low

1. >33% of studies were at moderate or high risk of bias
2. Model adjusted for age and sex
3. Study is at moderate risk of bias
4. 95% CIs cross both lines of the MID (0.8, 1.25)

Imaging prior to SLNB

PET-CT (per patient)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET-CT; Reference standard: SLNB; Analysis per patient; All studies (Figure 1 and Figure 2)										
3 (Kell 2007; Klode 2010; Singh 2008)	Retrospective	150	0.15 (0.06, 0.30)	0.93 (0.85, 0.97)	LR+ 2.80 (0.89, 8.77)	Serious[1]	Not serious	Not serious	Very serious[3]	Very low
					LR- 0.90 (0.79, 1.02)	Serious[1]	Not serious	Not serious	Serious[2]	Low
Index test: US; Reference standard: SLNB if pre-operative imaging is positive										
Stahlie 2021	Prospective	23	0.30 (0.12, 0.56)	0.95 (0.53, 0.98)	LR+ 6.00 (0.36, 99.66)	Serious[1]	Not serious	N/A	Very serious[3]	Very 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- 0.74 (0.51, 1.06)	Serious[1]	Not serious	N/A	Serious[2]	Low

1. Studies 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)

PET-CT (per node)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET-CT; Reference standard: SLNB; Analysis per node; All studies (Figure 3 and Figure 4)										
2 (Schaarschmidt 2018; Hinz 2013)	Retrospective	144	0.13 (0.04, 0.32)	0.96 (0.90, 0.89)	LR+ 0.73 (0.91, 15.26)	Very serious[1]	Serious[2]	Serious[3]	Very serious[5]	Very low
					LR- 0.96 (0.89, 1.04)	Very serious[1]	Serious[2]	Not serious	Serious[4]	Very low
Index test: PET-CT; Reference standard: SLNB; Analysis per node; Sensitivity analysis without studies at high risk of bias										
Hinz 2013	Retrospective	59	0.02 (0.00, 0.32)	0.98 (0.84, 0.99)	LR+ 2.38 (0.04, 115.8)	Not serious	Not serious	N/A	Very serious[5]	Low
					LR- 0.98 (0.90, 1.07)	Not serious	Not serious	N/A	Serious[4]	Moderate

1. >33.3% of weighted data from studies at high risk of bias
2. >33.3% of weighted data from indirect or partially indirect studies
3. i-squared between 33.3% and 66.7%
4. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)
5. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)

PET-CT (per patient, T4 only)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET-CT; Reference standard: SLNB; Analysis per patient (only patients with T4) (Figure 5 and Figure 6)										
2 (Maubec 2007; Singh 2008)	Prospective Retrospective	32	0.23 (0.07, 0.53)	0.89 (0.67, 0.97)	LR+ 1.59 (0.19, 12.87)	Serious[1]	Not serious	Not serious	Very serious[2]	Very low
					LR- 0.98 (0.78, 1.23)	Serious[1]	Not serious	Not serious	Serious[3]	Low
Index test: PET-CT; Reference standard: SLNB; Analysis per patient (only patients with T4); Sensitivity analysis without studies at high risk of bias										
Singh 2008	Retrospective	12	0.31 (0.09, 0.67)	0.91 (0.37, 0.99)	LR+ 3.75 (0.21, 64.56)	Serious[1]	Not serious	Not serious	Very serious[2]	Very low
					LR- 0.75 (0.44, 1.26)	Serious[1]	Not serious	Not serious	Very serious[2]	Very low
Index test: PET-CT; Reference standard: SLNB/CLND/clinical follow-up; Analysis per patient (only patients with T4) (Figure 29 and Figure 30)										
3 (Arrangoiz 2012; Maubec 2007; Wagner 2012)	Prospective Retrospective	119	0.40 (0.27, 0.54)	0.92 (0.80, 0.97)	LR+ 4.68 (1.48, 14.80)	Very serious[4]	Not serious	Not serious	Serious[3]	Very low
					LR- 0.74 (0.49, 1.12)	Very serious[4]	Not serious	Not serious	Very serious[2]	Very low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)
3. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)
4. >33.3% of weighted data from studies at high risk of bias

US to predict SLNB per patient

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: US; Reference standard: SLNB; Analysis per patient (Figure 31 and Figure 32)										
10	Prospective	2,919	0.36	0.88	LR+ 2.78	Serious[1]	Not serious	Very serious[2]	Not serious	Very 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
	Retrospective		(0.22, 0.52)	(0.81, 0.93)	(2.01, 3.85)					
					LR- 0.73 (0.61, 0.87)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
Index test: US; Reference standard: SLNB/CLND/FNAB/clinical follow-up; Analysis per patient (Figure 33 and Figure 34)										
2 (Cheng 2020; Riquelme 2019)	Retrospective Cross-sectional	342	0.59 (0.16, 0.91)	0.97 (0.90, 0.99)	LR+ 24.11 (2.40, 241.58)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					LR- 0.38 (0.11, 1.26)	Serious[1]	Not serious	Serious[3]	Very serious[4]	Very low
Index test: US; Reference standard: SLNB if pre-operative imaging is positive										
Stahlie 2021	Prospective	23	0.36 (0.16, 0.62)	0.89 (0.50, 0.99)	LR+ 3.21 (0.45, 23.21)	Serious[1]	Not serious	N/A	Very serious[4]	Very low
					LR- 0.72 (0.46, 1.14)	Serious[1]	Not serious	N/A	Very serious[4]	Low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. i-squared >66.7%
3. i-squared between 33.3% and 66.7%
4. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)

