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Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma (Review)

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Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma (Review)

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[Intervention Review]

Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma

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ABSTRACT

Background

Melanoma is the leading cause of skin cancer-associated mortality. The vast majority of newly diagnosed melanomas are confined to the primary cutaneous site. Surgery represents the mainstay of melanoma treatment. Treatment strategies include wide excision of the primary tumour and sentinel lymph node biopsy (SLNB) to assess the status of the regional nodal basin(s). SLNB has become an important component of initial melanoma management providing accurate disease staging.

Objectives

To assess the effects and safety of SLNB followed by completion lymph node dissection (CLND) for the treatment of localised primary cutaneous melanoma.

Search methods

We searched the following databases up to February 2015: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (2015, Issue 1), MEDLINE (from 1946), EMBASE (from 1974), and LILACS (Latin American and Caribbean Health Science Information database, from 1982). We also searched the following from inception: African Index Medicus, IndMED of India, Index Medicus for the South-East Asia Region, and six trials registers. We checked the reference lists of included and excluded studies for further references to relevant randomised controlled trials (RCTs). We searched ISI Web of Science Conference Proceedings from inception to February 2015, and we scanned the abstracts of major dermatology and oncology conference proceedings up to 2015.

Selection criteria

Two review authors independently assessed all RCTs comparing SLNB followed by CLND for the treatment of primary localised cutaneous melanoma for inclusion. Primary outcome measures were overall survival and rate of treatment complications and side effects.

Data collection and analysis

Two review authors independently extracted and analysed data on survival and recurrence, assessed risk of bias, and collected adverse effect information from included trials.

Main results

We identified and included a single eligible trial comparing SLNB with observation which was published in eight different reports (from 2005 to 2014) with 2001 participants. This trial did not report on our first primary outcome of overall survival (which was also the planned primary outcome of this trial). When contacted for this important data, the trial authors stated "there are numerous additional analyses that have yet to be reported for the trial". We were able however to estimate overall survival from data included in the appendix of the published report and found no evidence of benefit for SLNB for overall survival. The overall survival hazard ratio (HR) using ITT (intention-to-treat) analysis was 0.99 95% confidence interval [CI] 0.82 to 1.19, 1661 participants). The overall survival using ITT for intermediate thickness melanomas was (HR 0.92, 95% CI 0.73 to 1.16) and for thick melanomas it was (HR 1.15, 95% CI 0.82 to 1.61).

The study did report on our second primary outcome of rate of treatment complications: short-term surgical morbidity (30 days) in 1735 participants showed no difference between SLNB and observation (risk ratio [RR] 1.11, 95% CI 0.9 to 1.37) for wide excision of the tumour site but favoured observation for complications related to the regional nodal basin (RR 14.36, 95% CI 6.74 to 30.59).

Our secondary outcomes of disease-specific and disease-free survival, local recurrence and distant metastases were reported. There were 1347 participants in the intermediate-thickness melanoma group and 314 in the thick melanoma group. The study did not report the actual 10-year melanoma-specific survival rate for all included participants. Instead, melanoma-specific survival rates for each group of participants: intermediate-thickness melanoma (defined as 1.2 to 3.5 mm) and thick melanomas (defined as 3.50 mm or more) was reported.

In the intermediate-thickness melanoma group there was no statistically significant difference in disease-specific survival between study groups at 10 years ($81.4 \pm 1.5\%$ versus $78.3 \pm 2.0\%$, HR 0.84, 95% CI 0.65 to 1.09). In the thick melanoma group, again there was no statistically significant difference in disease-specific survival between study groups at 10 years ($58.9.3 \pm 4.1\%$ versus $64.4 \pm 4.6\%$, HR 1.12, 95% CI 0.77 to 1.64). Combining these groups there was some heterogeneity ($I^2 = 34\%$) but the total HR was not statistically significant (HR 0.92, 95% CI 0.74 to 1.14).

The summary estimate for disease-free survival at 10 years favoured SLNB over observation in participants with intermediate-thickness and thick melanomas (HR 0.75, 95% CI 0.63 to 0.89).

With regard to the rate of local and regional recurrence as the site of first recurrence, a benefit of SLNB uniformly existed in both groups of participants with intermediate-thickness and thick melanomas (RR 0.56, 95% CI 0.45 to 0.69). This is in contrast with a uniformly unfavourable effect of SLNB with regard to the rate of distant metastases as site of first recurrence, in both groups of participants with intermediate-thickness and thick melanomas (HR 1.33, 95% CI 1.03 to 1.72).

Authors' conclusions

We found no evidence of improved overall survival or melanoma-specific survival rates for participants with intermediate or thick melanomas who underwent SLNB compared with observation alone.

Disease-free survival and rate of local and regional recurrence favoured SLNB in both groups of participants with intermediate-thickness and thick melanomas but short-term surgical morbidity was higher in the SLNB group, especially with regard to complications in the nodal basin.

The evidence for the outcomes of interest in this review is of low quality due to the risk of bias and imprecision of the estimated effects. Further research may have an important impact on our estimate of the effectiveness of SLNB in managing primary localised cutaneous melanoma. Currently this evidence is not sufficient to document a benefit of SLNB when compared to observation in individuals with primary localised cutaneous melanoma.

PLAIN LANGUAGE SUMMARY

Lymph node biopsy followed by lymph node dissection for localised skin cancer

Background

Melanoma arises from the uncontrollable growth of cells in the skin that produce the pigment melanin; it is the leading cause of skin cancer-associated mortality. In invasive melanoma, the tumour has infiltrated into the dermis (a deep layer in the skin).

For invasive skin cancer that is localised, the treatment of choice is complete surgical excision of the tumour. Most international guidelines also recommend sentinel lymph node biopsy (SLNB) in the management of these tumours.

A sentinel lymph node is the first lymph node in the body to receive lymph that comes from the primary site of the tumour. It is therefore, theoretically, the first site to which cancer cells will spread (metastasise). Hence, detecting tumour cells in this node can predict the involvement of other nodes in the spread of the cancer and may help identify individuals who are candidates for complete removal of these lymph nodes (completion lymph node dissection or CLND). This should help eradicate the further spread of melanoma cells.

Review question

Does lymph node biopsy followed by lymph node dissection, compared with observation, improve survival for people with localised skin cancer?

Study characteristics

We found one published randomised controlled trial with 2001 participants with localised skin cancer who had undergone removal of the primary tumour and were then randomised to receive SLNB or observation. Participants testing positive for cancer cells in the sentinel lymph node then underwent CLND. Participants in the observation group underwent removal of the lymph nodes only on disease recurrence. The study did not report on our primary outcome of interest (overall survival), but it did report on our secondary outcomes of disease-specific survival (time to death only from melanoma), disease-free survival (time to first melanoma recurrence at any site), and recurrence.

Key results

Although the authors of the one included study did not report the primary outcome of overall survival, we were able to calculate it from data they included in their report appendix which showed no benefit of SLNB for people with intermediate or thick melanomas. Our one included study also did not report any difference in disease-specific survival for participants who underwent SLNB or observation. Disease-free survival was better in the SLNB treatment group. However, recurrence of the melanoma at a distant site in the body occurred more frequently in participants in the SLNB group than in those in the observation group.

Quality of the evidence

We assessed the quality of the evidence for this trial as low for the above outcomes. As indicated by the results of this one included study, there is no clear evidence at present to recommend that SLNB, followed by CLND, is a better means of improving overall or melanoma-specific survival than observation.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. SLNB versus Observation for localized primary cutaneous melanoma

SLNB versus observation for localised primary cutaneous melanoma

Patient or population: patients with localised primary cutaneous melanoma

Settings: Multicentre randomised controlled clinical trial

Intervention: SLNB

Comparison: Observation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Observation	SLNB				
Overall Survival Intention-to-treat Death from any cause during the study Follow-up: 10 years	278 per 1000	275 per 1000 (234 to 321)	HR 0.99 (0.82 to 1.19)	1661 (1 study)	⊕⊕⊕⊖ low ¹	
Surgical Morbidity (Within 30 d) Related to the Regional Nodal Basin in Patients Assigned to the 2 Treatment Arms of MSLT-I Any complication in the dissected basin, regional or systemic related to the surgical treatment in the regional nodal basin Follow-up: 30 days	9 per 1000	126 per 1000 (59 to 268)	RR 14.36 (6.74 to 30.59)	1735 (1 study ²)	⊕⊕⊕⊖ low ¹	
Surgical Morbidity (Within 30 d) Related to Wide Excision of the Primary Site in Patients Assigned to the 2 Treatment Arms of MSLT-I Any Surgical Complication related to the wide excision site Follow-up: 30 days	164 per 1000	182 per 1000 (148 to 225)	RR 1.11 (0.9 to 1.37)	1735 (1 study ²)	⊕⊕⊕⊖ low ¹	
Disease-specific Survival Death from melanoma Follow-up: 10 years	221 per 1000	205 per 1000 (169 to 248)	HR 0.92 (0.74 to 1.14)	1661 (1 study)	⊕⊕⊕⊖ low ¹	
Disease-free Survival First pathologically confirmed recurrence	360 per 1000	285 per 1000 (245 to 328)	HR 0.75 (0.63 to 0.89)	1661 (1 study)	⊕⊕⊕⊖ low ¹

Follow-up: 10 years					
Rate of pathologically confirmed locoregional recurrence following SLNB and curative CLND First pathologically confirmed local and/or regional recurrence Follow-up: 10 years	233 per 1000	130 per 1000 (105 to 161)	RR 0.56 (0.45 to 0.69)	1661 (1 study)	⊕⊕⊕⊖ low ¹
Rate of development of distant metastases following SLNB and curative CLND First pathologically confirmed distant metastasis Follow-up: 10 years	113 per 1000	151 per 1000 (117 to 195)	RR 1.33 (1.03 to 1.72)	1661 (1 study)	⊕⊕⊕⊖ low ¹

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Published evidence is limited to a single randomised trial, so the quality of evidence has been downgraded by one level; given that risk of bias has been rated as 'high' or 'unclear' for several components, we further downgraded the evidence because of this.

² As-treated analysis.

BACKGROUND

Melanoma is the leading cause of skin cancer-associated mortality, resulting from the uncontrollable proliferation of malignant melanocytes (cells within the epidermis that produce the pigment melanin) (Miller 2006; Tzellos 2014). The vast majority of newly diagnosed melanomas are confined to the primary cutaneous site, which is referred to as early-stage melanoma (Balch 2009). Surgery represents the mainstay of melanoma treatment, and standards of surgical treatment have evolved over the past few decades based on evidence acquired from randomised controlled trials (RCTs), large multicentre and single institutional databases, and consensus panels (Bichakjian 2011; Thompson 2009). Treatment strategies include the wide excision of the primary tumour (with margins dictated by important histological features, such as Breslow thickness (Mocellin 2011a)) and the use of sentinel lymph node biopsy (SLNB) to assess the status of the regional nodal basin(s) (Morton 2001; Ross 2011).

The use of SLNB for accurate disease staging is a key part of the preliminary management of many people with localised melanoma (Balch 2004); moreover, it is thought that early detection of occult metastatic disease in the regional lymph nodes followed by radical lymphadenectomy might lead to enhanced regional disease control and improved survival (Morton 2001; Ross 2010). In the USA, Western Europe, and Australia, SLNB is performed by most surgical specialists who treat individuals with melanoma, and its use is recommended in most evidence-based treatment guidelines for localised melanoma. However, because of a number of unresolved controversies relating to its usefulness (especially its therapeutic efficacy, safety, and costs), SLNB is not uniformly accepted by all specialised centres as the standard of care (Boland 2012; Thomas 2008a). In particular, the uncertainty regarding the therapeutic effect of this procedure stems from a lack of evidence with regard to whether or not SLNB can prolong survival either directly, through early identification and removal of micrometastatic disease in the regional lymph nodes, or indirectly, by staging individuals with melanoma more accurately for the use of potential adjuvant therapy, such as interferon alpha (Mocellin 2008; Mocellin 2011b).

Description of the condition

Although melanoma is the least common form of skin cancer, it accounts for 75% of skin cancer deaths (Ferlay 2010; Jemal 2011a; Jemal 2011b). In the 20th century, the incidence of melanoma in European populations increased faster than that of any other solid cancer, with the exception of lung cancer (Balch 2009; Bichakjian 2011; Fawzy 2012). An estimated 160,000 new cases and 41,000 deaths were reported worldwide in 2002 (Jemal 2011a). In 2007, the American Cancer Society estimated that the lifetime risk of melanoma was 1 in 49 for men and 1 in 73 for women. The number of deaths from melanoma was 8110 in the USA in 2007 (Mocellin 2011c). The incidence of melanoma also appears to be increasing, from 47,700 new cases recorded in 2001 to 59,940 new cases in 2007 (Mocellin 2011c). These factors underline the current important public health concerns about cutaneous melanoma (Bevona 2002; Erdmann 2012; Jemal 2011b; Mocellin 2011c).

