National Institute for Health and Care Excellence

Final

Melanoma: assessment and management

[D] Evidence review for Completion Lymphadenectomy for micrometastatic nodal disease in stage III melanoma

NICE guideline NG14

Evidence review underpinning recommendations 1.6.1 to 1.6.2 in the NICE guideline

July 2022

Final

These evidence reviews were developed by Guideline Updates Team

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 All NICE guidance is subject to regular review and may be updated or withdrawn.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:

Contents

Completion lymphadenectomy for micro metastatic nodal disease in stage 3 melanoma

1.1 Review question

RQ 4.1 What is the effectiveness of completion lymphadenectomy for micro metastatic nodal disease in stage 3 melanoma?

1.1.1 Introduction

Complete lymph node dissection is sometimes conducted following a positive sentinel lymph node biopsy. To date, the effect of complete lymph node dissection on prognosis is controversial. Completion lymph-node dissection is associated with higher morbidity than sentinel node biopsy alone. Therefore, there is a need to demonstrate the benefit of this more extensive surgical approach being used following sentinel lymph node biopsy before recommending its continued use.

Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update recommendations in this area due to new evidence from RCTs comparing completion lymphadenectomy to observation (clinical and imaging) only. This new evidence suggests no significant difference in melanoma specific survival.

1.1.2 Summary of the protocol

Table 1 PICO table for the effectiveness of completion lymphadenectomy for micro metastatic nodal disease in stage 3 melanoma

Population	People with a diagnosis of micro metastatic nodal disease (including aberrant lymph nodes) detected by sentinel lymph node biopsy
Intervention	Completion lymphadenectomy
Comparator	• Clinical observation or; • Clinical follow-up using imaging
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)

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 1068 references (see appendix B for the literature search strategy). Based on title and abstract screening against the review protocol, 41 references were ordered for screening based on their full texts.

Of the 41 references screened as full texts, 3 references (representing 2 distinct trials across 3 publications) 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 J for a list of references for excluded studies, with reasons for exclusion.

1.1.5 Summary of studies included in the clinical evidence

Table 2 Summary of included immunotherapy studies

Study	Sample size	Inclusion criteria	Interventions	Follow-up time	Risk of bias (notes)
MSLT-II trial (Faries 2017)	1939	Clinically localized cutaneous melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with 0 indicating an absence of disability and higher numbers indicating greater disability), a non–melanoma-related life expectancy of 10 years or more, and tumor-positive sentinel node.	Completion Lymphadenectomy vs observation	Up to 3 years	Moderate *Unclear if allocation concealment. A large proportion of those randomised to the surgery group did not consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed.*
DeCOG-SLT (Leiter 2016/2019)	483	Primary cutaneous melanoma of the torso, arms, or legs and a tumour thickness of at least 1 mm. Micrometastasis in the sentinel lymph node, including single cells.	Completion lymphadenectomy vs observation	Up to 6 years	Moderate *There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups.*

See appendix D for full evidence tables.

1.1.6 Summary of clinical effectiveness evidence

Table 3 Summary of survival outcomes for completion lymph node dissection vs observation

Study	size	GRADE Quality	Outcomes
Faries 2017 (MSLT-II)	1939	Low	Melanoma-specific survival at 3 years follow up (HR<1 favours the intervention group): aHR 1.08 [0.88 to 1.34]
Leiter 2016 (DeCOG-SLT)	473	Very Low	Overall survival at 3 years of follow up (HR<1 favours the intervention group): aHR 1·02 (0·68 to 1·52)
		Very Low	Melanoma-specific death at 3 years follow up (OR <1 favours intervention group): OR 0.91 [0.55, 1.49]
Leiter 2019 (DeCOG-SLT)	473	Very Low	Overall survival at 5-year follow up (HR<1 favours the intervention group): aHR 0.95 (0.70 to 1.36)
		Very Low	Melanoma-specific death at 5-years follow up (OR <1 favours intervention group): OR 1.01 [0.66, 1.53]

Table 4 Summary of local, regional, and distant recurrence outcomes for completion lymph node dissection vs observation

Study	size	GRADE Quality	Outcomes
Faries 2017 (MSLT-II)	1564	Very Low	Recurrence-free survival at 3 years follow up (OR >1 favours intervention group): **OR 0.81 [0.66, 0.99]**
		Very Low	Local-regional recurrence at 3 years follow up (OR <1 favours intervention group): OR 0.94 [0.71, 1.24]
		Moderate	Rate of nodal recurrence at 3 years follow up (HR <1 favours intervention group): **aHR 0.31 [0.24 to 0.41]**
		Low	Distant recurrence at 3 years follow up (OR <1 favours intervention group): OR 1.14 [0.92, 1.42]
		Low	Distant metastases-free survival at 3 years follow up (HR <1 favours intervention group): HR 1.10 [0.92 to 1.31]
Leiter 2016 (DeCOG-SLT)	473	Very Low	Recurrence-free survival at 3 years follow up (HR<1 favours intervention group): HR 0·96 (0·70 to 1·31)
		Very Low	Satellite/in-transit recurrences at 3 years follow up (OR <1 favours intervention group): OR 0.97 [0.38, 2.49]
		Low	Regional lymph node without distant metastases at 3 years follow up (OR <1 favours intervention group): OR 0.50 [0.21, 1.21]
		Very Low	Regional and distant recurrences at 3 years follow up (OR <1 favours intervention group): OR 0.59 [0.28, 1.25]
		Very Low	Distant without regional lymph node recurrences at 3 years follow up (OR <1 favours intervention group): OR 1.24 [0.70, 2.20]
		Low	Distant metastases-free survival at 3 years follow up (HR <1 favours intervention group): HR 1·19 (0·83 to 1·69)
Leiter 2019 (DeCOG-SLT)	473	Very Low	Recurrence-free survival at 5 years follow up (HR <1 favours intervention group): HR 1.01 (0.75 to 1.36)

Study	size	GRADE Quality	Outcomes
		Low	Regional lymph node recurrence at 5 years follow up (OR <1 favours intervention group): OR 0.62 [0.37, 1.06]
		Very Low	Distant metastases at 5 years follow up (OR <1 favours intervention group): OR 1.21 [0.79, 1.85]
		Very Low	Distant metastases-free survival at 5 years follow up (HR <1 favours intervention group): HR 1.09 (0.79 to 1.50)

Table 5 Summary of adverse events for completion lymph node dissection vs observation

Study	size	GRADE Quality	Outcomes
Faries 2017 (MSLT-II)	1755	Moderate	Lymphoedema at 3 years follow-up (OR<1 favours intervention group): **OR 4.71 [3.46, 6.40]**

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see 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.

1.1.7.2 Excluded studies

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

1.1.8 Summary of included economic evidence

There are no existing economic studies for this review question.

1.1.9 Economic model

No original modelling was completed for this review question.

1.1.10 Unit costs

No unit costs were supplied for this review question.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

Both identified trials reported mortality or survival figures, local, regional, and distant recurrence. The committee were particularly influenced by outcomes with clear clinical definitions and substantial implications for the patient, such as mortality rates and disease recurrence. Only one study provided follow up, for up to 5 years post intervention (the committee preference was for 5 and 10 year follow up. The committee were also particularly interested in the differences in adverse events occurring across studied surgical methods to provide a balanced view of the personal cost of treatment options, beyond disease control. However, only one trial compared each group for adverse surgical events, and only reported lymphoedema.

