National Institute for Health and Care Excellence

Final

Melanoma: assessment and management

[E] Evidence reviews for the use of sentinel lymph node biopsy for people with stage III melanoma with microsatellite lesions

NICE guideline NG14

Methods, evidence and recommendations

July 2022

Final

National Institute for Health and Care Excellence

Disclaimer

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

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-1322-0

Contents

Sentinel lymph node biopsy for people with stage III melanoma with microsatellite lesions

1.1 Review question

RQ 4.2. What is the utility of sentinel lymph node biopsy for people with stage 3 melanoma and micro-satellite lesions?

1.1.1 Introduction

Sentinel lymph node biopsy (SLNB) has prognostic utility in lower stage (I-II) melanoma, revealing whether metastases has spread to the sentinel lymph nodes. This allows for re-staging – progression to stage III if positive – and makes people eligible for additional therapies. There is a lack of consensus regarding whether there is a need to perform a SLNB for people who already have a diagnosis of stage III melanoma, in those people with microsatellite lesions for whom a SLNB has not previously been performed. Currently, some practices perform SLNB in this population of people in the hope that it will offer therapeutic and/or prognostic benefit.

1.1.2 Summary of the protocol

Table 1 PICO table for sentinel lymph node biopsy for people with stage III melanoma with microsatellite lesions

Population	People with a diagnostic of stage III melanoma with microsatellite lesions
Intervention (predictors)	SLNB
Comparator (predicted outcome)	No SLNB, with clinical observation

Outcomes	• Local Recurrence
	• Regional recurrence
	• All-cause and Melanoma-related mortality (5 & 10 yr)
	• Health related quality of life
	• Adverse events
	  ○ Short term (surgical adverse events)
	  ○ Long term (inc: Lymphoedema)

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.

1.1.4 Clinical evidence

1.1.4.1 Included studies

A systematic literature search was conducted for this review on systemic and localised treatment in people with melanoma. This returned 1,544 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 20 references were ordered for screening based on their full texts.

Of the 20 references screened as full texts, 0 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 Excluded studies

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

1.1.5 Economic evidence

1.1.5.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B). This search retrieved 7,545 studies. Based on title and abstract screening, 7,532 of the studies could confidently be excluded for this question. Thirteen studies were excluded following the full-text review. Thus, the review for this question did not include any studies from the existing literature.

1.1.5.2 Excluded studies

See **Error! Reference source not found.** for a list of references for excluded studies, with reasons for exclusion.

1.1.6 Summary of included economic evidence

There are no existing economic studies for this review question.

1.1.7 Economic model

No original modelling was completed for this review question

1.1.8 Unit costs

No unit costs were supplied for this review question.

1.1.9 Evidence statements

No existing economic studies or *de novo* economic modelling was included for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1 The outcomes that matter most

There are two speculated benefits for the use of SLNB in people with stage III melanoma with microsatellite lesions.

The first is that the SLNB will offer prognostic utility for the person with melanoma and will lead to more accurate staging, better treatment choices and improve outcomes of mortality and disease progression. The second is the direct therapeutic benefit of removing cancerous lymph nodes. The committee agreed that the current review on the use of SLNB should focus on downstream outcomes of mortality and disease progression.

1.1.10.2 The quality of the evidence

No studies were identified for the present evidence review.

1.1.10.3 Benefits and harms

The committee discussed the potential benefits and harms in the absence of evidence. The committee agreed that the presence of microsatellite lesions also means that there is evidence of progression past the lymph nodes and automatically upstages people to stage IIIIC disease. Therefore, conducting a SLNB would not lead to someone with microsatellite lesions being upstaged.

The committee advised that SLNB may sometimes be deemed useful at the discretion of the treating physician due to a desire to know whether disease has spread to the lymph nodes. However, its prognostic utility in this context is unclear.

The committee agreed that most hospitals in the UK do not currently perform SLNB for people with stage III disease. Therefore, the committee agreed to not make recommendations in this area.

1.1.10.4 Cost effectiveness and resource use

The committee did not prioritise this review for *de novo* economic modelling and there were no existing economic studies therefore, there was no economic evidence for the committee to consider.

1.1.11 Recommendations supported by this evidence review

No recommendations were made from this evidence review.

1.1.12 References – included studies

1.1.12.1 Clinical evidence

No studies were included in this review.

1.1.12.2 Economic

No studies were included in this review.

1.1.12.3 Other

No studies were included in this review.