People presenting with T1a melanoma, or T1b melanoma less than or equal to 0.5 mm thick, have a low risk of nodal micrometastasis and a 5-year survival rate of about 97% (Balch 2009). Those with T1b melanoma thicker than or equal to 0.76 mm comprise a subgroup that merits extra clinical attention, as the risk of occult nodal

disease increases to almost 10% (Balch 2009). A melanoma that is 0.5 to 0.75 mm thick with two or more mitoses/mm² might have an elevated risk of nodal micrometastasis, especially if cumulative adverse risk factors are present (Mocellin 2008).

The treatment of cutaneous melanoma is among the most difficult tasks for surgeons and oncologists (Thompson 2009). Advanced melanoma belongs to a group of solid malignancies that are resistant to medical therapy, thereby making timely diagnosis and surgical removal of the primary tumour the curative approach of choice (Divito 2010).

Description of the intervention

SLNB is a procedure in which the sentinel lymph node (SLN; the lymph node to which the cutaneous lymphatic vessels from the primary tumour site drain first) is identified, removed, and examined to determine whether cancer cells are present. The SLN is first identified by lymphatic mapping using lymphatic mapping by lymphoscintigraphy (imaging technique) prior to surgery and intraoperative injection of radioisotope, blue dye, or both (Bichakjian 2011; Morton 2006).

How the intervention might work

Currently available evidence argues that SLN status (the presence (SLNB-positive) or absence (SLNB-negative) of melanoma metastatic cells in the total lymph node basin) is the most important prognostic factor for the disease-specific survival of people with melanoma that is more than 1 mm thick (Balch 2011; Bichakjian 2011; Wen 2011). SLNB is considered the staging test with the best sensitivity and specificity to detect micrometastatic melanoma (occult disease) in regional lymph nodes (Bichakjian 2011). The technique is associated with an accuracy of about 95% (Bichakjian 2011). Despite the fact that this procedure is widely accepted as a useful tool for the prognostic staging of individuals with melanoma, particularly those in stages Ib to IIc (SLNB results have been incorporated in the latest version of the American Joint Committee on Cancer (AJCC) tumour, node, and metastasis (TNM) staging system (Balch 2011)), the systematic implementation of SLNB remains controversial, mainly due to the uncertainty regarding its therapeutic value (Boland 2012; Thomas 2008a). It is not known if early detection of occult nodal disease results in prolonged survival, control of regional disease, or both. Currently available evidence indicates a reduced rate of postoperative complications in those people who undergo completion lymph node dissection (CLND) for micrometastatic disease detected by SLNB-positive cells in the lymph node compared with those who undergo therapeutic lymph node dissection (LND) for clinically evident (palpable) disease (Bichakjian 2011; Leong 2011; Wen 2011).

Results from the prospective, randomised, controlled, Multicentre Selective Lymphadenectomy Trial I (MSLT-I) comparing SLNB (experimental arm) with observation (control arm) reported no significant difference in disease-specific survival between the biopsy and observation groups (Morton 2006). However, subgroup analysis of participants with nodal metastases showed higher five-year melanoma-specific survival in the group of individuals who underwent CLND following a positive SLNB than in those who underwent delayed therapeutic LND when they developed palpable nodal disease (Morton 2008). The MSLT-II is currently investigating whether CLND is necessary for all individuals with a positive SLNB (Bichakjian 2011; Wen 2011).

People with intermediate-thickness melanoma exhibit an overall rate of SLN positivity of approximately 20%, which decreases significantly when the thickness of the tumour is less than 1 mm (Bichakjian 2011; Fawzy 2012; Leong 2011).

Taking into account the important risk of regional lymph node micrometastatic disease involved when a tumour is thicker than 1 mm, SLNB is suggested (Wong 2012). For primary melanomas less than 1 mm thick, various negative predictive factors have been proposed to identify a subgroup of people whose risk of micrometastasis might justify the use of SLNB.

This risk could justify the use of SLNB, at least with the aim of better defining the prognosis of these individuals (Bichakjian 2011). In individuals with pathological stage I or II melanoma, additional adverse factors, besides the AJCC TNM staging factors, that have a predictive value linking or referring to SLN status include the following: Clark level IV or V, angiolymphatic invasion (presence of cancer cells in the small blood or lymph vessels), excision margin positivity, and younger age (Bichakjian 2011; Ross 2011). Finally, in the past it was thought that overall survival in people suffering from melanoma with a thickness of 4 mm or more (T4) was related to high rates of distant metastases and not to nodal status. However, the use of SLNB has been reported to be a potent independent predictor of outcome in these cases, confirming the potential usefulness of this procedure to personalise the prognosis even in this subgroup of individuals with melanoma (Balch 2011; Bichakjian 2011; Fawzy 2012; Leong 2011; Wen 2011).

Why it is important to do this review

This review aimed to assess the role of SLNB for the management of primary localised cutaneous melanoma through an evidence-based analysis in order to provide a basis for rational decision-making in the management of the disease.

In particular, it would be interesting to identify whether there is any survival benefit associated with early regional lymph node dissection; whether locoregional disease control is improved by treating nodal disease at the micrometastatic stage; or whether baseline factors (i.e. size of lesion, location) can affect treatment outcomes (in order to identify subgroups of individuals with melanoma who may have a prognostic benefit from SLNB).

Considering all of the above, it would be justifiable to discuss whether SLNB would be a beneficial treatment modality for individuals with primary cutaneous invasive melanoma. In those people who are candidates for SLNB, the value, cost-efficiency, complications, and limitations ought to be analytically discussed (Bichakjian 2011). When deemed appropriate, these individuals could be referred to a tumour board, with expertise in the surgical, radiologic, and pathological characteristics of SLNB (Bichakjian 2011). Significant comorbidities, personal preference, or other factors may contribute to the decision not to proceed with SLNB. In order to provide individuals and physicians with evidence-based information regarding the efficacy of SLNB, we planned, if possible, to perform a meta-analysis of the RCT results available on this subject.

The protocol for this review was entitled 'Sentinel lymph node biopsy followed by lymph node dissection for early cutaneous melanoma' (Kyrgidis 2013). For the review we changed the title to "Sentinel lymph node biopsy followed by lymph node

dissection for localised primary cutaneous melanoma". Please see the [Differences between protocol and review](#) section for our explanation of this change.

OBJECTIVES

To assess the effects and safety of SLNB followed by completion lymph node dissection (CLND) for the treatment of localised primary cutaneous melanoma.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs that reported the efficacy, safety, or tolerability of SLNB followed by CLND, alone or combined with adjuvant treatment (e.g. chemotherapy, chemoimmunotherapy, interferon-alpha immunotherapy), compared with other therapeutic approaches for the treatment of early malignant melanoma.

Types of participants

We included participants of all ages and both sexes, of any nationality, with a pathologically confirmed diagnosis of primary cutaneous melanoma with clinically negative lymph nodes and no confirmed distant metastatic disease.

Types of interventions

We included SLNB followed by CLND for the treatment of early melanoma. We considered all types of lymph node dissection (none, elective, comprehensive, etc), alone or combined with other treatment types (i.e. chemotherapy). Possible comparisons might be as follows: SLNB and observation versus SLNB and CLND, versus node dissection alone.

Types of outcome measures

Primary outcomes

1. Overall survival
2. Rate of treatment complications and side effects (short-term: up to 6 months; medium-term: up to 1 year; long-term: up to 10 years)

Secondary outcomes

1. Disease-specific survival
2. Disease-free survival
3. Rate of pathologically confirmed locoregional recurrence following SLNB and curative CLND (short-term: up to 6 months; medium-term: up to 1 one year; long-term: up to 10 years)
4. Rate of development of distant metastases following SLNB and curative CLND (short-term: up to 6 months; medium-term: up to 1 year; long-term: up to 10 years)

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

We searched the following databases up to 25 February 2015:

- the Cochrane Skin Group Specialised Register using the search strategy in [Appendix 1](#);
- the Cochrane Central Register of Controlled Trials (CENTRAL) 2015, Issue 1, in *The Cochrane Library* using the strategy in [Appendix 2](#);
- MEDLINE via Ovid (from 1946) using the strategy in [Appendix 3](#);
- Embase via Ovid (from 1974) using the strategy in [Appendix 4](#); and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in [Appendix 5](#).

We searched the following databases up to 1 February 2015:

- African Index Medicus (indexmedicus.afro.who.int/ from inception) using the strategy in [Appendix 6](#);
- IndMED of India (indmed.nic.in/ from inception) using the strategy in [Appendix 6](#); and
- Index Medicus for the South-East Asia Region (IMSEAR) (from inception) using the strategy in [Appendix 6](#).

Trials registers

We searched the following trials registers up to 1 February 2015 using the strategy in [Appendix 6](#):

- the metaRegister of Controlled Trials (www.controlled-trials.com/);
- the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov/);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/);
- the World Health Organization International Clinical Trials Registry platform (who.int/trialsearch/);
- the EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>);
- the South African National Clinical Trial Register (www.sanctr.gov.za/).

Searching other resources

References from published studies

We scanned the bibliographies of included and excluded studies for further references to relevant trials.

Conference proceedings

In order to identify eligible studies from conference proceedings, we searched ISI Web of Science Conference Proceedings up to 1 February 2015. We also scanned the abstracts of major dermatology and oncology conference proceedings up to 2015, such as those of the American Society of Clinical Oncology (ASCO) Annual Meeting, the Society of Surgical Oncology (SSO) Annual Cancer Symposium, and the Society for Melanoma Research (SMR) Annual Congress.

Adverse effects

We did not perform a separate search for adverse effects, but we did consider adverse and side effects described in included studies.

Data collection and analysis

Some parts of the methods section of this review uses text that was originally published in other Cochrane titles co-authored by one review author (TT; predominantly [Tzellos 2013](#), which is now withdrawn from *The Cochrane Library*) and by TT, AK, SM, PP, and ZA (predominantly [Tzellos 2014](#)), as well as text originally published in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Should sufficient studies be identified that met our inclusion criteria, we planned to perform meta-analyses following the information included in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines ([Moher 2009](#)).

Selection of studies

We examined the titles and abstracts of all references identified in each of the search phases. We obtained the full text of all papers that either met our inclusion selection criteria or for which we could not make a decision without looking at the full text. At least two reviewers (AK, TT) looked at these items independently. They resolved any differences by discussion or by consulting a third author (SM or AL).

We recorded the reasons for exclusion in the '[Characteristics of excluded studies](#)' table.

Data extraction and management

Two review authors (TT, AK) independently extracted data into a standard data extraction form, which was modified for the purposes of this review. Authors were not blinded to the journal title or to the names of the trial authors. We resolved differences by discussion with a third author (SM or AS). We extracted data according to the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#); Table 7.3.a). AK entered data into the '[Characteristics of included studies](#)' tables in Review Manager.

We extracted the following data: general study information, trial methodology information, key variables characterising the participants, key variables characterising the primary tumour, key variables characterising the intervention, the type of adjuvant medical therapy, and results information.

- General study information
 - Authors
 - Publication status (full report/abstract/unpublished data)
 - Starting year of the trial
 - Publication date
 - Source of study funding (if any)
 - Setting (single-centre or multicentre, national or international)
 - Place where the trial was conducted
 - Potential multiple publication (publication of partially or completely overlapping series)
 - Language of original publication
- Trial methodology
 - Study design

- Study duration
- Sequence generation
- Allocation sequence concealment
- Participant, provider, and outcome assessor blinding
- Number of participants allocated to each treatment group
- Number of dropouts and reason for dropouts
- Intention-to-treat analysis or not
- Method and duration of follow-up period
- Key variables characterising the participants
 - Age
 - Sex
 - Ethnicity
 - Inclusion and exclusion criteria
 - Number of participants enrolled
 - Previous treatment
 - Immunocompetent or not (e.g. B-cell lymphoma, transplantation)
- Key variables characterising the primary tumour
 - Site
 - Tumour Breslow thickness
 - Presence of ulceration
 - Histological subtype of melanoma
 - Mitotic rate
- Key variables characterising the intervention
 - Use of a dual approach to identify the SLN (use of isosulphan dye and technetium-99m-labelled sulphur)
 - Type of subsequent surgical intervention following SLNB:
 - CLND conducted the same day, after the intraoperative performance of a frozen section pathology (usually takes 40 to 60 minutes): the SLNB incision was extended, with the individual still in the operating theatre under anaesthesia
 - CLND performed some days after, when the final pathology report on the SLN status was available: the SLNB incision was sutured.
- Type of adjuvant medical therapy
 - Chemotherapy
 - Chemoimmunotherapy
 - Interferon immunotherapy
 - Other immunotherapy
 - None
- Results
 - The number of participants in each group and the denominator for categorical outcomes
 - Missing participants, number lost to follow up
 - TNM stage for each intervention group
 - Estimate of the treatment effect (with confidence intervals (CIs) for each outcome
 - Method and frequency used to identify clinically involved nodes (clinical, sonographic, computed tomography (CT) scans, magnetic resonance imaging, positron emission tomography - computed tomography
 - Means and standard deviations for continuous data
 - Subgroup analyses

Assessment of risk of bias in included studies

Two authors (TT, AK) independently assessed the quality and risk of bias of the eligible studies. They resolved any disagreement by discussion and consensus. We assessed quality and risk of bias by evaluating the following components for each included trial using the 'Risk of bias' tool detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- (a) method of generation of the randomisation sequence;
- (b) method of allocation concealment - we considered this adequate if the assignment could not be foreseen by either subjects or investigator;
- (c) blinding (who was blinded or not blinded) in order to assess performance bias - we considered this adequate if subjects, investigators, and assessors were blinded to who received the intervention and who received the placebo or other treatment;
- (d) proportion of participants lost to follow up (in each group); and
- (e) whether or not the reported results were analysed according to the groups to which the participants were originally allocated (intention-to-treat (ITT) analysis) in order to assess detection and attrition bias.