1.1.11.2 The quality of the evidence

The committee considered the quality of the two trials, both were rated as having "Moderate" for risk of bias. In the MSLT-II trial, a large proportion of those randomised to the surgery group did not consent to receive completion lymph node dissection (CLND) (140/971). In the DeCOG-SLT study there was also some deviation from treatment which was unbalanced between experimental groups - 36 participants in the CLND group requested to be in the observation arm and 3 in the observation arm asked for CLND. Neither trial performed blinding or blinded analysis.

Other aspects of study quality were considered. The committee considered the observation protocol described in the comparison groups. For both studies this was quite extensive. MSLT-II used clinical examination every 4 months during the first 2 years, every 6 months during years 3 through 5, and then annually. Nodal ultrasonographic assessment of the sentinel-node basin occurred at each visit for the first 5 years. DECOG-SLT used physical examinations, lymph node sonography, and blood tests with serum S100b were done every 3 months. Every 6 months, patients received section diagram imaging, e.g. CT scan, MRI, or PET-CT, or a chest x-ray and abdomen sonography at minimum. This procedure was done during the entire 3-year follow-up from the date of randomisation. The committee considered that where observations and monitoring were significantly greater in the research than in UK practice, this may lead to a false sense of the adequacy of the observation approach.

The committee noted that there were some differences in the inclusion/exclusion criteria of the two trials. In particular, the DeCOG-SLT trial excluded people with satellite, in-transit, or distant metastatic disease, those with involvement of the entire lymph node with capsular perforation (regional macrometastasis) or those with melanoma of the head and neck region.

1.1.11.3 Benefits and harms

The committee considered evidence from two trials. Neither trial found that CLND was associated with survival or melanoma-specific survival. While DeCOG-SLT found that there was no significant difference between comparison groups for recurrence (including regional and distant), the larger MSLT-II trial found that there was greater overall recurrence in the

observation group when compared to the CLND group. When the study authors considered the specific types of disease recurrence, they found that this was largely due to a statistically significant difference in the rate of nodal recurrence.

The committee discussed the importance of the finding that CLND resulted in reduced rates of nodal basin control. The committee noted that this was an expected finding due to the nature of the surgery (which removes a large amount of lymph nodes). The committee considered that the issue of key importance was whether disease control is lost in the nodal basin. In other words, if a person is monitored well, then nodal recurrence can be picked up and managed surgically before leading to more severe forms of metastasis. This was reflected in the lack of significant difference between comparison groups for survival or melanoma-specific survival.

The committee argued that the morbidity resulting from CLND surgery also needed to be taken into account. In the MSLT-II trial the risk of lymphoedema was significantly different across comparison groups. This complication of surgery could be highly disabling for patients and was greatly increased in the surgery group (24.1% vs 6.3% at 3 years).

The committee therefore recommended that CNLD is not routinely offered for the treatment of micro metastatic nodal disease detected by sentinel lymph node biopsy.

The committee then discussed whether there were ever good indications for performing CNLD. They considered situations where management of recurrent nodal disease may be difficult. For example, in melanoma of the head and neck, it may be difficult to surgically manage recurrent nodal disease, despite monitoring, and therefore a pre-emptive completion lymph node dissection makes more sense. Other aspects that could assist with the management of recurrent nodal disease may also be ruled out. For example, the use of stage-3 adjuvant therapies may be contraindicated in certain patients. With these treatments ruled out, it may make sense to pre-emptively perform CNLD. Finally, as mentioned above, monitoring is key to making sure that management of disease recurrence happens in good time and at a treatable stage. Therefore, the committee considered that there may be situations where regular follow up is simply not possible to the standard required for good control. In all cases, these deliberations should happen in discussion with the person with melanoma and the Specialist Skin MDT.

It was therefore recommended that the use of CLND be considered where management of recurrent nodal disease may be difficult – for example, in melanoma of the head and neck, where stage-3 adjuvant therapies are contraindicated, or where regular follow up is not possible. However, the committee felt it was important to note that even where regular follow up may be difficult, this should not preclude the provision of good monitoring – for example, through offering supported transport, or outreach clinics.

1.1.11.4 Cost effectiveness and resource use

No published economic evidence was identified from the systematic review. The committee noted how CLND is mostly used in very specific circumstances, and when the clinical need to prevent disease progression outweighs the associated adverse effects. Since the impact of the adverse effects can be managed, the committee believed that, on balance, CLND would likely be cost effective in these patients. The committee noted that, following the results of the trials included in the evidence review, most surgical teams have stopped routinely offering CLND, in favour of observation and monitoring. Therefore, the recommendations made by the committee were not expected to have a significant resource impact, and, given that CLND is now only recommended for a small subset of patients, there would potentially be cost savings.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 and 1.6.2.

1.1.13 References – included studies

Faries, Mark B, Thompson, John F, Cochran, Alistair J et al. (2017) Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. The New England journal of medicine 376(23): 2211-2222

Leiter, Ulrike, Stadler, Rudolf, Mauch, Cornelia et al. (2019) Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 37(32): 3000-3008

Leiter, Ulrike, Stadler, Rudolf, Mauch, Cornelia et al. (2016) Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. The Lancet. Oncology 17(6): 757-767

Appendices

Appendix A – Review protocols

Review protocol for completion lymphadenectomy for micro metastatic nodal disease in stage 3 melanoma

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Surgical treatment for stage 3 melanoma
2.	Review question	What is the effectiveness of completion lymphadenectomy for micro metastatic nodal disease in stage 3 melanoma?
3.	Objective	Determine the efficacy of completion lymphadenectomy for micro metastatic nodal disease
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: Date (of last update, 2015)

		The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Micro metastatic nodal disease melanoma
6.	Population	People with a diagnosis of micro metastatic nodal disease (including aberrant lymph nodes) detected by sentinel lymph node biopsy
7.	Intervention/Test	Completion lymphadenectomy
8.	Comparator/Reference standard	Clinical observation or; Clinical follow-up using imaging
9.	Types of study to be included	RCTs
10.	Other exclusion criteria	None
11.	Context	This review is part of an update of the NICE guideline on melanoma: assessment and management (NG14, 2105). This guideline covers adults and children with melanoma. Input from topic experts during the 2019 surveillance review of NG14 highlighted there was a need to update recommendations in this area due to new evidence from RCTs comparing completion

		lymphadenectomy to clinical observation/ follow-up. This new evidence suggests no significant difference in melanoma specific survival.
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 (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 Cochrane risk of bias tool (version 2), 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. Tumour site

18.	Type and method of review	☒
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	01/03.2021
22.	Anticipated completion date	01/09/2021
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	Completion lymphadenectomy Melanoma Skin cancer Skin tumour
33.	Details of existing review of same topic by same authors	Update of question 6.1 in **NICE Guideline NG14 Melanoma: assessment and management**

34.	Current review status	☒Completed
35..	Additional information	
36.	Details of final publication	**www.nice.org.uk**

1

Appendix B – Literature search strategies

Topic/question details: Melanoma

RQ 4.1 – What is the most effective surgical treatment for stage 3 melanoma?