Appendices

Appendix A – Review protocols

Review protocol for SLNB for stage III melanoma and microsatellite lesions

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Sentinel lymph node biopsy for people with stage 3 melanoma and micro-satellite lesions
2.	Review question	RQ 4.2 What is the utility of sentinel lymph node biopsy for people with stage 3 melanoma and micro-satellite lesions?
3.	Objective	Determine the utility of sentinel lymph node biopsy (SLNB) for people with stage 3 melanoma and micro-satellite lesions, who have not already had a SLNB.
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: • none 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 3 melanoma with micro-satellite lesions
6.	Population	People with a diagnosis of stage 3 melanoma with micro-satellite lesions who have not undergone a SLNB
7.	Intervention	SLNB
8.	Comparator	Clinical observation

9.	Types of study to be included	• RCTs • Cohort studies (prospective and retrospective) if attempts have been made to control for baseline differences between groups
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 create new recommendations regarding the use of SLNB in people with stage 3 melanoma with satellite lesions. These people will not have previously undergone SLNB and there is uncertainty whether performing one offers any prognostic utility or impact upon outcomes. It is possible that a SLNB may help inform on the benefit of adjuvant treatment.
12.	Primary outcomes (critical outcomes)	• Local Recurrence • Regional recurrence • All-cause and Melanoma-related mortality (5 & 10 yr) • Health related quality of life • Adverse events • Long term (inc: Lymphoedema) • Short term (surgical adverse events)
13.	Secondary outcomes	None

	(important outcomes)	
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 Cochrane risk of bias tool (version 2) for RCTs and the ROBINS-I checklist for cohort studies, as described in Developing NICE guidelines: the manual.

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

19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	01/03/21
22.	Anticipated completion date	01/09/21
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 • Hannah Lomax • Jenny Craven
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	• SLNB • Micro-satellite lesions • Melanoma • Skin cancer • Skin tumour

33.	Details of existing review of same topic by same authors	This is a new review question for this guideline.
34.	Current review status	☒Intervention
35..	Additional information	none
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Searches were run on the 27th April 2020 and updated on 14th July 2021 in Medline, Medline in Process, Medline epub, the Cochrane Database of Systematic Reviews (CRD/CENTRAL) and DARE (Wiley platform). These searches are presented below.

Database: Medline
1 exp Melanoma/ 97786
2 Skin Neoplasms/ 123844
3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. 106964
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. 63197
5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. 25629
6 (hutchinson* adj2 (freckle* or melano*)).tw. 69
7 dubreuilh*.tw. 74
8 (maligna* adj2 lentigo*).tw. 1088
9 LMM.tw. 933
10 or/1-9 257674
11 Sentinel Lymph Node Biopsy/ 11522

12	(sentinel adj2 node*).tw. 13465
13	(sentinel adj2 lymphadenectom*).tw. 363
14	(SLNB or SNB).tw. 3442
15	or/11-14 16534
16	(Microsatellit* or micro-satellit*).tw. 36790
17	Satellit*.tw. 24729
18	(In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*).tw. 9264
19	((Small* or tiny or micro* or thin* or subcutan* or aggressive*) adj4 (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)).tw. 198339
20	SITM.tw. 3
21	(Metasta* or advanc*).tw. 1083173
22	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three).tw. 40982
23	or/16-22 1327299
24	10 and 15 and 23 2568
25	limit 24 to english language 2347
26	animals/ not humans/ 4779874
27	25 not 26 2312
28	limit 27 to (letter or historical article or comment or editorial or news or case reports) 280

29	27 not 28	2032
30	randomized controlled trial.pt.	526759
31	randomi?ed.mp.	833628
32	placebo.mp.	201387
33	or/30-32	886424
34	Observational Studies as Topic/	6111
35	Observational Study/	96272
36	Epidemiologic Studies/	8612
37	exp Case-Control Studies/	1158898
38	exp Cohort Studies/	2114576
39	Cross-Sectional Studies/	360004
40	Controlled Before-After Studies/	604
41	Historically Controlled Study/	197
42	Interrupted Time Series Analysis/	1183
43	Comparative Study.pt.	1887335
44	case control$.tw.	117417
45	case series.tw.	63760
46	(cohort adj (study or studies)).tw.	188717
47	cohort analy$.tw.	7389

48	(follow up adj (study or studies)).tw.	46419
49	(observational adj (study or studies)).tw.	94767
50	longitudinal.tw.	217345
51	prospective.tw.	520610
52	retrospective.tw.	476397
53	cross sectional.tw.	309343
54	or/34-53	4535891
55	33 or 54	5055154
56	29 and 55	1080

