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Evidence-Based Series 8-6 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities

The Melanoma Disease Site Group

An assessment conducted in December 2025 deferred the review of Evidence-Based Series (EBS) 8-6 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 8-6 consists of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/806

Section 1: Guideline Recommendations (UPDATED [1b] and ENDORSED)
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review Summary and Tool

August 31, 2018

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original December 2012	Jan 1980 – Sept 2011	Full Report	Web publication	NA
Version 2 June 2016	Jan 2011 – April 2016	New evidence added to Section 1 and new data found in Section 4	Updated web publication	2012 recommendations ENDORSED
Update of version 2 August 2018	NA	MSLT-II trial added to Section 1 only	Updated web publication	Recommendation 1b updated with the data from the MSLT-II trial. For details see Appendix 3

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Evidence-Based Series 8-6 Version 2: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities: Guideline Recommendations

A.M. Easson, R. Cosby, D.R. McCready, C. Temple, T. Petrella, F. Wright, and the Melanoma Disease Site Group

Original Report Date: December 5, 2012

Evidence-Based Series (EBS) 8-6 was reviewed in 2018 and UPDATED by the Melanoma Disease Site Group. New evidence was added to Section 1 and recommendation 1b was updated based on new practice-changing evidence. All other recommendations have been ENDORSED and are relevant for decision making.

QUESTIONS

1. What is the optimal surgical management of patients with positive sentinel lymph nodes (SLNs) from cutaneous melanoma of the trunk or extremities with respect to:
   a. Factors for predicting non-sentinel lymph node (NSLN) positivity
   b. Completion lymph node dissection (CLND) at the time of SLN positivity versus observation
   c. Extent of nodal dissection

2. What is the optimal surgical management of patients with biopsy-proven clinically palpable or biopsy-proven radiologically detected lymph nodes from cutaneous melanoma of the trunk or extremities with respect to:
   a. Extent of nodal dissection

OUTCOMES OF INTEREST

The outcomes of interest for these guideline recommendations are local and regional recurrence, distant recurrence, overall survival (OS), and disease-free survival (DFS).

TARGET POPULATION

These recommendations apply to adult patients with truncal or extremity cutaneous melanoma with nodal metastases.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management or referral of patients with nodal metastases from truncal or extremity cutaneous melanoma.

DEFINITIONS

- **Completion Lymph Node Dissection (CLND) –** The surgical removal of the remaining lymph nodes within an axillary or inguinal nodal basin after the identification of metastatic melanoma within a previously removed sentinel lymph node (SLN) from that same nodal basin. The axillary nodal basin is divided into three levels: level 1 nodes lie below, level 2 nodes lie behind, and level 3 nodes lie above the pectoralis minor muscle. The inguinal nodal basin includes the nodes from below/superficial to the inguinal ligament to the apex of the femoral triangle. The nodes above the inguinal ligament in the pelvis along the iliac vessels up to the common iliac bifurcation can also be considered a part of the inguinal nodal basin. If they are also removed, this is an **ilioinguinal dissection**.
- **Therapeutic Lymph Node Dissection (TLND)** – The surgical removal of all lymph nodes within an axillary or inguinal nodal basin in the presence of biopsy-proven clinically palpable, or biopsy-proven radiologically detected lymph nodes.
- **Radiologically Detected Lymph Node** – A node that was not clinically palpable but that was biopsied under radiologic guidance after appearing abnormal on radiologic imaging.
- **Cloquet's node** - The node medial to the femoral vein at the level of the inguinal ligament.

RECOMMENDATIONS AND KEY EVIDENCE

1. Patients with a positive sentinel lymph node

a. Prognostic factors for predicting non-sentinel lymph node involvement

No consistent set of factors reliably predicts non-sentinel lymph node positivity in those patients with a positive SLN.

Thirty-nine [1-39] studies, mainly retrospective, have looked at many factors that might predict further node positivity at CLND. However, no core set of features among the studies is consistently examined nor does a core set of features consistently predict further nodal positivity at CLND.

New 2018

b. Completion lymph node dissection at the time of SLN positivity versus observation

Patients with sentinel node metastasis should be considered for nodal observation with ultrasonography rather than CLND. Monitoring with ultrasonography of the affected nodal basin and clinical exam will be required, at minimum, every 4 to 6 months for the first 2 years and every 6 months from 3-5 years. Suspicions of a nodal recurrence in a lymph node basin include any two of the following: lymph node length:depth ratio <2, hypoechoic centre, failure to identify a nodal hilar vessel and/or focal rounded area of low level echoes with increased vascularity in that area. Suspicions of nodal recurrence via ultrasound should be confirmed with a biopsy of the basin. For certain patients, a CLND may still be the best option for local control but should be discussed by a multi-disciplinary team (MDT).

Qualifying Statements for Recommendation 1b

- In MSLT-II [58] one third of patients had metastases greater than 1 mm in diameter and 72% of patients had one sentinel node with metastases. A subgroup evaluation of patients with a greater disease burden (maximal tumour diameter >1 mm) did not indicate that a benefit

from completion lymph-node dissection was more likely in high-risk groups than in low-risk groups [58].

- Patients in whom CLND would be a better option than nodal observation with ultrasonography are:
    - patients with extensive sentinel node metastasis in which CLND would be the only option for local control
    - patients unlikely to be compliant with an intensive surveillance protocol
- While this guideline is specific to the trunk and extremities, this recommendation can be applied to melanomas of the head and neck and their respective drainage basins.

Key Evidence Added in the 2018 Update of Recommendation 1b

One randomized trial, MSLT-II [58] evaluated the utility of CLND compared to observation with frequent nodal ultrasonography and dissection only in melanoma patients with positive sentinel lymph node metastasis. The majority of patients in MSLT-II had low-volume nodal tumour burden (1 positive sentinel lymph node, longest diameter of the largest tumor deposit measured and the mean diameter of nodal metastasis 1.1mm). Three year MSS for the CLND and the observation group was the same, 86±1.3% and 86±1.2% (p=0.42), respectively. The 3-year DFS rate was slightly higher in the CLND group (p=0.05) but the investigators caution the significance of this result based on the lack of significance of the MSS, which was the primary outcome. The DFS rate may be explained by the lower rate of nodal failure in the CLND group as compared to the observation group at 3 years (92±1% vs. 77±1.5%; p=0.001). Adverse events occurred with more frequency among the CLND patients than the observation group with lymphedema being the most common (24.1% of patients vs. 6.3% at last follow-up, p<0.001). Non sentinel-node metastases, which was identified in 11.5% of the patients in the CLND group was found to be an independent prognostic factor for melanoma related death. Overall, some regional control and prognostic value can be derived from CLND; however, this is at the expense of increased adverse events. The non-significant difference in MSS and increase in adverse events of the CLND group indicates that CLND may not be optimal for patients and does not offer a survival benefit. Although the majority of patients had low volume tumor metastases, sub set analysis did not demonstrate a benefit for any groups of patient receiving CLND. As a result of the publication of the MSLT-II trial, the original recommendation has been altered to reflect this new high-quality evidence.

Key Evidence added in the 2016 Endorsement

The literature search conducted in 2016 to assess the validity of the current recommendations identified one randomized controlled trial that evaluated the benefit of CLND [46]. The DeCOG-SLT trial found no difference in distant metastasis-free survival, overall survival, or recurrence-free survival when SLN positive patients who received CLND were compared to patients who were observed. In this study, the majority (68% of patients) had sentinel node metastasis of <1mm). Although this study indicates no benefit for CLND, the study was small (n=240 CLND; n=233 observation) and included a short median follow-up time of 35 months. Due to the limitations of this study, the current recommendation was not altered.

Original Key Evidence from 2012

There are three small non-randomized studies that have evaluated the benefit of CLND versus observation [40-42]. Three papers compared CLDN at time of positive SLN to those patients having a TLND for clinically palpable nodes. The largest of these (n=2633), a meta-analysis [43], does demonstrate a survival advantage for upfront CLND at the time of a positive

SLN (Risk of Death for TLND, hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.28 to 2.00; p<0.0001). This recommendation is based on this limited evidence and expert opinion.

Likewise, the few studies that evaluate the benefit of CLND over either observation or TLND with respect to recurrence are not randomized. No studies identified have reported significant differences in recurrence between CLND and observation [41-43] or CLND and TLND [40, 44, 45].

c. Extent of nodal dissection for sentinel node positive disease if being undertaken

A complete Level 1, 2 and 3 dissection in the axilla is recommended for patients with a positive SLN, pending the emergence of good quality randomized data.

An inguinal dissection is recommended for patients with a positive SLN in the groin, pending the emergence of good quality randomized data. The routine examination of Cloquet's node and the addition of iliac dissection are more controversial, and any decision regarding these procedures should be made on a case-by-case basis.

There is no clear advantage to ilioinguinal dissection [47-50] or the evaluation of Cloquet's node [51,52] with respect to survival or morbidity in the small dataset that is available. This recommendation is based on expert opinion.

2. Patients with biopsy-proven clinically or biopsy-proven radiologically detected positive nodes

A Level 1, 2 and 3 dissection in the axilla is recommended for patients with biopsy-proven clinically or biopsy-proven radiologically detected positive nodes, pending the emergence of good quality randomized data.

Extent of nodal dissection

No studies addressing this question were identified, resulting in no evidence to support or refute the extent of axillary dissection being found. However, these patients are more likely to have multiple positive nodes than those patients identified by a SLN biopsy. This recommendation is based on expert opinion.

Inguinal dissection is recommended for patients with biopsy-proven clinically or biopsy-proven radiologically detected positive inguinal lymph nodes, pending the emergence of good quality randomized data. Because there is a greater likelihood of positive ilioinguinal nodes in this clinical situation, Cloquet's node could be examined and ilioinguinal dissection undertaken if the node is positive.

In the small dataset currently available there is no clear advantage to ilioinguinal dissection [53] or the evaluation of Cloquet's node [54,55] with respect to survival or morbidity. Decisions regarding iliac dissection should be made on a case-by-case basis [56,57]. This recommendation is based on expert opinion.

FUTURE RESEARCH

The development of more consistency among studies of factors to predict additional disease in non-sentinel lymph nodes would be invaluable, not only in the selection of variables,

but also in the strict definition of the variables selected. Standardized synoptic reporting of the SLN would help bring consistency to these types of studies.

RELATED GUIDELINES

PEBC Evidence-Based Series Report (EBS):

- EBS 8-2: Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/51116

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Updating

All PEBC documents are maintained and updated
as described in the PEBC Document Assessment and Review Protocol at
https://www.cancercareontario.ca/en/cancer-care-ontario/programs/data-research/evidence-based-care

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Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities: Evidentiary Base

A.M. Easson, R. Cosby, D.R. McCready, C. Temple, T. Petrella, F. Wright, and the Melanoma Disease Site Group

Original Report Date: December 5, 2012

Please see Document Review Summary and Tool for a summary of updated evidence published between 2011 and 2016 and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTIONS

1. What is the optimal surgical management of patients with positive sentinel lymph nodes (SLNs) from cutaneous melanoma of the trunk or extremities with respect to:
   a. Factors for predicting non-sentinel lymph node (NSLN) positivity
   b. Completion lymph node dissection (CLND) at the time of SLN positivity versus observation
   c. Extent of nodal dissection

2. What is the optimal surgical management of patients with biopsy-proven clinically palpable or biopsy-proven radiologically detected lymph nodes from cutaneous melanoma of the trunk or extremities with respect to:
   a. Extent of nodal dissection

INTRODUCTION

Although cutaneous melanoma is an uncommon disease compared with other non-melanoma skin cancers, the incidence of melanoma is increasing. Approximately 5800 new cases of melanoma will be diagnosed in Canada in 2012 [1]. The majority of patients are diagnosed with a primary melanoma (clinically node negative and systemically negative), and for them the principal therapy is the surgical excision of the primary tumour and the assessment of the regional lymph node basin with sentinel node biopsy (see EBS 8-2; https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/51116). The optimal surgical management of nodal metastases identified either through SLN biopsy or clinical examination, however, remains uncertain.