Date limit of 2015 – 2021 applied to all databases (except EPub Ahead of Print and INAHTA – no date limit added)

McMaster Balanced RCT Filter applied to Ovid searches.

Databases	Date searched	Version/files	No. retrieved
Cochrane Central Register of Controlled Trials (CENTRAL)	27/04/2021	27/04/2021	452
Cochrane Database of Systematic Reviews (CDSR)	27/04/2021	27/04/2021	33
Database of Abstracts of Reviews of Effect (DARE)	26/04/2021	26/04/2021	1
HTA	26/04/2021	26/04/2021	13
INAHTA	27/04/2021	27/04/2021	30
Embase (Ovid)	26/04/2021	<1974 to 2021 April 23>	712
MEDLINE (Ovid)	26/04/2021	<1946 to April 23, 2021>	440
MEDLINE In-Process (Ovid)	26/04/2021	<1946 to April 23, 2021>	41
MEDLINE Epub Ahead of Print[a]	26/04/2021	<April 23, 2021>	23

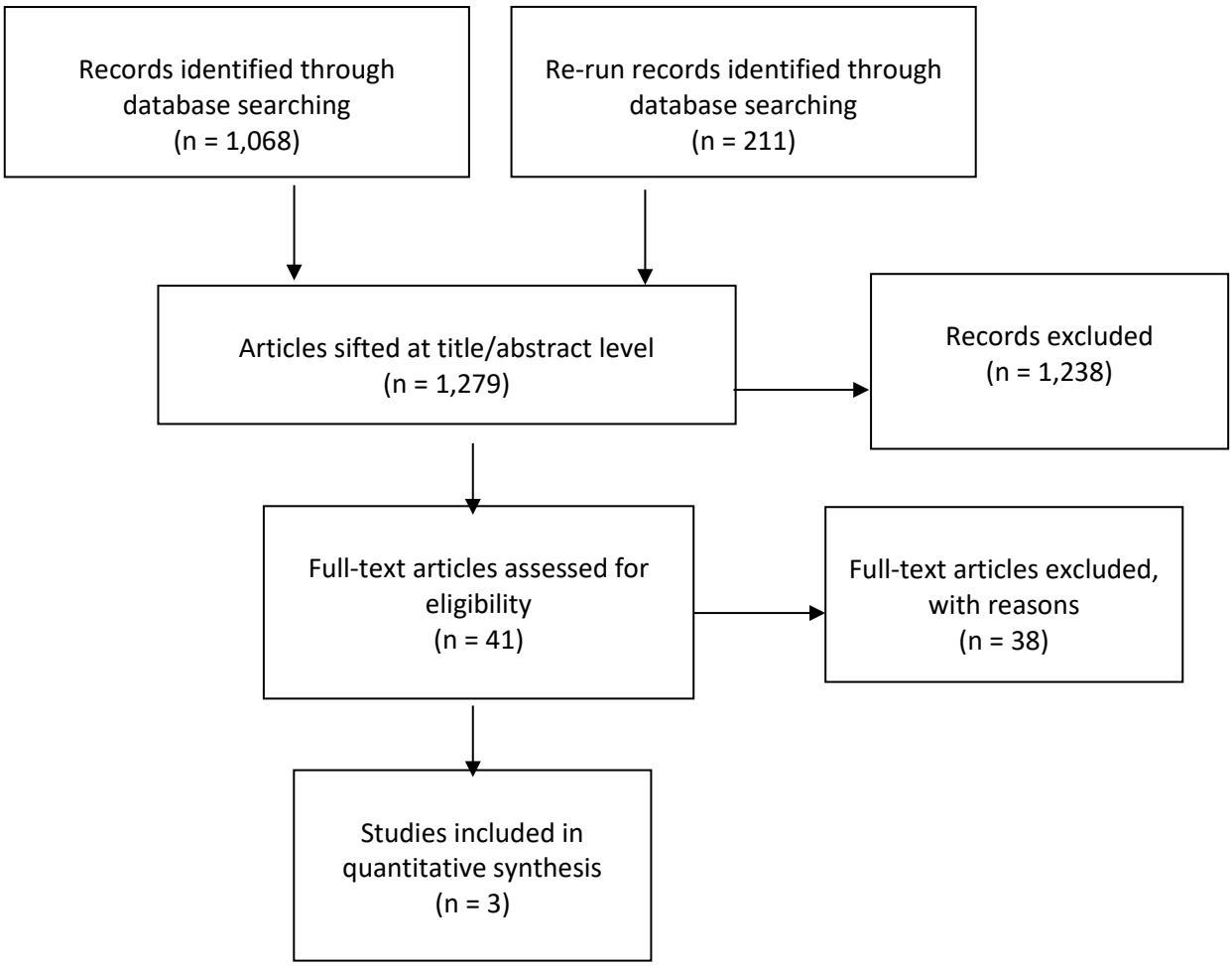
1 **Search strategy (Medline only)**

Database:
Database: Ovid MEDLINE(R) <1946 to April 23, 2021> Search Strategy: --- 1 exp Melanoma/ (97886) 2 Skin Neoplasms/ (123938) 3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (107117) 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. (63259) 5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (25649) 6 (hutchinson* adj2 (freckle* or melano*)).tw. (69) 7 dubreuilh*.tw. (74) 8 (maligna* adj2 lentigo*).tw. (1090) 9 LMM.tw. (934) 10 or/1-9 (257928) 11 Lymph Node Excision/ (34194) 12 exp Lymph Nodes/ (91576) 13 (surg* or resect* or remov* or ablat* or operat* or excision* or excised or dissection* or lymphadenectom* or CLND* or TLND*).tw. (3034192) 14 or/11-13 (3106687) 15 10 and 14 (50104) 16 animals/ not humans/ (4782806) 17 15 not 16 (47673) 18 limit 17 to "english language" (40599) 19 randomized controlled trial.pt. (527406) 20 randomi?ed.mp. (834943)

21	placebo.mp. (201653)
22	or/19-21 (887781)
23	18 and 22 (1450)
24	limit 23 to ed=20150101-20210426 (440)

1
2

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence

CLND vs observation

Faries 2017

Faries, 2017

Bibliographic Reference	Faries, Mark B; Thompson, John F; Cochran, Alistair J; Andtbacka, Robert H; Mozzillo, Nicola; Zager, Jonathan S; Jahkola, Tiina; Bowles, Tawnya L; Testori, Alessandro; Beitsch, Peter D; Hoekstra, Harald J; Moncrieff, Marc; Ingvar, Christian; Wouters, Michel W J M; Sabel, Michael S; Levine, Edward A; Agnese, Doreen; Henderson, Michael; Dummer, Reinhard; Rossi, Carlo R; Neves, Rogerio I; Trocha, Steven D; Wright, Frances; Byrd, David R; Matter, Maurice; Hsueh, Eddy; MacKenzie-Ross, Alastair; Johnson, Douglas B; Terheyden, Patrick; Berger, Adam C; Huston, Tara L; Wayne, Jeffrey D; Smithers, B Mark; Neuman, Heather B; Schneebaum, Schlomo; Gershenwald, Jeffrey E; Ariyan, Charlotte E; Desai, Darius C; Jacobs, Lisa; McMasters, Kelly M; Gesierich, Anja; Hersey, Peter; Bines, Steven D; Kane, John M; Barth, Richard J; McKinnon, Gregory; Farma, Jeffrey M; Schultz, Erwin; Vidal-Sicart, Sergi; Hoefer, Richard A; Lewis, James M; Scheri, Randall; Kelley, Mark C; Nieweg, Omgo E; Noyes, R Dirk; Hoon, Dave S B; Wang, He-Jing; Elashoff, David A; Elashoff, Robert M; Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma.; The New England journal of medicine; 2017; vol. 376 (no. 23); 2211-2222

Study details

Trial registration number and/or trial name	MSLT-II NCT00297895
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	An international, multicenter trial conducted in 63 settings
Study dates	The trial opened in December 2004 and was registered on February 27, 2006.