Database: Medline in Process		
1	exp Melanoma/	0
2	Skin Neoplasms/	0
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw.	3426

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.	1544
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.	606
6	(hutchinson* adj2 (freckle* or melano*)).tw.	1
7	dubreuilh*.tw.	0
8	(maligna* adj2 lentigo*).tw.	41
9	LMM.tw.	71
10	or/1-9	5015
11	Sentinel Lymph Node Biopsy/	0
12	(sentinel adj2 node*).tw.	462
13	(sentinel adj2 lymphadenectom*).tw.	7
14	(SLNB or SNB).tw.	144
15	or/11-14	493
16	(Microsatellit* or micro-satellit*).tw.	748
17	Satellit*.tw.	626
18	(In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*).tw.	281
19	((Small* or tiny or micro* or thin* or subcutan* or aggressive*) adj4 (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)).tw.	8729
20	SITM.tw.	1

21	(Metasta* or advanc*).tw.	45257
22	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three).tw.	1497
23	or/16-22	53940
24	10 and 15 and 23	74
25	limit 24 to english language	72
26	animals/ not humans/	0
27	25 not 26	72

Database: Medline Epub

1	exp Melanoma/	0
2	Skin Neoplasms/	0
3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw.	1583
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.	923
5	((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.	409
6	(hutchinson* adj2 (freckle* or melano*)).tw.	1
7	dubreuilh*.tw.	0
8	(maligna* adj2 lentigo*).tw.	19

9	LMM.tw.	24
10	or/1-9	2611
11	Sentinel Lymph Node Biopsy/	0
12	(sentinel adj2 node*).tw.	274
13	(sentinel adj2 lymphadenectom*).tw.	6
14	(SLNB or SNB).tw.	93
15	or/11-14	305
16	(Microsatellit* or micro-satellit*).tw.	338
17	Satellit*.tw.	423
18	(In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*).tw.	208
19	((Small* or tiny or micro* or thin* or subcutan* or aggressive*) adj4 (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)).tw.	3538
20	SITM.tw.	0
21	(Metasta* or advanc*).tw.	24299
22	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three).tw.	851
23	or/16-22	28352
24	10 and 15 and 23	41
25	limit 24 to english language	40
26	animals/ not humans/	0

27	25 not 26	40

Database: Embase

1 exp melanoma skin cancer/ or melanoma/ or cutaneous melanoma/ or metastatic melanoma/ or superficial spreading melanoma/ or skin carcinoma/ 163816

2 skin tumor/ or skin cancer/ or epithelium tumor/ 69039

3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. 170199

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. 96898

5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. 41265

6 (hutchinson* adj2 (freckle* or melano*)).tw. 81

7 dubreuilh*.tw. 73

8 (maligna* adj2 lentigo*).tw. 1762

9 LMM.tw. 1615

10 or/1-9 344547

11 sentinel lymph node biopsy/ 17530

12 (sentinel adj2 node*).tw. 25325

13	(sentinel adj2 lymphadenectom*).tw. 537
14	(SLNB or SNB).tw. 6932
15	or/11-14 31552
16	satellite lesion/ or "satellitosis"/ 63
17	(Microsatellit* or micro-satellit*).tw. 48668
18	Satellit*.tw. 37538
19	in-transit metastasis/ 532
20	(In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*).tw. 14511
21	((Small* or tiny or micro* or thin* or subcutan* or aggressive*) adj4 (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)).tw. 336084
22	SITM.tw. 9
23	(Metasta* or advanc*).tw. 1861628
24	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three).tw. 86136
25	or/16-24 2252959
26	10 and 15 and 25 4668
27	limit 26 to english language 4310
28	nonhuman/ not human/ 4863383
29	27 not 28 4265

30	limit 29 to (letter or historical article or comment or editorial or news or case reports)	85
31	29 not 30	4180
32	random:.tw.	1677077
33	placebo:.mp.	479132
34	double-blind:.tw.	222322
35	or/32-34	1941039
36	Clinical study/	156131
37	Case control study/	172408
38	Family study/	25556
39	Longitudinal study/	155052
40	Retrospective study/	1073037
41	comparative study/	898502
42	Prospective study/	685258
43	Randomized controlled trials/	203726
44	42 not 43	677572
45	Cohort analysis/	702624
46	cohort analy$.tw.	14582
47	(Cohort adj (study or studies)).tw.	342462
48	(Case control$ adj (study or studies)).tw.	147800