We also assessed the length of follow up, and how disease clearance (partial or complete) and local recurrence were recorded (by imaging techniques, by tumour biopsy, or by other means).

We summarised the information for each included study in the 'Risk of bias' section in the '[Characteristics of included studies](#)' table and in a 'Risk of bias' graph.

Measures of treatment effect

For survival outcomes (and, thus, time-to-event data), we used the natural logarithm of the hazard ratio (HR) and the corresponding 95% CIs as data points for the meta-analysis. We calculated the survival time from the date of randomisation. In studies that performed multivariate survival analyses (using Cox proportional hazards regression models) and reported HRs and CIs, we utilised these as summary data for describing trial findings and for meta-analysis purposes. For studies not reporting HRs, we estimated HRs and the associated statistics for individual trials, based on the information presented in the trial report according to the methodology reported by Tierney et al. (Tierney 2007). For studies performing (or reporting) only univariate survival analysis (log-rank test-based comparison of Kaplan-Meier survival curves), we planned to extrapolate HR and 95% CIs from survival curves, adopting the hierarchical series of steps proposed by Parmar et al. (Parmar 1998) but we were unable to do so as no such studies were found. We also intended to express results as the number needed to treat for an additional beneficial outcome (the number of participants needed to be treated with SLNB to avoid one event of interest, such as death), as appropriate (Altman 1999).

We summarised the incidence of events of interest (e.g. postoperative complications, local recurrences, distant recurrences) with trial-specific rates (i.e. number of events per 1000 participants) and their corresponding 95% CIs.

Unit of analysis issues

If multiple-treatment-group trials were eligible, we aimed to combine groups to create a single pairwise comparison following recommendations in the *Cochrane Handbook for Systematic*

Reviews of Interventions (Higgins 2011; Chapter 16). If no relevant intervention groups could be combined, we planned to conduct multiple-treatment meta-analyses. If any cluster trials were considered eligible for inclusion in this review, we aimed to analyse these trials as a distinct group from other study designs.

Dealing with missing data

We analysed the data of a trial as such if the analysis was conducted according to the principle of ITT. If data necessary for performing meta-analyses were missing, we contacted the trial authors. We planned to exclude individual studies from the meta-analysis if we were unable to obtain sufficient data.

We contacted the authors of the single study (MSLT-I) included in this review asking for missing overall survival and ITT data. The authors stated that "we do not feel we can reasonably disseminate the data at this time". Therefore, we proceeded to ITT analysis using imputation. For this approach we assumed that all missing participants did not experience the event (Higgins 2011, 16.2.2 Intention-to-treat issues for dichotomous data). For survival data, where ITT HRs were not available, we considered that the HRs reported for the per-protocol analysis would also apply in the ITT analysis.

Assessment of heterogeneity

We aimed to investigate result consistency (effect sizes) among studies by means of two heterogeneity analyses: Cochran's Q-test (heterogeneity test), based on the χ^2 statistic, and the I^2 statistic ($[Q - df]/Q \times 100$, where Q is the Cochran statistic and df are the degrees of freedom (i.e. the number of studies minus 1); it indicates the percentage of the variability in effect estimates due to heterogeneity rather than to sampling error) (Higgins 2011; Sutton 2000). To be more conservative, we considered heterogeneity to be significant when the Cochran's Q-test P value was less than 0.1. In addition, we intended to quantify inconsistency across studies by the use of the I^2 statistic, which is generally considered notable (i.e., heterogeneity has a notable impact on the results of the meta-analysis) at values of 50% or higher (Mocellin 2008).

Assessment of reporting biases

If more than 10 studies were to be included in the meta-analysis, we intended to use funnel plots to visually analyse the existence of publication bias. Additionally, we intended to perform the Egger's test (Egger 1997) to formally assess the symmetry of funnel plots.

Selective reporting bias

We sought the protocols of the included studies. When available, we compared outcomes mentioned in the protocol with those in the published report. If not available, then we compared the outcomes listed in the methods section of the article with those for which results were reported (Higgins 2011, Table 8.5d).

Other sources of bias

We examined the included studies for other sources of bias (Higgins 2011, Table 8.5d).

Data synthesis

If there was no evidence of statistically significant or notable heterogeneity between eligible studies, we intended to synthesise data using the fixed-effect model, which assumes that all

the studies share the same common treatment effect (Higgins 2011; Sutton 2000). When statistically significant or notable heterogeneity was apparent, we planned to perform meta-analysis by applying the random-effects model (DerSimonian 1986), which assumes that studies are a random sample of a hypothetical population of studies and assigns a weight to each study, taking into account variance not only within but also between studies.

We intended to use HRs and corresponding 95% CIs to summarise the results of each trial and to perform meta-analyses for the following outcomes: overall participant survival (our primary outcome) and the following secondary outcomes: disease-specific and disease-free survival, rate of pathologically confirmed locoregional recurrence following SLNB and curative CLND, and rate of development of distant metastases following SLNB and curative CLND.

We summarised other events of interest, including postoperative complications, local recurrences, and distant recurrences, using trial-specific rates (i.e. number of events per 1000 participants) and their corresponding 95% CIs.

Subgroup analysis and investigation of heterogeneity

Following the assessment of heterogeneity, we planned, when sufficient numbers of studies were available, to perform subgroup analyses and meta-regression in order to identify factors associated with any observed heterogeneity that could potentially affect treatment efficacy, safety, or tolerability.

Potential subgroups identified included lesion factors and treatment factors.

- Lesion factors
 - Site
 - Size
 - Tumour thickness or depth of invasion
 - Mitotic rate
- Treatment factors
 - Number of nodes biopsied

We also intended to consider any other factor that may have been identified. We planned not to assume that any subgroup effect existed unless there was strong evidence of an interaction. However, if subgroup effects had been judged credible, we aimed to conduct separate meta-analyses for the relevant subgroups and produce separate 'Summary of findings' tables for these subgroups.

Sensitivity analysis

We planned to perform sensitivity analyses to examine the effects of excluding study subgroups, studies of low methodological quality, or studies for which there was ambiguity as to whether they met the inclusion criteria. We also intended to consider study design factors.

In sensitivity analyses, we imputed data as if:

1. all missing participants did not experience the event;
2. all missing participants experienced the event;
3. according to the event rate observed in the control group;

4. according to event rates among completers in the separate groups.

We also performed available case analysis using as a denominator the total number of people who had data recorded for the particular outcome in question. We present ITT analyses, where we assumed that all missing participants did not experience the event; this choice was based on clinical judgement but also on the results of the sensitivity analyses (also see [Potential biases in the review process](#)).

RESULTS

Description of studies

We identified a single RCT in which, following surgical excision of the primary cutaneous melanoma, SLNB was compared with observation ([MSLT-I](#)). The study recruited 2001 people; 1973 participants were included in the safety analysis and 1661 participants were randomised in the efficacy analysis: 1347 had intermediate-thickness (1.2 to 3.5 mm) primary melanomas and 314 had thick (3.5 mm or higher) primary melanomas.

We found no additional studies (comparing SLNB with any different modality) which further assessed adverse event or quality of life outcomes.

One month after the first search we conducted (28 January 2014), the authors of the single included study published a "final" (10-year) interim analysis, which we immediately located and included

in this review. We contacted the authors of this analysis for further information; they stated that "there are numerous additional analyses that have yet to be reported for the trial". We therefore refer to this publication as a 10-year analysis rather than the "final" analysis (as the authors clearly state in the title of their definitive study manuscript). The study considered melanomas of different thickness and different tumour sites. In the trial, pathologists histologically verified a diagnosis of melanoma. The definition used for recurrence was not always stated plainly and accurately in the reports.

One of the references we identified as relating to the [MSLT-I](#) study ([MSLT-I](#): Morton 2012) reports on MSLT-I and MSLT-II. MSLT-II was not included in this review as all the participants in that study received SLNB. SLNB-positive participants were then either followed using ultrasound or underwent CLND. This treatment did not meet our inclusion criteria.

We were not able to identify any unpublished studies which would be eligible for inclusion in this systematic review.

Results of the search

Our database searches identified 263 records. We identified a further 19 from other sources. After removing duplicates, we had 223 records. We excluded 211 records and assessed 12 full-text records for eligibility. Of these, we excluded four. The remaining eight references all related to one study, [MSLT-I](#), which we included in this review. See our study flow diagram ([Figure 1](#)) for more details on our screening process.

Figure 1. Study flow diagram.

Figure 1. (Continued)

1 study included
in quantitative
synthesis

Included studies

We identified a single randomised trial ([MSLT-I](#)), published in eight different reports (between 2005 and 2014). We have listed below, in brief, the characteristics of the study, and describe them in detail in the '[Characteristics of included studies](#)' table.

The trial was multicentre and multinational. The final study sample included 2001 participants, 1347 with intermediate-thickness melanomas (defined as 1.2 to 3.5 mm), 340 in the group with thin melanomas (defined as 1.20 mm or less), and 314 in the group with thick melanomas (defined as 3.50 mm or more). From 2001 participants screened, 1973 participants were randomly allocated to receive either SLNB (and CLND if SLNB-positive, $n = 1191$) or observation (and LND upon clinical relapse, $n = 782$). In the MSLT-I, 39 (5.0%) participants assigned to wide local excision and observation (WEO) actually received wide excision plus SLNB whereas 57 (4.8%) participants assigned to wide excision plus SLNB actually received WEO ([MSLT-I](#): Morton 2005). These numbers of participants were assessed for safety and quality of life outcomes. With regard to overall survival, disease-specific survival and disease-free survival, 1347 participants with intermediate-thickness melanomas were selected as the primary study group, of whom 814 were allocated to the SLNB group and 533 to the observation group. The authors state that "The sentinel nodes were examined in multiple permanent sections of tissue stained with hematoxylin and eosin and by immunohistochemical analysis with the use of antibodies to the melanoma-associated antigens S-100, HMB-45, and MART-1 or Melan-A" ([MSLT-I](#): Morton 2014).

Local and intransit metastases were reported but not specifically defined in the methods section of any of the study publications. The site of first recurrence ("nodal, distant, local/in-transit") was reported ([MSLT-I](#): Morton 2014). SLNB was performed in the experimental group (SLNB group) but not in the control group (observation group). The study publications report that in the observation group (control group), nodal surgery (LND) was performed only in those cases in which disease manifested clinically within the follow-up period. Clinical manifestation comprised either palpable disease or disease detected via CT or high-resolution ultrasound (US). The latter is discussed further below.

For all outcomes (see [Effects of interventions](#)) with the exception of rate of treatment complications and side effects (short-term: up to six months), we have used [MSLT-I](#): Morton 2014, as its data supersede those in any previous publications. For the rate of treatment complications and side effects (short-term: up to six months), we have used [MSLT-I](#): Morton 2005, as the short-term data published in this report have not been published elsewhere.

Given the number of missing participants between the per-protocol and ITT analyses (SLNB: 44/814 versus observation: 33/533 (intermediate-thickness melanomas); SLNB: 13/186 versus observation: 11/128 (thick melanomas)) ([MSLT-I](#): Morton 2014), we

performed ITT analysis using the imputation of the events in the participants with missing data for some outcomes.

Excluded studies

We excluded four studies ([Hauschild 2010](#); [Korovin 2013](#); [McMasters 2010](#); [Reintgen 2004](#)) because they did not fulfil our inclusion criteria, mainly with regard to the administration of the intervention. The studies are reported in the [Characteristics of excluded studies](#) tables.

Risk of bias in included studies

Random sequence generation (selection bias)

Randomisation was carried out centrally, in random permuted blocks of four, six, and eight participants. This is an acceptable method of randomisation for RCTs.