Melanoma may spread to regional lymph nodes, with the risk of nodal involvement increasing with primary tumour thickness. Ninety percent of stage I and II patients exhibit no clinical evidence of lymph node involvement at their initial presentation, yet approximately 20% have subclinical involvement [2,3]. Sentinel lymph node biopsy (SLNB) is a surgical procedure that identifies the sentinel node, the first lymph node(s) that drain the primary

melanoma site. The advantage of SLNB is that it provides accurate nodal staging with limited morbidity. Less than 25% of patients with a positive SLN have further NSLN involvement [4-6]. Currently, no reliable set of factors predict which patients with a positive SLN will have further positive non-SLNs within the nodal basin, unlike in breast cancer.

Furthermore, whether early intervention with a CLND following a positive SLNB offers a survival advantage over observation is unknown. That question is currently under study in the Multicentre Selective Lymphadenectomy Trial II (MSLT-II), the results of which are not expected for several years. What is known is that lymph node status is the most important predictor of survival and recurrence in patients with localized melanoma [7], and long-term survival after therapeutic dissection for clinically palpable nodes is achievable (15-year survival = 34% in a recent large series [8]).

Regardless of the level of evidence that exists in the literature, there is an immediate clinical need for guidelines that examine the best currently available evidence. Treatment decisions must be made even in the absence of good evidence, and expert opinion based on the best information that is available becomes the best guidance obtainable. The management of cutaneous melanoma patients with lymph node metastases is one such situation.

Development of this systematic review and clinical practice guideline was undertaken by the Melanoma Disease Site Group (DSG) with the intention of providing health practitioners with recommendations on the optimal surgical management of their adult patients with lymph node metastases from cutaneous melanoma of the trunk or extremities. The issue of postoperative radiation to the nodal basin was not included in this review as this topic will be the topic of an independent guideline.

DEFINITIONS

- **Completion Lymph Node Dissection (CLND) –** The surgical removal of the remaining lymph nodes within an axillary or inguinal nodal basin after identification of metastatic melanoma within a previously removed SLN from that nodal basin. The axillary nodal basin is divided into three levels: level 1 nodes lie below, level 2 nodes lie behind and level 3 nodes lie above the pectoralis minor muscle. The inguinal nodal basin includes the nodes from below/superficial to the inguinal ligament to the apex of the femoral triangle. The nodes above the inguinal ligament in the pelvis along the iliac vessels up to the common iliac bifurcation can also be considered a part of the inguinal nodal basin. If they are also removed, this is an **ilioinguinal dissection**.
- **Therapeutic Lymph Node Dissection (TLND)** – The surgical removal of all lymph nodes within an axillary or inguinal nodal basin in the presence of biopsy-proven clinically palpable, or biopsy-proven radiologically detected lymph nodes.
- **Radiologically Detected Lymph Node** – A node that was not clinically palpable but that was biopsied under radiologic guidance after appearing abnormal on radiologic imaging.
- **Cloquet's node** - The node medial to the femoral vein at the level of the inguinal ligament.

METHODS

The evidence-based series (EBS) guidelines developed by the PEBC, CCO, use the methods of the Practice Guidelines Development Cycle [9]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by members of the project Working Group and one methodologist (Appendix 1).

The systematic review is a convenient and up-to-date source of the best available evidence on the surgical management of lymph node metastases from cutaneous melanoma of the trunk or extremities. The body of evidence in this review is primarily comprised of retrospective cohort studies. That evidence forms the basis of the recommendations developed

by the Melanoma DSG (Appendix 2) and presented in Section 1. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through CCO. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (1980 through Sep [week 1] 2011) and EMBASE (1980 through week 37 2011) databases were searched for relevant evidence. The full MEDLINE and EMBASE literature search strategies can be found in Appendix 3. The reference lists from retained articles were also searched for additional relevant trials.

Study Selection Criteria

Inclusion Criteria

Articles were included if they were published English-language reports involving human participants of phase II or III randomized controlled trials (RCTs), other comparative studies, single-arm studies, practice guidelines, and systematic reviews, with or without meta-analyses, that related to the surgical management of node-positive cutaneous melanoma. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.

Single-arm studies were specifically included, because it was known that there were few randomized studies that addressed the research questions, particularly Question 1. It was thought a critical mass of evidence from single-arm studies with congruent results may potentially affect the recommendations made.

Exclusion Criteria

Letters, editorials, notes, case reports, commentaries, and non-systematic reviews were not eligible.

Synthesizing the Evidence

Owing to the varying designs of the identified studies and the lack of fully published RCTs, data were not pooled using meta-analytic techniques.

RESULTS

Literature Search Results

The MEDLINE search yielded 2516 hits, of which 194 were potentially relevant and were fully reviewed; 51 were retained. The EMBASE searched yielded 3243 hits, of which 57 were potentially relevant and were fully reviewed; three were retained (Table 1, Appendix 4).

Table 1. Literature search results.

Database	Dates Searched	Hits	Fully reviewed	Retained
MEDLINE	1980 – Sep (week 1) 2011	2516	194	51
EMBASE	1980 – Week 37 2011	3243	57	3
ASCO	Up to 2011	82	0	0
SSO	Up to 2011	59	0	0
Reference Mining	NA	0	0	0

Note: ASCO, American Society for Clinical Oncology; NA, not applicable; SSO, Society of Surgical Oncology

In total, 50 documents from the literature search met the eligibility criteria for this systematic review and are listed in Table 2.

Table 2. Evidence included in the report by topic.

	Topic	Number of Documents	Reference Numbers
Patients with Positive Sentinel Lymph Nodes	Predicting NSLN Positivity	39	[4-6,10-45]
	CLND versus Observation	3	[46-48]
	CLND versus Delayed TLND	3	[49-51]
	Extent of Nodal Dissection (Axilla)	0	----
	Extent of Nodal Dissection (Inguinal)	4	[52-55]
	Extent of Nodal Dissection (Cloquet)	2	[56,57]
Patients with Clinically Palpable Nodes	Extent of Nodal Dissection (Axilla)	0	----
	Extent of Nodal Dissection (Inguinal)	1	[58]
	Extent of Nodal Dissection (Cloquet)	2	[59,60]

Note: CLND, completion lymph node dissection; NSLN, non-sentinel lymph node; TLND, therapeutic lymph node dissection

Study/Trial Design and Quality

Inclusion Criteria

Articles were included if they were published English-language reports involving human participants of phase II or III randomized controlled trials (RCTs), other comparative studies, single-arm studies, practice guidelines, and systematic reviews, with or without meta-analyses, that related to the surgical management of node-positive cutaneous melanoma. If more than one study evaluated the same data set, only the most recent paper was selected for inclusion.

Single-arm studies were specifically included, because it was known that there were few randomized studies that addressed the research questions, particularly Question 1. It was thought a critical mass of evidence from single-arm studies with congruent results may potentially affect the recommendations made.

Exclusion Criteria

Letters, editorials, notes, case reports, commentaries, and non-systematic reviews were not eligible. The quality of the cohort studies was evaluated based on four criteria: whether or not funding, control details, and power calculations were reported, and whether blinded assessment was used. Funding source was reported in only 15 studies. Control details, blinded assessment, and power calculations were mostly not applicable for the types of studies included in this systematic review. See Appendix 5 for the full details.

The quality of each systematic review (with or without meta-analysis) was evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [61]. This instrument has good face and content validity [62] and has been externally validated [61,63]. Each item has a value of one point, for a maximum total of 11 AMSTAR points. The Pasquali et al. [49] meta-analysis scored 10 AMSTAR points, and the Hughes et al. [52] systematic review scored two AMSTAR points, with two questions being 'not applicable' as meta-analysis was not done. The Hughes [52] systematic review did not provide much methodological detail.

Outcomes

1. Patients with Positive Sentinel Lymph Nodes

a. Factors for Predicting Non-Sentinel Lymph Node (NSLN) Positivity

Thirty-nine studies [4-6,10-45] were identified that looked at factors that would predict a positive CLND (i.e., further positive NSLN). These studies were almost all retrospective analyses. Table 3 describes how the CLND sample was pathologically assessed in each of the studies and if this was reported. Only half of the studies described the sectioning technique used. All studies that reported how the CLND samples were evaluated used hematoxylin and eosin (H & E) staining. Only a few studies routinely evaluated all specimens with immunohistochemistry (IHC), and a few studies used IHC staining for confirmation purposes only. Only eleven studies reported the number of nodes removed during the CLND. This lack

of detail is not surprising given that NSLNs from CLND specimens are not routinely evaluated with the same pathologic rigour as are SLNs. Given the amount of work that this scrutiny would involve (serial sectioning and IHC staining at 2 mm intervals of all nodes retrieved at CLND [up to 30]), it is unlikely that NSLNs will ever be evaluated in the same detailed manner as are SLNs. It is possible, therefore, that small nodal metastases in the CLND sample will be under-reported.

Table 3. Pathological assessment of CLND specimens.

Study	H & E	IHC	Sectioning Technique	Number of Nodes Removed
Joseph 1998 [10]	Yes	NR	NR	NR
Starz 2001 [11]	Yes	Anti-S100 HMB-45 (for confirmation only)	Specimens formalin fixed and cut into slices a few mm thick, 1-mm slices then paraffin embedded	Evaluable Nodes: Neck – 2 Axillary – 22 Inguinoiliac – 12 Inguinal – 4
McMasters 2002 [4]	Yes	No	Serial sectioning not done	NR
Reeves 2003 [5]	Yes	No	Bivalved	Mean >20
Salti 2003 [12]	Yes	No	NR	NR
Cochran 2004 [13]	Yes	S-100, HMB-45	NR	NR
Dewar 2004 [14]	NR	NR	NR	NR
Elias 2004 [15]	Yes	S-100, HMB-45, NKIC3, MART-1	Serial sectioning	NR
Lee 2004 [6]	Yes	No	NR	NR
Scolyer 2004 [16]	Yes	No	Whole nodes embedded in paraffin, sliced if >3mm diameter	Median - 14
Starz 2004 [17]	Yes	S-100	Specimen formalin fixed, cut into thin slices	Mean - 29
Fink 2005 [18]	Yes	No	Specimen formalin fixed, cut into thin slices	NR
Sabel 2005 [19]	Yes	No	Bivalved	Mean number of nodes removed: Axillary – 18 Inguinal – 10 Neck – 33
Vuylsteke 2005 [20]	Yes	No	LNs lamellated and embedded in paraffin. LN <0.5 cm - embedded whole LN 0.5-1.0 cm - halved LN >1.0 cm - lamellated into sections approximately 0.5 cm in size	Median - 11.5 nodes
Pearlman 2006 [21]	Yes	No	Bivalved	NR
van Akkooi 2006 [22]	NR	NR	NR	NR
Govindarajan 2007 [23]	Yes	For confirmation only	Bisected or trisected depending on size	Mean - 18.5 nodes
Debarbieux 2007 [24]	Yes[1]	For confirmation only	NR	NR
Page 2007 [25]	NR	NR	NR	NR
Frankel 2008 [26]	NR	NR	NR	NR
Glumac 2008 [27]	Yes	No	NR	Mean number of nodes removed: Axillary – 18.4 Parotidectomy – 31.4 Inguinal – 10.4 Inguino-iliac – 21.2
Guggenheim 2008 [28]	NR	NR	NR	NR
Roka 2008 [29]	Yes	No	Bivalved	NR
Rossi 2008 [30]	Yes	For confirmation only	LN diameter ≤4 mm - embedded whole in paraffin LN diameter >4 mm - cut into 3-4-mm thick slices, which were each embedded in paraffin	Median - 18.5
Satzger 2008 [31]	Yes	NR	NR	NR
van Akkooi 2008 [32]	NR	NR	NR	NR
Cadili 2009 [33]	Yes	No	Bivalved	NR
Gershenwald 2008 [34]	NR	NR	Specimens analysed using 'standard procedures'	NR
Ollila 2009 [35]	NR	NR	NR	NR
Santinami 2009 [36]	Yes	For confirmation only	Fixed and paraffin embedded	NR
Cadili 2010 [37]	Yes	No	LN diameter <3mm – embedded whole in paraffin LN diameter >3mm – sliced into 3-mm slices first	Median - 18
Cadili 2010 [38]	Yes	No	Bivalved	NR
Murali 2010 [39]	Yes	No	LNs embedded in paraffin and sectioned at one level	NR

Study	H & E	IHC	Sectioning Technique	Number of Nodes Removed
Wiener 2010 [40]	Yes	No	NR	NR
Younan 2010 [41]	Yes	No	Bivalved	NR
Bogenrieder 2011 [42]	Yes	S-100, HMB-45 – if sectioned	Halved, sectioned occasionally	Mean - 12
Fink 2011 [43]	NR	NR	NR	NR
Kunte 2011 [44]	NR	NR	NR	NR
van der Ploeg 2011 [45]	NR	NR	NR	NR

Note: CLND, completion lymph node dissection; H & E, hematoxylin and eosin; IHC, immunohistochemistry; LN, lymph node; NR, not reported

[1]HES (hematoxylin-eosin-saffron) staining.