US (per node)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: US; Reference standard: SLNB; Analysis per node (Figure 35 and Figure 36)										
3 (Hinz 2013; Sanki 2009; Thompson 2019)	Prospective Retrospective	4,232	0.13 (0.04, 0.33)	0.97 (0.97, 0.98)	LR+ 5.21 (2.44, 11.12)	Serious[1]	Not serious	Very serious[2]	Not serious	Very low
					LR- 0.86 (0.74, 1.01)	Serious[1]	Not serious	Serious[3]	Serious[4]	Very 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

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. i-squared >66.7%
3. i-squared between 33.3% and 66.7%
4. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)

PET alone

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET alone; Reference standard: SLNB; Analysis per patient										
Hafner 2004	Prospective	100	0.09 (0.02, 0.27)	0.99 (0.90, 1.00)	LR+ 13.88 (0.68, 280.17)	Serious[1]	Not serious	N/A	Very serious[2]	Very low
					LR- 0.91 (0.80, 1.03)	Serious[1]	Not serious	N/A	Serious[3]	Low
Index test: PET alone; Reference standard: SLNB; Analysis per basin										
Wagner 2005	Prospective	184	0.20 (0.11, 0.35)	0.97 (0.92, 0.98)	LR+ 7.37 (2.39, 22.77)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.81 (0.69, 0.95)	Serious[1]	Not serious	N/A	Not serious	Moderate

1. Study at moderate risk of bias
2. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)
3. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)

PET-US

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET-US; Reference standard: SLNB; Analysis per patient										
	Prospective	100	0.11	0.83	LR+ 0.71	Serious[1]	Not serious	N/A	Very serious[2]	Very 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
Hafner 2004			(0.03, 0.30)	(0.73, 0.90)	(0.21, 2.32)					
					LR- 1.05 (0.89, 1.25)	Serious[1]	Not serious	N/A	Serious[3]	Low

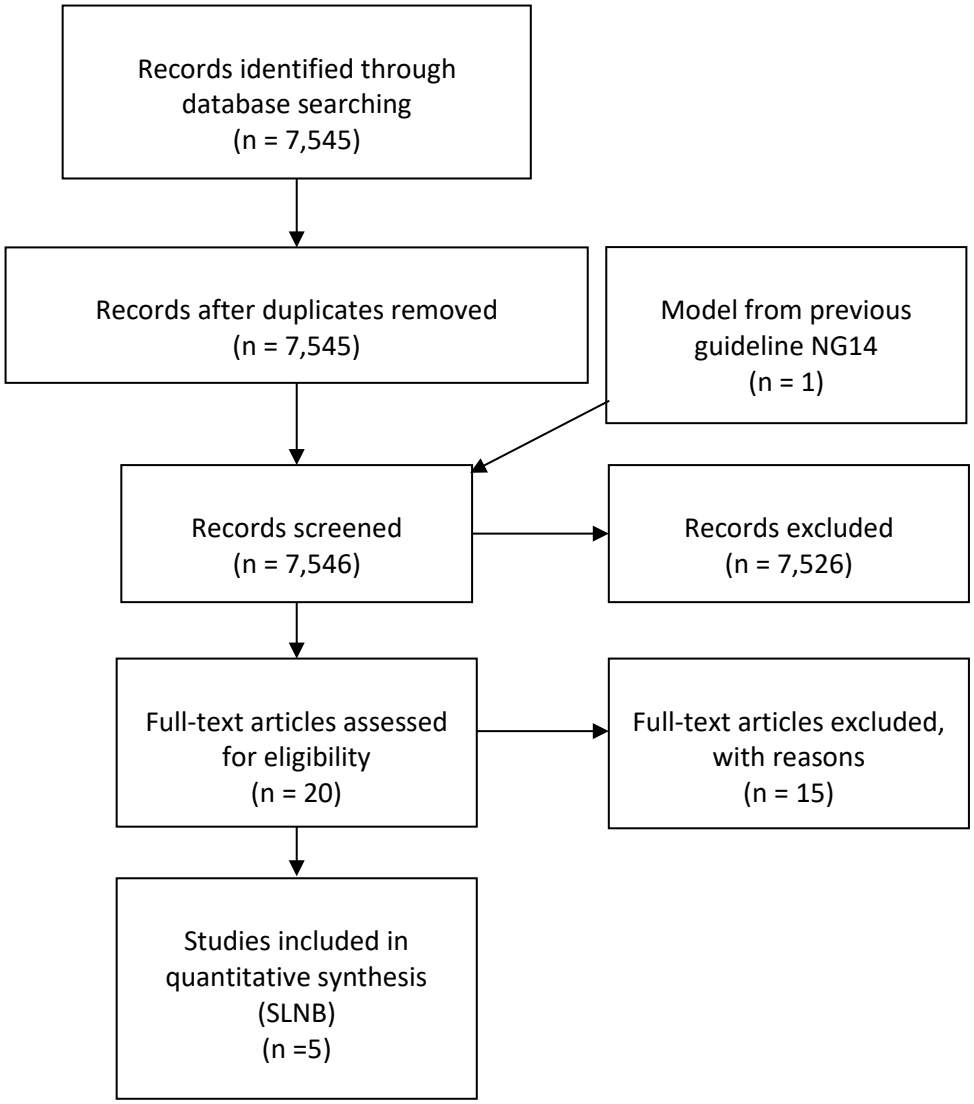
1. Study at moderate risk of bias
2. 95% confidence interval for likelihood ratio crosses two lines of a defined MID interval – (0.5, 1, 2)
3. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)