The study also used stratification to achieve balance. Stratification factors were Breslow thickness (1.20 mm or less versus 1.20 to 1.79 mm versus 1.80 to 3.50 mm versus 3.50 mm or higher) and the primary site of the melanoma (group or leg versus another site).

Allocation

MSLT-I was a randomised study. Randomisation was carried out using a recognised method. However, whether this was sufficient to achieve allocation concealment is unclear as the study reports do not include sufficient information in their methods sections to confirm adequate concealment of allocation. There was no mention of the use of envelopes or their opaqueness.

Blinding

Blinding of participants or treating clinicians in RCTs of SLNB is impossible because of the manner of the intervention, but detection bias could probably be reduced if outcome assessors are blinded. However, with no blinding, considerable detection bias is still unlikely in terms of overall survival. In no report of the MSLT-I study was blinding of outcome assessors mentioned; therefore, one could assume that assessors were not blinded.

Incomplete outcome data

The MSLT-I study results were not reported according to ITT principles but as a per-protocol analysis in the 10-year interim analysis of the MSLT-I ([MSLT-I](#): Morton 2014). [MSLT-I](#): Morton 2006 reports that parallel analyses conducted according to the ITT principle, which included all randomised participants, produced results that were consistent with those of the per-protocol analysis. In the group with intermediate-thickness melanomas, participants were excluded due to not meeting eligibility criteria (one participant in the SLNB group), for opting for the other group procedure ($n = 36$ in the SLNB group and $n = 22$ in the observation group), and for withdrawing prior to treatment ($n = 8$ in the SLNB group and $n = 11$ in the observation group). In the group with thick melanomas, participants were excluded due to not meeting eligibility criteria (one participant in the SLNB group), for opting for

the other group procedure ($n = 12$ in the SLNB group and $n = 9$ in the observation group) and for withdrawing prior to treatment ($n = 2$ in the observation group).

Follow up

The trial had lost or missing data, or incomplete follow up. There were 83 dropouts in the SLNB group at five years: 8 dropped out before treatment and 21 after treatment, 38 were lost to follow up (LFU), and 16 were unable to continue due to other reasons. There were 52 dropouts in the observation group: 11 dropped out before treatment and 8 after treatment, 23 were LFU, and 10 were unable to continue due to other reasons. At the 10-year analysis, the unable to continue group was merged with the LFU group: the numbers were 120 and 68 for the SLNB and observation groups, respectively. We did not seek to contact the study authors with regard to the minor amount of missing data and few variations in reported study denominator numbers.

Selective reporting

The original trial registration document for MSLT-I on [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT00275496) at <https://clinicaltrials.gov/ct2/show/NCT00275496> clearly states:

“Primary Outcome Measures: To determine whether wide excision of the primary with intraoperative lymphatic mapping (LM) followed by selective lymphadenectomy will effectively prolong **overall survival** [emphasis added] compared to wide excision of the primary melanoma alone. [Time Frame: 10 years] [Designated as safety issue: No]”. The fact that the authors have not reported this primary outcome of overall survival in the main 10-year paper

(MSLT-I: Morton 2014) is a typical example of selective reporting outcome bias. Notably, they claim in this paper that “the primary end point was melanoma-specific survival”. However, disease-free survival is listed as a secondary, not primary, outcome in the trial registration document. This selective reporting outcome bias did not allow us to examine the prespecified primary outcome of this review.

For the other outcomes reported in the MSLT-I publications, reporting bias is unlikely to have affected the conclusions of the present review with the exception of overall survival (first primary outcome), as noted above.

Other potential sources of bias

In the MSLT-I 10-year analysis (MSLT-I: Morton 2014), disease-free survival was calculated as time-to-event data, using local or intransit, nodal and distant-metastases as sites of first recurrence. Of note, previously, the National Cancer Institute (NCI), the sponsor of MSLT-I, had recommended the exclusion of nodal recurrence from disease-free survival calculations in future reports of MSLT-I (Thomas 2009). The reason for this was the possibility of lead-time bias because earlier diagnosis of a positive node (via SLNB) would allow those diagnosed with a positive node to survive longer as opposed to observation where a positive node would have to manifest clinically; thus, the portion of disease-free survival owing to nodal recurrence would be expected to favour the SLNB group.

The trial had lost or missing data, or incomplete follow up in few participants. We report other sources of bias in the 'Risk of bias' section of the [Characteristics of included studies](#) table (Figure 2).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Effects of interventions

See: [Summary of findings for the main comparison SLNB versus Observation for localized primary cutaneous melanoma](#)

Primary outcomes

1. Overall survival (time to death from any cause)

Our one included study did not report on overall survival in the 10-year trial analysis (MSLT-I: Morton 2014). Instead disease-specific survival was reported. Of note, the trial protocol lodged

with www.clinicaltrials.gov reported overall survival as the primary outcome of the study. June 2012 is reported as the final data collection date for the primary outcome measure. We contacted the trial authors querying this issue. They stated "there are numerous additional analyses that have yet to be reported for the trial". We expect that overall survival data will be available in a future update of this review.

Using data from the 10-year interim analysis (MSLT-I: Morton 2014) there were 180 deaths in the SLNB group versus 128 in the observation group in participants with intermediate-thickness melanomas, and 87 deaths in the SLNB group and 52 in the observation group in those with thick melanomas. Death rates from other causes were 47/180 versus 25/128, and 19/87 versus 9/52 in participants with intermediate-thickness and thick melanomas, respectively (Mantel-Haenszel RR 1.32, 95% CI 0.91 to 1.90). Hence, more deaths from other causes were seen in the SLNB group than in the observation group, but this difference was not statistically significant. Given these data, and since no statistically significant favourable effect of SLNB on disease-specific survival was reported (see Secondary outcome 1 below), we believe that a statistically significantly favourable effect of SLNB in overall survival is even more unlikely.

Following publication of the commentary by [Sladden 2015](#), we have made a minor revision to this review by calculating overall survival on a per protocol and intention-to-treat basis and found no difference between SLNB and observation: the hazard ratio for overall survival using a per protocol and intention-to-treat analysis was 0.98 (95% CI 0.81 to 1.18 [Analysis 1.1](#)) and 0.99 (95% CI 0.82 to 1.19 [Analysis 1.2](#)) respectively. For ITT analysis, we also conducted best and worst case scenarios, as described in the methods of this review ([Sensitivity analysis](#)). The best case analysis showed the benefit of SLNB with a hazard ratio of 0.68 (95% CI 0.57 to 0.81 [Analysis 1.3](#)), was largely due to the intermediate group. The worse-case analysis showed benefit in favour of the observation group with a hazard ratio of 1.46 (95% CI 1.24 to 1.73 [Analysis 1.4](#)).

2. Rate of treatment complications and side effects (short-term: up to six months)

The preliminary safety and accuracy of staging study (MSLT-I: Morton 2005), in which 1973 participants were randomly allocated to either SLNB (and CLND if SLNB-positive, n = 1191) or observation

(and LND upon clinical relapse, n = 782), reported on short-term surgical complications. Of the 1973 eligible participants, 1969 were included in the morbidity analysis, on an as-treated basis; the remaining four participants (two in the SLNB group and two in the observation group) were excluded as a result of a lack of surgical toxicity forms. Two hundred and thirty-four participants who were SLNB-positive received CLND. For these participants, 30-day surgical morbidity related to the wide excision of the primary site was not reported, probably because the time-frame overlapped with the CLND procedure. The CLND procedure was reported to dramatically increase surgical morbidity in the regional nodal basin to 37.2% (87/234, wound separation = 7, seroma/hematoma = 54, infection = 37) compared with 10.1% in SLNB-negative participants. Four of 234 participants treated with CLND developed systemic complications (pulmonary = 3, other = 1). These 234 participants who received SLNB followed by CLND were excluded from the analysis due to a lack of comparable data, as the complications of the CLND procedure would eclipse the complications and side effects analysed below.

We thus compared 798 participants treated with wide excision and observation versus 937 participants treated with wide excision plus SLNB (which was negative and did not proceed to CLND) and calculated risk ratios. Safety outcomes were:

1. Surgical morbidity (within 30 days) related to wide excision of the primary site in participants assigned to the two treatment groups in MSLT-I ([Analysis 1.5](#));
2. Complications in the dissected basin (part of surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection) ([Analysis 1.6](#));
3. Regional complications (part of surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection) ([Analysis 1.7](#)); and
4. Systemic complications (part of surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection) ([Analysis 1.8](#)).

Results are reported in the table below.

For dichotomous data		
Outcomes	SLNB not followed by CLND, n = 937	Observation, n = 798
Surgical morbidity (within 30 days) related to wide excision of the primary site in participants assigned to the two treatment groups of MSLT-I (Analysis 1.5)		
Wound separation	31	28
Seroma/haematoma	41	22
Infection	78	67
Skin graft failure	21	14

Surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection

Complications in the dissected basin (Analysis 1.6)

Wound separation	11	0
Seroma/haematoma	52	0
Infection	43	0

Surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection

Regional complications (Analysis 1.7)

Leg oedema	6	2
Thrombophlebitis	4	3
Other	4	1

Surgical morbidity (within 30 days) related to the regional nodal basin in participants undergoing wide excision with or without nodal dissection

Systemic complications (Analysis 1.8)

Pulmonary	3	1
Urinary	3	0
Other	3	0

The total surgical morbidity related to the nodal basin (dissected basin + regional + systemic) is summarised in Analysis 1.9. In MSLT-I: Morton 2014, the authors quote that "The incidence of allergic reactions to the blue dye administered at the time of [SLNB] was [reported to be] 0.17% (2 of 1173) and consisted of blue-coloured urticaria (hives). No patient developed an anaphylactic reaction to blue dye". Non-surgical treatment complications (e.g. length of hospital inpatient stay, local versus general anaesthetic, adverse drug reactions (e.g. to antibiotics, analgesics, anaesthetics)) have not been recorded in MSLT-I study publications.

A sub-study of this trial evaluated the impact of mood state on survival (MSLT-I: Garreau 2009). Participants were asked to complete a 65-question form within 6 months of enrolment (baseline) and every 12 months thereafter. This questionnaire measured six identifiable mood states (vigour-activity, tension-anxiety, depression, anger-hostility, fatigue-inertia, confusion-bewilderment) of the Profile of Mood States (POMS), a validated mood scale for assessing response to therapy. Self-reported data from the questionnaires were linked to demographic and clinical variables. The baseline distribution of POMS variables was similar in the two treatment groups. Participants with more vigour at baseline were reported to have a statistically significantly longer period of disease-free and overall survival, even after adjusting for age, tumour thickness, site, and ulceration status.

Secondary outcomes

1. Disease-specific survival

The study did not report the actual 10-year melanoma-specific survival rate for all participants included. Instead, melanoma-specific survival rates for each group of participants (intermediate-thickness and thick melanoma) are reported.

In the intermediate-thickness melanoma group, there was no statistically significant difference in disease-specific survival between study groups at 10 years (SLNB: $81.4 \pm 1.5\%$ versus Obs: $78.3 \pm 2.0\%$, reported HR 0.84, 95% CI 0.64 to 1.09; P value = 0.18 in the per-protocol analysis; HR 0.84, 95% CI 0.65 to 1.09 in the ITT analysis). We performed ITT analysis using the imputation of the events in the participants with missing data for some outcomes, as I amended above.

In the thick melanoma group, there was again no statistically significant difference in disease-specific survival between study groups at 10 years ($58.9.3 \pm 4.1\%$ versus $64.4 \pm 4.6\%$, reported HR 1.12, 95% CI 0.76 to 1.67; P value = 0.56 in the per-protocol analysis; HR 1.12, 95% CI 0.77 to 1.64 in the ITT analysis).

We calculated disease-specific survival from study data on an ITT basis, combining intermediate-thickness and thick melanomas; heterogeneity was measurable ($I^2 = 34\%$) (Analysis 1.10: HR 0.92,

95% CI 0.74 to 1.14). Of note, the CI of the HR crosses 1, indicating a lack of statistical significance, which implies that the absolute risk reduction is not significant and SLNB may actually increase risk.

2. Disease-free survival

It must be emphasized that because disease-free survival is bound to be different if disease is removed earlier in one group, disease-free survival may not be a proper outcome to examine the efficacy of SLNB. More discussion on this follows in [Summary of main results](#).

The study did not report the actual 10-year disease-free survival rate for all participants included, instead, disease-free survival rates for each group of participants (intermediate-thickness and thick melanoma) are reported. We calculated disease-free survival from study data on an ITT basis, for both intermediate-thickness and thick melanoma groups ([Analysis 1.11](#)).

