



Review

Complications of sentinel lymph node biopsy for melanoma – A systematic review of the literature

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Abstract

Purpose: The complications reported after sentinel lymph node biopsy (SLNB) for melanoma is highly variable in the worldwide literature; the overall complication rate varies between 1.8% and 29.9%. With heterogeneous reporting of morbidity data, no ‘average’ complication rates of this procedure have been reported. This systematic review aims to determine the complications rates associated with SLNB.

Methods: A systematic review of English-language literature from 2000 to 2015, which reported morbidity information about SLNB for melanoma, was performed. The methodological quality of the included studies was performed using the methodological index for non-randomised studies (MINORS) instrument and Detsky score. Pooled proportions of specific post-operative complications were constructed using a random effects statistical model, and subgroups including lymph node basin and continent of origin of the study were compared.

Results: After application of inclusion and exclusion criteria, 21 articles progressed to the final analysis. 9047 patients were included. The overall complication rate was 11.3% (95% CI: 8.1–15.0). The incidence of infection was 2.9% (95% CI 1.5–4.6); seroma 5.1% (95% CI: 2.5–8.6); haematoma 0.5% (95% CI: 0.3–0.9) lymphoedema 1.3% (95% CI: 0.5–2.6) and nerve injury 0.3% (95% CI: 0.1–0.6). There was no statistically significant difference in morbidity between the sites of SLNB or between continents.

Discussion: This study provides information about the incidence of complications after SLNB. It can be used to counsel patients about the procedure and it sets a benchmark against which surgeons can audit their practice.

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Keywords: Complications; Sentinel; Lymph node; Biopsy; Melanoma; Infection; Seroma; Haematoma; Lymphoedema

Introduction

The incidence of melanoma across the developed world is increasing; in England, the incidence has almost doubled from 6000 cases in 2000 to 11,000 cases in 2011.¹ The 5-year disease specific survival rate for localised melanoma is 80%² and for patients with regional (stage III) and distant (stage IV) disease it is 39% and 33% respectively.³ Sentinel lymph node biopsy (SLNB) is a minimally invasive

technique that identifies patients who have occult lymph node micrometastasis.⁴ Research shows that regional lymph node status is the most powerful predictor of survival,⁵ and since 2009 the American Joint Committee on Cancer (AJCC) classification for melanoma has incorporated it into the staging system.³ Since SLNB with dynamic lymph node mapping was introduced in 1992, it is considered the gold standard of staging for melanoma.^{6,7}

The practice of SLNB has high sensitivity and specificity for diagnosing subclinical regional lymph node involvement and the sentinel lymph node can be identified in 95% of patients. The British Association of Dermatologists recommends that SLNB be carried out in patients with a melanoma of ≥ 1 mm thickness,⁴ of whom 20% will have

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lymph node micrometastasis.⁶ However, it is worth noting, that studies have shown 5% of patients with melanoma of thicknesses 0.5 mm or less will also have micrometastasis.⁴

With SLNB being a well-established investigation, there is huge variation in the reporting of early post-operative morbidity. The overall complication rates range from 1.8%⁸ to 29.9%,⁹ with infection rates ranging from 0.3%¹⁰ to 19.0%.¹¹ Many of the studies presenting morbidity data are small in scale and are retrospective in design, with paucity of high quality evidence available. Although considered a relatively safe procedure with little reported morbidity by a number of studies,^{8,10,12–15} there is no overall ‘average’ complication rates with which we can use to counsel patients prior to the procedure. The aim of this study is to pool the outcomes from international literature, such that the worldwide incidence of specific complications for SLNB can be reported.

Materials and methods

Data sources

A systematic literature review of publications in English of the following electronic databases was conducted: Cochrane Database of Systematic Reviews, MEDLINE and EMBASE. The following keywords were used: (complications) AND (sentinel) AND (lymph node) AND (biopsy) AND (melanoma). The publication date range for studies was from 01/01/2000 to 31/12/2015.