Sources of funding	Supported by grants (CA189163 and CA29605, to Dr. Faries) from the National Cancer Institute and by funding from the Borstein Family Foundation, the Amyx Foundation, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, and the John Wayne Cancer Institute Auxiliary.
Inclusion criteria	Age 18 to 75 years of age Clinical features of melanoma Clinically localized cutaneous melanoma, an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale, with 0 indicating an absence of disability and higher numbers indicating greater disability) Life expectancy a non–melanoma-related life expectancy of 10 years or more Metastases Tumor-positive sentinel node.
Outcome measures	Melanoma-specific survival For the primary end point, melanoma-specific survival, authors used the log-rank test to compare the rates among patients in the dissection group and the observation group in the intention-to-treat population with three-year follow up from the point of randomisation. Melanoma-specific survival was determined at the time of melanoma-related death. Disease-free survival Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up. Disease-free survival was the time to any recurrence. Survival without nodal recurrence was the time to recurrence within the draining nodal basin Distant-metastases-free survival Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up. Overall survival

	Secondary end points included overall survival, disease-free survival, survival without recurrence of regional nodal metastases, distant metastasis–free survival, and the extent of nodal involvement. Time zero was the time of randomization until 3 years of follow up.
Number of participants	1939
Duration of follow-up	3 years
Loss to follow-up	4 and 1 (in the treatment and observation group, respectively) were ineligible for analysis in the ITT analysis, 147 and 37 were not eligible for per protocol analysis
Methods of analysis	Intention to treat

1 **Study arms**

Completion Lymph Node Dissection (N = 971) Follow-up of the dissection group involved the same schedule as in the observation group (see below), but without protocol-mandated nodal ultrasonography.
Observation (N = 968) Patients who were assigned to the observation group were monitored by means of clinical examination every 4 months during the first 2 years, every 6 months during years 3 through 5, and then annually. Nodal ultrasonographic assessment of the sentinel-node basin occurred at each visit for the first 5 years; findings were considered to be abnormal on the basis of a length:depth ratio of less than 2, a hypoechoic center, an absence of hilar vessels, or focal nodularity with increased vascularity.

2 **Arm-level characteristics**

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
Sex (male)		
Sample Size	n = 478 ; % = 58	n = 549 ; % = 59
Smoking status		
Current		
Sample Size	n = 147 ; % = 18.3	n = 158 ; % = 17.4
Previous		
Sample Size	n = 193 ; % = 24	n = 227 ; % = 25
Never		
Sample Size	n = 463 ; % = 57.7	n = 522 ; % = 57.6
Breslow thickness (mm)		
Mean/SD	2.76 (2.34)	2.7 (2.11)
Primary site		
Arm or Leg		
Sample Size	n = 327 ; % = 39.7	n = 382 ; % = 41
Head or neck		
Sample Size	n = 113 ; % = 13.7	n = 128 ; % = 13.7
Trunk		

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
Sample Size	n = 384 ; % = 46.6	n = 421 ; % = 45.2
Ulceration present		
Sample Size	n = 316 ; % = 38.3	n = 353 ; % = 37.9
Number of positive sentinel lymph nodes		
0, RT-RCT positive		
Sample Size	n = 80 ; % = 9.7	n = 111 ; % = 11.9
one		
Sample Size	n = 596 ; % = 72.3	n = 643 ; % = 69.1
two		
Sample Size	n = 121 ; % = 14.7	n = 162 ; % = 17.4
three		
Sample Size	n = 18 ; % = 2.2	n = 10 ; % = 1.1
more than 3		
Sample Size	n = 9 ; % = 1.1	n = 5 ; % = 0.5
Diameter of sentinel lymph node metastases		
Mean/SD	1.07 (*empty data*)	1.11 (*empty data*)
Received adjuvant treatment		

	Completion Lymph Node Dissection (N = 971)	Observation (N = 968)
Sample Size	n = 66 ; % = 8.1	n = 60 ; % = 6.5
Age		
Mean/SD	52.5 (12.9)	53.2 (13.6)
Size of sentinel lymph node metastases (mm)		
<0.1 mm		
Sample Size	n = 45 ; % = 8	n = 65 ; % = 10.4
0.1 - 1.0 mm		
Sample Size	n = 333 ; % = 58.8	n = 343 ; % = 55.1
>1.0 mm		
Sample Size	n = 188 ; % = 33.2	n = 215 ; % = 34.5

1 **Risk of bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information

Section	Question	Answer
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
	Risk of bias judgement for the randomisation process	Moderate *(Unclear if allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure	Not applicable

Section	Question	Answer
	to analyse participants in the group to which they were randomized?	
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate *(In the treatment arm 140 Declined dissection 3 Did not undergo dissection for unknown reason. In the observation group, 9 Declined observation 7 Did not undergo observation for unknown reason. It does not appear that deviations from the intended treatment were due to the experimental context - however this was not stated directly. Intent-to-treat analysis was used.)*
	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Moderate *(little evidence was provided on "adherence to intervention" among those who had received surgery)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	No
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	No
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Probably no
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable

Section	Question	Answer
	Risk-of-bias judgement for missing outcome data	Moderate *(Risk of bias was high for per protocol analysis but low for intent to treat. Many more declined intervention in the treatment group, however this is unlikely to be related to the risk of survival. 4 and 1 (in the treatment and observation group, respectively) were ineligible for analysis in the ITT analysis, 147 and 37 were not eligible for per protocol analysis)*
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Probably yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
	Risk-of-bias judgement for measurement of the outcome	Moderate *(all aspects of the trial were unblinded)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Unclear if allocation concealment. A large proportion of those randomised to the surgery group did not consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed.)*
	Overall Directness	Directly applicable

1 **Leiter 2016/2019**

Leiter, 2019

Bibliographic Reference	Leiter, Ulrike; Stadler, Rudolf; Mauch, Cornelia; Hohenberger, Werner; Brockmeyer, Norbert H; Berking, Carola; Sunderkotter, Cord; Kaatz, Martin; Schatton, Kerstin; Lehmann, Percy; Vogt, Thomas; Ulrich, Jens; Herbst, Rudolf; Gehring, Wolfgang; Simon, Jan-Christoph; Keim, Ulrike; Verver, Danielle; Martus, Peter; Garbe, Claus; German Dermatologic Cooperative Oncology, Group; Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2019; vol. 37 (no. 32); 3000-3008