In the intermediate-thickness melanoma group, there were 161 recurrences (nodal 73 (14.6%), distant 56 (11.2%), local or intransit 32 (6.4%)) in the observation group and 199 (nodal 38 (4.9%), distant 107 (13.7%), local or intransit 54 (7.0%)) in the SLNB group (per-protocol analysis). In the reported ITT analysis, these numbers are 170 (instead of 161) and 213 (instead of 199), but no subgroupings (nodal, distant, local, or intransit) are reported. The disease-free survival rate was significantly higher in the biopsy group than in the observation group at 10 years (SLNB: $71.3 \pm 1.8\%$ versus Obs: $64.7 \pm 2.3\%$; HR 0.76, 95% CI, 0.62 to 0.94; P value = 0.01 in the per protocol analysis; HR 0.77, 95% CI 0.63 to 0.95 in the ITT analysis).

Number needed to treat for an additional beneficial outcome (NNTB): using the reported ITT analysis in the intermediate-thickness melanoma group, at the 10-year interim, given the 68.1% recurrence-free probability in the observation group and a 0.77 HR, NNTB = 18 (95% CI 10 to 134), which means we must perform SLNB in 18 people with intermediate-thickness melanoma to prevent one melanoma recurrence that would have occurred at 10 years under observation.

In the group of participants with thick melanomas, there were 80 recurrences (nodal 15 (8.7%), distant 43 (24.9%), local or intransit 22 (12.7%)) in those treated with SLNB versus 68 recurrences (nodal 40 (34.2%), distant 19 (16.2%), local/intransit 9 (7.7%)) in those in the observation group (per-protocol analysis) (HR 0.70, 95% CI 0.50 to 0.97, P value = 0.03). The HR remained exactly the same in the reported ITT analysis ([Analysis 1.11](#); HR 0.70, 95% CI 0.50 to 0.97, P value = 0.03).

When combining the intermediate-thickness and thick melanoma groups, the overall effect on disease-free survival was more robust statistically with no heterogeneity ($I^2 = 0\%$). It appears that a favourable effect of SLNB with regard to disease-free survival is apparent in individuals with either intermediate-thickness or thick melanomas (ITT: HR 0.75, 95% CI 0.63 to 0.89, P value = 0.001, [Analysis 1.11](#)).

3. Rate of pathologically confirmed locoregional recurrence as site of first recurrence following SLNB and curative CLND (long-term: up to 10 years)

The study reported locoregional recurrence as the site of first recurrence.

In the group with intermediate-thickness melanomas, there were 105 local and nodal recurrences as the site of first recurrence in the observation group versus 92 in the SLNB group. The rate of locoregional recurrence as site of first recurrence was lower in the SLNB group (ITT; RR 0.57, 95% CI 0.44 to 0.74, [Analysis 1.12](#)).

In the group of participants with thick melanomas, there were 37 pathologically confirmed locoregional recurrences as site of first recurrence in those treated with SLNB versus 49 in the observation group (ITT; RR 0.52, 95% CI 0.36 to 0.75, [Analysis 1.12](#)).

The overall effect on the rate of locoregional recurrence as site of first recurrence when combining the intermediate-thickness and thick melanoma groups was more robust statistically with no heterogeneity ($I^2 = 0\%$). It appears that a favourable effect of SLNB with regard to the rate of locoregional recurrence as site of first recurrence is apparent in individuals with either intermediate-thickness or thick melanomas (ITT: RR 0.56, 95% CI 0.45 to 0.69, [Analysis 1.12](#)).

4. Rate of development of distant metastases as site of first recurrence following SLNB and curative CLND (long-term: up to 10 years)

The study reported distant metastases as the site of first recurrence. In the group with intermediate-thickness melanomas, distant metastasis was the first site of recurrence in 56 participants in the observation group versus 107 in the SLNB group (ITT: RR 1.25, 95% CI 0.92 to 1.70, [Analysis 1.13](#)).

In the group of participants with thick melanomas, distant metastasis was the first site of recurrence in 19 in the observation group versus 43 in the SLNB group (ITT: RR 1.56, 95% CI 0.95 to 2.54, [Analysis 1.13](#)).

When distant metastases as the site of first recurrence for intermediate-thickness and thick melanomas were combined there was no statistical heterogeneity ($I^2 = 0\%$). The rate of development of distant metastases as the site of first recurrence did not favour SLNB (ITT: RR 1.33, 95% CI 1.03 to 1.72, [Analysis 1.13](#)).

5. Rates of local, intransit and distant recurrences as site of first recurrence

Because it has been suggested by the NCI (who sponsored MSLT-I) that nodal recurrences should be excluded from the disease-free survival calculation in future updates of MSLT-I ([Thomas 2009](#)), we calculated the risk ratio for local, intransit and distant metastasis as the site of first recurrence in a sensitivity analysis. In a second sensitivity analysis we also calculated the risk ratio for local and intransit metastases as the site of first recurrence.

The study reported that in the intermediate-thickness melanoma group there were 161 recurrences (nodal 73 (14.6%), distant 56 (11.2%), local or intransit 32 (6.4%)) in the observation group and 199 (nodal 38 (4.9%), distant 107 (13.7%), local and intransit 54 (7.0%)) in the SLNB group.

In the group of participants with thick melanomas, there were 80 recurrences (nodal 15 (8.7%), distant 43 (24.9%), local or intransit 22 (12.7%)) in those treated with SLNB versus 68 recurrences (nodal 40 (34.2%), distant 19 (16.2%), local and intransit 9 (7.7%)) in the observation group. We calculated the following risk ratios, using

the numbers for the above-mentioned distant, local and in-transit recurrences.

Rate of development of local, intransit and distant recurrences as site of first recurrence

The rate ratio for local, in-transit and distant metastases as the site of first recurrence (RR 1.29, 95% CI 1.06 to 1.58; [Analysis 1.14](#)) favoured observation.

Rate of development of local and intransit recurrences as site of first recurrence

The risk ratio for local and intransit metastases as the site of first recurrence in MSLT-I did not differ significantly between study groups (RR 1.23, 95% CI 0.85 to 1.77; [Analysis 1.15](#)).

DISCUSSION

The observation period allows extension of metastases within the nodal basin ([MSLT-I](#)), which correlates with an increased risk of death ([Balch 2001](#)) and therefore the observation period of the study is appropriate to monitor the outcomes. The publication ([MSLT-I: Morton 2006](#)) reported that parallel analyses according to the ITT principle, which included all randomised participants, produced results that were consistent with those of the reported per-protocol analysis ([MSLT-I: Morton 2006](#)). Our ITT analyses confirm this statement.

Summary of main results

This systematic review summarises the evidence regarding the value of SLNB for the treatment of localised primary cutaneous melanoma. The sole included trial did not show a statistically significant difference in disease-specific survival when comparing SLNB with observation. Overall survival was not reported in the final trial report, although it was the primary study outcome according to the study protocol. Because more deaths from other causes (M-H RR 1.32, 95% CI 0.91 to 1.90) occurred in the SLNB group than in the observation group it is anticipated that the HR for overall survival between study groups would be higher than that for disease-specific survival, providing a less favourable (non-statistically significant) effect of SLNB compared to the findings for disease-specific survival (discussed below). We were able to extract required numbers and calculate overall survival in a PP and ITT basis ([Analysis 1.1](#); [Analysis 1.2](#)). Best and worst case scenarios have also been calculated ([Analysis 1.3](#); [Analysis 1.4](#)). Both PP and ITT analyses, are nowhere close in favouring any modality over the other. In fact, the HR is always marginally close to 1. In the best case scenario a 32% reduced statistically significant hazard exists in favour of SLNB. In the worst case scenario a 46% reduced statistical significant hazard exists in favour of observation. These results are not expected to change in any future update of [MSLT-I](#) or in other future studies. It has been suggested that additional analyses on overall survival with and without positive SLNB may further only confirm their utility as a prognostic tool ([Yang 2014](#)).

Although non-surgical treatment complications (e.g. length of hospital inpatient stay, local versus general anaesthesia, adverse drug reactions (e.g. to antibiotics, analgesics, anaesthetics)) have not been reported for the MSLT-I, short-term surgical complications were reported in the preliminary safety and staging accuracy study ([MSLT-I: Morton: 2005](#)) ([Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.7](#); [Analysis 1.8](#); [Analysis 1.9](#)). Short-term surgical morbidity was, as expected, higher in the SLNB group (who did not undergo

CLND) than in the observation group, especially with regard to complications in the nodal basin. In the MSLT-I, 39 (5.0%) participants assigned to wide local excision and observation (WEO) actually received wide excision plus SLNB whereas 57 (4.8%) participants assigned to wide excision plus SLNB actually received WEO ([MSLT-I: Morton 2005](#)). Analysis of surgical morbidity was neither on an ITT nor a per-protocol basis. Rather, those 800 participants who received WEO were compared to the 1173 participants who received wide excision plus SLNB in an as-treated analysis. The study authors noted that because their purpose was "to evaluate the surgical procedure in regard to morbidity and accuracy in staging the regional nodal basin, this analysis is based on treatment actually received" ([MSLT-I](#)). We were not able to calculate rates for this outcome on an ITT basis, because we could not impute data for those participants who crossed over to the opposite group. Therefore we elected to present available cases from the as-treated analysis, as they had been reported. For this outcome, we also excluded SLNB followed by CLND because measuring and reporting short-term surgical morbidity was, as expected, not feasible in this group.

Our review does not show a statistically significant difference in disease-specific survival between the two groups treated with SLNB or observation ([Analysis 1.10](#)). In the intermediate-thickness melanoma group, the point estimate for disease-specific survival favoured SLNB by a small degree at 10 years (HR 0.84, 95% CI 0.64 to 1.09; P value = 0.18) (per-protocol analysis), but the result was nowhere near statistically significant. This non-statistically significant result is compatible with both a 36% relative reduction in disease-specific mortality favouring SLNB and a 9% relative increase in risk of mortality in those receiving SLNB compared with observation. This means that SLNB may either prolong or reduce the disease-specific survival of individuals with melanoma. However, a small difference, such as a 15-year survival rate of 95% compared to one of between 91% and 97% (which could be clinically important) in disease-specific survival between SLNB and observation cannot be ruled out with confidence for those participants with intermediate-thickness melanomas. In the case of thick melanomas, SLNB does not appear to have any effect on disease-specific survival (HR 0.92, 95% CI 0.74 to 1.14), due to the heterogeneity between the intermediate-thickness and thick melanoma groups ($I^2 = 34\%$).

In intermediate-thickness melanomas, the point estimate for disease-free survival favoured SLNB at 10 years in both the per-protocol ($71.3 \pm 1.8\%$ versus $64.7 \pm 2.3\%$; HR 0.76, 95% CI 0.62 to 0.94; P value = 0.01) and ITT (HR 0.77, 95% CI 0.63 to 0.95; [Analysis 1.11](#)) analyses. This result is compatible with a 6% to 38% relative reduction in disease-free mortality favouring SLNB.

As expected, the most common site of first recurrence in the observation group was the nodal basin (73 cases (14.6%) versus 38 cases (4.9%) in the SLNB group. This can be logically anticipated because a large proportion of subclinical nodal disease (that would eventually progress) would be diagnosed earlier through SLNB compared with clinical observation. Therefore, the longer disease-free survival in the SLNB group might represent a typical example of lead-time bias. This lead-time bias has been previously discussed: the NCI, who sponsored MSLT-I, recommended excluding nodal recurrence from disease-free survival calculations in future updates of MSLT-I ([Thomas 2009](#)).

Overall the rate of locoregional recurrences as the site of first recurrence was higher in the SLNB group than in the observation group (RR 0.56, 95% CI 0.45 to 0.69). This effect is in the same direction for both thick and intermediate-thickness melanomas ([Analysis 1.12](#)).

By contrast, the rate of development of distant metastases as the site of first recurrence, combining both the intermediate-thickness and thick melanoma groups, demonstrated a statistically significant 33% increased risk of distant metastases as the site of first recurrence for participants in the SLNB group of MSLT-I (RR 1.33, 95% CI 1.03 to 1.72; [Analysis 1.13](#)). Thus, participants in the observation group had a measurable benefit with regard to distant metastases as the site of first recurrence. A serious limitation of this analysis is that those people who developed nodal disease as the site of first recurrence are counted as such and censored for the rest of the follow-up period. Within the remainder of the follow up, however, they might have also developed a second metastasis at a distant site. Taking into account the lead-time bias described above with regard to nodal recurrences, it may be more prudent to consider distant metastases to be a more appropriate time-point for measuring potential SLNB morbidity. In a reply to an appeal from Meirion Thomas, the Chief of the Clinical Investigations Branch of the NCI stated that "in a Trial where one group has nodal disease removed at the outset and the other group does not, calculation of either distant disease-free survival or exclusion of nodal recurrences from the DFS calculation is appropriate" ([Thomas 2009](#)). Therefore, distant metastasis-free survival (time to first distant metastasis or death from any cause, with censoring of participants who are lost to follow up) may be a more appropriate measure by which to document the benefit of SLNB. In this regard, and because calculation of distant metastasis-free survival and corresponding HRs was not feasible with the data available, we calculated the rate ratio of local, intransit and distant metastases as the site of first recurrence. This latter ratio, similarly to that for distant metastasis as the site of first recurrence, favoured observation (RR 1.29, 95% CI 1.06 to 1.58; [Analysis 1.14](#)). Calculation of disease-free survival using only local, intransit and distant metastasis as endpoints would eliminate the censoring of participants who developed nodal disease as the site of first recurrence, thereby allowing us to reject the hypothesis that SLNB increases the rate of distant metastases, at least as the site of first recurrence.