Study selection

Two researchers independently conducted the literature search. Study eligibility was defined using the population, intervention, comparator, outcome, and study design approach (PICOS),¹⁶ which is summarised with the inclusion and exclusion criteria in Table 1. Articles were included if a subgroup of patients fulfilling the inclusion criteria could be extracted from the reported cohort (e.g. complications of SLNB extracted from a mixed cohort of SLNB and wide excision). If SLNB data was not extractable, or incomplete from a mixed cohort, it was excluded. In the initial literature search, abstracts were excluded if they failed to mention morbidity; we included abstracts that contained numbers or percentage of reported complications, or abstracts that alluded to the reporting of morbidity data. In order to minimise inclusion of studies at high risk of selection bias, papers were excluded if the study arms contained fewer than 100 patients.

According to the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),¹⁶ our study selection was performed through three levels of screening. Initially, title screening included studies with the following word combinations: 1) SLNB and melanoma; 2) sentinel lymph node, melanoma, and morbidity or complications; 3) sentinel lymphadenectomy and melanoma. Studies were excluded if these phrases were omitted, or if the study title stated the number of participants were fewer than 100. In the second level of screening, abstracts were

Table 1

Inclusion and exclusion criteria applied to the screened articles and data selected for extraction.

| | Inclusion criteria | Exclusion criteria | Data extracted |
|--------------|---|--|--|
| Population | Patients undergoing SLNB for melanoma. Patients with any type of primary melanoma. Any anatomical site or lymph node basin. Human patients of all ages and both sexes. | Patients undergoing SLNB for other malignancies. Non-melanoma skin cancer or extra-cutaneous malignancy. Non-human or experimental studies. | Patients (n). Site of primary melanoma and/or lymph node basin. Males (n); females (n); age at operation. |
| Intervention | SLNB for melanoma. Randomized and non-randomized studies; Non-comparative studies; Case series. English language literature. | Complications reported together with wide excision or complete lymphadenectomy. Single case reports; Review articles. Primary language other than English. | Surgical technique; SLNB extraction rate; Number of lymph node basins. Year of publication; continent of origin of population; type of study; years of study. |
| Comparator | Study cohort of >100 patients in SLNB arm. | Study cohort of <100 patients in SLNB arm. | Comparison group. |
| Outcome | All reported complications. | No complication numbers or percentages reported. Morbidity data presented in conjunction with another procedure. | Overall complications (n); Specific complications (infection, haematoma, etc.). |
| Study design | Any clinical study design (randomised, or non-randomised; comparative or non-comparative). | Non-clinical study; meta-analyses. | Study design; method of randomisation; year of study; length of follow up. |

reviewed according to our inclusion and exclusion criteria. The papers that proceeded to the third level of screening were read in their entirety and screened according to the same inclusion and exclusion criteria. Studies were only included if they succeeded all levels of screening. With the consensus of all authors that the included studies fulfilled the inclusion and exclusion criteria, the finalised list of articles were agreed upon.

Assessment of methodological quality

The methodological quality of the included non-randomised studies was performed using the methodological index for non-randomised studies (MINORS) instrument.¹⁷ Non-comparative and comparative studies were given a score out of 16 and 24 respectively. The included RCTs were assessed according to the Detsky score, the maximum result of which is 20.¹⁸ Consistent with other research, the studies that were assigned a score of >75% were considered high quality.^{19,20}

Data extraction and statistical analysis

A summary of the extracted data, recorded using Microsoft Excel (Redmond, WA, USA), is presented in Table 1. A kappa statistic was calculated to provide an estimate of agreement between reviewers with regard to the final list of articles reviewed. We performed multiple analyses to pool proportions in each dataset corresponding to the continent of origin of the study and lymph node basin. Prior to the analysis, we tested the significance of heterogeneity between studies using the Cochran Q test.²¹ These tests indicated the presence of heterogeneity, hence random effects models were used throughout. All statistical models were produced and presented using Stats Direct (StatsDirect Ltd, Cheshire, UK). In order to make comparisons between subgroups, the pooled values, and confidence intervals, from the models were transformed using the Freeman-Tukey double arcsine method.^{22,23} The resulting values were converted into means and standard errors, which were compared by t-test. The threshold considered for statistical significance was $p < 0.05$.