Predictive factors for further positive nodes from these 39 studies are included in Tables 4, 5, and 6. Table 4 looks at the patient features that might predict a positive CLND; Table 5 looks at the primary tumour features that might predict a positive CLND; and Table 6 (a, b and c) looks at SLN features that might predict a positive CLND. All the data presented in these tables are the results of univariate analyses. Although many, but not all, of these studies conducted multivariate analyses (MVA), these data are not included, as many did not have enough participants to justify the use of MVA.

Collectively, no core set of features is consistently evaluated for predicting a positive CLND, nor does any core set of features consistently predict a positive CLND. Each of these 39 studies looks at very different features, and in fact, some studies only look at one particular feature. Even looking at the data by feature, the results are mixed among the studies that evaluate that feature. The outcomes reported in Tables 4, 5, 6a, 6b, and 6c were thought to be the most important for developing recommendations.

The only patient features evaluated were age and gender (Table 4). Of the studies that evaluated older age, only six studies [6,24,33,34,37,45] found it to be predictive of the presence of positive NSLNs. Gender (male) was only found to be predictive of positive NSLNs in one study [19].

Table 4. Factors predictive of a positive CLND from univariate analysis: patient features.

Study	Number of SLNB Positive Patients	Number (%) of Patients Undergoing CLND	Number (%) of Patients with Positive CLND	p-values	
				Age	Gender
Joseph 1998 [10]	83	64(77.1)	5(7.8)	ns	-
Starz 2001 [11]	62	39(62.9)	-	-	-
McMasters 2002 [4]	274	274(100.0)	45(16.4)	ns	-
Reeves 2003 [5]	98	98(100.0)	16(16.3)	ns	ns
Salti 2003 [12]	56	56(100.0)	8(14.3)	ns	ns
Cochran 2004 [13]	90	90(100.0)	19(21.1)	-	-
Dewar 2004 [14]	146	146(100.0)	24(16.4)	ns	ns
Elias 2004 [15]	87	80(92.0)	12(15.0)	-	-
Lee 2004 [6]	191	191(100.0)	46(24.1)	0.025	ns
Scolyer 2004 [16]	175	140(80.0)	24(17.1)	-	-
Starz 2004 [17]	65	45(69.2)	12(26.7)	ns	ns
Fink 2005 [18]	26	26(100.0)	4(15.4)	-	-
Sabel 2005 [19]	232	221(95.3)	34(15.4)	ns	0.001
Vuylsteke 2005 [20]	71	71(100.0)	19(26.8)	-	-
Pearlman 2006 [21]	90	80(88.9)	17(21.3)	ns	ns
van Akkooi 2006 [22]	77	67(87.0)	10(14.9)	ns	ns
Govindarajan 2007 [23]	127	127(100.0)	20(15.8)	ns	ns

Study	Number of SLNB Positive Patients	Number (%) of Patients Undergoing CLND	Number (%) of Patients with Positive CLND	p-values	
				Age	Gender
Debarbieux 2007 [24]	98	98(100.0)	-	0.001	ns
Page 2007 [25]	70	70(100.0)	19(27.1)	ns	ns
Frankel 2008 [26]	136	136(100.0)	29(21.3)	ns	ns
Glumac 2008 [27]	74	73(98.6)	16(21.9)	-	-
Guggenheim 2008 [28]	107	100(93.5)	22(22.0)	-	-
Roka 2008 [29]	85	85(100.0)	18(21.2)	ns	ns
Rossi 2008 [30]	101	96(95.0)	20(20.8)	ns	ns
Satzger 2008 [31]	180	180(100.0)	28(16.0)	-	-
van Akkooi 2008 [32]	388	360(92.8)	92(25.6)	-	-
Cadili 2009 [33]	92	68(73.9)	12(17.6)	0.01	ns
Gershenwald 2008 [34]	359	343(95.5)	48(14.0)	0.02	ns
Ollila 2009 [35]	90	86(95.6)	18(20.9)	-	-
Santinami 2009 [36]	150	150(100.0)	36(24.0)	-	-
Cadili 2010 [37]	606	606(100.0)	-	0.0046	-
Cadili 2010 [38]	144	140(97.2)	19(17)	ns	-
Murali 2010 [39]	409	309(75.6)	53(17.2)	ns	ns
Wiener 2010 [40]	501	323 (65)	61(18.9)	ns	ns
Younan 2010 [41]	82	82 (100)	10(12.2)	ns	ns
Bogenrieder 2011 [42]	70	70(100)	18(25.7)	ns	ns
Fink 2011 [43]	124[a]	124(100)[a]	30(24.2)[a]	-	-
Kunte 2011 [44]	213	176(82.6)	26(14.8)	ns	ns
van der Ploeg 2011 [45]	1080	1009(93.4)	212(21.0)	0.032	ns

Note: Dash(-), not evaluated; CLND, completion lymph node dissection; ns, not significant; SLNB, sentinel lymph node biopsy

[a]based on number of nodal basins, not number of patients.

Several primary tumour features have been evaluated by at least one study (Table 5) to determine if they are predictive of positive CLND. Breslow thickness, ulceration, location of primary, Clark level, and mitotic rate are among the features most commonly evaluated. Once again, there is no single feature or group of features that is consistently predicative of positive NSLNs. Other features such as regression, satellitosis, and angiolymphatic invasion were only evaluated by a very few studies.

Table 5. Factors predictive of a positive CLND from univariate analysis: Primary tumour features.

Study	p-values							
	Breslow Thickness	Ulceration	Primary Site	Clark Level	Mitotic Rate	Satellitosis	Angio-lymphatic Invasion	Regression
Joseph 1998 [10]	NR	ns	-	-	-	-	-	-
McMasters 2002 [4]	ns	ns	-	ns	-	-	-	-
Reeves 2003 [5]	0.05	0.04	ns	-	ns	ns	-	0.02
Salti 2003 [12]	ns	ns	ns	ns	ns	-	-	-
Cochran 2004 [13]	0.0001	-	-	-	-	-	-	-
Dewar 2004 [14]	ns	-	-	-	-	-	-	-
Lee 2004 [6]	0.001	ns	0.023	<0.001	ns	-	-	-
Starz 2004 [17]	ns	-	0.039	-	-	-	-	-

Study	p-values							
	Breslow Thickness	Ulceration	Primary Site	Clark Level	Mitotic Rate	Satellitosis	Angio-lymphatic Invasion	Regression
Sabel 2005 [19]	0.03	0.005	ns	-	0.02	ns	ns	-
Vuylsteke 2005 [20]	ns	-	-	-	-	-	-	-
Pearlman 2006 [21]	0.003	-	0.027	-	-	-	-	-
van Akkooi 2006 [22]	ns	0.05[a]	-	ns	-	-	-	-
Govindarajan 2007 [23]	ns	ns	-	-	-	-	-	-
Debarbieux 2007 [24]	ns	ns	-	-	-	-	-	-
Page 2007 [25]	ns	ns	ns	-	ns	-	-	-
Frankel 2008 [26]	0.0013	ns	<0.02	-	ns	0.0038	<0.001	ns
Roka 2008 [29]	ns	ns	ns	ns	-	-	-	-
Rossi 2008 [30]	ns	-	-	-	-	-	-	-
Cadili 2009 [33]	ns	ns	0.05	ns	-	-	ns	-
Gershenwald 2008 [34]	0.0001	ns	-	0.01	-	-	-	-
Santinami 2009 [36]	-	ns	-	ns	-	-	-	-
Cadili 2010 [38]	ns	-	-	-	-	-	-	-
Murali 2010 [39]	ns	ns	-	ns	ns	ns	ns	0.02
Wiener 2010 [40]	ns	0.006	-	-	ns	-	-	-
Younan 2010 [41]	ns	ns	ns	ns	-	-	ns	ns
Bogenrieder 2011 [42]	ns	ns	-	ns	-	-	-	-
Fink 2011 [43]	0.04	ns	ns	0.01	-	-	-	-
Kunte 2011 [44]	0.022	‡	ns	ns	-	-	-	‡
van der Ploeg 2011 [45]	<0.001	ns	0.011	0.011	-	-	-	-

Note; Dash(-), not evaluated; NR, not reported; ns, not significant

[a] *Absence* of ulceration

‡significant but study authors report that the p-value is questionable

Many different SLN features have been evaluated by at least one study (Table 6) to determine if they are predictive of positive CLND. Table 6a shows SLN features related to the size of the tumour in the SLN. Unfortunately, no consistent measure of tumour size in the SLN has been used, and definitions vary from study to study. For example, SLN tumour burden is defined as: less than versus greater than 2 mm in some studies [21,25,28,36]; less than 0.1 mm versus 0.1 to 1.00 mm versus greater than 1.00 mm in other studies [22,35]; and as a mean in another study [33].

Tumour size as measured on a glass slide was found to be predictive of a positive CLND seven of the nine times it was evaluated; tumour burden has also been evaluated seven times, but the results have been mixed in terms of its predicative ability; and the area of the tumour in the SLN has been evaluated five times and been found to be predictive each time. The depth of the SLN metastases has been evaluated six times and has been deemed to be predictive of positive NSLNs in each case. Other measures of tumour size in the SLN(s) have rarely been evaluated.

Table 6a. Factors predictive of a positive CLND from univariate analysis: Features related to size of tumour in SLN.

Study	p-values								
	Tumour Size in SLN	Size of largest tumour deposit in SLN	Diameter of SLN metastasis	SLN tumour burden	SLN tumour burden (Rotterdam Criteria)	Area of tumour	Relative area of tumour	No. Of SLN metastatic foci	Depth of SLN metastases
Reeves 2003 [5]	0.04	-	-	-	-	-	-	-	-
Salti 2003 [12]	-	-	-	-	-	-	-	-	-
Cochran 2004 [13]	-	-	-	-	-	0.0001	-	-	-

Study	p-values								
	Tumour Size in SLN	Size of largest tumour deposit in SLN	Diameter of SLN metastasis	SLN tumour burden	SLN tumour burden (Rotterdam Criteria)	Area of tumour	Relative area of tumour	No. Of SLN metastatic foci	Depth of SLN metastases
Dewar 2004 [14]	-	-	-	-	-	-	-	-	<0.0001
Lee 2004 [6]	<0.001	-	-	-	-	-	-	-	-
Scolyer 2004 [16]	-	-	ns	-	-	<0.01	ns	ns	0.05
Vuylsteke 2005 [20]	-	-	-	-	-	0.003	-	-	-
Pearlman 2006 [21]	<0.001	-	-	<0.0001	-	-	-	-	-
van Akkooi 2006 [22]	-	-	-	ns	-	-	-	-	-
Govindarajan 2007 [23]	-	0.02	-	-	-	-	-	ns	-
Debarbieux 2007 [24]	-	-	0.004[a]	-	-	-	-	-	0.009
Page 2007 [25]	-	-	-	ns	-	-	-	-	-
Frankel 2008 [26]	0.0041	-	-	-	-	-	-	-	-
Glumac 2008 [27]	-	-	-	-	-	-	-	0.05	-
Guggenheim 2008 [28]	-	-	-	ns	-	-	-	-	-
Roka 2008 [29]	ns	-	-	-	-	-	-	-	-
Rossi 2008 [30]	ns	-	-	-	-	-	-	-	0.009
Satzger 2008 [31]	-	-	0.001	-	-	<0.001	<0.001	-	<0.001
van Akkooi 2008 [32]	-	-	-	-	0.001	-	-	-	-
Cadili 2009 [33]	0.01	-	-	0.01	-	-	-	-	-
Gershenwald 2008 [34]	-	<0.0001	-	-	-	<0.0001	-	0.004	-
Santinami 2009 [36]	-	-	-	<0.0001	-	-	-	-	-
Cadili 2010 [37]	0.0293	-	-	-	-	-	-	-	-
Cadili 2010 [38]	0.0023	0.045	-	-	-	-	-	-	-
Murali 2010 [39]	-	0.049	0.02	-	-	-	-	ns	0.02
Bogenrieder 2011 [42]	-	-	0.021	-	0.007	0.014	-	-	0.023
van der Ploeg 2011 [45]	-	-	-	-	<0.001[b]	-	-	-	-

Note: Dash(-), not evaluated; NR, not reported; ns, not significant; SLN, sentinel lymph node
[a]Diameter 2 – shortest diameter of the largest metastasis observed in serial sections
[b]Rotterdam Criteria calculated four different ways

Table 6b shows the features related to the number of positive SLNs, the location of the metastases within the SLN, and the method of identification of positive SLNs. All of these features have mixed results with respect to being predictive of a positive CLND or are rarely evaluated.