49	(follow up adj (study or studies)).tw. 66655
50	(observational adj (study or studies)).tw. 190248
51	(epidemiologic$ adj (study or studies)).tw. 112075
52	(cross sectional adj (study or studies)).tw. 251576
53	case series.tw. 115787
54	prospective.tw. 928311
55	retrospective.tw. 981816
56	or/36-41,44-55 4404794
57	35 or 56 5884173
58	31 and 57 1569
59	(conference abstract or conference paper or conference proceeding or "conference review").pt. 4871802
60	58 not 59 1034

Database: Cochrane Wiley (CDSR/CENTRAL)	
#1	MeSH descriptor: [Melanoma] explode all trees 1843
#2	MeSH descriptor: [Skin Neoplasms] explode all trees 1599
#3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*):ti,ab,kw 5579

#4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)):ti,ab,kw 4117

#5 ((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*)):ti,ab,kw 709

#6 (hutchinson* NEAR/2 (freckle* or melano*)):ti,ab,kw9

#7 dubreuilh*:ti,ab,kw 0

#8 (maligna* NEAR/2 lentigo*):ti,ab,kw 40

#9 LMM:ti,ab,kw 129

#10 {or #1-#9} 8774

#11 MeSH descriptor: [Sentinel Lymph Node Biopsy] explode all trees 280

#12 (sentinel NEAR/2 node*):ti,ab,kw 1455

#13 (sentinel NEAR/2 lymphadenectom*):ti,ab,kw 30

#14 (SLNB or SNB):ti,ab,kw 466

#15 {or #11-#14} 1636

#16 (Microsatellit* or micro-satellit*):ti,ab,kw 416

#17 Satellit*:ti,ab,kw 554

#18 (In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*):ti,ab,kw 605

#19 ((Small* or tiny or micro* or thin* or subcutan* or aggressive*) NEAR/4 (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)):ti,ab,kw 5758

#20	SITM:ti,ab,kw 1
#21	(Metasta* or advanc*):ti,ab,kw 98728
#22	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three).:ti,ab,kw 1596
#23	{or #16-#22} 105153
#24	#10 and #15 and #23 180