In the 10-year analysis of MSLT-I ([MSLT-I: Morton 2014](#)) the authors report on average-treatment-effects (ATE) from latent subgroup analyses. ATE measure the difference in mean (average) outcomes between units assigned to the treatment and units assigned to the control; but since units can be exposed to only one level of the treatment it is impossible to measure treatment effects at the individual level ([Austin 2011](#)). If treatment is randomised across individuals, then estimation of ATE may be considered appropriate. In non-randomised comparisons, treated individuals may differ systematically from untreated individuals ([Austin 2011](#)); thus, an unbiased estimate of ATE cannot be obtained by comparing outcomes between the two post-hoc subgroups with nodal metastases used in MSLT-I ([MSLT-I: Morton 2014](#)). The semiparametric accelerated failure time mixture model used to compensate for lack of randomisation has been modelled and tested only on MSLT-I data and requires a number of assumptions that may not be fulfilled ([Altstein 2013](#)) (see the 'Risk of bias' section in the [Characteristics of included studies](#)

table). Nevertheless, Morton and colleagues reported an estimated ATE on distant metastasis-free survival of 0.73 in the post-hoc subgroup comparisons of participants with nodal metastasis ([MSLT-I: Morton 2014](#)). Although causality cannot be documented by this evidence (assuming that it is in the right direction, which would mean better distant metastasis-free survival in participants with nodal metastasis between the two treatment groups), it might be suggested that the higher rate of distant metastases as the site of first recurrence found in the baseline stratified and randomly allocated to SLNB or Observation groups in MSLT-I could be attributable to the subgroup of SLNB negative participants in the SLNB treatment group. To test this hypothesis, another post-hoc analysis of the MSLT-I data would be required. Such an analysis would aim with regard to nodal negative participants, to count those who develop nodal disease in both groups as losses. Although these results would still be observational in nature, they could provide some information on the possible existence of a higher rate of distant metastases in the subgroup of SLNB negative participants as compared with those in the observation group who did not experience nodal metastasis. Upon confirmation of such a finding, the possible role of removing the sentinel nodes (SLNB) thereby potentially reducing host immune response and favouring development of distant metastases could be discussed.

In other words removing nodal tissue when this is not actually needed (which is what is done in SLNB negative patients), leaves SLNB negative patients (who were not going to develop nodal disease anyway) with reduced regional immunity when compared to those Observation patients who also were not going to develop nodal disease. This advantage in regional immunity in the Observation patients could be the reason for them to have fewer distant metastasis. In simple terms: Local Disease (site of melanoma) -> Regional Disease (guardian lymph nodes) -> Distant Disease (remote organs, i.e. brain) which is how melanoma spreads. If following Wide Local Excision there is remaining disease then in those who were SLNB negative, there is no regional barrier (lymph nodes), thus melanoma will progress distantly but in those in the observation group, remaining disease will first stop at the regional barrier prior to metastasising distantly.

Higher rates of local, intransit recurrence following SLNB versus Wide Local Excision (WLE) were reported a decade ago ([Thomas 2004](#)). However, survival in individuals with melanoma aged younger than 30 years does not appear to be lower compared to the survival in individuals older than 30 years despite a higher rate of SLNB positivity in the younger patients ([Chagpar 2007](#)). In an attempt to rationalise this controversy, it has been proposed that a more generally capable immune system would remove small micrometastases before they manifest clinically ([Chao 2004](#); [Thomas 2004](#)). In [MSLT-I: Morton 2014](#), the rate of local and in-transit metastases as the site of first recurrence did not differ significantly between study groups (RR 1.23, 95% CI 0.85 to 1.77; [Analysis 1.15](#)). Although non-significant, it should be noted that the result is in the same direction as the results reported a decade ago ([Thomas 2004](#)).

[MSLT-I: Morton 2006 and 2014](#) both included a comparison between post-hoc groups with nodal metastasis: those among observation participants who developed clinical nodal disease and underwent delayed LND versus those among SLNB participants who were SLNB-positive and underwent immediate CLND. Another 31 SLNB participants developed clinical disease and were submitted to

LND in the SLNB group. We elected not to analyse these post-hoc subgroups as their selection may be taken as observational in nature (Higgins 2011, Section 9.6.6). In a case-control study with 381 participants who underwent SLNB, of whom 103 were positive, there were no recurrences or deaths were recorded in the subgroup of SLNB positive who had SLN metastatic deposits 0.2 mm or smaller (n=6 patients); these patients also had no additional positive non-sentinel lymph nodes (Francischetto 2010). The latter finding indicates that the prognosis of those 6 patients was similar to that of participants with negative SLNs (Francischetto 2010). This has been previously described as the prognostic false-positivity of SLNB (Thomas 2008b). Because in the MSLT-I, acceptable evidence of a nodal tumour was made, "even if cells were identified by immunohistochemical analysis alone and even if only one such cell was identified" (MSLT-I: Morton 2014), it could be such nodal nevocytes that are the underlying cause of this "prognostic false-positivity of SLNB". The latter effect has been reported as a possible confounder (or "latent" as reported in MSLT-I: Morton 2014), rendering the post-hoc comparison problematic (Thomas 2008b; Thomas 2009). This effect of prognostic false positivity has been debated on the occasion of the 10-year interim publication of MSLT-I: Morton 2014. Due to the MSLT study design, disease-free survival in the observation group ends when the patient develops a nodal metastasis even if lymphadenectomy is performed, whereas in the SLNB group the disease-free survival interval continues despite the finding of micrometastases identified by the SLNB (Sladden 2015). Thomas argued that the cumulative nodal metastatic curves are parallel from 8 to 10 years and suggested that this proves the presence and incidence of prognostic false positivity (Thomas 2014). The study authors however, in their reply state that "more than one fourth of the remaining minimal numerical difference between the curves evaporates during those 2 years" (Thompson 2014). In any case, because the curves may converge but to a limited degree, the fact remains that disease-free survival is bound to be different if disease is removed earlier in one group. One could even argue that disease-free survival should have not been among the outcomes of this review, because of this evident discrepancy. We still elected to report the disease-free survival outcome because it was pre-specified in our review protocol. See the 'Risk of bias' section in the [Characteristics of included studies](#) table.

Another issue with regard to the utility of SLNB would be the potential superiority of CLND over LND with regard to morbidity and survival. Results from the subgroup post-hoc analysis of the MSLT-I suggest such a survival and reduced morbidity benefit (MSLT-I: Morton 2014). However, a randomised study would be required to confirm or reject this hypothesis. This is the aim of the MSLT-II study, which randomised SLNB-positive participants to either observation (and LND upon relapse) or CLND. The study's primary endpoint is disease-specific survival and the completion date is 2020. If the hypothesis of MSLT-II is proved, then the SLNB procedure might be justifiably considered as standard practice because SLNB is a prerequisite to detect individuals eligible for CLND. The inclusion of SLNB-positive participants in MSLT-II requires the inclusion of approximately a fourfold higher number (MSLT-I; Thomas 2009) of participants proven to be SLNB-participants prior to screening for eligibility. Because a higher rate of distant metastases (at least as the site of first recurrence) cannot be confidently ruled out in this post-hoc subgroup of SLNB participants in MSLT-I compared with those in the observation group (see above), it might be prudent to further explore the possibility that the higher rate of distant metastases as the site

of first recurrence found between the groups in MSLT-I could be attributable to those SLNB-participants in the treatment group.

Finally, high-resolution ultrasound has been proposed as a measure to augment the efficacy of observation in cases where no suspicious lymph nodes are found by ultrasonography after WLE of the primary tumour. If individuals were assessed periodically by ultrasound of the regional lymph nodes, lymphadenectomy could be delayed until nodal recurrence has been detected (Thomas 2008b). It has been reported that this utility of ultrasound could have been used in participants in MSLT-I to document clinical metastases. This has been reported for the 946 participants of the Sydney Melanoma Unit, which was the study centre with the most participants involved in MSLT but it may also be the case for other study centres as noted by Thompson 2006. Participating sites were permitted to use their routine follow-up procedure, which could include nodal ultrasonography (MSLT-I: Morton 2014). This might have reduced the possible survival benefit of SLNB between the two treatment groups in MSLT-I (Thomas 2009).

Although most international guidelines suggest SLNB for localised primary cutaneous melanomas, the results of this review demonstrate the paucity of data on which this advice is based.

Overall completeness and applicability of evidence

Since only one trial was eligible, no meta-analyses could be undertaken. Further, there are limited RCT data assessing the efficacy of SLNB in the treatment of thin melanomas (less than 1.2 mm thick) and thick melanomas (3.5 mm or more thick). The MSLT-I reported on outcomes from 314 participants with thick melanomas (186 assigned to SLNB, 128 assigned to observation), which were included in this review. The MSLT-I does not satisfactorily handle melanomas in particular sites of the body (e.g. head and neck, distal extremities, hands (including fingers and subungual melanomas), and feet) that present site specific differences in terms of treatment and prognosis. More specifically, the total lack of available RCT data does not provide clinicians with any evidence-based information on the clinical management of head and neck melanomas in which lower survival rates have been reported (Callender 2011) and SLNB sensitivity and specificity have been reported to be inferior (Wong 2012).

Quality of the evidence

We assessed the quality of the evidence for this trial as low for the outcomes specified in the review protocol ([Summary of findings for the main comparison](#)). As indicated by our findings, there is no clear evidence at present to recommend that SLNB, followed by CLND, is a good means of improving overall or melanoma-specific survival. The quality of evidence has been downgraded by one level for all outcomes because evidence is limited to a single RCT. We have also further downgraded the evidence because we have rated the risk of bias as 'high' or 'unclear' for several components.

Because we have identified only one reported RCT that has examined SLNB safety and efficacy in individuals with melanoma, we were unable to perform any meta-analyses. This review has the limitation of solely depending on a single study to identify genuine variation in outcomes, which reduces the strength of our results. However, the number of participants identified through this systematic review is fairly large (2001 participants screened for inclusion in the safety analysis). Due to the statistical power

of the above-mentioned number of participants, which would be adequate to statistically significantly document some difference in outcomes, it can be assumed that if a true difference exists, then it would be relatively small. Of course we acknowledge that even such a small difference may be very important for a single individual (Sladden 2009).

Potential biases in the review process

There are certain limitations of this systematic review that need to be discussed. We contacted the trial authors querying the lack of data on overall survival which was the primary outcome of their important study. We also asked for ITT data for outcomes that were not available. The authors did not give us any new data; instead they stated "there are numerous additional analyses that have yet to be reported for the trial".

The rates of treatment complications and side effects are reported on an as-treated basis because we could not impute data for those participants who crossed over to the opposite group. However, we would not anticipate any change in the estimated effects of surgical morbidity in the nodal basin between the two treatment groups. For the survival analyses, we used the reported HRs from the per-protocol analysis to estimate the number of expected events in each group for participants with thick melanomas. For participants with intermediate-thickness melanomas HRs were available on an ITT and per-protocol basis and were identical. It is unlikely that this would be different for participants with thick melanomas. We assumed that all missing participants did not experience the event in the presented ITT analyses. Sensitivity analyses showed that in all cases changes to HRs and risk ratios were minimal, mostly in the second decimal digit, whereas statistical significance was in no case altered. We therefore believe that our decision to assume that all missing participants did not experience the event cannot have changed the estimated effects. Using this approach may have rendered our analysis even more susceptible to type II error, and thus more conservative.

Agreements and disagreements with other studies or reviews

No systematic reviews including only RCTs examining SLNB for cutaneous melanomas have previously been published. In contrast, a number of systematic and narrative reviews focusing on SLNB and including observational and non-randomised clinical studies have been published, the most complete being published in 2011 (Valsecchi 2011) on which the current ASCO and SSO joint guideline is based (Wong 2012). However, this review was aimed at measures of test performance, namely the proportion of nodes successfully mapped (PSM), false-negative rate (FNR), post-test probability negative (PTPN), and predictive value positive (PVP) using same nodal basin recurrence as the outcome of interest. The probability of distant or any recurrence in individuals with a negative SLNB averaged 4.4% or 10.5%, respectively, while the probability of distant or any recurrence, inclusive of CLND in individuals with a tumour-positive SLNB, averaged 21% or 36%, respectively. Of note, no outcomes with regard to overall, disease-specific or disease-free survival were examined in this meta-analysis. The expert-panel guideline concluded that for individuals with intermediate-thickness cutaneous melanomas (Breslow thickness 1 to 4 mm) of any anatomical site, SLNB was recommended because it provides accurate staging, with high estimates for PSM and acceptable estimates for FNR, PTPN, and

PVP. With regard to thicker melanomas, although few studies were identified, the panel concluded that "use of SLN biopsy in this population may be recommended for staging purposes and to facilitate regional disease control" (Wong 2012). In thin melanomas, the panel concluded that there was insufficient evidence to support the routine use of SLNB (Wong 2012). These recommendations were based solely on the accuracy of SLNB as a diagnostic modality and not a therapeutic one.