Table 6b. Factors predictive of a positive CLND from univariate analysis: Other SLN features.

Study	p-values								
	No. of SLNs removed	No. of positive SLNs	Micro-anatomic Location	Effacement of Nodal Architecture	Perinodal lymphatic involvement present	Extranodal extension	S-classifi-cation	Positive H & E vs. Positive IHC	Extra-capsular extension in SLN
Starz 2001 [11]	-	-	-	-	-	-	0.0012	-	-
McMasters 2002 [4]	-	ns	-	-	-	-	-	-	-
Reeves 2003 [5]	ns	ns	-	-	-	-	-	ns	-
Salti 2003 [12]	-	0.008	-	-	-	-	-	-	-
Dewar 2004 [14]	-	-	0.003	-	-	-	-	-	-
Lee 2004 [6]	-	0.016	-	-	-	-	-	-	-
Scolyer 2004 [16]	-	ns	-	0.05	<0.01	-	-	-	ns
Starz 2004 [17]	-	-	-	-	-	-	0.01	-	-
Fink 2005 [18]	-	-	-	-	-	-	0.02	-	-
Sabel 2005 [19]	ns	0.035	-	-	-	0.0002	-	-	-
van Akkooi 2006 [22]	-	0.02	ns	-	-	-	ns	-	-
Govindarajan 2007 [23]	ns	ns	-	-	-	-	-	-	-
Debarbieux 2007 [24]	-	ns	-	-	-	-	-	-	ns

Study	p-values								
	No. of SLNs removed	No. of positive SLNs	Micro-anatomic Location	Effacement of Nodal Architecture	Perinodal lymphatic involvement present	Extranodal extension	S-classifi-cation	Positive H & E vs. Positive IHC	Extra-capsular extension in SLN
Page 2007 [25]	ns	ns	-	-	-	-	-	-	-
Frankel 2008 [26]	ns	0.0198	ns	-	-	0.0002	-	-	-
Roka 2008 [29]	-	ns	-	-	-	-	-	-	-
Rossi 2008 [30]	-	ns	-	-	-	-	0.017	-	-
Satzger 2008 [31]	-	ns	-	-	<0.001	<0.001	-	<0.001	-
van Akkooi 2008 [32]	-	-	ns	-	-	-	-	-	-
Cadili 2009 [33]	ns	ns	ns	-	-	ns	-	-	-
Gershenwald 2008 [34]	0.0006	ns	<0.04	-	-	-	-	-	0.0001
Santinami 2009 [36]	-	-	ns	-	-	-	-	-	-
Murali 2010 [39]	ns	ns	0.007	-	<0.001	ns	-	-	-
Wiener 2010 [40]	ns	-	-	-	-	-	-	-	-
Younan 2010 [41]	-	-	-	-	-	-	0.04	-	-
Bogenrieder 2011 [42]	-	ns	ns	-	-	-	NR	-	-
Fink 2011 [43]	-	-	0.004	-	-	-	0.001	-	-
van der Ploeg 2011 [45]	-	-	<0.001[a]	-	-	-	-	-	-

Note: Dash(-), not evaluated; H & E, hematoxylin and eosin; IHC, immunohistochemistry; No, number; NR, not reported; ns, not significant; SLN, sentinel lymph node; vs., versus

[a]Calculated two different ways

Table 6c shows the various miscellaneous features of SLNs that were evaluated in only one study. Although each of these factors was a significant predictor for positive NSLNs, each feature has only been evaluated by one study in this group of 39 studies.

Table 6c. Factors predictive of a positive CLND from univariate analysis: Rarely evaluated sentinel lymph node features.

Study	p-values						
	All SLNs positive	Proportion of positive SLNs	Area of dendritic cells	Density of dendritic cells/mm^2	Pattern of SLN involvement	Capsular involvement	SLN sub-capsular
Reeves 2003 [5]	-	-	-	-	-	-	0.01
Cochran 2004 [13]	-	-	0.0245	0.008	-	-	-
Elias 2004 [15]	0.04	-	-	-	-	-	-
Rossi 2008 [30]	-	-	-	-	0.015	-	-
Satzger 2008 [31]	-	-	-	-	-	0.001	-
Murali 2010 [39]	-	0.009	-	-	-	-	-

Dash(-)=not evaluated; CLND=completion lymph node dissection; SLN=sentinel lymph node

Several of the studies looking for factors to predict CLND status attempted to develop a scoring system or risk-stratification model using the various factors that they evaluated [5,6,13,31,33,34,37-39,45]. Many of these scoring systems are based on multivariate analyses, a questionable action given the large number of factors evaluated and the small number of events (i.e., CLND positive).

b. Completion Lymph Node Dissection at the Time of Sentinel Lymph Node Positivity versus observation

Three studies were found that compared CLND to observation in patients with positive SLNs [46-48].

Survival

Wong et al. [46] compared a group of 134 SLN-positive patients from 16 institutions who did not have CLND to a group of 164 SLN-positive patients from the Memorial Sloan-Kettering Cancer Centre (MSKCC) database who did have CLND. They report no significant difference in

three-year disease-specific survival (DSS) in these two groups of patients although the follow-up was shorter in the group who did not have CLND (Table 7). Also, the group that did have CLND had more primary lesions with ulceration and fewer SLNs with micrometastatic disease, thus making them a population with possibly a poorer prognosis, Similarly, Kingham et al [47], using the MSKCC database, found that DSS was not significantly different when he compared 271 who did and 42 who did not undergo immediate CLND. Patient refusal was the most common reason for not doing the CLND. van der Ploeg et al. [48] also compared a group of SLN-positive patients who either did or did not go on to have CLND. However, they divided the groups by the Starz [11,17] classification, which is based on the penetrative depth of the metastasis from the capsule into the SLN. Patients who were categorized as SI or SII (invasion ≤1.0 mm) did not undergo CLND, whereas patients categorized as SIII (invasion >1.0 mm) did undergo CLND. These authors report a significant difference in overall three-year survival but not in three-year disease-free survival (DFS). Details of surgical or other treatments that were provided once the disease recurred were not specifically reported.

Table 7. Survival outcomes for patients with positive SLNs who undergo CLND versus observation.

Study	Type of Study	Arm	Number of Patients	Median Follow-Up (months)	Disease-Specific Survival (%)	DFS (%)	OS (%)
Wong 2006 [46]	retro	no CLND CLND	134 164	20 36	3-yr DSS 80 74 p=0.65 (log-rank)	NR	NR
Kingham 2010 [47]	retro	no CLND CLND	42 271	32 43	Median DSS Not yet reached 73 months p=0.26	NR	NR
Van de Ploeg 2009 (48)	retro	No CLND (Starz-III) CLND (Starz I,II)	50 20	33	NR	60 83 p=0.40	80- 100 p=0.04

CLND=completion lymph node dissection; DFS=disease-free survival; DSS=disease-specific survival; NR=not reported; ns=not significant; OS=overall survival; prosp=prospective; retro=retrospective; yr=year; the Starz [11,17] classification: SI or SII (≤1.0 mm invasion of metastasis from the capsule into the SLN), SIII (invasion >1.0 mm).

Recurrence

All three studies of CLND versus observation in SLN-positive patients show similar recurrence rates and/or patterns of recurrence between the CLND and observation arms (Table 8) in the respective studies [46-48]. For the sake of consistency, the percentage of patients with a given type of recurrence is calculated using the number of patients in each arm as the denominator rather than the number of patients with a recurrence. Percentages were recalculated, when needed, to ensure this consistency across each of these studies.

Table 8. Recurrence in patients with positive SLNs who undergo CLND versus observation.

Study	Arm	No. of Patients	Recurrence N(%)	Type of Recurrence[1]							Nodal Recurrence-Free Survival (%)	Median Relapse-Free Survival (months)
				LR Only N(%)	Nodal Only N(%)	Nodal +/- LR N(%)	LR as a Component N(%)	Nodal as a Component N(%)	Systemic Only N(%)	Systemic as a Component N(%)		
Wong, 2006[2] [46]	no CLND CLND	134 164	49(37) 85(52)	7(5) 29(18)	14(10) 12(7)	17(13) 14(9)	NR	20(15) 17(10)	NR	25(19) 42(26)	At 36 months 80 88 p=0.07 (log-rank)	NR
Kingham, 2010[2] [47]	no CLND CLND	42 271	20(48) 146(54)	7(17) 48(18)	2(5) 15(6)	NR	7(17) 45(17)	3(7) 17(6)	9(21) 73(27)	11(26) 78(29)	NR	35 36 p=0.63
van der Ploeg, 2009 [48]	no CLND (SI/SII)[3] CLND (SIII)	20 50	NR	NR	NR	NR	0(0) 1(2)	0(0) 2(4)	NR	0(0) 1(2)	NR	NR

Note: CLND, completion lymph node dissection; LR, locoregional; NE, not evaluable because of a low number of events; NR, not reported; SLN, sentinel lymph node
[1]Not mutually exclusive
[2]Pattern of first recurrence
[3]Patients divided by Starz classification (2001, 2004)

Three studies were identified that compared CLND with patients having a TLND for positive nodes [49-51]. These two patient populations are clearly different, with the latter having a poorer prognosis. Pasquali et al. [49] conducted a published literature meta-analysis of five studies, plus they included their own institutional data (n=2633). None of the data from the included studies was randomized. As expected, they report that the risk of death is significantly greater for patients undergoing TLND than CLND (hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.28 to 2.00) (see Table 9). Recurrence data is not reported [49]. Rutkowski et al. [50] report on data collected from one cancer centre in Poland. They found that overall survival (OS) from the date of relapse in patients with an in-transit/local recurrence (IT/LR) as a first recurrence was not significantly different in patients undergoing TLND or CLND. However, OS from the date of relapse was not a particularly useful measure. They also report that the rate of IT/LR as a first recurrence was not significantly different in the two arms of the study [50]. Veenstra [51] compared various measures of recurrence and found that there were no significant differences on any measure of recurrence between the TLND and CLND arms.

It is therefore difficult to make any definitive conclusions about the benefit of CLND at time of SLN positivity based on the limited data available and since most patients do go on to have a completion dissection. However, those patients do have a better survival than those presenting with bulky nodal disease. Since the ability to predict further nodal positivity in the

lymph node basin is limited (Question 1), patients are generally recommended to have a CLND at time of SLN positivity.