Results

Study selection and assessment of methodological quality

The literature search yielded 991 articles; after removal of duplicates, and application of inclusion and exclusion criteria, 29 articles progressed to full text screening. Ultimately, 21 articles were included in the final analysis^{8–15,24–37} (kappa = 0.9; Fig. 1). Of the 21 papers, there was one RCT and 20 non-randomized studies, which included one comparative and 19 non-comparative studies. The RCT scored ten on the Detsky score and was not

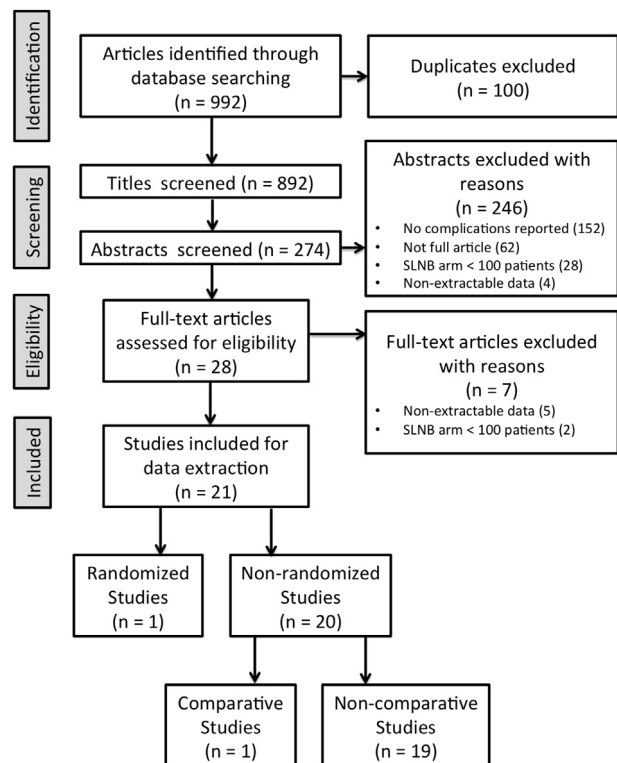


Figure 1. Flow diagram depicting the search strategy for inclusion of articles into the systematic review.

considered high quality. The mean MINORS score for non-comparative studies was 7.8, with two studies considered as high quality. The MINORS score for the comparative study was 14, which was not considered high quality (Appendix 1).

Data extraction

A total of 9047 patients were included from the 21 selected studies. With regards to continent of origin, 14 of the studies were located in Europe (n = 4087 patients), three were from America (n = 2856 patients), two were from Australasia (n = 917 patients), one was from Asia (n = 250 patients) and there was one multi-centre international study (n = 937 patients) (Fig. 2).

The average age of patients at time of SLNB was presented in 17 studies and age at melanoma diagnosis was presented in two studies. There was no predominance of average modality (median, mean or range) presented for average age. Some studies omitted which modality they have used and just refer to their values as an ‘average’. Therefore, no valid comparison or conclusions can be made regarding the age of the patients and complication rates.

The location of the primary melanoma was recorded in 19 of the 21 studies. The most common site of primary melanoma was on the extremities (n = 4229 melanomas); 15 papers reported the number of melanomas separately on