1 **Study details**

Other publications associated with this study included in review	Leiter 2017 and 2019
Trial registration number and/or trial name	DeCOG-SLT NCT02434107
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Multicentre: 41 German skin cancer centres
Study dates	Recruitment occurred from between Jan 1, 2006, and Dec 1, 2014
Sources of funding	German Cancer Aid
Inclusion criteria	Age aged between 18 and 75 years Clinical features of melanoma Primary cutaneous melanoma of the torso, arms, or legs and a tumour thickness of at least 1 mm Metastases

	micrometastasis in the sentinel lymph node, including single cells
Exclusion criteria	Metastases Evidence of satellite, in-transit, or distant metastatic disease, or involvement of the entire lymph node with capsular perforation (regional macrometastasis) Location of skin tumour Patients with melanoma of the head and neck region Past medical history Patients with a history of previous or concurrent (ie, second primary) invasive melanoma, solid tumours, or haematological malignancy during the past 5 years (except non-melanoma skin cancer), treated with oral or parenteral immunosuppressive agents during study participation or within 6 months before enrolment) Pregnancy pregnant or lactating women Allergies patients allergic to vital blue dye or any radio colloid
Outcome measures	Disease-free survival Secondary endpoints included recurrence-free survival (defined as time between randomisation and the date of diagnosis of first recurrence, the date of last follow-up visit, or date of death by any cause), and recurrence of regional lymph node metastases. Distant-metastases-free survival The primary endpoint was distant metastasis-free survival, calculated from the date of randomisation to the date of diagnosis of first distant metastases, date of latest follow-up visit, or date of death by any cause. Overall survival overall survival (time between randomisation and date of last follow-up visit or date of death by any cause), Adverse events

	For patients allocated to the complete lymph node dissection group, adverse events and surgical complications were collected immediately postoperatively and 3 and 6 months after complete lymph node dissection. Grade 3 and 4 adverse events of surgical complications were reported in the complete lymph node dissection group during the entire follow-up. Grade 3 and 4 events were delayed wound healing (grade 3 moderate, >2 months; grade 4 severe, >3 months); infection (grade 3 moderate, cellulitis; grade 4 severe, sepsis); seroma (grade 3 moderate, seroma size of >7 cm; grade 4 severe, seroma size of >10 cm); lymph fistula (grade 3 moderate, >3 months; grade 4 severe, persistent); lymphoedema (grade 3 moderate, >3 months; grade 4 severe, persistent); and persistent staining of the skin due to injection of patent vital blue dye (grade 3 moderate, <9 months; grade 4 severe, persistent).
Number of participants	483
Duration of follow-up	3 year and 6 year follow up
Loss to follow-up	10 were lost to follow up, 8 in the observation group and 2 in the CLND group
Methods of analysis	Intention to treat

1 **Study arms**

Observation group (N = 233) Identical follow-up schedules were applied for both study groups. Physical examinations (whole body and palpation of primary scar to and including the regional lymph node basin), lymph node sonography (primary scar to and including regional lymph node basin), and blood tests with serum S100b were done every 3 months. Every 6 months, patients received section diagram imaging, such as whole body CT scan, MRI, or PET-CT, or a chest x-ray and abdomen sonography at minimum. This procedure was done during the entire 3-year follow-up from the date of randomisation.
Completion Lymph Node Dissection (N = 240)

Randomisation and complete lymph node dissection in patients who were randomly assigned to the complete lymph node dissection group had to be completed within 120 days after the sentinel lymph node biopsy. Standard operating procedures for the sentinel lymph node biopsy, for the complete lymph node dissection, and for the histopathological processing of the lymph nodes were done.

1 **Arm-level characteristics**

	Observation group (N = 233)	**Completion Lymph Node Dissection (N = 240)**
Sex (male)		
Sample Size	n = 150 ; % = 64	n = 141 ; % = 59
Median age at diagnosis		
MedianIQR	56 (45 to 66)	57 (47 to 67.8)
Body site of tumour		
Trunk		
Sample Size	n = 119 ; % = 51	n = 128 ; % = 53
Upper extremity		
Sample Size	n = 31 ; % = 13	n = 35 ; % = 15
Lower extremity		
Sample Size	n = 83 ; % = 36	n = 77 ; % = 32
Median tumour thickness (mm)		
MedianIQR	2.4 (1.5 to 3.85)	2.4 (1.6 to 4)

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
Ulceration present		
Sample Size	n = 95 ; % = 41	n = 90 ; % = 38
Sentinel node biopsy positives per patient		
one		
Sample Size	n = 213 ; % = 91	n = 222 ; % = 93
two or more		
Sample Size	n = 20 ; % = 9	n = 16 ; % = 7
not applicable		
Sample Size	n = 0 ; % = 0	n = 2 ; % = 1
Positive sentinel node biopsies per patient		
Histological criteria		
Haematoxylin and eosin stain positive		
Sample Size	n = 144 ; % = 62	n = 140 ; % = 58
Immunhistochemistry positive (S100, HMB45, Melan A)		
Sample Size	n = 73 ; % = 31	n = 77 ; % = 32
Size of metasteses in the sentinel lymph node biopsy		

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
Single cells or <0.5		
Sample Size	n = 76	n = 68
0.5 to 1.0		
Sample Size	n = 82	n = 85
1.01 - 2.0		
Sample Size	n = 43	n = 48
2.01 to 5.0		
Sample Size	n = 12	n = 11
more than 5		
Sample Size	n = 4	n = 3
no size specified		
Sample Size	n = 16	n = 25
Adjuvant interferon-a		
No therapy		
Sample Size	n = 82 ; % = 35	n = 103 ; % = 43
Low dose		
Sample Size	n = 105 ; % = 45	n = 89 ; % = 37

	Observation group (N = 233)	Completion Lymph Node Dissection (N = 240)
High dose		
Sample Size	n = 40 ; % = 17	n = 37 ; % = 15
Pegylated interferon		
Sample Size	n = 6 ; % = 3	n = 11 ; % = 5

1 **Risk of Bias**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	1. 1. Was the allocation sequence random?	Yes
	1. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	Yes
	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Yes
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Yes

Section	Question	Answer
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	Yes/Probably yes
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	No
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	No information
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable
	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Moderate *(36 participants in the CLND group requested to be in the observation arm and 3 in the observation arm asked for CLND. These patients were included in the ITT analysis but excluded from the per-protocol analysis.)*
Domain 3. Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Not applicable
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Not applicable

Section	Question	Answer
	3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	Not applicable
	3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Not applicable
	Risk-of-bias judgement for missing outcome data	Low *(nearly all data was available at follow up for ITT analysis)*
Domain 4. Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	No
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	Probably no
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	Yes
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Probably no
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Probably no
	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalised before unblinded outcome data were available for analysis ?	Yes

Section	Question	Answer
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No/Probably no
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	No/Probably no
	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups)*
	Overall Directness	Directly applicable

Appendix E - Forest plots

No forest plots were generated from the evidence review as meta-analysis was not possible.