PET-MRI

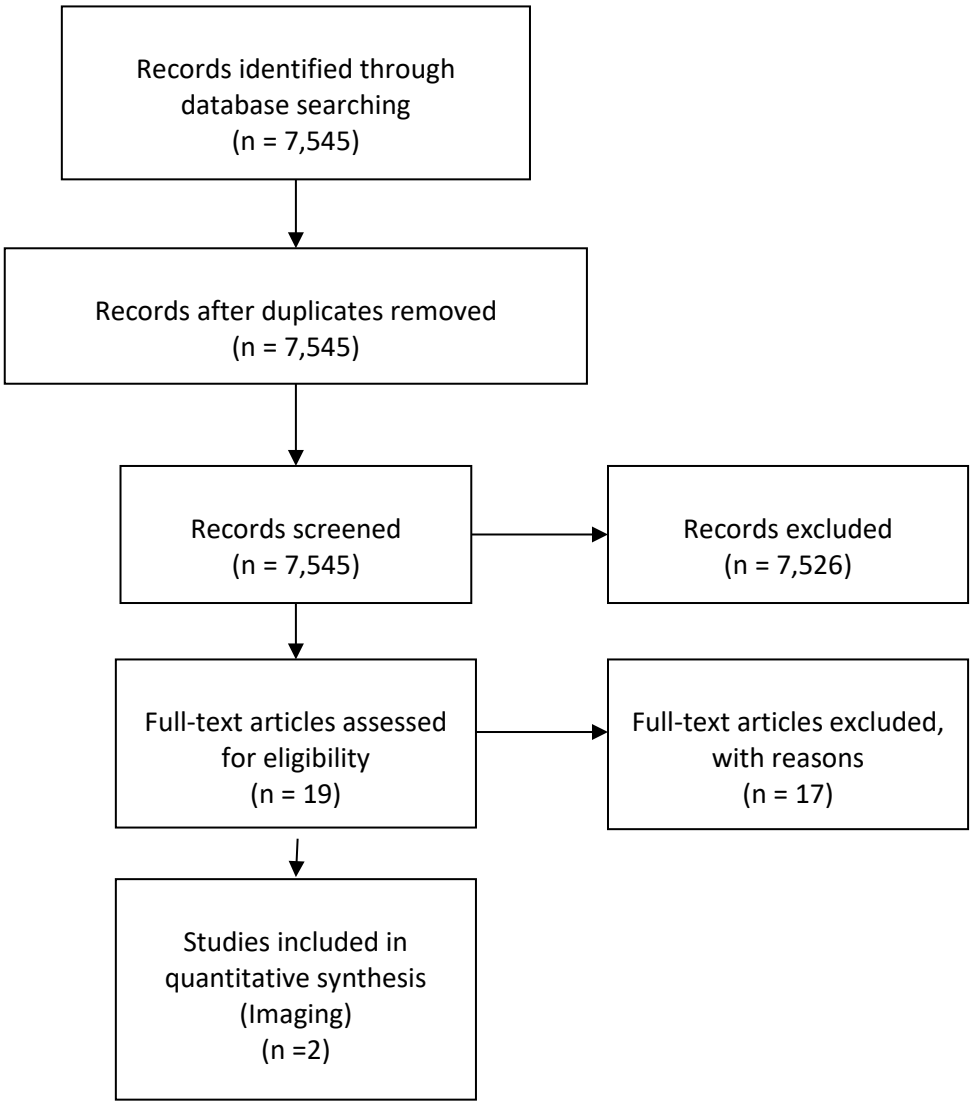
No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: PET-MRI; Reference standard: SLNB; Analysis per node										
Schaarschmidt 2018	Retrospective	82	0.23 (0.09, 0.48)	0.96 (0.88, 0.99)	LR+ 7.64 (1.52, 38.30)	Very serious[1]	Serious[2]	N/A	Serious[3]	Very low
					LR- 0.78 (0.60, 1.03)	Very serious[1]	Serious[2]	N/A	Serious[3]	Very low

1. Study at high risk of bias
2. Partially applicable study
3. 95% confidence interval for likelihood ratio crosses one line of a defined MID interval – (0.5, 1, 2)

Appendix I – Economic evidence study selection (predictors of SLNB review)



Appendix J – Economic evidence study selection (imaging review)