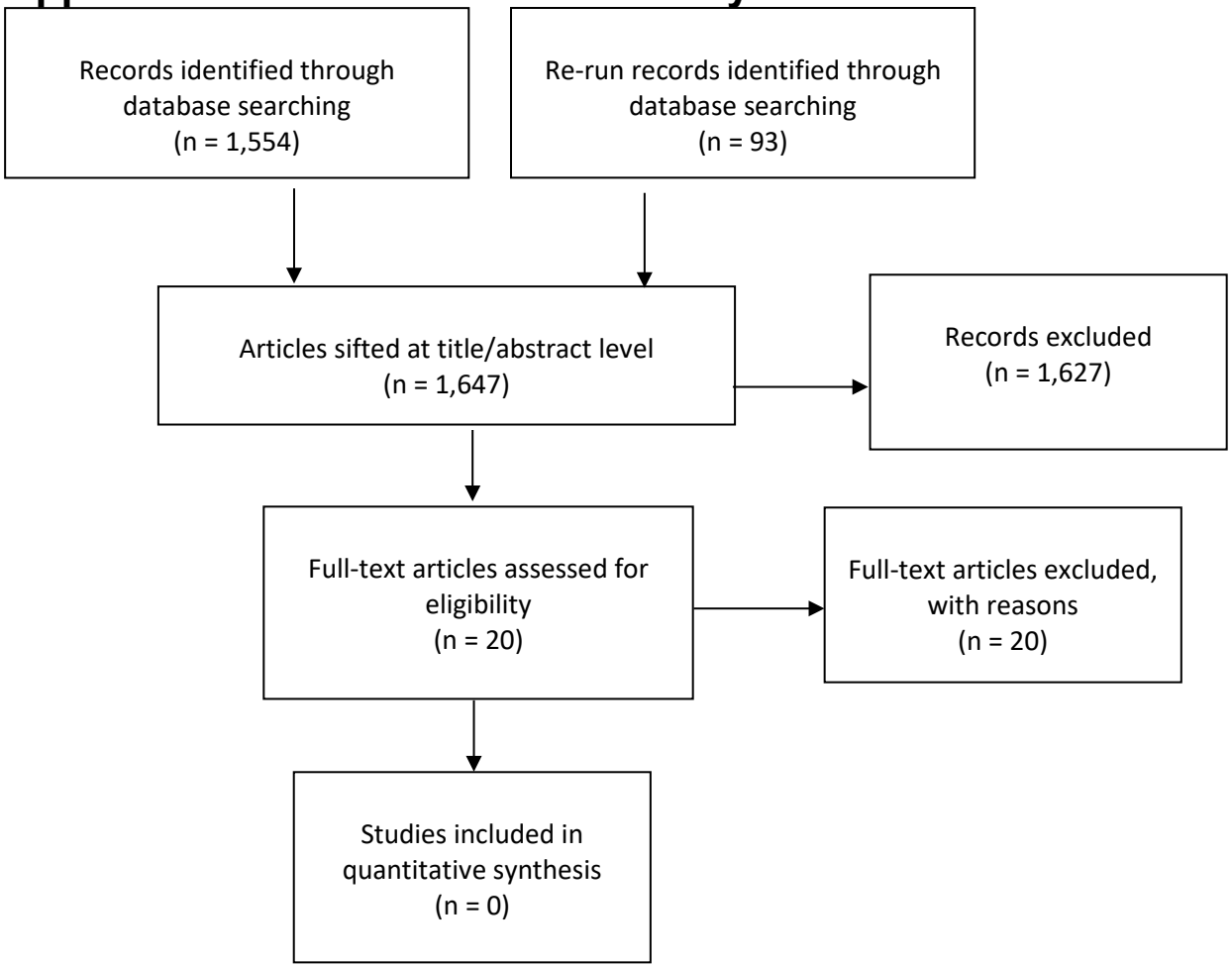
Database: CRD (DARE/HTA)
1 MeSH DESCRIPTOR Melanoma EXPLODE ALL TREES 221 Delete
2 MeSH DESCRIPTOR Skin Neoplasms EXPLODE ALL TREES 194 Delete
3 ((melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*)) 329 Delete
4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)) 476 Delete
5 ((maligna* or melano*) NEAR (freckle* or lesion* or mole* or nev* or naev*)) 123 Delete
6 (hutchinson* NEAR (freckle* or melano*)) 0 Delete
7 (dubreuilh*) 0 Delete
8 (maligna* NEAR lentigo*) 0 Delete

9	(LMM)	0	Delete
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	731	Delete
11	MeSH DESCRIPTOR Sentinel Lymph Node Biopsy EXPLODE ALL TREES	119	Delete
12	(sentinel NEAR node*)	149	Delete
13	(sentinel NEAR lymphadenectom*)	5	Delete
14	(SLNB or SNB)	20	Delete
15	#11 OR #12 OR #13 OR #14	154	Delete
16	(Microsatellit* or micro-satellit*)	27	Delete
17	(Satellit*)	95	Delete
18	(In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*)	22	Delete
19	((Small* or tiny or micro* or thin* or subcutan* or aggressive*) NEAR (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*))	223	Delete
20	(SITM)	0	Delete
21	(Metasta* or advance*)	4872	Delete
22	("Stage-3" or "stage3" or stage-iii or stageiii or stage-three)	291	Delete
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	514	Delete
24	#10 AND #15 AND #23	20	

INAHTA		
24	#23 AND #15 AND #10	1
23	#22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16	2867
22	"Stage-3" or "stage3" or stage-iii or stageiii or stage-three	1917
21	Metasta* or advance*	1148
20	SITM	0
19	(Small* or tiny or micro* or thin* or subcutan* or aggressive*) NEAR (lesion* or nodal* or nodule* or recurren* or re-curren* or structure* or tumour* or tumor* or deposit*)	18
18	In-transit* or Intransit* or In-tralymphatic* or Intralymphatic*	72
17	Satellit*	7
16	Microsatellit* or micro-satellit*	45
15	#14 OR #13 OR #12 OR #11	24
14	SLNB or SNB	7
13	sentinel NEAR lymphadenectom*	0
12	sentinel NEAR node*	0
11	"Sentinel Lymph Node Biopsy"[mh]	20
10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	168
9	LMM	0
8	maligna* NEAR lentigo*	0

7	dubreuilh*	0
6	hutchinson* NEAR (freckle* or melano*)	0
5	(maligna* or melano*) NEAR (freckle* or lesion* or mole* or nev* or naev*)	1
4	(skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)	5
3	melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*	122
2	"Skin Neoplasms"[mh]	64
1	"Melanoma"[mh]	104