Table 9. Outcomes for patients who undergo CLND versus TLND

Study	Type of Study	Arm	Number of Patients	Survival Outcomes	Recurrence
Pasquali 2010 [49]	MA (PL)	TLND CLND	1488 1145	Risk of Death for TLND HR=1.60, 95% CI, 1.28-2.00; p<0.0001	NR
Rutkowski 2006 [50]	Retro?	TLND CLND	306 224	OS[a] in patients with IT/LR as first recurrence, p=ns	IT/LR as first recurrence 17.0% 20.1% p=ns
Veenstra 2010 [51]	Retro	TLND CLND	178 141	NR	TLND vs. CLND Local – 3% vs. 5%, ns Satellite – 2% vs. 2%, ns In-transit – 14% vs. 15%, ns Node field – 4% vs. 4%, ns Total – 19% vs. 22%, ns

CLND=completion lymph node dissection; IT=in transit; LR=local recurrence; MA=meta-analysis; NR=not reported; ns=nonsignificant; PL=published literature; retro=retrospective; TLND=therapeutic lymph node dissection; vs.=versus
[a]from the date of relapse

Extent of Nodal Dissection

Axilla

No studies pertaining to extent of axillary dissection were found.

Inguinal

One systematic review [52] and three other unique retrospective studies [53-55] were identified that evaluated the extent of inguinal node dissection (Table 10). Disease-free survival and five-year survival were not significantly different in those who had radical ilioinguinal LND or inguinal LND in the van der Ploeg et al. [55] study. However, in the Karakousis et al. [54] study, five-year survival significantly favoured those in the inguinal LND group, but these researchers limited their analysis to those who had histologically positive nodes. Two studies [52,55] reported on recurrence although no p-values are reported. Three studies [52-54] also reported on morbidity of radical versus inguinal LND, and all reported no significant differences either in general [52] or with respect to wound complications [53] or lymphedema [53,54].

It should be noted that these papers are not homogenous with respect to the nodal status of the patients included in the studies. The Hughes [52] systematic review includes some papers in which the patients had palpable nodes, some papers in which the patients had clinically negative nodes, and some papers with a mix of patients. Zoltie et al. [53] does not report on the nodal status of the patients included in their study. In Karakousis et al. [54] patients in the radical ilioinguinal LND arm had palpable nodes, whereas the patients in the inguinal LND arm had clinically negative nodes.

The van der Ploeg et al. [55] study only included patients with positive SLNs, and thus is the only paper in this group that does not have a case-mix issue. They report no significant difference in either DFS or five-year survival in those undergoing ilioinguinal versus inguinal dissection. Those in the ilioinguinal LND arm had more local recurrence and satellite

metastases, although p-values are not provided. Those in the inguinal LND arm had more lymph node recurrence, more in-transit metastases and more distant metastases. Again, no p-values are reported. Morbidity data is not provided.

Table 10. Outcomes for extent of inguinal node dissection for SLN positive patients.

Study	Type of Study	Arm	Nodal Status of Pts Included	No. of Pts	DFS	Median Survival	5-year Survival	Recurrence	Morbidity
Hughes 1999 [52]	SR	Ilioinguinal LND Inguinal LND	Some studies included: Clinically Palpable Nodes or Clinically Negative Nodes or Mixture	34 studies	NR	NR	Not reported by arm. Estimated 5-yr survival after pelvic LN mets 0-35%	<5% 9%-23%, p=NR	Report no difference in morbidity in the two arms
Zoltie 1991 [53]	Retro	Ilioinguinal LND Inguinal LND	NR	20 22	NR	24 mos 18 mos, p=ns	40% 35%, p=NR	NR	Wound Complications (Ilioinguinal vs. Inguinal LND) 65 vs. 50%, p=ns Lymphedema (Ilioinguinal vs. Inguinal LND) 35 vs. 18%, p=ns
Karakousis 1994 [54]	Retro	Ilioinguinal LND Inguinal LND	Ilioinguinal Arm – Palpable Nodes Inguinal Arm – Clinically Negative Nodes	104 94	5-yr DFS - Pts with Histologically Positive Nodes 17% 33%	NR	Pts with Histologically Positive Nodes 28% 41%, p=0.006	NR	Lymphedema 42% 37%, p=ns
van der Ploeg 2008 [55]	Retro	Ilioinguinal LND Inguinal LND	Positive SLNs	24 18	5-yr DFS 61% (95%CI: 39-96) 53% (95%CI: 31-90), p=ns	NR	80% (95%CI: 61-100) 76% (95%CI: 56-100), p=ns	**Event - Ilioinguinal vs. Inguinal (%)** Lymph node recurrence – 0 vs. 5.6 Local recurrence – 8.3 vs. 5.6 In-transit mets – 20.8 vs. 38.9 Satellite mets – 8.3 vs. 5.6 Distant mets – 20.8 vs. 33.3	NR

Note: CI, confidence interval; DFS, disease-free survival; LN, lymph node; LND, lymph node dissection; mets, metastases; mos, months; no., number; NR, not reported; ns, not significant; pts, patients; retro, retrospective; SLN, sentinel lymph node; SR, systematic review; vs., versus

Node of Cloquet

Two studies evaluating the value of the node of Cloquet in predicting pelvic lymph node metastases in patients with positive SLNs were identified [56,57] (Table 11). Essner et al. [56]

evaluated 93 patients in whom the node of Cloquet had been examined by H & E staining only. The staining had a poor positive predictive value (PPV) but a very high negative predictive value (NPV). They suggest that the Cloquet node may be useful in determining the status of iliac pelvic lymph nodes. Chu et al. [57] evaluated 53 patients for whom the node of Cloquet had been identified during groin or groin and pelvic dissection. Only six patients had positive iliac nodes, and of these, only two patients had a positive Cloquet's node. These authors concluded that routine evaluation of the node of Cloquet, in the era of SLNB, is unnecessary because a positive node of Cloquet is rare, and those with a positive node will likely have other indications for undergoing an iliac dissection.

Table 11. Diagnostic parameters for the node of Cloquet in predicting positive pelvic iliac nodes in patients with positive SLNs.

Study	Type of Study	Number of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Essner 2006 [56]	Retrospective	93	NR	NR	66	97
Chu 2010 [57]	Retrospective	53	NR	NR	NR	NR

NPV=negative-predictive value; PPV=positive-predictive value; SLN=sentinel lymph node

2. Patients with Biopsy Proven, Clinically Palpable, or Radiologically Detected Positive Nodes

a. Extent of Nodal Dissection

Axilla

No RCTs were found where evidence-based examination of the extent of dissection on the axilla was performed. The current clinical standard is to perform a complete Level 1,2,3 dissection, removing all nodes along the axillary/subclavian vein until the subclavian vein goes under the clavicle to enter the chest at the costoclavicular or "Halsted's" ligament [64-66]. Full dissection is recommended because the axilla is considered to be one nodal basin and the levels somewhat arbitrarily defined by the location of the pectoralis major. Because the location of the melanoma may be anywhere on the skin, a systematic pattern of spread throughout the axilla is unpredictable (unlike the situation in breast cancer).

Inguinal

One paper was identified that only included patients with palpable lymph nodes [58]. There was no significant difference in either median or five-year survival in those undergoing ilioinguinal LND versus inguinal LND. These authors reported that 33.6% of all patients relapsed in the dissection lymph node basin but did not report the relapse rate by study arm. Morbidity data is not provided. A distinction is made between inguinal and iliac dissection; while both are considered locoregional disease, the inguinal ligament separates them.

Node of Cloquet

Two studies evaluating the value of the node of Cloquet in predicting pelvic lymph node metastases were identified [59,60]. Shen et al. [59] retrospectively evaluated 68 patients for whom the node of Cloquet had been identified using H & E staining and reported on within the surgical pathology report. Thirty patients had a positive Cloquet node, and 20(67%) of these had positive iliac nodes, whereas thirty-five patients had a negative Cloquet node, and 8 (23%) of these patients had positive iliac nodes (odds ratio [OR], 6.8; p=0.0019). Shen et al. [59] went on to use immunohistochemistry (IHC) to re-evaluate the eight negative Cloquet nodes that were associated with positive iliac nodes and found that three of these Cloquet nodes were actually tumour positive. This increased the odds ratio of iliac node involvement from 6.8 to 12.4 and improved the sensitivity, positive predictive value (PPV), and negative predictive value

(NPV) for the node of Cloquet (see Table 12). Shen et al. [59] concluded that the status of the node of Cloquet significantly indicated the tumour status of the iliac/obturator nodes especially when the Cloquet node is evaluated using IHC. Strobbe et al. [60] evaluated a larger group of patients either retrospectively, in which the status of the node of Cloquet happened to be reported, or prospectively, in which the node of Cloquet was actively looked for during surgery. This group of researchers found the sensitivity of the node of Cloquet to be much poorer than that of Shen et al. [59], and they conclude that this particular node does not accurately predict the tumour status of the iliac nodes.

It should be noted that these papers are not homogenous with respect to the nodal status of the patients included in the studies. Shen et al. [59] included patients both with and without clinically palpable nodes, whereas Strobbe et al. [60] mostly included patients with clinically palpable nodes.

Table 12. Diagnostic parameters for the node of Cloquet in predicting positive pelvic iliac nodes.

Study	Type of Study	Nodal Status of Included Patients	Number of Patients	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Shen 2000 [59]	Retro	Palpable nodes - 81% Non-palpable nodes - 17% Metastatic - 2%	68	71 82[a]	73 73[a]	67 70[a]	77 84[a]
Strobbe 2001 [60]	Retro & prosp	Palpable nodes - 91% Non-palpable nodes - 6% Positive SLN - 4%	194	54	90	69	82

NPV=negative-predictive value; PPV=positive-predictive value, prosp=prospective; retro=retrospective
[a]calculated after eight negative Cloquet nodes were re-evaluated with immunohistochemistry and three were found to be positive.

ONGOING TRIALS

The National Cancer Institute (NCI) clinical trials database was searched on September 21, 2011 (http://www.cancer.gov/clinicaltrials/search) for reports of new or ongoing trials that met the inclusion criteria for this review. One relevant phase III trial was identified and is described in Table 13.

Table 13. Ongoing randomized trials of surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities.

Title	Complete lymph node dissection or observation in treating patient with localized melanoma and sentinel node metastasis who have undergone sentinel lymphadenectomy (MSLT-II)
Protocol ID	NCT00297895 ; NIH P01 CA029605
Date last modified	August 09, 2011
Type of trial	Phase III RCT, open-label, active control
Comparison	CLND vs US observation + delayed CLND if recurrence detected
Primary endpoint	Melanoma-specific survival
Accrual	Target enrolment 1925
Sponsorship	John Wayne Cancer Institute; National Institutes of Health
Status	Recruiting

DISCUSSION

There is a definite lack of randomized data that addresses the issue of the surgical management of patients with positive lymph nodes from cutaneous melanoma. The MSLT-II

trial has been designed to address this issue by comparing CLND to observation in patients with positive SLNs. Unfortunately, the results of this trial are not expected for some years to come. In the interim, there is still a need for guidance with respect to the management of this group of patients.

Less than 25% of patients with a positive SLN have further NSLN involvement. Given that there are morbidities associated with lymph node dissection, it would be advantageous if one could identify, in advance, those patients who are most likely to have positive NSLNs. To this end, many researchers have conducted studies to identify specific features that could predict those who are more likely to have positive NSLNs [4-6,10-45]. Most of these studies are small, and almost all are single-arm retrospective cohorts. In addition, each study seems to assess a different set of features. Interpretation of these features is difficult as they may be defined differently between studies making development of recommendations problematic at best. Of the 25 SLN features reported, only two were evaluated in more than 25% of the studies (see Tables 6a,b, and c). Additionally, when a given feature is evaluated in several studies, the results have not been consistent. Some studies will conclude that a particular feature is a good predictor of positive NSLNs, whereas other studies will conclude that the same feature is not a good predictor. There have also been attempts to create nomograms, similar to what has been done in breast cancer. Many of these scoring systems are based on multivariate analyses, which are questionable at best given the large number of factors evaluated and the small number of events (i.e., positive CLND). Consequently, it is not yet possible to identify in advance patients who are unlikely to have positive NSLNs and, therefore, can be spared CLND.