Appendix F – GRADE tables

CLND vs Observation

Survival

Table 6 Survival

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival at 3 years of follow up (HR<1 favours the intervention group)								
Leiter 2016 (DeCOG-SLT)	473	N/A	aHR 1·02 (90%CI 0·68 to 1·52)[1], p=0.95	Serious[2]	Not serious	N/A	NE[3]	Low
Overall survival at 5-year follow up (HR<1 favours the intervention group)								
Leiter 2019 (DeCOG-SLT)	473	N/A	aHR 0.95 (90%CI 0.70 to 1.36)[1], p=0.80	Serious[2]	Not serious	N/A	NE[3]	Low
Melanoma-specific survival at 3 years follow up (HR<1 favours the intervention group)								
Faries 2017 (MSLT-II)	1939	N/A	aHR 1.08 [0.88 to 1.34][4]	Serious[5]	Not serious	N/A	Serious[6]	Low
Melanoma-specific death at 3 years follow up (OR <1 favours intervention group)								
Leiter 2016 (DeCOG-SLT)	473	N/A	OR 0.91 [0.55 to 1.49]	Serious[2]	Not serious	N/A	Very Serious[7]	Very Low
Melanoma-specific death at 5-years follow up (OR <1 favours intervention group)								

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Leiter 2019 (DeCOG-SLT)	473	N/A	OR 1.01 [0.66 to 1.53]	Serious[2]	Not serious	N/A	Very Serious[7]	Very Low

1. Adjusted for tumour load in sentinel lymph node biopsy, tumour thickness, ulceration, positive sentinel lymph node biopsy nodes, adjuvant interferon therapy
2. Study was at serious risk of bias and was marked down one level: There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups
3. Study was downgraded one level as it was not possible to estimate imprecision since 90% confidence intervals were reported, rather than 95%CI.
4. Unclear how adjusted but likely adjusted for sex, age, Breslow thickness, ulceration, primary site, number of positive sentinel nodes, and sentinel node positive
5. Study was at serious risk of bias and was marked down one level: Unclear if allocation concealment. A large proportion of those randomised to the surgery group did nc consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed. Overall survival was not reported in the study or appendix. Unclear how multivariable adjustments were made.
6. Serious risk of imprecision as confidence intervals for study estimate crossed one line of minimum important effect (0.8 and 1.25 for hazard ratios and odds ratios)
7. Study was downgraded two levels due to very serious imprecision as confidence intervals crossed two lines of minimum important difference (0.8 and 1.25 for hazard ra and odds ratios)

Local, regional, and distant recurrence

Table 7 Local, regional, and distant recurrence

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Recurrence-free survival over 3 years follow up (HR<1 favours intervention group)								
Leiter 2016 (DeCOG-SLT)	483	N/A	HR 0·96 (90%CI 0·70 to 1·31), p=0.83 [1]	Serious[2]	Not serious	N/A	NE[3]	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Recurrence-free survival at 3 years follow up (OR <1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	**OR 0.81 [0.66 to 0.99]** [4]	Very Serious[5]	Not serious	N/A	Serious[6]	Very Low
Recurrence-free survival over 5 years follow up (HR <1 favours intervention group)								
Leiter 2019 (DeCOG-SLT)	473	N/A	HR 1.01 (90%CI 0.75 to 1.36), p=0.94 [3]	Serious[2]	Not serious	N/A	NE[3]	Low
Local-regional recurrence at 3 years follow up (OR <1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	OR 0.94 [0.71 to 1.24][4]	Very Serious[5]	Not serious	N/A	Serious[6]	Very Low
Satellite/in-transit recurrences at 3 years follow up (OR <1 favours intervention group)								
Leiter 2016 (DeCOG-SLT)	483	N/A	OR 0.97 [0.38 to 2.49]	Serious[2]	Not serious	N/A	Very Serious[3]	Very Low
Rate of nodal recurrence at 3 years follow up (HR <1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	**aHR 0.31 [0.24 to 0.41]**[8]	Serious[9]	Not serious	N/A	Not Serious	Moderate
Regional lymph node without distant metastases at 3 years follow up (OR <1 favours intervention group)								
Leiter 2016 (DeCOG-SLT)	483	N/A	OR 0.50 [0.21 to 1.21]	Serious[2]	Not serious	N/A	Serious[6]	Low

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Regional lymph node recurrence at 5 years follow up (OR <1 favours intervention group)								
Leiter 2019 (DeCOG-SLT)	473	N/A	OR 0.62 [0.37 to 1.06]	Serious[2]	Not serious	N/A	Serious[6]	Low
Distant recurrence at 3 years follow up (OR <1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	OR 1.14 [0.92 to 1.42][4]	Very Serious[5]	Not serious	N/A	Serious[6]	Very Low
Distant metastases at 5 years follow up (OR <1 favours intervention group)								
Leiter 2019 (DeCOG-SLT)	473	N/A	OR 1.21 [0.79 to 1.85]	Serious[2]	Not serious	N/A	Very Serious[3]	Very Low
Distant metastases-free survival at 3 years follow up (HR <1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	HR 1.10 [0.92 to 1.31][8]	Serious[5]	Not serious	N/A	Serious[6]	Low
Leiter 2016 (DeCOG-SLT)	483	N/A	HR 1·19 (90%CI 0·83 to 1·69), p=0·43 [1]	Serious[2]	Not serious	N/A	NE[3]	Low
Distant metastases-free survival at 5 years follow up (HR <1 favours intervention group)								
Leiter 2019 (DeCOG-SLT)	473	N/A	HR 1.09 (90%CI 0.79 to 1.50), p= 0.62 [1]	Serious[2]	Not serious	N/A	NE[3]	Low

1. Adjusted for tumour load in sentinel lymph node biopsy, tumour thickness, ulceration, positive sentinel lymph node biopsy nodes, adjuvant interferon therapy

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

2. Study was at serious risk of bias and was marked down one level: There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups.
3. Study was downgraded one level as it was not possible to judge imprecision since study reported 90% confidence intervals.
4. Per-protocol analysis
5. Study was at very serious risk of bias and was marked down two levels: Unclear if allocation concealment. A large proportion of those randomised to the surgery group not consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysi performed. Overall survival was not reported in the study or appendix. Unclear how multivariable adjustments were made.
6. Serious risk of imprecision as confidence intervals for study estimate crossed one line of minimum important effect (0.8 and 1.25 for hazard ratios and odds ratios)
7. Study was downgraded two levels due to very serious imprecision as confidence intervals crossed two lines of minimum important difference (0.8 and 1.25 for hazard ra and odds ratios)
8. Unclear how adjusted but likely adjusted for sex, age, Breslow thickness, ulceration, primary site, number of positive sentinel nodes, and sentinel node positive

Adverse events

Table 8 adverse events

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Lymphoedema at 3 years follow-up (OR<1 favours intervention group)								
Faries 2017 (MSLT-II)	1564	N/A	**OR 4.71 [3.46, 6.40]**[1]	Serious[2]	Not serious	N/A	Not Serious	Moderate