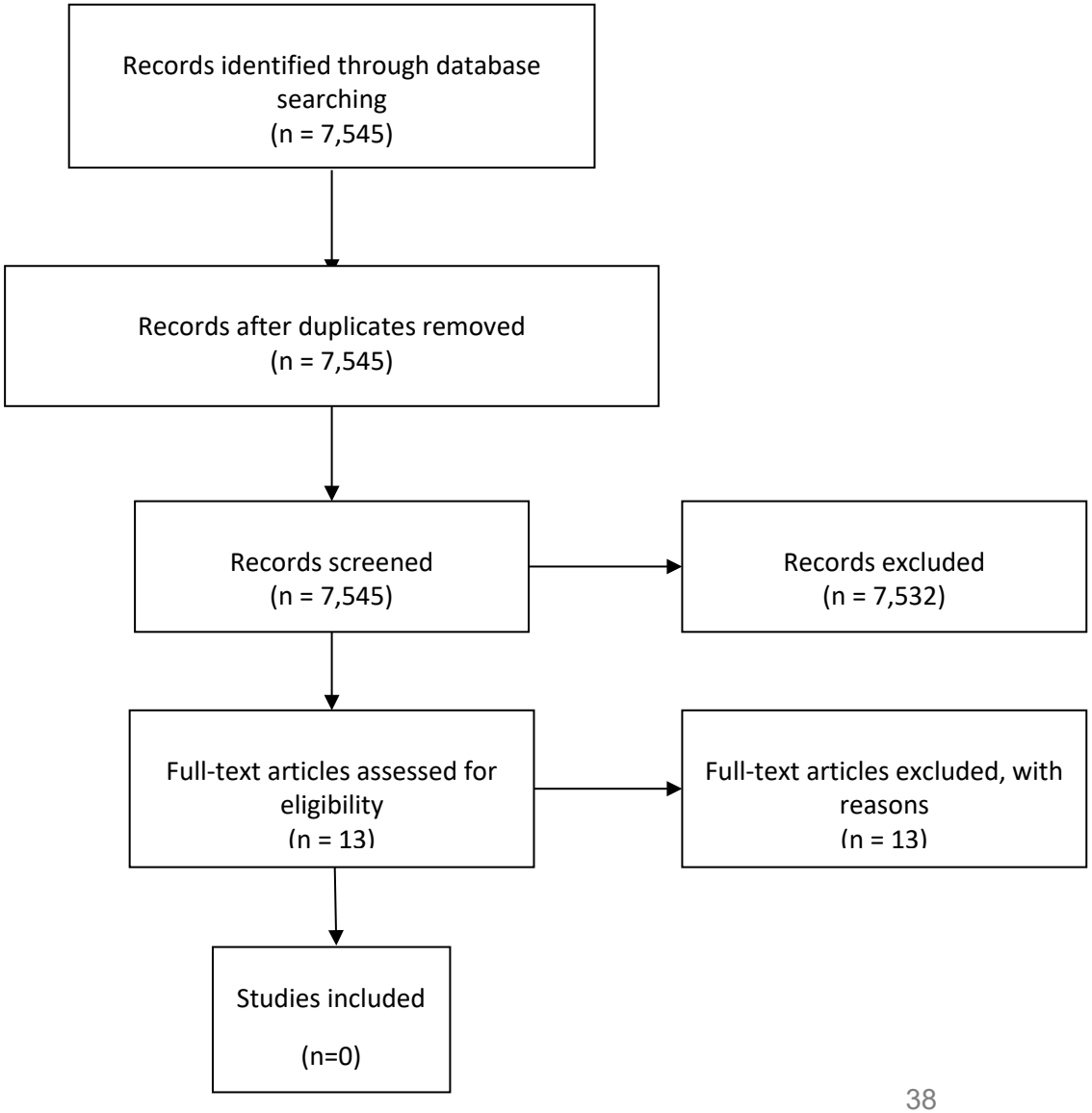
Appendix C – Clinical evidence study selection



Appendix D - Forest plots

No forest plots were generated from the evidence reviewed

Appendix E -Economic evidence study selection



Appendix F – Economic evidence tables

No economic evidence was found for this review question.

Appendix G – Health Economic model

No original health economic modelling was completed for this review question.

Appendix H – Research recommendations – full details

No research recommendations were made for this review.