MSLT-II will determine what, if any, the benefits of CLND are at the time of a positive SLN compared to observation and possible later TLND. In the meantime, CLND is the standard of care in North America. Single-arm studies of patients undergoing CLND have demonstrated significantly poorer survival in those with a positive NSLN than in those with negative NSLNs [67,68]. The only comparative data currently available are a few small, retrospective studies [46,47] that do not demonstrate a survival or recurrence advantage to CLND versus not having CLND. In these studies, the reasons for electing not to have CLND were often based on patient preference or on physician and patient preference. It could be that patients with less extensive SLN disease were not advised to have a CLND by their physicians. van der Ploeg et al. [48] does demonstrate a survival advantage for those who do *not* have CLND, but these authors pre-selected their patients based on the Starz classification such that only those with more extensive SLN disease are provided with CLND. Therefore, this result is not surprising. Looking at the totality of the evidence, there is no strong evidence for or against CLND with respect to either survival or recurrence.

A direct comparison of patients who undergo CLND at the time of a positive SLN to those who undergo TLND only after nodes become clinically apparent also yielded mixed results. The meta-analysis by Pasquali et al. [49] included five studies as well as their own institutional data set. They report a significantly higher risk of death for those in the TLND arm compared to the CLND arm (HR, 1.60; 95% CI, 1.28 to 2.00; $p<0.0001$) but do not report on recurrence. Two other retrospective studies that were identified [50,51] did not demonstrate an advantage for CLND with respect to survival [50] or recurrence [50,51]. The results from a subgroup in the MSLT-1 study [69], which is included in the Pasquali et al. [49] meta-analysis, did demonstrate that those who did not undergo SLN biopsy but later presented with palpable nodes did have more bulky disease at TLND than did those who had CLND at the time of a positive SLN. These patients also had a significantly higher 5-year survival than patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm) (72.3% versus 52.4%; P=0.004). The strength of this finding is limited because this was a subgroup analysis, and overall survival in the MSLT-1 trial comparing immediate SLN biopsy versus delayed

dissection for node positive disease was not significant. However, this does suggest that there is a risk associated with waiting to do a LND until there is clinically apparent disease.

There is a paucity of data on the extent of dissection in patients with positive SLNs. There are no studies on extent of axillary dissection in this group of patients. There is very little data on the extent of inguinal dissection, and the results are mixed with respect to survival and recurrence. Finally, the papers are not homogenous with respect to the nodal status of the patients included in the studies. Only the van der Ploeg et al. [55] study solely included patients with positive SLNs. They reported no significant difference in either DFS or five-year survival in those undergoing ilioinguinal versus inguinal dissection. Those in the ilioinguinal LND arm had more local recurrence and satellite metastases, although p-values are not provided. Those in the inguinal LND arm had more lymph node recurrence, more in-transit metastases and more distant metastases, but, again, no p-values are reported [55]. There are no significant differences in morbidity in those undergoing inguinal versus ilioinguinal dissection in those studies that report this outcome. Finally, only two small retrospective studies were found that looked at the node of Cloquet in patients with positive SLNs [56,57]. The results of these studies are conflicting, with one concluding that evaluating the node of Cloquet might be useful in determining the status of iliac pelvic nodes [56] and the other concluding that routine evaluation of the node of Cloquet is unnecessary [57].

Few studies address the extent of LND in patients with clinically palpable nodes and no studies on axillary dissection. The one study looking at the extent of inguinal dissection in this group of patients [58] reported no significant difference in the median or five-year survival in those patients undergoing ilioinguinal LND versus inguinal LND. Two studies evaluated the role of the node of Cloquet in predicting pelvic lymph node metastases [59,60]. Again, one study had more promising results [59] than the other [60]. As a result, the value in locating and dissecting the node of Cloquet remains controversial.

We have not included the topic of postoperative radiation to the nodal basin in our review, but evidence exists that suggests that postoperative radiation to an involved nodal basin is beneficial, especially with large or numerous nodes [70]. CLND may offer the benefit, therefore, of selecting patients for postoperative radiation, and that finding could be the topic of a future guideline.

CONCLUSIONS

The surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities must be based on the best available evidence. Although there is a lack of RCT evidence that could address all possible issues, the evidence that is available shows that survival is possible for patients with node positive, and that this can be achieved with regional node dissection. The results of the MSLT-II trial, which will provide randomized evidence of the benefits (if any) of upfront CLND and possible delayed TLND, is eagerly awaited. Nevertheless, these patients present needing treatment. There is evidence that some patients have long-term survival after surgery for nodal disease, but, unfortunately, there are few alternative treatments. The recommendation is, therefore, that CLND be offered to patients at the time of positive SLNB. Based on the expert opinion of the authors, this should be a Level 1, 2 and 3 axillary dissection or a complete inguinal dissection, depending on the location of the melanoma. However, Cloquet's node and ilioinguinal dissection is much more controversial. The authors do recognize the need for resource allocation for such a recommendation, in that CLND requires referral to a surgeon with expertise in this procedure.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

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Appendix 1. Members of the Melanoma DSG Working Group Panel.

Chair:

Alexandra Easson	Surgeon	Princess Margaret Hospital, Toronto, ON

Panel Members:

Roxanne Cosby	Methodologist	PEBC, McMaster University, Hamilton, ON
David McCready	Surgeon	Princess Margaret Hospital, Toronto, ON
Teresa Petrella	Medical Oncologist	Odette Regional Cancer Centre, Toronto, ON
Claire Temple	Plastic Surgeon	Tom Baker Cancer Centre, Calgary, AB
Frances Wright	Surgeon	Odette Regional Cancer Centre, Toronto, ON

Appendix 2. Members of the Melanoma Disease Site Group.

Co-Chairs:

Teresa Petrella	Medical Oncologist
Frances Wright	Surgical Oncologist

Members:

Tara Baetz	Medical Oncologist
Pablo Cano	Medical Oncologist
Roxanne Cosby	Methodologist
Alexandra Easson	Surgical Oncologist
Danny Ghazarian	Pathologist
Caroline Hamm	Medical Oncologist
Anthony Joshua	Medical Oncologist
Oliver Keller	Medical Oncologist
Adam Mamelak	Dermatologist
David McCready	Surgical Oncologist
Elaine McWhirter	Medical Oncologist
Christian Murray	Dermatologist
Sudha Rajagopal	Medical Oncologist
R. Bryan Rumble	Methodologist
Alexander Sun	Radiation Oncologist
Claire Temple	Plastic Surgeon
John Toye	Plastic Surgeon
Shailendra Verma	Medical Oncologist

Appendix 3. Literature search strategy.

MEDLINE – Primary Research Papers

1. exp Melanoma/
2. melanoma.mp. or Melanoma/
3. (maligna: adj2 lentigo).tw.
4. (malignant adj1 (nev: or naev:)).tw.
5. (malignan: adj5 melanoma:).tw.
6. or/1-5
7. exp Sentinel Lymph Node Biopsy/
8. (sentinel adj3 biops:).tw.
9. exp Lymph Node Excision/
10. (lymph adj2 excision).tw.
11. (lymph adj2 biops:).tw.
12. (lymph adj2 dissection).tw.
13. (lymph node adj2 surgery).tw.
14. (SLNB or SNB).tw.
15. completion lymph node dissection.mp.
16. (complet: adj1 lymph node dissection).tw.
17. completion lymphadenectomy.mp.
18. therapeutic lymph node dissection.mp.
19. (therap: adj1 lymph node dissection).tw.
20. therapeutic lymphadenectomy.mp.
21. extent of dissection.mp.
22. extent of excision.mp.
23. deep inguinal node dissection.mp.
24. deep inguinal node.mp.
25. superficial inguinal node dissection.mp.
26. superficial inguinal node.mp.
27. level 3 axillary dissection.mp.
28. level 3 axillary node.mp.
29. cloquet's node dissection.mp.
30. cloquet's node.mp.
31. iliac node dissection.mp.
32. iliac node.mp.
33. obturator node dissection.mp.
34. obturator node.mp.
35. or/7-34
36. 6 and 35
37. comment.pt.
38. letter.pt.
39. editorial.pt.
40. case report.tw.
41. historical article.pt.
42. or/37-41
43. 36 not 42
44. limit 43 to english language

EMBASE – Primary Research Papers

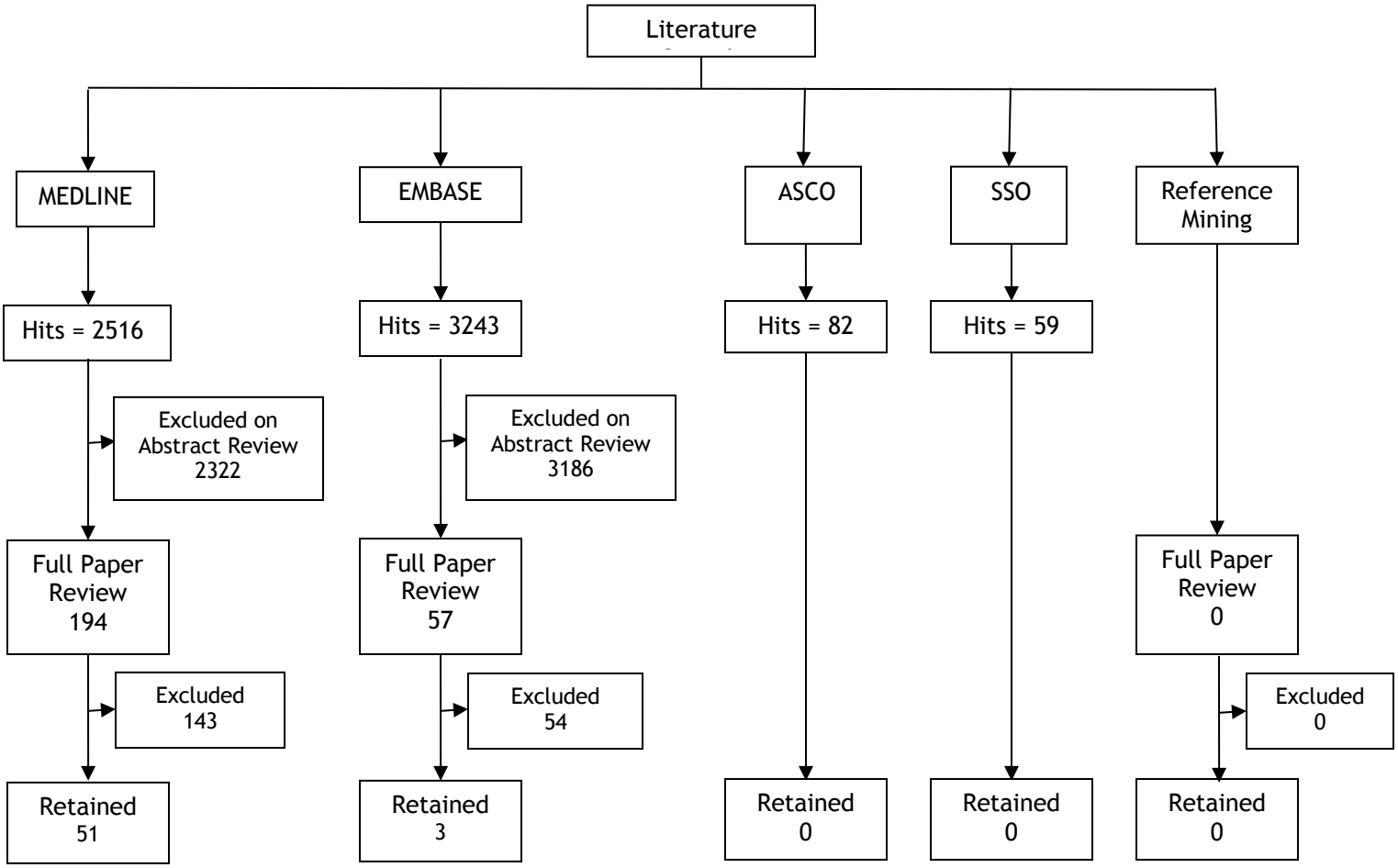
1. exp melanoma/
2. melanoma.mp.
3. (maligna: adj2 lentigo).tw.
4. (malignant adj1 (nev: or naev:)).tw.
5. (malignan: adj5 melanoma:).tw.
6. or/1-5
7. exp sentinel lymph node biopsy/
8. (sentinel adj3 biops:).tw.
9. lymph node excision.mp. or exp lymphadenectomy/
10. (lymph adj2 excision).tw.
11. (lymph adj2 biops:).tw.
12. (lymph adj2 dissection).tw.
13. (lymph node adj2 surgery).tw.
14. (SLNB or SNB).tw.
15. completion lymph node dissection.mp.
16. (complet: adj1 lymph node dissection).tw.
17. completion lymphadenectomy.mp.
18. therapeutic lymph node dissection.mp.
19. (therap: adj1 lymph node dissection).tw.
20. therapeutic lymphadenectomy.mp.
21. extent of dissection.mp.
22. extent of excision.mp.
23. deep inguinal node dissection.mp.
24. deep inguinal node.mp.
25. inguinal lymph node/
26. superficial inguinal node dissection.mp.
27. superficial inguinal node.mp.
28. level 3 axillary dissection.mp.
29. level 3 axillary node.mp.
30. axillary lymph node/
31. cloquet's node dissection.mp.
32. cloquet's node.mp.
33. iliac node dissection.mp.
34. iliac node.mp.
35. obturator node dissection.mp.
36. obturator node.mp.
37. or/7-36
38. 6 and 37
39. comment.pt.
40. letter.pt.
41. editorial.pt.
42. case report.tw.
43. historical article.tw.
44. or/39-43
45. 38 not 44
46. limit 45 to english language**MEDLINE – Guidelines**