Appendix K – Economic evidence tables

Predictors of SLNB – summary of studies and results

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
NG14 Model (2014)	Cost-utility study Decision Tree and Markov model	United Kingdom Hospital	Wide excision and sentinel lymph node biopsy (SNB) Wide excision (WE)	Stage 1A to 2C Age: 52 Female: 43%	**Health states:** Disease free, local metastases, nodal metastases, distant metastases, dead from melanoma, dead other causes **Data Sources:** *Baseline/natural history* – based on the literature, including MSLT-1 trial *Effectiveness* – based on the literature; main differentiating parameter between interventions was disease-free survival from MSLT-1 trial *Costs* - NHS reference costs, based on literature *Utilities* – based on the literature **Time horizon:** 20 Years **Discount rates:** 3.5%	Cost[1]: SNB: £33,320 WE: £31,682 QALY: SNB: 11.34 WE:11.29 Incremental (SNB vs. WE) Cost: £1,638 QALY: 0.048 ICER: £34,402	**Deterministic:** SNB becomes cost effective if the difference in cost between SNB and WE is reduced. All other changes do not result in SNB becoming cost effective. **Probabilistic:** 1000 iterations done, SNB is preferred 43.8% of the time at £20,000/QALY threshold	**Source of funding:** Built as part of the 2014 update to NG14 **Authors' conclusions:** SNB is not cost effective at £20,000/QALY threshold
Hu et al. (2015)	Cost-utility study Markov model	United States of America Hospital	Wide excision and sentinel lymph node biopsy (SNB) Wide excision (WE)	Patients presenting with melanoma (more than one site or concurrent visceral or nodal melanoma were excluded) Age: 64.9 Female: 50%	**Health states:** Surveillance, Complete Lymphadenectomy, Stage 3 (Edema), Stage 3 (No Edema) and Death **Data Sources:** *Baseline/natural history* – based on the literature *Effectiveness* – from a review of a prospectively collected database *Costs* - derived from the Medicare physician fee	Absolute discounted costs[2]: SNB $26,221 WE $22,557 Absolute discounted QALYs: SNB 3.85 WE 3.66	**Deterministic:** SNB is no longer cost effective if more than 23% of nodes are positive or 15% of SNB patients experience regional recurrence. **Probabilistic:** SNB is cost effective in 78-95% of cases over $50,000 - $100,000/QALY	**Source of funding:** National Institute of Health **Limitations identified by authors:** SNB clinical outcomes are highly variable due to its rarity, utility of different health states vary across patients, stage 4 was not modelled due to lack of data. **Authors' conclusions:** SNB should be used for patients presenting with melanoma.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					schedule and Hospital Outpatient Prospective Payment System. *Utilities* - based on the literature. **Time horizon:** 5 Years **Discount rates:** unknown	Incremental (SNB vs. WE) discounted costs: $3,664 Incremental discounted QALYs: 0.19 ICER: $19,102		
Morton et al. (2009)	Cost-utility study Markov model	Australia Hospital Health system	Wide excision and sentinel lymph node biopsy (SNB) Wide excision (WE)	Primary tumour greater or equal to 1 mm Starting age: 52 Followed: 20 years	**Health States:** Melanoma, Disease free, Local metastasises, Nodal metastasises, Distant metastasises, Dead, Dead other causes. **Data Sources:** *Baseline/natural history* – based on the MSLT-1 trial *Effectiveness* – based on the literature *Costs* - derived from Australian refined diagnosis related groups and the Australian Medicare benefits schedule. *Utilities* - **Time horizon:** 20 years **Discount rate:** 5%	Total cost[3]: SNB AU$24,045 WE AU$23,182 Total QALYs SNB 10.34 WE 9.90 Incremental (SNB vs. WE) Cost: AU$863 QALYs 0.44 ICER AU$1,983	**Deterministic:** Variables that affected cost effectiveness were cost of SNB, cost of delayed complete lymph node dissection and probability of nodal or distant metastases. **Probabilistic:** Not completed	**Source of funding:** not reported. **Limitations identified by authors:** It was assumed that there was constant probability of progression every year. All SNB positive patients had immediate complete lymph node dissection. **Authors conclusions:** SNB is highly cost-effective for patients with tumours ≥ 1mm.
Serra-Arbeloa et al. (2016)	Cost-utility study Decision Tree	Spain Hospital Health care system	Wide excision and sentinel lymph node biopsy (SNB) Wide excision (WE)	Patients aged 18 years and over. Population divided into 3 sub-groups, thin (≤1 mm), intermediate (1-4mm) and thick (≥4mm) melanoma	**Benefits and harms in model:** Disease free, nodal relapse, distant relapse, death Data Sources**:** *Baseline/natural history* – based on the literature *Effectiveness* – based on the literature *Costs* - extracted from Spanish government publications.	**Thin:** Total cost[4]: SNB €25,980 WE €7,800 Total QALYs SNB 0.72 WE 0.83 Incremental (SNB vs. WE)	**Deterministic:** One way and two-way sensitivity analysis was done. No changes altered the preference for WE. **Probabilistic:** Not completed	**Source of funding:** not reported. **Limitations identified by authors:** Time dependant progression data not found in the literature. The outcomes in the decision tree are assumed to be mutually exclusive when in reality there is overlap in 12 % of cases. Spanish costs are lower than the USA and most other European countries.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					Utilities - obtained from a melanoma population study that used the time trade off method to obtain values for the different disease states. **Time horizon:** 10 years **Discount rate:** 0% in base case, 3% in sensitivity analysis	Cost: €18,180 QALYs -0.11 ICER: WE dominated **Intermediate:** Total cost: SNB €25,823 WE €22,683 Total QALYs SNB 0.70 WE 0.67 Incremental (SNB vs. WE) Cost: €3,140 QALYs 0.03 ICER €130,508 **Thick:** Total cost: SNB €36,101 WE €18,185 Total QALYs SNB 0.46 WE 0.49 Incremental (SNB vs. WE) Cost: €17,916 QALYs -0.03 ICER: WE dominates SNB		**Authors conclusions:** SNB is not cost-effective for any thickness of melanoma.