Appendix I – Excluded studies

Study	Reason for exclusion
Ahmed, Tasnia, El Sharouni, Mary-Ann, Sigurdsson, Vigfus et al. (2021) Development and Validation of Nomograms to Predict Local, Regional, and Distant Recurrence in Patients With Thin (T1) Melanomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 39(11): 1243-1252	- Included in another review
Anwar, Sumadi Lukman, Cahyono, Roby, Budiman, Heru Yudanto et al. (2021) Regional lymph node infiltration and thick lesions are associated with poor prognosis in high-risk resected melanomas: A retrospective cohort study. Annals of Medicine and Surgery 61: 132-138	- Included in another review
Bartlett, Edmund K, Gupta, Meera, Datta, Jashodeep et al. (2014) Prognosis of patients with melanoma and microsatellitosis undergoing sentinel lymph node biopsy. Annals of surgical oncology 21(3): 1016-23	- Included in another review
Baum, Cornelia, Weiss, Christel, Gebhardt, Christoffer et al. (2017) Sentinel node metastasis mitotic rate (SN-MMR) as a prognostic indicator of rapidly progressing disease in patients with sentinel node-positive melanomas. International journal of cancer 140(8): 1907-1917	- Included in another review

Study	Reason for exclusion
Bertolli, Eduardo, de Macedo, Mariana Petaccia, Calsavara, Vinicius Fernando et al. (2019) A nomogram to identify high-risk melanoma patients with a negative sentinel lymph node biopsy. Journal of the American Academy of Dermatology 80(3): 722-726	- Included in another review
El Sharouni, M A, Ahmed, T, Witkamp, A J et al. (2020) Predicting recurrence in patients with sentinel node-negative melanoma: validation of the EORTC nomogram using population-based data. The British journal of surgery	- Included in another review
Garbe, Claus, Keim, Ulrike, Amaral, Teresa et al. (2020) Prognosis of patients with stage III melanoma according to American joint committee on cancer version 8: A reassessment on the basis of 3 independent stage III melanoma cohorts. Journal of Clinical Oncology 38(22): 2543-2551	- No outcomes of relevance to this review - Included in another review
Karakousis, Giorgos C, Gimotty, Phyllis A, Leong, Stanley P et al. (2019) Microsatellitosis in Patients with Melanoma. Annals of surgical oncology 26(1): 33-41	- Not a RCT
Kimsey, Troy F, Cohen, T, Patel, A et al. (2009) Microscopic satellitosis in patients with primary cutaneous melanoma: implications for nodal basin staging. Annals of surgical oncology 16(5): 1176-83	- Not a RCT
Kretschmer, Lutz, Bertsch, Hans Peter, Zapf, Antonia et al. (2015) Nodal Basin Recurrence After Sentinel Lymph Node Biopsy for Melanoma: A Retrospective Multicenter Study in 2653 Patients. Medicine 94(36): e1433	- Included in another review

Study	Reason for exclusion
Lo, Serigne N, Ma, Jiawen, Scolyer, Richard 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: official journal of the American Society of Clinical Oncology 38(24): 2719-2727	- Included in another review
Nijhuis, Amanda A G, Spillane, Andrew J., Stretch, Jonathan R. et al. (2020) Current management of patients with melanoma who are found to be sentinel node-positive. ANZ journal of surgery 90(4): 491-496	- No outcomes of relevance to this review
O'Connell, Emer P, O'Leary, Donal P, Fogarty, Katrina et al. (2016) Predictors and patterns of melanoma recurrence following a negative sentinel lymph node biopsy. Melanoma research 26(1): 66-70	- Included in another review
Pasquali, S, Mocellin, S, Campana, L G et al. (2011) Maximizing the clinical usefulness of a nomogram to select patients candidate to sentinel node biopsy for cutaneous melanoma. European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 37(8): 675-80	- No outcomes of relevance to this review
Patel, Ronak A., Borrelli, Mimi R., Wan, Derrick C. et al. (2020) Compounding Benefits of Sentinel Lymph Node Biopsy for Perineal Melanoma: A Population-Based Retrospective Cohort Analysis. Annals of plastic surgery 84(5ssuppl4): 257-s263	- Included in another review
Pinero, Antonio, Canteras, Manuel, Ortiz, Eduardo et al. (2008) Validation of a nomogram to predict the presence of sentinel lymph node metastases in melanoma. Annals of surgical oncology 15(10): 2874-7	- Included in another review