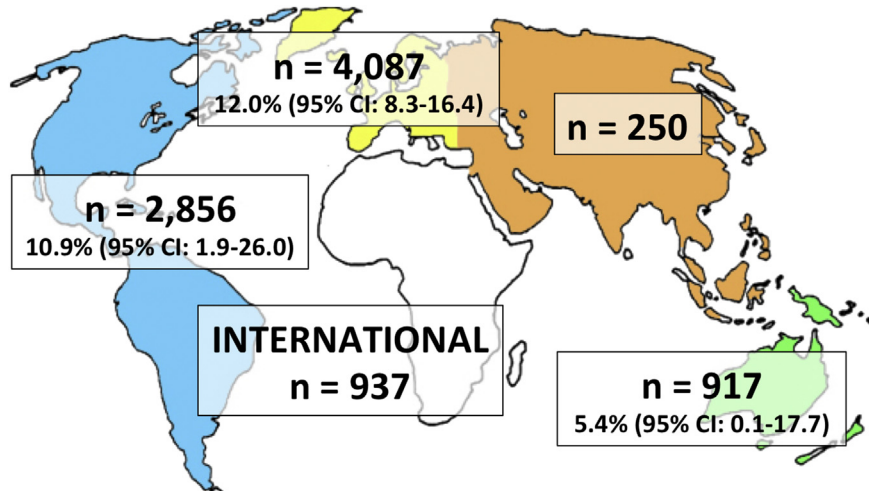


Figure 2. Continent of origin of the included studies. The data is presented as total number of patients (n) and the pooled proportion of complications from each on the continents. A single study from Asia and a single International study do not allow for pooled proportions of complications.

the upper and lower extremities ($n = 1289$ and $n = 1677$ respectively); five papers reported the number on melanomas together on both upper and lower extremities ($n = 1263$). The trunk was the second most common site with 3549 melanomas, followed by the head and neck with 982 melanomas. Five papers reported 62 melanomas on ‘other’ sites.

The most common reported complications were seroma in 16 articles ($n = 386$ of 6750 patients); infection in 17 articles ($n = 242$ of 7687 patients) and lymphoedema in 18 reports ($n = 135$ of 7770 patients). The crude seroma rate ranged from 0% to 38%; infection ranged from 0.3% to 19% and lymphoedema ranged from 0% to 17%. Other reported but not fully enumerated local complications included nerve injury (motor or sensory dysfunction), wound dehiscence, post-operative pain, keloid scar, suture granuloma, lymphatic fistula and persistent skin staining of blue dye. Other, rare, systemic reported complications included allergy to the blue dye (13 patients), urinary complications including infection (five patients), deep vein thrombosis (four patients), myocardial infarction (two patients), pulmonary embolism (one patient) and cerebral vascular accident (one patient). There were no deaths secondary to SLNB reported.

The percentage of complications reported in each lymph node basin (axilla, groin, neck, other) was extractable from 5 studies. Overall, there were 257 complications reported in 3541 biopsies. There were 118 complications in 1922 axilla biopsies; 110 complications in 992 groin biopsies; 21 complications in 594 neck biopsies and eight complications in 73 ‘other’ site biopsies.

The length of follow up across the studies is heterogeneously presented as the median, mean or range. Some studies omit their length of follow up, or it is not transparently presented. Therefore, as conducted by previous studies,³⁸ the minimum follow-up was extracted from the data. The minimum follow up was reported in 12 studies,

ranging from 11 days³⁶ to 12 months,^{30,37} although the study reporting a minimum follow-up of 11 days did have a mean follow-up of 24 months overall in 187 patients. Several papers report complete resolution of complications within the follow-up time period.^{10,11,13,26} One study reported that 3% of their patients had ‘permanent’ lymphoedema³³ and together, two papers reported two cases of persistent staining from the blue dye.^{9,36} The majority of the studies, however, partially reported or failed to report whether or not the complications had resolved.

Data synthesis and analysis

Pooled proportions estimates of the overall complication rate, seroma, infection, lymphoedema, haematoma and nerve injury were calculated. The overall incidence of complications was 11.3% (95% CI: 8.1–15.0; Fig. 3). The incidence of seroma was 5.1% (95% CI: 2.5–8.6); infection was 2.9% (95% CI: 1.5–4.6); lymphoedema was 1.3% (95% CI: 0.5–2.6); haematoma was 0.5% (95% CI: 0.3–0.9) and nerve injury was 0.3% (95% CI: 0.1–0.6).

Separate pooled estimates were calculated for the rate of complications per lymph node basin site in order to identify any significant differences. The site with the highest incidence of complications was the groin with a rate of 14.9% (95% CI: 6.1–26.7), followed by the axilla at 9.8% (95% CI: 4.7–16.6). The neck had the fewest complications with a rate of 5.1% (95% CI: 2.2–9.3). There was no significant difference in complication rate between the lymph node basins.