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Wilson et al (2002)	Cost Utility study Decision tree	USA Hospital	Treat no one with IFN, surgery and clinical observation only Test with time horizon. SLNB. Treat patients with a positive result with high dose IFN and those with a negative low dose IFN (test and treat appropriately) Treat all with low dose IFN following surgery. Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative with surgery alone (Test and treat some)	Hypothetical cohort of patients with Stage II malignant melanoma after surgical excision. Age, performance status and other demographic details were not reported for this cohort	**Benefits and harms in model:** Recurrence, no recurrence Data Sources**:** *Baseline/natural history* – based on the literature *Effectiveness* – based on the literature *Costs* – from the literature, Massachusetts General Hospital Melanoma Centre, Boston University Medical centre *Utilities* – based on the literature **Time horizon: 5** years **Discount rate:** 3%	Treat no one: Cost[5]: $18,400 QALY: 3.06 Test and treat appropriately: Cost: $24,200 QALY: 3.37 ICER: $18,700 Treat all: Cost: $30,500 QALY: 3.48 Extended dominated Test and treat some: Cost: $33,800 QALY: 3.68 ICER: $31,100	**Deterministic:** For test and treat some versus surgery and test and treat appropriately versus test and treat some reducing the cost of relapse to $10,000 increased the ICER to $21,900/QALY and $35,900/QALY respectively. Increasing the cost of relapse to $50,000 reduced the ICERs by $14,500/QALY and $26,100/QALY respectively Sensitivity and specificity of SLNB and the probability of dose changing toxicities were reported to have an insignificant effect on the ICER for both comparisons. **Probabilistic:** Varying across all variables for test and treat some versus surgery the median, 25th and 75th percentiles of the PSA are $19,605,$10,291 and $36,659 per QALY respectively. For test and treat appropriately versus test and treat some the median, 25th and 75th percentiles $30,229, $16,766 and $58,823 per QALY respectively	**Source of funding:** educational grant from the manufacturer. **Limitations identified by authors:** Short time horizon, explicitly differentiates patients and adjuvant dosing by sentinel lymph node mapping **Authors conclusions:** combining more accurate staging with either high dose IFN treatment of SLM-positive patients only or appropriate adjuvant IFN dosing for stage II melanoma are both cost-effective strategies

1 Costs in GBP in 2014, costs uprated to GBP in 2020 in summary in main text.
2 Costs in USD in 2015, costs uprated to GBP in 2020 in summary in main text
3 Costs in AUD in 2009, costs uprated to GBP in 2020 in summary in main text
4 Costs in EUR in 2016, costs uprated to GBP in 2020 in summary in main text
5 Costs in USD in 2002, costs uprated to GBP in 2020 in summary in main text

Imaging Review – summary of studies and results

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Look Hong (2015)	Cost-effectiveness study Decision Tree	Canada Hospital Healthcare system	Physical exam with chest radiography (PE/Radiography)	Patients with pathologically detected node-positive melanoma, with nonpalpable	**Benefits and harms in model:** True positive for distant metastases, true negative for distant metastases, test positive for	**Total cost[1]:** CT: CAD69,931.93 PE/Radiography: CAD70,623.52	**Deterministic:** When comparing CT and PE/radiography, CT dominates for all sensitivity analyses except high	**Source of funding:** not reported. **Limitations identified by authors:** Drug

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
			Computed Tomography (CT) Positron emission tomography and computed tomography (PET/CT)	nodal or in transit disease by clinician.	metastatic disease, test negative for metastatic disease, BRAF mutation, no BRAF mutation, surgery, no surgery, chemotherapy, no chemotherapy, Interferon and no Interferon **Data Sources:** *Baseline/natural history* – based on observational studies and expert opinion *Effectiveness* – based on observation trials and expert opinion *Costs* – Ontario Schedule of Benefits, New Drug Funding program of Ontario *Utilities* – not included **Time horizon:** Completion of a patient's initial medical and surgical options **Discount rate:** None as time horizon less than a year	PET/CT: CAD70,834.74 **Total effectiveness:** Probability of accurate diagnosis: CT: 0.90 PE/Radiography: 0.74 PET/CT: 0.94 **ICER**[2] CT vs. PE/Radiography: CT Dominates PET/CT vs CT: CAD22,570.25	probability of surgery (after any imaging technique) and high probability of adjuvant therapy (after any imaging technique). However, these are still below the threshold. When comparing CT and PET/CT, PET/CT is the preferred option for most sensitivity analyses except when the sensitivity of PET/CT is increased likely due to more patients receiving expensive treatment when it is not always required. **Probabilistic:** From a WTP of CAD0 to CAD22,570 CT is the preferred option, CAD22,570 and above PET/CT is preferred.	regimens and cost of hospital-based treatments are different between countries; the model does not address survival. **Authors conclusions:** PET/CT is the most cost-effective option as it reduces the need for unnecessary surgeries.
Olmedo et al. (2017)	Cost-effectiveness study CEA alongside retrospective observational study January 2004 - December 2015	Spain Hospitals Health service perspective	All patients received SLNB All patients received a regional lymph node ultrasound, with indeterminate or positive results receiving a core needle biopsy. If biopsy confirmed presence of lymph node metastasis, patient did not undergo SLNB.	All patients had received lymph node ultrasound for staging before SLNB. SLNB performed on patients with melanomas ≥0.75mm, with ulceration, at least 1 mitosis, microscopic satellite lesions or vascular invasion. 384 patients included.	**Benefits and harms in model:** Melanoma≥T1b, Physical examination, SLNB, Lymph node ultrasound, Tru-cut biopsy. **Data Sources:** *Baseline/natural history* – not included *Effectiveness* – based on the retrospective observational study *Costs* – based on invoices to a third party, including direct and indirect costs *Utilities* – not included	Total cost[3]: SLNB: €1700 Ultrasound: €1716.30 Total effectiveness (probability of identifying lymph node metastasis): SLNB: 0.06 Ultrasound: 0.21 Incremental[4] Cost: €16.30 Effectiveness: 0.15	**Deterministic:** Not completed. **Probabilistic:** Not completed.	**Source of funding:** not reported. **Limitations identified by authors**: Single centre, retrospective study. **Authors conclusions**: Ultrasound when necessary is a useful tool for staging melanoma before SLNB

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
					Time horizon: Not reported **Discount rate:** Not reported	ICER: €108.67		