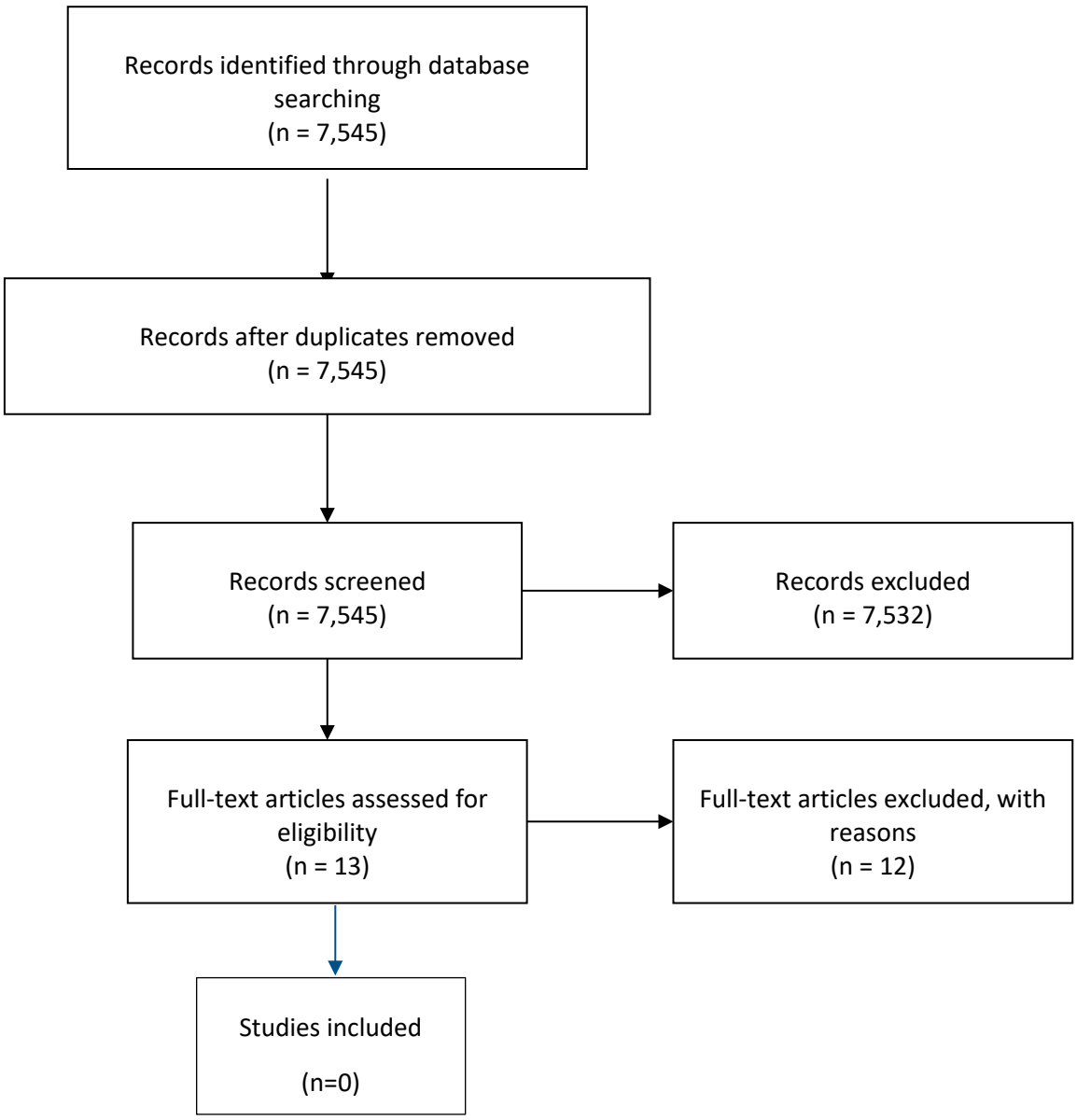
1. Only percentages were reported, analyst used the total number of patients in each arm as the denominator to calculate the number with adverse events in each arm

Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2. Study was at serious risk of bias and was marked down one level: Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or ITT participants were excluded for ineligibility but details not provided.								

1

2

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was found for this review question.

Appendix I – Health economic model

No original health economic modelling was completed for this review question

Appendix J – Excluded studies

Clinical studies

Study	Code [Reason]
(2015) Models of Melanoma Spread and Final Results of the Multicenter Selective Lymphadenectomy Trial-I. Actas dermo-sifiliograficas 106(2): 82-85	- Review article but not a systematic review
Angeles, Christina V. and Wong, Sandra L. (2020) Management of Regional Nodal Melanoma. Surgical Oncology Clinics of North America 29(3): 415-431	- Review article but not a systematic review
Ascierto, Paolo Antonio, Borgognoni, Lorenzo, Botti, Gerardo et al. (2019) New paradigm for stage III melanoma: From surgery to adjuvant treatment. Journal of Translational Medicine 17(1): 266	- Review article but not a systematic review
Bartlett, Edmund K (2019) Current management of regional lymph nodes in patients with melanoma. Journal of surgical oncology 119(2): 200-207	- Review article but not a systematic review
Bello, Danielle M and Faries, Mark B (2020) The Landmark Series: MSLT-1, MSLT-2 and DeCOG (Management of Lymph Nodes). Annals of surgical oncology 27(1): 15-21	- Review article but not a systematic review
Carr, Michael J., Boulware, David, Kirichenko, Dennis A. et al. (2021) Surveillance of Sentinel Node-Positive Melanoma Patients with Reasons for Exclusion from MSLT-II: Multi-Institutional Propensity Score Matched Analysis. Journal of the American College of Surgeons 232(4): 424-431	- non-randomised study *Propensity score matching*

Study	Code [Reason]
Costa Svedman, F, Spanopoulos, D, Taylor, A et al. (2017) Surgical outcomes in patients with cutaneous malignant melanoma in Europe - a systematic literature review. Journal of the European Academy of Dermatology and Venereology : JEADV 31(4): 603-615	- Systematic review used as source of primary studies
Da Cunha Cosme, Maribel L., Liuzzi Samaterra, Juan F., Siso Cardenas, Saul A. et al. (2021) Lymphadenectomy after a positive sentinel node biopsy in patients with cutaneous melanoma. A systematic review. Surgical and Experimental Pathology 4(1): 2	- Systematic review used as source of primary studies
de Bree, E and de Bree, R (2015) Implications of the MSLT-1 for sentinel lymph node biopsy in cutaneous head and neck melanoma. Oral oncology 51(7): 629-33	- Review article but not a systematic review
Delgado, Alberto Falk and Delgado, Anna Falk (2017) Complete Lymph Node Dissection in Melanoma: A Systematic Review and Meta-Analysis. Anticancer research 37(12): 6825-6829	- Systematic review used as source of primary studies - 2nd opinion *see two older studies*
Delman, Keith A and Wong, Sandra L (2018) Completion Node Dissection After Sentinel Node Biopsy in Melanoma. JAMA surgery 153(11): 1045-1046	- Review article but not a systematic review
Downs, Jennifer S and Gyorki, David E (2019) An evidence-based approach to positive sentinel node disease: Should we ever do a completion node dissection?. Melanoma Management 6(3): mmt24	- Review article but not a systematic review