No statistically significant difference was found between the pooled estimates comparing the complication rates across the different continents. Europe had the highest rate of reported complications at 12.0% (95% CI: 8.3–16.4), followed by USA with 10.9% (95% CI: 1.9–26.0) and Australasia had the fewest at 5.4% (95%

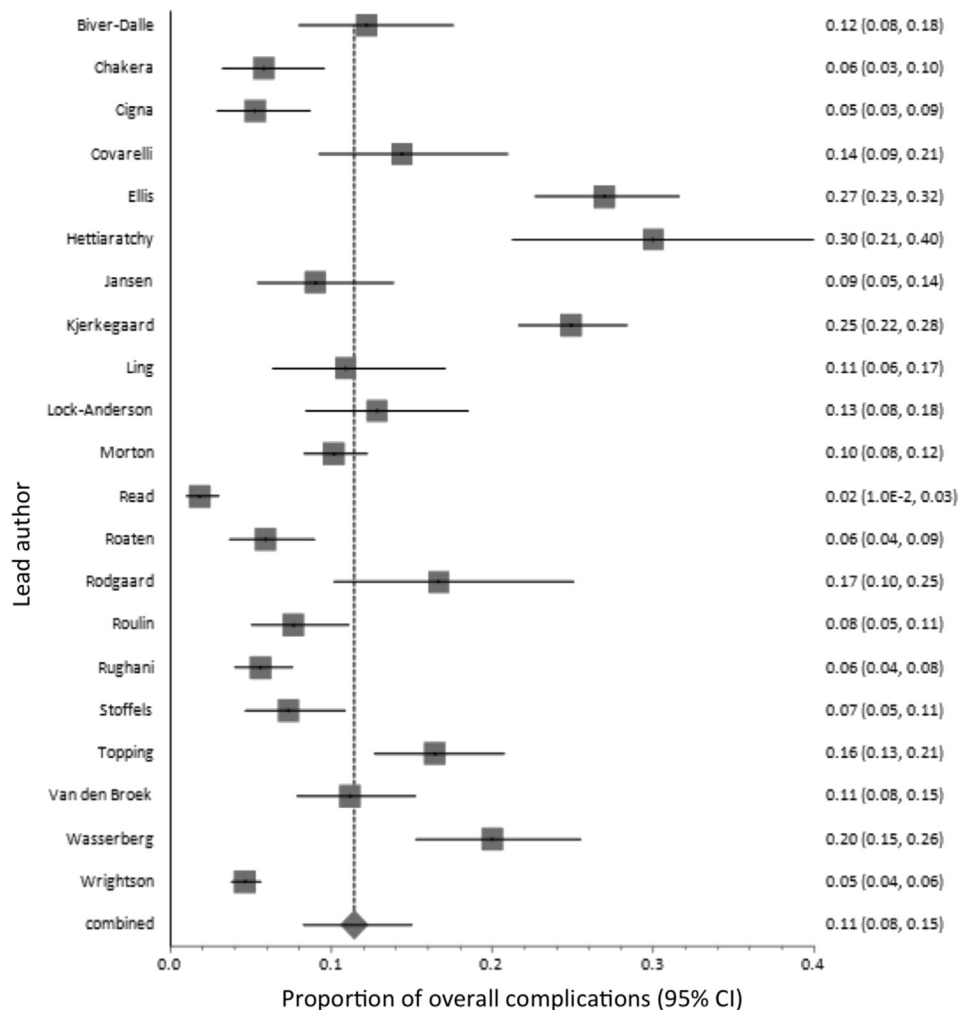


Figure 3. Forest plot showing the proportion of reported complications after sentinel lymph node biopsy for melanoma (9047 patients in 21 studies). Individual studies and their results are given in the body of the figure; the summary statistic of the random-effects model shows the pooled proportion of complications (0.1134) when all studies are combined in the meta-analysis model.

CI: 0.1–17.7). There was only one study from Asia, therefore it was not included in the pooled proportion analysis.