1 Costs in CAD in 2015, costs uprated to GBP in 2020 in summary in main text.
2 ICERs reported were not calculated using a full incremental analysis (i.e., compared to the next best alternative) not correctly reported, but absolute costs and benefit outcomes effects were reported and therefore ICERs based on a full incremental analysis were calculated by the technical analyst
3 Costs in EUR in 2017, costs uprated to GBP in 2020 in summary in main text.
4 Incremental average cost-effectiveness reported, but absolute costs and effects were reported and therefore ICERs based on a full incremental analysis were calculated by the technical analyst

Predictors of SLNB – study quality assessment

Study identification **NG14 model (2014)**		
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?	Partly	Treatment after sentinel lymph node biopsy included complete lymph node dissection, which is not routinely conducted in current UK clinical practice.
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	

Study identification NG14 model (2014)		
Category	**Rating**	**Comments**
1.8 OVERALL JUDGEMENT	**PARTLY 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?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Study identification Hu et al. (2015)		
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?	Partly	US system different however it is an OECD country and investigation appear to be the same as the UK. Treatment after sentinel lymph node biopsy however included complete lymph node dissection, which is not routinely conducted in current UK clinical practice.
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?	Unclear	The values are discounted but a discount value is not stated.
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).	Partly	Some values obtained from investigator approximation, the other values were obtained from the literature.
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 Hu et al. (2015)		
Category	**Rating**	**Comments**
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Some utilities were obtained from investigator approximation, this included the more severe disease states. Does not state how the investigator valued these.
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?	Partly	Sourced from the available evidence, but does not state if these costs were adjusted to account for inflation.
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?	Unclear	Not stated.
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Study identification Morton et al. (2009)		
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	

Study identification Morton et al. (2009)		
Category	**Rating**	**Comments**
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Australian healthcare system, patients also received complete lymph node dissection after sentinel lymph node biopsy, which is not routinely conducted in current UK clinical practice.
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?	Partly	Cost and outcomes discounted at 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).	Yes	
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	
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 Morton et al. (2009)		
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	No probabilistic sensitivity analysis was done, only one way and two-way sensitivity analysis was conducted.
2.11 Has no potential financial conflict of interest been declared?	No	
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Study identification Serra-Arbeloa et al. (2016)		
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?	Partly	Spanish healthcare system, patients also received complete lymph node dissection after sentinel lymph node biopsy, which is not routinely conducted in current UK clinical practice.
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?	No	Discounting was only done in sensitivity analysis and 3% was used for both costs and outcomes.

Study identification Serra-Arbeloa et al. (2016)		
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	**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	
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	No probabilistic sensitivity analysis was done, only one way and two-way sensitivity analysis was conducted.
2.11 Has no potential financial conflict of interest been declared?	Yes	

Study identification Serra-Arbeloa et al. (2016)		
Category	**Rating**	**Comments**
2.12 OVERALL ASSESSMENT	**POTENTIALLY SERIOUS LIMITATIONS**	

Study identification Wilson L S, Reyes C M, Lu C, Lu M, Yen C (2002)		
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?	Partly	Includes the treatment of Melanoma
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	USA
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	**PARTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	

Study identification Wilson L S, Reyes C M, Lu C, Lu M, Yen C (2002)		
Category	**Rating**	**Comments**
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	Inappropriate time horizon, 5 years
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?	Yes	
2.11 Has no potential financial conflict of interest been declared?	No	Manufacture funded
2.12 OVERALL ASSESSMENT	**VERY SERIOUS LIMITATIONS**	

Imaging Review – study quality assessment

Study identification Look Hong et al. (2015)		
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?	Partly	Canadian 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?	No	No QoL outcomes
1.6 Are all future costs and outcomes discounted appropriately?	Partly	Discounting not done as the time horizon is a year however treatment of Stage 3 may last over a year in practice
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	No QoL outcomes
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?	No	Time horizon is a year and therefore does not take into account full benefits of treatments
2.3 Are all important and relevant outcomes included?	No	QoL outcomes not included
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	

Study identification Look Hong et al. (2015)		
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?	Partly	They are unless treatment were to last longer than a year
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?	Partly	Not available for QoL data but is available for 'per accurate diagnoses' etc
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?	No	Not stated
2.12 OVERALL ASSESSMENT	**VERY SERIOUS LIMITATIONS**	

Study identification Olmedo et al. (2017)		
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?	Partly	Spanish healthcare system
1.4 Is the perspective for costs appropriate for the review question?	Partly	Included non-direct costs

Study identification Olmedo et al. (2017)		
Category	**Rating**	**Comments**
1.5 Is the perspective for outcomes appropriate for the review question?	Partly	Did not appear to use QALYs
1.6 Are all future costs and outcomes discounted appropriately?	No	No discounting is reported
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	Used different effectiveness method but does not report how it was obtained
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?	Partly	Does not report time horizon but all patients received a staging diagnosis
2.3 Are all important and relevant outcomes included?	Unclear	Does not explain how effectiveness was assessed
2.4 Are the estimates of baseline outcomes from the best available source?	Unclear	Does not explain how effectiveness was assessed
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?	Partly	Does not explain how effectiveness was assessed, the ICER that was reported was incorrectly done

Study identification Olmedo et al. (2017)		
Category	**Rating**	**Comments**
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analysis done
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**VERY SERIOUS LIMITATIONS**	