We performed our analyses differently to those of Valsecchi 2011. We focused on survival outcomes and the safety of the SLNB intervention compared with observation.

AUTHORS' CONCLUSIONS

Implications for practice

Neither the MSLT-I, nor our review, have shown a statistically significant difference in disease-specific survival between the groups of participants with localised primary melanoma allocated to undergo observation or SLNB. Current RCT evidence cannot confirm the potential therapeutic benefit of SLNB. Despite this fact, a number of expert international committees have published relatively consistent guidelines for the treatment of individuals with melanoma that recommend SLNB for those with intermediate-thickness melanomas. "It is important to determine whether the absence of any statistically significant overall survival difference in randomised studies (or meta-analyses thereof) conducted to date preclude the possibility that there may actually be a real but very small difference in survival" (Sladden 2009), also for individuals treated with SLNB (Kretschmer 2006). Of note, there is little likelihood of worsening disease-specific survival by performing SLNB.

It may be important to inform each individual with melanoma about the additional low morbidity following SLNB, the possibility of a slight increase in the rate of distant metastases as the site of first recurrence, and the clear benefit with regard to the rate of nodal recurrences as the site of first recurrence and in disease-free survival. In those individuals who decline SLNB, close observation supplemented by ultrasound may be a non-inferior modality.

Implications for research

One could assume that observation would probably not provide better survival outcomes than SLNB; hence, the aim of a future review about the efficacy of SLNB in melanoma could be to examine the evidence available regarding the equivalence or non-inferiority of observation compared with SLNB. In the latter case, the research hypothesis would be "is observation not associated with lower survival rates than SLNB?" rather than superiority of treatment with SLNB. Because the aim of this review was to quantify the uncertainty around the benefits and risks of each therapeutic modality so that people can choose - with the support of their doctors - the appropriate decision for them, it is not focused on non-inferiority. The single RCT included in this review has not been reported as a formal non-inferiority or equivalence study.

Further randomised trials which are properly designed and adequately powered are needed to fully investigate the therapeutic potential of SLNB in individuals with melanoma, and to determine whether observation alone is associated with worse survival outcomes. Currently, it appears that observation produces similar survival outcomes to SLNB. We agree with Sladden 2009, that a

large study would be the only way to find a difference between these two methods, because "only a very small survival deficit (if any) would be acceptable".

Primary outcomes of future trials should preferably focus on overall survival and further report on numbers of events. Because the final MSLT-I analysis did not report on overall survival, such an analysis is warranted. Future study authors need to use the term 'recurrence' consistently, to allow for the comparison of results. In MSLT-I, reporting of distant metastasis-free survival on an ITT basis and reporting of disease-free survival (excluding nodal disease from the endpoint, as proposed by the NCI, to eliminate lead-time bias) along with further exploring the probability of a higher distant-metastasis rate (at least as the site of first recurrence) for SLNB participants in a post-hoc subgroup analysis, would be important to negate any safety concerns for those individuals who had been screened with SLNB and proved to be SLNB-negative.

In future trials, as well as including and assessing quality-of-life outcomes, it might be useful if detailed outcome data were provided for each participant. From these, the impact of Breslow thickness and other information about the spread of the disease could be used to undertake individual patient data meta-analyses to learn more about the best way to manage this disease.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

MSLT-I

Methods	Open-label, interventional, randomised, parallel-assignment controlled efficacy study
Participants	<p>Adults with melanoma</p> <p>Inclusion criteria:</p> <p>The participant consented to be in the study.</p> <p>The participant must have had invasive melanoma with: 1) Clark level III and Breslow thickness greater than or equal to 1.00 mm; or 2) Clark level IV or V with any Breslow thickness. A confirmation of diagnosis and thickness must have been made by the institutional pathologist.</p> <p>The primary cutaneous melanoma site must have been on the head, neck, trunk, extremity, scalp, palm of the hand, sole of the foot, or subungual skin.</p> <p>The participant's biopsy must have been completed no more than 10 weeks before the initial visit to the clinic. (Surgery must have been scheduled within three months of the biopsy.)</p> <p>The participant must have been between 18 and 75 years old.</p> <p>The participant must have had a life expectancy of at least 10 years from the time of diagnosis, excluding the diagnosis of melanoma.</p> <p>Exclusion criteria:</p> <p>The participant had had a prior wide excision of the primary with a diameter of excision greater than or equal to 3.0 cm and the shortest margin from the tumour edge to the excision edge had been measured by a pathologist to have been greater than or equal to 1.5 cm; or the participant had an elliptical excision and the margin beyond the tumour edge had been greater than or equal to 1.5 cm at the narrowest margin.</p> <p>The primary cutaneous melanoma involved the eye, ear, mucous membranes.</p> <p>The participant had clinical evidence of satellite lesions, intransit, regional nodal or distant metastases.</p> <p>The participant had a second primary invasive melanoma.</p> <p>The participant had had any type of solid tumour or haematological malignancy during the past 5 years. Exceptions were if the participant had been treated for T1 lesions (e.g. squamous cell carcinoma of the skin, basal cell carcinoma or in situ carcinoma of the uterine cervix) during the past 5 years, but had not received treatment within the last 6 months.</p> <p>The participant had had prior skin grafts, tissue transfers or flaps, or lymph node dissections that may alter the lymphatic drainage pattern from a primary cutaneous melanoma to the adjacent regional lymph node basins.</p> <p>The participant had had previous chemotherapy, immunotherapy or radiation therapy.</p>

MSLT-I (Continued)

The participant had had an organ transplantation and was receiving immunosuppressive agents as a result of the transplantation.
The participant had taken oral or parenteral steroids or immunosuppressive drugs within the past 6 months.
The participant had any known primary or secondary immune deficiencies.
The participant had another medical condition that would affect life expectancy.
The participant was pregnant.
Evidence that the participant could not undergo selective lymph node dissection for any reason.

Interventions	Wide excision alone (661 participants randomised)/wide excision and SLNB and/or CLND if SLNB-positive (1000 participants randomised)
Outcomes	Overall survival (primary); disease-free survival; incidence, timing, and anatomic distribution of distant metastases; morbidity of procedures; significance of TA90 levels; incidence of sentinel node metastases (biopsy) vs clinical metastases (observation); accuracy of lymphatic mapping
Notes	The MSLT-I study was funded by the National Cancer Institute, National Institutes of Health, and the Australia and New Zealand Melanoma Trials Group; ClinicalTrials.gov number, NCT00275496.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out centrally, in a stratified fashion, in random permuted blocks of four, six, and eight participants. Stratification was for Breslow thickness (1.20 to 1.79 mm vs 1.80 to 3.50 mm vs > 3.5 mm) and the primary site of the melanoma (group or leg vs other site).
Allocation concealment (selection bias)	Unclear risk	This is not reported in the relevant publications.
Blinding (performance bias and detection bias) All outcomes	High risk	Because of the open-label design and since participating centres were permitted to use their routine follow-up procedure, which could include periodic positron-emission tomographic and computed tomographic scanning, nodal ultrasonography, and testing for melanoma markers such as S-100 and lactate dehydrogenase, a similar amount of attention, ancillary treatment and diagnostic investigations cannot be warranted for every participant.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the intervention (SLNB) this was an open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Detection bias was not likely due to the standardised follow up for all included participants.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>In the group of participants with intermediate-thickness melanomas, people were excluded due to not meeting eligibility criteria (n = 1 in the SLNB group), for opting for the other group procedure (n = 36 in the SLNB group and n = 22 in the observation group), for withdrawing prior to treatment (n = 8 in the SLNB group and n = 11 in the observation group) and those lost to follow up (n = 120 in the SLNB group and n = 68 in the observation group).</p> <p>In the group of participants with thick melanomas, people were excluded due to not meeting eligibility criteria (n = 1 in the SLNB group), for opting for the other group procedure (n = 12 in the SLNB group and n = 9 in the observation group), for withdrawing prior to treatment (n = 2 in the observation group) and those lost to follow up (n = 18 in the SLNB group and n = 9 in the observation group). Different loss of subjects appears to be unlikely from these num-</p>

Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma (Review)

MSLT-I (Continued)

		<p>bers. However the exclusion of participants with thin melanomas despite outcome data being available did not allow for a low risk assessment. In the safety analyses, although all participants with thin, intermediate and thick melanomas were included, analysis was based on treatment actually received.</p>
Selective reporting (reporting bias)	High risk	<p>Overall survival (OS) was NOT reported in the 2006 <i>New England Journal of Medicine (NEJM)</i> paper. For intermediate-thickness melanomas, 122 CLND (CLND or LND for those false negative) participants were compared with 78 LND participants. In the 2014 <i>NEJM</i> paper (final trial analysis), OS is still not reported. The post-hoc comparison of 122 with 87 (at 10 years) participants is reported and commented on. An average treatment effect is also modelled for this post-hoc analyses, based on a custom model which has been developed based on the results of the 5-year interim analysis (Altstein 2013). In the 2006 <i>NEJM</i> paper, the authors reported this comparison to be prespecified, but this dose not appear anywhere in the NCT study protocol. Selection of these subgroups cannot be taken as random. Rather, it may be taken as observational in nature (Higgins 2011, Section 9.6.6 Interpretation of subgroup analyses and meta-regressions).</p>
Other bias	High risk	<p>Use of ultrasound to document clinical metastases. This has been reported for the 946 participants from the Sydney Melanoma Unit, but it may also be the case for other study centres as the authors noted (Thompson 2006). This might have reduced the survival benefit of SLNB (Thomas 2009).</p> <p>Disease-free survival calculation on nodal disease may not have been appropriate as the SLNB group would have few (or if CLND performed, most) regional nodes removed. It has been reported and suggested by the NCI that disease-free survival ought to be calculated on a distant- rather than a nodal-metastasis basis (Thomas 2009)</p>

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Hauschild 2010	635 participants received SLNB versus 197 who did not, but that was not in a random allocation scheme and subgroups differed statistically in terms of age and tumour thickness.
Korovin 2013	SLNB not followed by CLND.
McMasters 2010	All enrolled participants underwent wide local excision of the primary melanoma and sentinel node biopsy.
Reintgen 2004	All participants in the study received SLNB.

DATA AND ANALYSES

Comparison 1. SLNB versus Observation for melanoma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival PP	1	1638	Hazard Ratio (95% CI)	0.98 [0.81, 1.18]
1.1 Intermediate Melanomas	1	1327	Hazard Ratio (95% CI)	0.91 [0.72, 1.15]
1.2 Thick Melanomas	1	311	Hazard Ratio (95% CI)	1.14 [0.81, 1.60]
2 Overall Survival ITT	1	1661	Hazard Ratio (95% CI)	0.99 [0.82, 1.19]
2.1 Intermediate Melanomas	1	1347	Hazard Ratio (95% CI)	0.92 [0.73, 1.16]
2.2 Thick Melanomas	1	314	Hazard Ratio (95% CI)	1.15 [0.82, 1.61]
3 Overall Survival Best Case ITT	1	1661	Hazard Ratio (95% CI)	0.68 [0.57, 0.81]
3.1 Intermediate Melanomas	1	1347	Hazard Ratio (95% CI)	0.59 [0.48, 0.73]
3.2 Thick Melanomas	1	314	Hazard Ratio (95% CI)	0.98 [0.71, 1.36]
4 Overall Survival Worst Case ITT	1	1661	Hazard Ratio (95% CI)	1.46 [1.24, 1.73]
4.1 Intermediate Melanomas	1	1347	Hazard Ratio (95% CI)	1.50 [1.23, 1.82]
4.2 Thick Melanomas	1	314	Hazard Ratio (95% CI)	1.37 [1.00, 1.89]
5 Surgical Morbidity (Within 30 d) Related to Wide Excision of the Primary Site in Patients Assigned to the 2 Treatment Groups of MSLT-I	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Surgical Morbidity (Within 30 d): Nodal Basin Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Surgical Morbidity (Within 30 d): Regional Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Surgical Morbidity (Within 30 d): Systemic Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Surgical Morbidity (Within 30 d) Related to the Regional Nodal Basin in Patients Assigned to the 2 Treatment Groups of MSLT-I	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Disease-specific survival	1	1661	Hazard Ratio (95% CI)	0.92 [0.74, 1.14]
10.1 Intermediate Melanomas	1	1347	Hazard Ratio (95% CI)	0.84 [0.65, 1.09]
10.2 Thick Melanomas	1	314	Hazard Ratio (95% CI)	1.12 [0.77, 1.64]
11 Disease-free survival	1	1661	Hazard Ratio (95% CI)	0.75 [0.63, 0.89]
11.1 Intermediate Melanomas	1	1347	Hazard Ratio (95% CI)	0.77 [0.63, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Thick Melanomas	1	314	Hazard Ratio (95% CI)	0.70 [0.50, 0.97]
12 Rate of pathologically confirmed loco-regional recurrence as site of first recurrence	1	1661	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.45, 0.69]
12.1 Intermediate Melanomas	1	1347	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.44, 0.74]
12.2 Thick Melanomas	1	314	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.36, 0.75]
13 Rate of development of distant metastases as site of first recurrence	1	1661	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.03, 1.72]
13.1 Intermediate Melanomas	1	1347	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.92, 1.70]
13.2 Thick Melanomas	1	314	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.95, 2.54]
14 Rate of development of local, In-transit and distant recurrences as site of first recurrence	1	1661	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.06, 1.58]
14.1 Intermediate Melanomas	1	1347	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.95, 1.52]
14.2 Thick Melanomas	1	314	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.09, 2.34]
15 Rate of development of local and In-transit recurrences as site of first recurrence	1	1661	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.85, 1.77]
15.1 Intermediate Melanomas	1	1347	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
15.2 Thick Melanomas	1	314	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.80, 3.53]

Analysis 1.1. Comparison 1 SLNB versus Observation for melanoma, Outcome 1 Overall Survival PP.