Discussion

The key findings of this study include the average pooled complication rate of 11.3%, and the most commonly reported early post-operative complications: seroma and infection which had a reported average of 5.1% and 2.9% respectively. No deaths occurred as a result from SLNB. There were very few definitive ‘permanent’ complications, with many studies reporting resolution within the follow-up period. There were 13 cases of ‘allergy’ to the radiocolloid or blue dye, however, often ‘allergy’ was not defined, and therefore the true rate of hypersensitivity or anaphylaxis cannot be reported. There were several serious systemic sequelae reported, including myocardial infarction, thromboembolism and stroke. One study attributed their case of iliofemoral vein thrombosis to a hypercoagulability state and multiple metastatic groin nodes.³⁴ Interrogation of

epidemiological statistics from the Centre for Disease Control and Prevention, the incidence of patients with acute myocardial infarction from 1999 to 2014 for adults was 61.8 per 100,000 and for ‘stroke’ it was 31.6 per 100,000.³⁹ Therefore, in a sample size of over 9000 patients, it is unlikely that the few reported cases of MI and CVA are directly attributable to the SLNB procedure.

The data presented by studies investigating complication rates for SLNB is incredibly heterogeneous; there is little uniformity in the definition of variables and there is inconsistency in what is chosen to be presented or omitted. For example, only two studies define ‘infection’^{8,35} and a precise definition is necessary for conclusive comparison. Although accepted definitions are available,⁴⁰ they are not made reference to in most of the studies. Some authors chose to present only the complications that required intervention, some chose to present all reported complications, but most failed to mark this distinction in their reporting. Indeed, only a minority of studies included in this analysis had a primary outcome of complication rate; the majority

reported complications as a secondary measure, which is commonly poorly documented. As an example of further poor documentation, few papers report the timings of the reported complications, for example into ‘early’ and ‘late’, so we have been unable to present our results in such manner. This limitation is likely a result of the retrospective study design of the majority of studies. Some studies amalgamate complication results, for example, one study presented data as ‘wound complications’,³⁴ the definition of which is not stated. This renders the information impractical for the purpose of meta-analysis. Additionally, dissimilar to the majority of studies who presented their morbidity data as the number of patients who had complications, two studies^{9,34} reported the number of biopsies that incurred complications. The number of biopsies for these studies, were approximately 1.2 times greater than the number of patients. In order to include the studies’ findings, the dataset needed to be standardised to complications per patient. Therefore, the average (mean) number of biopsies per patient was used to calculate this information. The heterogeneity of our dataset therefore is a limitation, which is important to consider when interpreting our results. Nevertheless, this systematic review attempts to standardise the information such that an estimate of complication rate can be used to counsel patients prior to the procedure, and to aid surgeons to assess their practice.

Stringent search terms and inclusion/exclusion criteria were applied to provide the best account of the available literature. The literature search was conducted twice, the second widened the inclusion criteria from ‘complication rate reported in the abstract’ to ‘any mention of morbidity data written in the abstract’ in order to prevent relevant data from being excluded. The rationale for the exclusion of patient cohorts fewer than 100 was to reduce the possibility of including studies that were at high risk of selection bias. Based on the range of complication rates that are reported in the literature, papers with fewer than 100 patients have the potential to underreport morbidity. With the exclusion of papers before the year 2000, we attempted to reflect modern practice and reduce the incidence of the effects of the ‘learning curve’ associated with the development of the technique, whilst maintaining a sufficiently large cohort of patients. One paper⁴¹ was excluded on full text screening because a large proportion of their patient cohort overlapped with patients enrolled on the MSLT-1 trial.²⁹

Wilke et al. published international, multi-centre trial results of breast SLNB complications within 30 days of the procedure for 4069 patients in 2006.⁴² Their results are consistent with this study’s findings. Wound infection was present in 1% of cases, haematoma in 1.4% of cases, seroma in 7.1% of cases and nerve injury of 0.2% of cases. However, lymphoedema reported within six months was considerably greater at 7.9% than our findings of 1.3%. In 2015, the Cochrane Collaboration published a systematic review⁴¹ with the primary outcome measure being overall

survival after lymph node dissection for melanoma in 2001 patients. A subgroup analysis was performed comparing complications within the lymph node basin between SLNB versus observation, which unsurprisingly showed zero complications in the unoperated observation group versus 106 complications in 937 patients in the SLNB group (11.3%). This result is identical to the pooled proportion of complications in our present study, although in a much smaller sample size. The review included eight individual studies that contributed to one overall RCT, which was included in our analysis.²⁹