Appendix L – Health economic model

No original health economic modelling was undertaken for this review question

Appendix M– Excluded studies

Diagnostic studies

Study	Reason for exclusion
Antonialli, A.Z., Bertolli, E., de Macedo, M.P. et al. (2020) How does the mitotic index impact patients with T1 melanoma? Comparison between the 7th and 8th edition of the American Joint Committee on Cancer melanoma staging system. Anais Brasileiros de Dermatologia	- data relevant to this review is not in extractable format
Aubuchon, M M F, Bolt, L J J, Janssen-Heijnen, M L G et al. (2017) Epidemiology, management and survival outcomes of primary cutaneous melanoma: a ten-year overview. Acta chirurgica Belgica 117(1): 29-35	- data relevant to this review is not in extractable format
Bellomo, D., Arias-Mejias, S.M., Ramana, C. et al. (2019) Model combining tumor molecular and clinicopathologic risk factors predicts sentinel lymph node metastasis in primary cutaneous melanoma. JCO Precision Oncology 3: 319-334	- data relevant to this review is not in extractable format
Borghi, A, Corazza, M, Minghetti, S et al. (2015) Malignant melanoma in Ferrara, Northern Italy: epidemiologic survey focusing on tumor thickness. Giornale italiano di dermatologia e venereologia : organo ufficiale, Societa italiana di dermatologia e sifilografia 150(6): 655-62	- data relevant to this review is not in extractable format
Conic, Rosalynn R Z, Ko, Jennifer, Damiani, Giovanni et al. (2019) Predictors of sentinel lymph node positivity in thin melanoma using the National Cancer Database. Journal of the American Academy of Dermatology 80(2): 441-447	- Study uses data from the National Cancer Database. To avoid double counting the same participants this study was excluded and another, larger study was included.
Egger, Michael E, Stevenson, Megan, Bhutiani, Neal et al. (2019) Should Sentinel Lymph Node Biopsy Be Performed for All T1b Melanomas in the New 8th Edition American Joint Committee on Cancer Staging System?. Journal of the American College of Surgeons 228(4): 466-472	- Study uses data from the National Cancer Database. To avoid double counting the same participants this study was excluded and another, larger study was included.
Hayek, Sarah A, Munoz, Amanda, Dove, James T et al. (2018) Hospital-Based Study of Compliance with NCCN Guidelines and Predictive Factors of Sentinel Lymph Node Biopsy in the Setting of Thin Melanoma Using the National Cancer Database. The American surgeon 84(5): 672-679	- Study uses data from the National Cancer Database. To avoid double counting the same participants this study was excluded and another, larger study was included.
Isom, Chelsea, Wheless, Lee, Hooks, Mary A et al. (2019) Early Melanoma Nodal Positivity and Biopsy Rates Before and After Implementation of the 7th Edition of the AJCC Cancer Staging Manual. JAMA dermatology 155(5): 572-577	- data relevant to this review is not in extractable format
Lo, S.N., Ma, J., Scolyer, R.A. et al. (2020) Improved risk prediction calculator for sentinel node positivity in patients with melanoma: The melanoma institute australia nomogram. Journal of Clinical Oncology 38(24): 2719-2727	- Prediction model not validated on thin melanomas

Study	Reason for exclusion
Sinnamon, Andrew J, Neuwirth, Madalyn G, Yalamanchi, Pratyusha et al. (2017) Association Between Patient Age and Lymph Node Positivity in Thin Melanoma. JAMA dermatology 153(9): 866-873	- Study uses data from the National Cancer Database. To avoid double counting the same participants this study was excluded and another, larger study was included.
Sinnamon, Andrew J, Sharon, Cimarron E, Song, Yun et al. (2018) The prognostic significance of tumor-infiltrating lymphocytes for primary melanoma varies by sex. Journal of the American Academy of Dermatology 79(2): 245-251	- Predictors assessed do not meet protocol
Verver, D., Louwman, W.J., Koljenovic, S. et al. (2018) Improved stratification of pT1 melanoma according to the 8th American Joint Committee on Cancer staging edition criteria: A Dutch population-based study. European Journal of Cancer 92: 100-107	- Does not predict SLNB positivity Data specific to thin melanomas is not reported. Prediction tool evaluated including genetic information and does not meet protocol

Diagnostic evidence

In addition to the studies listed below, the 10 studies included in the evidence review for 6.2 (Diagnostic accuracy of imaging during follow-up) were screened at full text for this review but were excluded.

Study	Reason for exclusion
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	- Does not contain a relevant population mucosal melanoma is out of scope
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
Bloemendal, Martine, van Willigen, Wouter W, Bol, Kalijn F et al. (2019) Early Recurrence in Completely Resected IIIB and IIIC Melanoma Warrants Restaging Prior to Adjuvant Therapy. Annals of surgical oncology 26(12): 3945-3952	- Not a relevant study design Not a diagnostic accuracy study
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

Study	Reason for exclusion
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
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 participants underwent imaging for reasons other than staging. 2 x 2 data not available for these groups separately.
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	- Data not reported in an extractable format 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.
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
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 melanoma (CMM): a pilot study. International journal of clinical oncology 19(4): 716-21	- Reference standard in study does not match that specified in protocol No mention of SLNB being performed
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	- Not possible to calculate a contingency table from the data specified in the protocol
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
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	- Study not reported in English

Study	Reason for exclusion
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	
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	- Not possible to calculate a contingency table from the data specified in the protocol
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

Economic Studies (prognostic review)

Study reference	Reason for exclusion
(2012) MelanoSITEâ„¢. Lansdale, PA: HAYES, Inc	- No costs or QoL data included, also no discounting done
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, (DECIT-CGATS) (2009) [Rapid HTA on the use of Positron Emission Tomography (PET) in the diagnosis, staging and re-staging of malignant melanoma]. Brasilia: Department of Science and Technology - Brazilian Health Technology Assessment General Coordination (DECIT-CGATS)	-Published in Portuguese
Goydos J S, Ravikumar T S, Germino F J, Yudd A, Bancila E (1998) Minimally invasive staging of patients with melanoma: sentinel lymphadenectomy and detection of the melanoma-specific proteins MART-1 and tyrosinase by reverse transcriptase	- Not a full economic evaluation, costs of test were the only values included, no outcomes were included