Study	Reason for exclusion
Sun, James, Carr, Michael J., Kim, Youngchul et al. (2021) Active surveillance of patients who have sentinel node positive melanoma: An international, multi-institution evaluation of adoption and early outcomes after the Multicenter Selective Lymphadenectomy trial II (MSLT-2). Cancer	- Included in another review
van Akkooi, Alexander C. J., Franke, Viola, Haferkamp, Sebastian et al. (2021) A Retrospective Chart Review Study of Real-World Use of Talimogene Laherparepvec in Unresectable Stage IIIB-IVM1a Melanoma in Four European Countries. Advances in Therapy 38(2): 1245-1262	- Included in another review
Verver, D., Grunhagen, D.J., Verhoef, C. et al. (2019) Development and validation of a nomogram to predict recurrence and melanoma-specific mortality in patients with negative sentinel lymph nodes. British Journal of Surgery 106(3): 217-225	- Included in another review
Verver, Danielle, Rekkas, A, Garbe, Claus et al. (2020) The EORTC-DeCOG nomogram adequately predicts outcomes of patients with sentinel node-positive melanoma without the need for completion lymph node dissection. European journal of cancer (Oxford, England : 1990) 134: 9-18	- Included in another review

Economic Studies

Study	Reason for exclusion
Aiken, Taylor J, Stahl, Christopher C, Schwartz, Patrick B et al. (2021) Sentinel lymph node biopsy is associated with increased cost in higher risk thin melanoma. Journal of surgical oncology 123(1): 104-109	- Non economic evaluation, No ICER or able to be calculated. No explanation on source of costs.
Alberta Heritage Foundation for Medical, Research (1997) Radiosurgery in the treatment of malignant melanoma. Alberta Heritage Foundation for Medical Research (AHFMR): 7	-Bibliographic record only
Azzopardi, E A, Abdelrahman, W, Azzopardi, E et al. (2021) Treatment of cutaneous basal cell carcinoma with combined laser extirpation and methyl aminolevulinic acid: five-year success rates. Annals of the Royal College of Surgeons of England 103(4): 263-271	-Different decision problem, does not include melanoma.
Covarelli P, Badolato M, Tomassini GM, Poponesi V, Listorti C, Castellani E, Boselli C, Noya G (2012) Sentinel lymph node biopsy under local anaesthesia versus general anaesthesia: reliability and cost-effectiveness analysis in 153 patients with malignant melanoma. In Vivo 26(2): 315-318	-Non economic evaluation
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	-Different decision problem
Hu, Yinin, Shah, Puja, Stukenborg, George J et al. (2015) Utility of sentinel lymph node biopsy for solitary dermal melanomas. Journal of surgical oncology 111(7): 800-7	-Different decision problem

Study	Reason for exclusion
Morton RL, Howard K, Thompson JF (2009) The cost-effectiveness of sentinel node biopsy in patients with intermediate thickness primary cutaneous melanoma. Annals of Surgical Oncology 16(4): 929-940	-Different decision problem
Ollila, David W., Stitzenberg, Karyn B., Meyers, Michael O. et al. (2021) ASO Visual Abstract: Use and Costs of Sentinel Lymph Node Biopsy in Nonulcerated T1b Melanoma: Analysis of a Population-Based Registry. Annals of surgical oncology 28(7): 3479	-Abstract only
Serra-Arbeloa, Patricia, Rabines-Juarez, Angel Orlando, Alvarez-Ruiz, Maria Soledad et al. (2016) Sentinel node biopsy in patients with primary cutaneous melanoma of any thickness: A cost-effectiveness analysis. Surgical oncology 25(3): 205-11	-Different decision problem
Standage, Hayley and Han, Dale (2021) ASO Author Reflections: What is the Cost-Effective Treatment of Melanoma Patients with a Positive Sentinel Node?. Annals of surgical oncology 28(5): 2923-2924	-Editorial only, author reflection
Standage, Hayley, Hersh, Alyssa R, Caughey, Aaron et al. (2021) What is the Cost-Effective Treatment for Melanoma Patients with a Positive Sentinel Node?. Annals of surgical oncology 28(5): 2913-2922	-Different decision problem
Stoffels I, Dissemond J, Schulz A, Hillen U, Schadendorf D, Klode J (2012) Reliability and cost-effectiveness of complete lymph node dissection under tumescent local anaesthesia vs. general anaesthesia: a retrospective analysis in patients with malignant melanoma AJCC stage III. Journal of the European Academy of Dermatology and Venereology 26(2): 200-206	-Cost analysis only

Study	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