1. exp Melanoma/
2. exp Skin Neoplasms/
3. 1 or 2
4. limit 3 to (consensus development conference or consensus development conference, nih or guideline or practice guideline)
5. limit 4 to english language

EMBASE – Guidelines

1. exp melanoma/
2. exp skin cancer/
3. 1 or 2
4. exp practice guideline/
5. 3 and 4
6. limit 5 to yr="1980 - 2010"
7. (melanoma: or (skin and (tumor: or tumour: or neoplasm: or cancer:))).ti.
8. 6 and 7
9. limit 8 to english language

Appendix 4. Flow diagram of literature search results.



Appendix 5. Quality attributes of studies used to inform each of the topics addressed in this guidance report.

	Topic	Study	Design	N Undergoing CLND	Funding Reported	Control Details	Blinded Assessment	Power Calc
Patients with Positive Sentinel Lymph Nodes	**Predicting NSLN Positivity**	Joseph, 1998	Prospective cohort	64	No	NA	NA	NA
		Starz 2001	Retrospective cohort	39	No	NA	NA	NA
		McMasters 2002	Subgroup analysis of an RCT	274	Yes	NR	No	NR
		Reeves 2003	Retrospective cohort	98	No	NA	NA	NA
		Salti 2003	Retrospective cohort	56	No	NA	NA	NA
		Cochran 2004	Retrospective cohort`	90	No	NA	NA	NA
		Dewar 2004	Retrospective cohort	146	No	NA	NA	NA
		Elias 2004	Retrospective cohort	80	No	NA	NA	NA
		Lee 2004	Retrospective cohort	191	Yes	NA	NA	NA
		Scolyer 2004	Retrospective cohort	140	Yes	NA	NA	NA
		Starz 2004	Retrospective pre/post cohort	45	No	Yes	NR	NA
		Fink 2005	Retrospective cohort	26	No	NA	NA	NA
		Sabel 2005	Retrospective cohort	221	No	NA	NA	NA
		Vuylsteke 2005	Prospective cohort	71	Yes	NA	NA	NA
		Pearlman 2006	Retrospective cohort	80	No	NA	NA	NA
		van Akkooi 2006	Retrospective cohort	67	No	NA	NA	NA
		Govindarajan 2007	Retrospective cohort	127	No	NA	NA	NA
		Debarbieux 2007	Retrospective cohort	98	Yes	NA	NA	NA
		Page 2007	Retrospective cohort	70	No	NA	NA	NA
		Frankel 2008	Retrospective cohort	136	No	NA	NA	NA
		Glumac 2008	Retrospective cohort	73	No	NA	NA	NA
		Guggenheim 2008	Retrospective cohort	100	No	NA	NA	NA
		Roka 2008	Retrospective cohort	85	No	NA	NA	NA
		Rossi 2008	Retrospective cohort	96	Yes	NA	NA	NA
		Satzger 2008	Retrospective cohort	180	No	NA	NA	NA
		van Akkooi 2008	Retrospective cohort	360	Yes	NA	NA	NA
		Cadili 2009	Retrospective cohort	68	Yes	NA	NA	NA
		Gershenwald 2008	Retrospective cohort	343	Yes	NA	NA	NA
		Ollila 2009	Retrospective cohort	86	No	NA	NA	NA
		Santinami 2009	Retrospective cohort	150	No	NA	NA	NA
		Cadili 2010	Retrospective cohort	606	No	NA	NA	NA
		Cadili 2010	Retrospective cohort	140	No	NA	NA	NA
		Murali 2010	Retrospective cohort	309	Yes	NA	NA	NA
		Wiener 2010	Retrospective cohort	323	No	NA	NA	NA
		Younan 2010	Retrospective cohort	82	No	NA	NA	NA
		Bogenrieder 2011	Retrospective cohort	70	No	NA	NA	NA
		Fink 2011	Retrospective cohort	121	Yes	NA	NA	NA
		Kunte 2011	Retrospective cohort	176	Yes	NA	NA	NA
		van der Ploeg	Retrospective cohort	1009	No	NA	NA	NA
	CLND vs O	Wong 2006	Retrospective cohorts - comparison	298	No	Yes	NR	NA
		Kingham 2010	Retrospective cohorts - comparison	313	No	Yes	NR	NA
		van der Ploeg 2009	Prospective cohorts- comparison	70	No	Yes	NR	NA
	CLND vs TLND	Pasquali 2010	Meta-analysis[a]	NA	NA	NA	NA	NA
		Rutkowski 2006	Prospective cohorts - comparison	530	No	Yes	NR	NA
		Veenstra 2010	Retrospective cohorts - comparison	319	No	Yes	NR	NA
	Nodal Dissection (Inguinal)	Hughes 1999	Systematic review[a]	NA	NA	NA	NA	NA
		Zoltie 1991	Retrospective cohorts - comparison	42	No	Yes	NR	NA
		Karakousis 1994	Retrospective cohorts – comparison	198	No	Yes	NR	NA

	Topic	Study	Design	N Undergoing CLND	Funding Reported	Control Details	Blinded Assessment	Power Calc
		van der Ploeg 2008	Retrospective cohorts – comparison	42	No	Yes	NR	NA
	Nodal Dissection (Cloquet)	Essner 2006	Retrospective cohort	93	Yes	NA	NA	NA
		Chu 2010	Retrospective cohort	53	Yes	NA	NA	NA
Patients with Clinically Palpable	**Nodal Dissection (Inguinal)**	Kretschmer 2001	Retrospective cohorts – comparison	104	No	Yes	NR	NA
	Nodal Dissection (Cloquet)	Shen 2000	Retrospective cohort	65	Yes	NA	NA	NA
		Strobbe 2001	Retrospective & Prospective cohorts	195	No	NA	NA	NA

CLND=completion lymph node dissection; NA=not applicable; NR=not reported; NSLN=non-sentinel lymph node;) O=observations; TLND=therapeutic lymph node dissection

[a]Quality of the meta-analysis and systematic review evaluated by AMSTAR tool. See page 4 of Evidentiary Base.

Evidence-Based Series 8-6 Version 2: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities: Development Methods, Recommendations Development and External Review Process

A. Easson, R. Cosby, D.R. McCready, C. Temple, T. Petrella, F. Wright, and the Melanoma Disease Site Group

Original Report Date: December 5, 2012

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle [1,2]. The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group

or Panel.

- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF this Evidence-based Series

Development and Internal Review

This EBS was developed by the Melanoma Disease Site Group of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the surgical management of lymph node metastases from cutaneous melanoma of the trunk or extremities, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, a panel that includes oncologists and whose members have clinical and methodological expertise. Key issues raised by the Report Approval Panel included the following (with the Working Group responses italicized):

- a comment that the need for this guideline, in the absence of strong evidence, was not as strongly articulated as it could be. Another comment that perhaps the guideline should not be written until the MSLT-II data are available. *More information about the need and impetus of the guideline was added to the Introduction.*
- a query that the Questions 1bi and 1bii were redundant. *A section with definitions was added to Sections 1 and 2 as a means of clarification.*
- a query that portions of Questions 1 and 2 were redundant. *Question 2 was reworded to provide clarity.*
- an observation that even though there are currently no statistically significant findings regarding CLND, the pattern in the outcomes do not favour CLND and in fact appear to favour not having CLND. *More interpretation and explanation of these results were added to the Discussion.*
- a comment that in the absence of good quality evidence several of the recommendations were based on expert opinion and that a modified Delphi method should be considered. *This suggestion was not implemented. Delphi is also expert opinion, and the pool of melanoma surgeons is small.*
- an observation that perhaps the Tables 6a and 6b do demonstrate that some SLN features may predict a positive CLND. *More interpretation of this data is provided in the Discussion section to address this.*
- a comment that the guideline does not cover radiation to the nodal basin for patients with a positive CLND. *A reference for this was added to the Discussion, as well as a statement that it could be the topic of a separate guideline.*
- a comment that the tables (particularly tables 6a, 6b and) are too large with too many blank cells and that removing many of the rows would make the document more readable. *The Working Group believed strongly that all the tables were important to the telling of the story. However, it was agreed that there were many empty rows, particularly in Table 6c. Therefore, the empty rows from each table were removed.*

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified

content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Melanoma DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Melanoma DSG.

BOX 1:
QUESTIONS

1. What is the optimal surgical management of patients with positive sentinel lymph nodes (SLNs) from cutaneous melanoma of the trunk or extremities with respect to:
   a. Factors for predicting non-sentinel lymph node (NSLN) positivity
   b. Completion lymph node dissection (CLND) at the time of SLN positivity versus:
      i. observation and
      ii. delayed therapeutic lymph node dissection (TLND) when a clinically positive node is detected
   c. Extent of nodal dissection

2. What is the optimal surgical management of patients with biopsy-proven clinically palpable or radiologically detected lymph nodes from cutaneous melanoma of the trunk or extremities with respect to:
   a. Extent of nodal dissection

OUTCOMES OF INTEREST

The outcomes of interest for these guideline recommendations are local and regional recurrence, distant recurrence, overall survival (OS), and disease-free survival (DFS).

TARGET POPULATION

These recommendations apply to adult patients with truncal or extremity cutaneous melanoma with nodal metastases.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management or referral of patients with nodal metastases from truncal or extremity cutaneous melanoma.

RECOMMENDATIONS AND KEY EVIDENCE

1. Patients with a positive sentinel lymph node

a. Prognostic factors for predicting non-sentinel lymph node involvement

> No consistent set of factors reliably predicts non-sentinel lymph node positivity in those with a positive SLN. Hence, it is recommended that all patients with a positive SLN be offered either a completion lymph node dissection (CLND) of the involved nodal basin or enrolment in a relevant clinical trial.

Thirty-nine (1-39) studies, mainly retrospective, have looked at many factors that might predict further node positivity at CLND. However, no core set of features among the studies is consistently examined nor does a core set of features consistently predict a positive CLND. Therefore, it is not possible to identify a group of patients who can reliably be spared CLND.

b. Completion lymph node dissection

> All patients with a positive SLN should be offered CLND of the appropriate nodal basin or be offered enrolment in a relevant clinical trial pending the emergence of good quality randomized data.

Currently, of the few studies that have evaluated the benefit of CLND over either observation or delayed TLND with respect to survival, none are randomized. One published literature meta-analysis (40) of more than 2500 patients does demonstrate a survival advantage for upfront CLND at the time of a positive SLN versus delayed TLND once nodes are clinically palpable (Risk of Death for TLND, hazard ratio [HR], 1.60; 95% confidence interval [CI], 1.28 to 2.00; p<0.0001). This recommendation is based on the limited evidence and expert opinion.