Study reference	Reason for exclusion
polymerase chain reaction. Journal of the American College of Surgeons 187(2): 182-188	
Herb, J.N., Ollila, D.W., Stitzenberg, K.B. *et al.* Use and Costs of Sentinel Lymph Node Biopsy in Non-Ulcerated T1b Melanoma: Analysis of a Population-Based Registry. *Ann Surg Oncol* **28,** 3470–3478 (2021). https://doi.org/10.1245/s10434-021-09998-6	- Not a full economic evaluation, no incremental analysis, No ICER provided or possible to work out
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; 2002; 87 (2); 151-157	- Not clear how outcomes are calculated and not possible to calculate an ICER
Hu, Y., Briggs, A., Gennarelli, R.L. et al. (2020) Sentinel Lymph Node Biopsy for T1b Melanoma: Balancing Prognostic Value and Cost. Annals of Surgical Oncology	- No QoL outcomes and indirect costs are included. Costs are reported as Medicare-proportional costs
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
IQWiG (2011) [Positron emission tomography (PET) in malignant melanoma]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	- No costs included
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
Look Hong N, Petrella T, Chan K (2015) Cost-effectiveness analysis of staging strategies in patients with regional metastatic melanoma. Journal of surgical oncology	- Intervention is not SLNB
Olmedo, D; Brotons-Segui, M; Del Toro, C; Gonzalez, M; Requena, C; Traves, V; Pla, A; Bolumar, I; Moreno-Ramirez, D; Nagore, E (2017) Use of Lymph Node Ultrasound Prior to Sentinel Lymph Node Biopsy in 384 Patients with Melanoma: A Cost-Effectiveness Analysis. Actas dermo-sifiliograficas	- Intervention is not SLNB
Tosteson ANA, Tapp S, Titus LJ, et al. Association of Second-Opinion Strategies in the Histopathologic Diagnosis of Cutaneous Melanocytic Lesions With Diagnostic Accuracy and Population-Level Costs. *JAMA Dermatol.* Published online June 02, 2021. doi:10.1001/jamadermatol.2021.1779	- Noneconomic analysis, no incremental analysis or explanation of the source of costs
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

Study reference	Reason for exclusion
van der Velde-Zimmermann D, Schipper M I, de Weger R A, Hennipman A, Borel Rinkes I H (2000) Sentinel node biopsies in melanoma patients: a protocol for accurate, efficient, and cost-effective analysis by preselection for immunohistochemistry on the basis of Tyr-PCR. Annals of Surgical Oncology 7(1): 51-54	- Cost analysis only

Economic Studies

Study reference	Reason for exclusion
(2012) MelanoSITEâ„¢. Lansdale, PA: HAYES, Inc	- No costs or QoL data included, also no discounting done
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, (DECIT-CGATS) (2009) [Rapid HTA on the use of Positron Emission Tomography (PET) in the diagnosis, staging and re-staging of malignant melanoma]. Brasilia: Department of Science and Technology - Brazilian Health Technology Assessment General Coordination (DECIT-CGATS)	-Published in Portuguese
Goydos J S, Ravikumar T S, Germino F J, Yudd A, Bancila E (1998) Minimally invasive staging of patients with melanoma: sentinel lymphadenectomy and detection of the melanoma-specific proteins MART-1 and tyrosinase by reverse transcriptase polymerase chain reaction. Journal of the American College of Surgeons 187(2): 182-188	- Not a full economic evaluation, costs of test were the only values included, no outcomes were included
Herb, J.N., Ollila, D.W., Stitzenberg, K.B. *et al.* Use and Costs of Sentinel Lymph Node Biopsy in Non-Ulcerated T1b Melanoma: Analysis of a Population-Based Registry. *Ann Surg Oncol* **28,** 3470–3478 (2021). https://doi.org/10.1245/s10434-021-09998-6	- Not a full economic evaluation, no incremental analysis, No ICER provided or possible to work out
Hofmann U, Szedlak M, Rittgen W, Jung E G, Schadendorf D (2002) Primary staging and follow-up in melanoma patients:	- Not clear how outcomes are calculated and not possible to calculate an ICER

Study reference	Reason for exclusion
monocenter evaluation of methods, costs and patient survival British Journal of Cancer; 2002; 87 (2); 151-157	
Hu, Y., Briggs, A., Gennarelli, R.L. et al. (2020) Sentinel Lymph Node Biopsy for T1b Melanoma: Balancing Prognostic Value and Cost. Annals of Surgical Oncology	- No QoL outcomes and indirect costs are included. Costs are reported as Medicare-proportional costs
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
IQWiG (2011) [Positron emission tomography (PET) in malignant melanoma]. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)	- No costs included
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
Tosteson ANA, Tapp S, Titus LJ, et al. Association of Second-Opinion Strategies in the Histopathologic Diagnosis of Cutaneous Melanocytic Lesions With Diagnostic Accuracy and Population-Level Costs. *JAMA Dermatol.* Published online June 02, 2021. doi:10.1001/jamadermatol.2021.1779	- Noneconomic analysis, no incremental analysis or explanation of the source of costs
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
van der Velde-Zimmermann D, Schipper M I, de Weger R A, Hennipman A, Borel Rinkes I H (2000) Sentinel node biopsies in melanoma patients: a protocol for accurate, efficient, and cost-effective analysis by preselection for immunohistochemistry on the basis of Tyr-PCR. Annals of Surgical Oncology 7(1): 51-54	- Cost analysis only