Study or subgroup	SLNB n/N	Observation n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
1.1.1 Intermediate Melanomas					
MSLT-I	180/805	128/522		68.69%	0.91[0.72,1.15]
Subtotal (95% CI)	805	522		68.69%	0.91[0.72,1.15]
Total events: 180 (SLNB), 128 (Observation)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.8(P=0.42)					
<div> <div>SLNB</div> <div>0.010.1110100</div> <div>Observation</div> </div>

Analysis 1.2. Comparison 1 SLNB versus Observation for melanoma, Outcome 2 Overall Survival ITT.

Analysis 1.3. Comparison 1 SLNB versus Observation for melanoma, Outcome 3 Overall Survival Best Case ITT.

Analysis 1.4. Comparison 1 SLNB versus Observation for melanoma, Outcome 4 Overall Survival Worst Case ITT.

Analysis 1.5. Comparison 1 SLNB versus Observation for melanoma, Outcome 5 Surgical Morbidity (Within 30 d) Related to Wide Excision of the Primary Site in Patients Assigned to the 2 Treatment Groups of MSLT-I.

Analysis 1.6. Comparison 1 SLNB versus Observation for melanoma, Outcome 6 Surgical Morbidity (Within 30 d): Nodal Basin Complications.

Analysis 1.7. Comparison 1 SLNB versus Observation for melanoma, Outcome 7 Surgical Morbidity (Within 30 d): Regional Complications.

Analysis 1.8. Comparison 1 SLNB versus Observation for melanoma, Outcome 8 Surgical Morbidity (Within 30 d): Systemic Complications.

Analysis 1.9. Comparison 1 SLNB versus Observation for melanoma, Outcome 9 Surgical Morbidity (Within 30 d) Related to the Regional Nodal Basin in Patients Assigned to the 2 Treatment Groups of MSLT-I.

Analysis 1.10. Comparison 1 SLNB versus Observation for melanoma, Outcome 10 Disease-specific survival.

Analysis 1.11. Comparison 1 SLNB versus Observation for melanoma, Outcome 11 Disease-free survival.

Analysis 1.12. Comparison 1 SLNB versus Observation for melanoma, Outcome 12 Rate of pathologically confirmed locoregional recurrence as site of first recurrence.

Analysis 1.13. Comparison 1 SLNB versus Observation for melanoma, Outcome 13 Rate of development of distant metastases as site of first recurrence.

Analysis 1.14. Comparison 1 SLNB versus Observation for melanoma, Outcome 14 Rate of development of local, In-transit and distant recurrences as site of first recurrence.

Analysis 1.15. Comparison 1 SLNB versus Observation for melanoma, Outcome 15 Rate of development of local and In-transit recurrences as site of first recurrence.

APPENDICES

Appendix 1. Skin Group Specialised Register search strategy

(lymphadenectom* or (lymph and node* and excision) or (lymph and node* and dissection)) and ((sentinel and lymph and node* and biops*) or (sentinel node procedure)) and melano*

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Sentinel Lymph Node Biopsy] explode all trees
#2 sentinel and lymph and node* and biops*
#3 sentinel node procedure
#4 #1 or #2 or #3
#5 MeSH descriptor: [Lymph Node Excision] explode all trees
#6 lymph and node* and dissection
#7 lymph and node* and excision
#8 lymphadenectom*
#9 #5 or #6 or #7 or #8
#10 MeSH descriptor: [Melanoma] explode all trees
#11 melano*
#12 #10 or #11
#13 #4 and #9 and #12

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Sentinel Lymph Node Biopsy/
2. (sentinel and lymph and node\$ and biops\$).ti,ab.
3. sentinel node procedure.ti,ab.
4. 1 or 2 or 3
5. exp Lymph Node Excision/
6. (lymph and node\$ and dissection).ti,ab.
7. (lymph and node\$ and excision).ti,ab.
8. lymphadenectom\$.ti,ab.
9. 5 or 6 or 7 or 8
10. exp Melanoma/
11. melano\$.ti,ab.
12. 10 or 11
13. randomised controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 4 and 9 and 12 and 22

Appendix 4. EMBASE (Ovid) search strategy

1. exp sentinel lymph node biopsy/
2. (sentinel and lymph and node\$ and biops\$).ti,ab.
3. sentinel node procedure.ti,ab.
4. 1 or 2 or 3
5. exp lymph node dissection/
6. (lymph and node\$ and dissection).ti,ab.
7. (lymph and node\$ and excision).ti,ab.
8. lymphadenectom\$.ti,ab.
9. 5 or 6 or 7 or 8
10. exp melanoma/ or exp melanoma skin cancer/

11. melano\$.ti,ab.
12. 10 or 11
13. crossover procedure.sh.
14. double-blind procedure.sh.
15. single-blind procedure.sh.
16. (crossover\$ or cross over\$).tw.
17. placebo\$.tw.
18. (doubl\$ adj blind\$).tw.
19. allocat\$.tw.
20. trial.ti.
21. randomised controlled trial.sh.
22. random\$.tw.
23. or/13-22
24. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
25. human/ or normal human/
26. 24 and 25
27. 24 not 26
28. 23 not 27
29. 4 and 9 and 12 and 28

Appendix 5. LILACS search strategy

(lymphadenectom\$ or (lymph and node\$ and excision) or (lymph and node\$ and dissection)) and ((sentinel and lymph and node\$ and biops\$) or (sentinel node procedure)) and melano\$

Appendix 6. African Index Medicus, IndMED of India, Index Medicus for the South-East Asia Region (IMSEAR), ISI Web of Science Conference Proceedings and trials registers search strategy

"sentinel lymph node" and "melanoma"

FEEDBACK

Conclusion on Survival Advantage, 31 July 2017

Summary

The comment was that authors came to the wrong conclusion in this review. Based on the data in MSLT-I, there was no real survival advantage of any kind for SLNB followed by complete lymph node dissection compared to wide excision and observation. This result is abundantly clear with the publication of MSLT-II where SLNB and immediate complete lymph node dissection did not even improve survival for patients with positive sentinel nodes. The review should be amended quickly so readers stop advocating SLNB and CLND.

The authors agreed that there was no real survival advantage of any kind and explain in further detail.

Reply

The comment claims that we report some survival advantage for SLNB followed by CLND compared to WLO followed by observation. Our review's primary endpoint was overall survival. No advantage was found. Second primary endpoint was short term morbidity. Obviously CLND scored worse. Secondary outcomes were disease specific survival, in which we report "no statistically significant difference in disease-specific survival between study groups at 10 years".

ONLY the summary estimate for disease free survival was better for CLND. But when we split it to locoregional or distant failure, locoregional favored SLNB + CLND and distant favored WLO + observation.

So basically, our review is 100% agreeable to the comment received that there was no real survival advantage of any kind. The only difference was in the time to develop recurrence and the site to first develop it. [I feel that the commenter might be confused between disease specific and disease free survival which are of course entirely different things].

The time had come to update the review but we were waiting for the MSLT-II publication released this summer. We will amend our review to include the latter study. However, I need to point out that the MSLT-II randomized patients with sentinel-node metastases to immediate completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group), which is a different group and modality for MSLT-I. So the main findings of the current review are not expected to be changed with regard to the utility of SLNB. [Basically MSLT-II design arbitrarily suggests SLNB for everybody. Then the study examines what to do if SLNB is positive. I feel the commenter has not clearly perceived this too.]

Contributors

Michael Bigby, who made the comment. Our Feedback Editor, Urbà González, and the lead author Athanassios Kyrgidis who replied.

WHAT'S NEW

Date	Event	Description
16 October 2017	Feedback has been incorporated	Authors responded to feedback referring to the conclusion of the review. Please see Feedback section for details.

HISTORY

Protocol first published: Issue 1, 2013

Review first published: Issue 5, 2015

Date	Event	Description
28 October 2016	Amended	A search of MEDLINE, PubMed, and Embase in October 2016 found only one relevant study, which our Co-ordinating Editor and the lead author decided did not merit an update at this time as it supports the conclusions of the current review. Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.
13 October 2015	Amended	Author information (affiliation) updated
5 August 2015	Amended	Changes in results of analyses without a change of conclusions: addition of effect estimates for primary outcome

CONTRIBUTIONS OF AUTHORS

AK was the contact person with the editorial base.

AK co-ordinated the contributions from the co-authors and wrote the final draft of the protocol and the review.

SM, TT, and AK worked on the methods sections.

SM, AS, ZA, AL, TT, and AK drafted the clinical sections of the background and responded to the clinical comments of the referees.

SM, AS, ZA, TT, and AK responded to the methodology and statistics comments of the referees.

SM, TT, and AK contributed to writing the protocol.

PP was the consumer co-author and checked the protocol for readability and clarity. He also ensured that the outcomes are relevant to consumers.

AK and TT screened papers against eligibility criteria.

AK and TT obtained data on ongoing and unpublished studies.

AK, TT, AL, ZA, AS, and SM appraised the quality of papers.

AK, TT, AL, ZA, AS, and SM extracted data for the review and sought additional information about papers.

AK and TT entered data into RevMan.

AK, TT, and SM analysed and interpreted data.

AK, TT, and SM worked on the methods sections.

AK, TT, SM, AL, ZA, and AS drafted the clinical sections of the background and responded to the clinical comments of the referees.

AK is the guarantor of the update.

Disclaimer

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DECLARATIONS OF INTEREST

Athanassios Kyrgidis: nothing to declare

Thrasivoulos Tzellos: nothing to declare

Simone Mocellin: nothing to declare

Zoe Apalla: nothing to declare

Aimilios Lallas: nothing to declare

Pierluigi Pilati: nothing to declare

Alexander Stratigos: nothing to declare

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Internal sources

- Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece.

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- Arcispedale Santa Maria Nuova, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Reggio Emilia, Italy.

Provided online literature access to full text articles.

External sources

- The National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of the Cochrane Skin Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the final drafting and writing of the manuscript, the team uniformly agreed to change the title of the protocol (Sentinel lymph node biopsy followed by lymph node dissection for early cutaneous melanoma) to 'Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma'. Because we included thick melanomas in the analyses, the team felt that it may not be appropriate to characterise 'early' as a non-metastatic stage IIc melanoma (some may have possibly been included in the MSLT-I trial). This is a wording issue rather than an actual change, because in the protocol we had defined "early-stage melanoma" as "confined to the primary cutaneous site", therefore making all individuals with stage I and stage II melanoma eligible for inclusion in the review.

With regard to the timeframe of recording outcome rates, the long-term time point has been changed from 5 years to 10 years, because of the publication of the 10-year analysis of the MSLT-I.

NOTES

A search of MEDLINE, PubMed, and Embase in October 2016 found only one relevant study, which our Co-ordinating Editor and the lead author decided did not merit an update at this time, as it supports the conclusions of the current review. Thus, an update of this review has been postponed. Our Information Specialist will run a new search in October 2017 to re-assess whether an update is needed.

INDEX TERMS

Medical Subject Headings (MeSH)

*Lymph Node Excision; *Sentinel Lymph Node Biopsy; Disease-Free Survival; Melanoma [mortality] [*pathology] [*surgery]; Randomized Controlled Trials as Topic; Skin Neoplasms [mortality] [*pathology] [*surgery]; Survival Rate; Watchful Waiting

MeSH check words

Humans