Study	Code [Reason]
Falk Delgado, Alberto; Zommorodi, Sayid; Falk Delgado, Anna (2019) Sentinel Lymph Node Biopsy and Complete Lymph Node Dissection for Melanoma. Current oncology reports 21(6): 54	- Review article but not a systematic review
Franke, Viola and van Akkooi, Alexander C J (2019) The extent of surgery for stage III melanoma: how much is appropriate?. The Lancet. Oncology 20(3): e167-e174	- Systematic review used as source of primary studies
Hieken, Tina J; Kane, John M 3rd; Wong, Sandra L (2019) The Role of Completion Lymph Node Dissection for Sentinel Lymph Node-Positive Melanoma. Annals of surgical oncology 26(4): 1028-1034	- Systematic review used as source of primary studies
Hui, Jane Yuet Ching, Burke, Erin, Broman, Kristy K et al. (2021) Surgeon decision-making for management of positive sentinel lymph nodes in the post-Multicenter Selective Lymphadenectomy Trial II era: A survey study. Journal of surgical oncology 123(2): 646-653	- non-randomised study
Jakub, JW, Terando, AM, Sarnaik, A et al. (2017) Safety and feasibility of minimally invasive inguinal lymph node dissection in patients with melanoma (SAFE-MILND): report of a prospective multi-institutional trial. Annals of surgery 265(1): 192-196	- Not intervention of interest *minimally invasive inguinal lymph node dissection* - non-randomised study
Kudchadkar, Ragini R.; Michielin, Olivier; Van Akkooi, Alexander C. J. (2018) Practice-Changing Developments in Stage III Melanoma: Surgery, Adjuvant Targeted Therapy, and Immunotherapy. American Society of Clinical Oncology Educational Book: 759-762	- Review article but not a systematic review

Study	Code [Reason]
Kyrgidis, Athanassios, Tzellos, Thrasivoulos, Mocellin, Simone et al. (2015) Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma. The Cochrane database of systematic reviews: cd010307	- not a comparator of interest *MSLT - I*
Macedo, Francisco Igor, Fayne, Rachel A., Azab, Basem et al. (2019) The Role of Completion Lymphadenectomy in Positive Regional Lymph Nodes in Melanoma: A Meta-analysis. Journal of Surgical Research 236: 83-91	- Systematic review used as source of primary studies
Masoud, Sabran J., Farrow, Norma E., Mosca, Paul J. et al. (2018) Sentinel Lymph Node Biopsy and Completion Lymph Node Dissection for Melanoma. Current Treatment Options in Oncology 19(11): 55	- non-randomised study
McMasters, Kelly M, Egger, Michael E, Edwards, Michael J et al. (2016) Final Results of the Sunbelt Melanoma Trial: A Multi-Institutional Prospective Randomized Phase III Study Evaluating the Role of Adjuvant High-Dose Interferon Alfa-2b and Completion Lymph Node Dissection for Patients Staged by Sentinel Lymph Node Biopsy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34(10): 1079-86	Population was negative SLN and positive RT-PCR
Moreno-Ramirez, David, Vidal-Sicart, Sergi, Puig, Susana et al. (2018) Should immediate lymphadenectomy be discontinued in patients with metastasis of a melanoma in the sentinel lymph node? Report of the results of the Multicenter Selective Lymphadenectomy Trial-II. Medicina clinica 150(8): 323-326	- Review article but not a systematic review
Nakamura, Yasuhiro (2019) The Role and Necessity of Sentinel Lymph Node Biopsy for Invasive Melanoma. Frontiers in Medicine 6: 231	- Review article but not a systematic review

Study	Code [Reason]
Peach, H, Board, R, Cook, M et al. (2020) Current role of sentinel lymph node biopsy in the management of cutaneous melanoma: A UK consensus statement. Journal of plastic, reconstructive & aesthetic surgery : JPRAS 73(1): 36-42	- Review article but not a systematic review
Schmalbach, Cecelia E. and Bradford, Carol R. (2018) Completion lymphadenectomy for sentinel node positive cutaneous head & neck melanoma. Laryngoscope Investigative Otolaryngology 3(1): 43-48	- Review article but not a systematic review
SIM, FRANKLIN H., PRITCHARD, DOUGLAS J., TAYLOR, WILLIAM F. et al. (1986) Lymphadenectomy in the Management of Stage I Malignant Melanoma: A Prospective Randomized Study. Mayo Clinic Proceedings 61(9): 697-705	- Not population of interest *Stage 1 melanoma - RCT*
Stadler, R; Leiter, U; Garbe, C (2019) Kein Überlebensvorteil beim Sentinel-Lymphknoten-positiven Melanom mit sofortiger kompletter Lymphadenektomie – eine Übersicht. JDDG - journal of the german society of dermatology 17(1): 7-14	- Study not reported in English
Stadler, Rudolf; Leiter, Ulrike; Garbe, Claus (2019) Lack of survival benefit in sentinel lymph node-positive melanoma with immediate complete lymphadenectomy - a review. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG 17(1): 7-13	- Review article but not a systematic review
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	- non-randomised study *retrospective cohort linked with the MSLT-2*

Study	Code [Reason]
Testori, Alessandro A E; Blankenstein, Stephanie A; van Akkooi, Alexander C J (2019) Surgery for Metastatic Melanoma: an Evolving Concept. Current oncology reports 21(11): 98	- Review article but not a systematic review
van Akkooi, A C J and Hayes, A (2019) Recent developments in lymph node surgery for melanoma. The British journal of dermatology 180(1): 5-7	- Review article but not a systematic review
van Akkooi, Alexander C J (2014) Sentinel node followed by completion lymph node dissection versus nodal observation: staging or therapeutic? Controversy continues despite final results of MSLT-1. Melanoma research 24(4): 291-4	- Review article but not a systematic review *editorial*
Winstanley, Joseph; Cervenak, Emma; Harmston, Christopher (2019) Cost and resource implications of introducing intensive nodal surveillance for sentinel node positive melanoma in provincial New Zealand. The New Zealand medical journal 132(1499): 43-48	- non-randomised study
Woeste, Matthew R.; McMasters, Kelly M.; Egger, Michael E. (2021) Stage IIIa Melanoma and Impact of Multiple Positive Lymph Nodes on Survival. Journal of the American College of Surgeons 232(4): 517	- not a comparator of interest *linked to the sunbelt trial*
Wong, Sandra L, Faries, Mark B, Kennedy, Erin B et al. (2018) Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 36(4): 399-413	- Systematic review used as source of primary studies
Wright, F C, Souter, L H, Kellett, S et al. (2019) Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in	- Review article but not a systematic review

Study	Code [Reason]
cutaneous melanoma: a clinical practice guideline. Current oncology (Toronto, Ont.) 26(4): e541-e550	
Wysocki, Wojciech M. and Rutkowski, Piotr (2019) Management of metastases in regional lymph nodes in melanoma patients in 2019. Nowotwory 69(34): 108-110	- Review article but not a systematic review

1

2 Economic studies

Study	Code [Reason]
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	-Not an economic evaluation, No ICER or 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	-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 et al. (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	-Not an economic evaluation

Study	Code [Reason]
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
Hu Y, Shah P, Stukenborg G, (2015) Utility of sentinel lymph node biopsy for solitary dermal melanomas. Journal of surgical oncology. 111(7) 800-7	-Not relevant for this review question
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	-Not relevant for this review question, included in 2.1
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 P; Rabines-Juarez A, Alvarez-Ruiz M 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	- Not relevant for this review question, included in 2.1
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 (not a *de novo* analysis, commentary on the model in the record below)
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	-Inappropriate setting and perspective (US healthcare system with a societal perspective which meant that all costs, including directly to the patient were included), 3% discount rate

Study	Code [Reason]
Stoffels I, Dissemond J, Schulz A, (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
van der Velde-Zimmermann D, Schipper M I, de Weger R A (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

1