It must be acknowledged that the pooled proportions include only the extractable reported data. The issue of heterogeneity and poor reporting means that these average figures of complications rates may be an under-estimation. Contrastingly, only a minority of papers failed to report their follow-up and generally the follow up times were more than sufficient for early post-operative complications. However, few papers reported their loss to follow up, and few had a loss of <5%, therefore the likelihood of attrition bias is high. Accurate and uniform definitions of complications are needed in order to collect comparable data, and timings of reported complications needs to be more commonly reported to allow analysis of early and late morbidity. The results can be used to inform patients of their risks of morbidity prior to the procedure, and it sets a benchmark for audit to help advance that surgical practice.

Conflict of interest

The authors state no conflict of interest.

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None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Appendix 1

Summary of studies included in the meta-analysis.

| Author | Year | Participants included in systematic review (n) | Summary of study |
|----------------|------|--|---|
| Biver-Dalle, C | 2012 | 197 | Observational cohort reports 8 years of SLNB experience; they evaluated disease progression and mortality. |
| Chakera AH | 2004 | 241 | Mixed retrospective and prospective cohort study investigated distribution of SNs, rate of positive nodes, recurrence, complications and reasons for failure of SLNB. |

(continued)

| Author | Year | Participants included in systematic review (n) | Summary of study |
|------------------|------|--|---|
| Cigna, E | 2012 | 266 | Retrospective cohort evaluated post-operative SLNB morbidity with a long-term follow up. |
| Covarelli, P | 2012 | 153 | Retrospective cohort study investigated reliability, cost and complications of SLNB under local anaesthesia. |
| Ellis, M | 2010 | 397 | Mixed retrospective & prospective cohort study presents indications, predictive factors and the outcomes of NO cutaneous melanoma having SLNB. |
| Hettiaratchy, SP | 2000 | 100 | Retrospective cohort study investigated sentinel lymph node identification, complications of SLNB and costs incurred from SLNB. |
| Jansen, L | 2000 | 200 | Prospective cohort study investigated the reliability of SLNB for staging melanoma. |
| Kjerkegaard, U | 2015 | 659 | Retrospective cohort study reports outcomes on node positivity rate, post-operative complications, recurrence and overall survival of patients. |
| Ling, A | 2010 | 147 | Retrospective cohort study analysed the morbidity and risk factors for developing complications after SLNB. |
| Lock-Anderson, J | 2006 | 187 | Prospective cohort study presents its institution's SLNB technique, positivity and complications, and melanoma recurrence and mortality. |
| Morton, D | 2005 | 937 | Phase III RCT evaluated the accuracy, use and morbidity of SLNB for staging regional nodal basins. |
| Read, RL | 2014 | 770 | Melanoma Institute Australia self-reported audit data compared to set surgical standards of SLNB. |
| Roaten, JB | 2005 | 339 | Retrospective cohort study investigated complications after SLNB. |
| Rødgaard, J | 2013 | 108 | Retrospective cohort study compared delayed SLNB with same day procedure. |
| Roulin, D | 2007 | 327 | Prospective cohort study reports SLNB accuracy and morbidity, and investigated predictors of SN status and prognostic factors. |
| Rughani, MG | 2011 | 697 | Prospective cohort study reports institute's 10 year clinical outcome of SLNB. |

(continued)

| Author | Year | Participants included in systematic review (n) | Summary of study |
|---------------|------|--|---|
| Stoffels, I | 2010 | 300 | Retrospective study reports effectiveness and reliability of SLNB under local anaesthesia, assessing it's cost and morbidity. |
| Topping, A | 2004 | 347 | Retrospective cohort study presents institute's 5 year SLNB clinical outcomes. |
| Van den Broek | 2013 | 305 | Mixed prospective & retrospective cohort study reporting 10 years' clinical experience in two hospitals. |
| Wasserberg, N | 2004 | 250 | Prospective cohort study presents SLNB morbidity data and node identification rate. |
| Wrightson, WR | 2003 | 2120 | Randomised prospective comparative study presents morbidity data after SLNB and complete lymph node dissection. |

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