Likewise, the few studies that evaluate the benefit of CLND over either observation or delayed TLND with respect to recurrence are not randomized. No studies identified have reported significant differences in recurrence between CLND and observation (41-43) or CLND and delayed TLND (40,44,45).

c. Extent of nodal dissection

A complete Level 1, 2 and 3 dissection in the axilla is recommended for patients with a positive SLN, pending the emergence of good quality randomized data.

No studies addressing this question were identified, resulting in no evidence to support or refute the extent of axillary dissection being found. This recommendation is based on expert opinion only.

An inguinal dissection is recommended for patients with a positive SLN in the groin, pending the emergence of good quality randomized data. The routine examination of Cloquet's node and the addition of iliac dissection are much more controversial, and any decision regarding these procedures should be made on a case-by-case basis.

There is no clear advantage to ilioinguinal dissection (46-49) or the evaluation of Cloquet's node (50,51) with respect to survival or morbidity in the small dataset that is available. This recommendation is based on expert opinion.

2. Patients with biopsy-proven clinically or radiologically detected positive nodes

a. **Extent of nodal dissection**

A Level 1, 2 and 3 dissection in the axilla is recommended for patients with biopsy-proven clinically or radiologically detected positive nodes, pending the emergence of good quality randomized data.

No studies addressing this question were identified, resulting in no evidence to support or refute the extent of axillary dissection being found. However, these patients are more likely to have multiple positive nodes. This recommendation is based on expert opinion only.

Inguinal dissection is recommended for patients with biopsy-proven clinically or radiologically detected positive inguinal lymph nodes, pending the emergence of good quality randomized data. Because there is a greater likelihood of positive ilioinguinal nodes in this clinical situation, Cloquet's node should be examined and ilioinguinal dissection undertaken if the node is positive.

In the small dataset currently available there is no clear advantage to ilioinguinal dissection (52) or the evaluation of Cloquet's node (53,54) with respect to survival or morbidity. This recommendation is based on expert opinion.

QUALIFYING STATEMENTS

- Cloquet's node is defined as the highest node of the inguinal basin at the apex of the femoral triangle. The node is medial to the femoral vein at the level of the inguinal ligament (55,56).
- Decisions regarding iliac dissection should be made on a case-by-case basis.

Methods

Targeted Peer Review: Three individuals (one each from British Columbia, Alberta, and Nova Scotia) considered to be clinical and/or methodological experts on the topic were identified by the Melanoma DSG during the guideline development process and were invited to participate as Targeted Peer Reviewers. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Three reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on June 6, 2012. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Melanoma DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All surgeons, dermatologists, and medical oncologists that treat skin cancers in the PEBC database were contacted by email to inform them of the survey. One hundred and forty-one were from Ontario, and one was from outside Ontario. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on June 15, 2012. The consultation period ended on July 16, 2012. The Melanoma DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	1
2. Rate the guideline presentation.				2	1
3. Rate the guideline recommendations.			1	2	
4. Rate the completeness of reporting.			2	1	
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	2	
6. What are the barriers or enablers to the implementation of this guideline report?	No barriers were identified in the responses				
	Lowest Quality (1)	**(2)**	**(3)**	**(4)**	**Highest Quality (5)**
7. Rate the overall quality of the guideline report			1	2	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
8. I would make use of this guideline in my professional decisions.			2	1	
9. I would recommend this guideline for use in practice.			2	1	

Summary of Written Comments

The main points contained in the written comments were:

Q2 Comments

- The evidence supporting 2b(i) and (ii) needs clarification. Specifically, one of the studies included in the Pasquali meta-analysis contributed to the estimate of effect but did not include an SLN biopsy arm.
- The level of supporting evidence for each recommendation should be included along with the narrative description.

Q3 Comments

- The opening explanation stating that node dissection is recommended for node positive disease pending RCT evidence may be misleading as no RCTs have been performed nor are planned according to the all-or-none criterion. Until an effective non-surgical therapy is an option, it would be unethical to randomize node-positive patients to a non-dissection treatment arm.
- The guideline statement on Cloquet's node may be too strong for the current evidence. First, the recommendation does not take modern imaging into account. Second, the authors used immunohistochemistry to evaluate the node and raise its positive predictive value, but this is not practical for intra-operative decision-making (requires a second procedure to dissect the iliac chain).
- Recommendation 1b doesn't follow from the data. While covered in the Discussion, the logical leap from evidence to recommendation needs clarification.

Q4 Comments

- The guideline states that there was no survival advantage to completion node dissection after a positive sentinel node biopsy compared to those patients who presented with bulky disease after observation only (page 20), but this is not actually true. The subset of node positive patients from at least one trial (MSLT-I) showed statistically significant superior survival in the SNB group.

Q5 Comments

- Although the guideline is entitled "Surgical management" it really only addresses the surgical procedure. Equally important issues such as pre-operative staging are not only important in selecting patients for surgery but also dictate the extent of the surgery. For example, the data cited on using Cloquet's node to determine the need for iliac node dissection do not take modern imaging into account. Although the document acknowledges the importance of adjuvant nodal basin radiotherapy and suggests a second guideline, this topic cannot be excluded from decision making for surgery. For example, completion node dissection results in fewer and less bulky lymph nodes than delayed node dissection for recurrence (Section 2, ref 69). This may obviate the need for adjuvant radiotherapy with its incumbent morbidity and therefore argues in favour of CLND. This clinical guideline addressed a clinical procedure, and this topic represents a clinical problem that should consider more than one therapeutic modality.
- A second problem is the exclusion of all studies related to interval nodes such as epitrochlear, popliteal or other ectopic sentinel nodes. Although data are scarce, these patients also present problems in deciding the need and extent for node dissection. The first statement in the Conclusions (page 21) could be clarified. It states that management cannot be based on available evidence, but on the contrary, it must be based on available evidence. Although there are inadequate RCTs to address all potential issues,

trials such as MSLT-I and the intergroup melanoma trial on elective lymph node dissection show that survival is possible for patients with node positive disease and that this can be achieved with regional node dissection. Variance from this gold standard therapy requires high-level evidence, and that is the question being addressed by this document.

Modifications/Actions

Q2 Comment Responses

- Question Two has been revised for clarity and 2(ii) no longer appears. This change was made to reinforce the fact that 2(i) and 2(ii) referred to different patient populations. Only patients with extensive nodal dissection were retained, and are addressed under question 1B.
- Evidence is not graded according to PEBC methods; therefore, no changes were made to address this comment.

Q3 Comment Responses

- The Melanoma DSG agreed with this comment, and the relevant section in the Introduction section was changed to reflect this. It now reads, "Regardless of the level of evidence that exists in the literature, there is an immediate clinical need for guidelines that examine the best currently available evidence."
- The Melanoma DSG agreed with this comment, and Recommendation 2 has been changed from "Cloquet's node should be examined and ilioinguinal dissection undertaken if the node is positive" to "Cloquet's node could be examined and ilioinguinal dissection undertaken if the node is positive."
- The Melanoma DSG agreed with this comment, and the patient population was clarified by changing "Completion lymph node dissection" to "Completion lymph node dissection at the time of SLN positivity versus observation."

Q4 Comment Responses

- The Discussion section was changed to address this comment, and now reads, "These patients also had a significantly higher 5-year survival than patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm) (72.3% versus 52.4%; P=0.004). The strength of this finding is limited because this was a subgroup analysis, and overall survival in the MSLT-1 trial comparing immediate SLN biopsy versus delayed dissection for node positive disease was not significant. However, this does suggest that there is a risk associated with waiting to do a LND until there is clinically apparent disease."

Q5 Comment Responses

- The Melanoma DSG agreed that these issues were important, but acknowledged that these management issues were also out-of-scope and would not be addressed in this guideline.
- Regarding internal nodes, the Melanoma DSG did not address these as it was considered out-of-scope. Regarding the second point this reviewer submitted, the Melanoma DSG agreed and has changed the Conclusions to reflect this. It now reads, "The surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities must be based on the best available evidence. Although there is a lack of RCT evidence that could address all possible issues, the evidence that is available shows that survival is possible for patients with node positive, and that this can be achieved with regional node dissection."

Professional Consultation: Eighteen responses were received. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.		*1 (6%)*	*2 (12%)*	*8 (47%)*	*6 (35%)*
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			*1 (6%)*	*8 (47%)*	*8 (47%)*
3. I would recommend this guideline for use in practice.			*1 (6%)*	*8 (47%)*	*8 (47%)*

4. What are the barriers or enablers to the implementation of this guideline report?

- It might be hard to get acceptance for the morbidity related to level 3 axillary dissection without clear evidence for increased survival (overall or especially disease free).
- Most recommendations are based on expert opinion in this document.
- There is no consideration of the surgical completion of lymphadenectomy -- especially in the lower extremity.
- Head & neck melanoma should be discussed.

Summary of Written Comments

Only one point was returned on the written comments:

- Recommendations should be graded to reflect the level of evidence

Modifications/Actions

- While it might be difficult to get acceptance for level 3 dissection, this remains standard treatment, as there is no evidence of a survival benefit from less extensive surgery. No changes were made.
- The Melanoma DSG acknowledges that most of the recommendations are based on expert opinion.
- The Melanoma DSG agreed that this was not well described, and lymphadenectomy has been better defined in the Introduction section.
- While head and neck melanoma are important topics, the Melanoma DSG did not address them in this guideline, as they are out-of-scope.
- Recommendations were not graded as per PEBC methods.

Peer Review Feedback

Two members of the PEBC reviewed this document prior to the External Review process (NC, GF), and submitted feedback. All of the feedback obtained pertained to either formatting or presentation of the recommendations, and were retained or rejected as the Working Group saw fit. No substantial changes were made based on the Peer Review process.

CONFLICT OF INTEREST

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Melanoma DSG members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Two of the four authors declared they had no conflicts. Two others (AE, DM) declared conflicts and reported being published on the topic in the last five years (AE, DM), and on providing either public advice and/or guidance (DM).

For the Melanoma DSG, all 16 members declared they had no conflicts of interest. For CCO/PEBC staff involved in this EBS, neither of the two members reported any conflicts. For the RAP reviewers, none of the three reported any conflicts. One of the three Targeted Peer Reviewers (GM) reported that if this guideline resulted in more nodal dissections being performed then he could potentially see an increase in income, as this is a billable procedure. This same respondent reported being an investigator on a trial (MSLT-II), and in having provided advice and/or guidance in a public capacity (Province of Alberta guidelines).

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca

References

1. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. Journal of Clinical Oncology. 1995;13(2):502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

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Evidence-Based Series 8-6 Version 2: Section 4

Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities: Document Review Summary and Tool

A.M. Easson, J. Salerno,and the Melanoma Disease Site Group

October 3, 2016

The 2012 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2012. In 2015, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist [JS] conducted an updated search of the literature. A clinical expert [AE] reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Melanoma DSG decided to endorse the recommendations found in Section 1 (Guideline Recommendations) in September of 2016.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1a. What are the factors predicting non-sentinel lymph node positivity among melanoma patients with positive sentinel lymph nodes?

1b. What is the clinical effectiveness of completion lymph node dissection at the time of sentinel lymph node positivity on outcomes including local and regional recurrence, distant recurrence, overall survival, and disease-free survival compared with observation?

1c. What is the extent of nodal dissection for melanoma patients with positive sentinel lymph nodes (including biopsy-proven or radiologically detected positive nodes) in the following:
(a) Axilla?
(b) Groin?

(Note: slight modified wording [AE] from original 2012 guideline)

Literature Search and New Evidence

The new search* yielded a total of 2,573 publications. After assessing study eligibility, there were six practice guidelines [1-6], two systematic reviews [7,8], two randomized controlled trials [9,10], and four observational studies [11-14] that met the inclusion criteria (Figure 1). A summary of the included studies and their findings can be found in the Document Review Tool (see below).

*Note: the literature search was conducted in planned stages: performed on April 14, 2016 to identify systematic reviews, on April 21, 2016 to identify clinical studies and randomized controlled trials, on April 29, 2016 to identify practice guidelines, and on May 10, 2016 to identify observational studies (Question 1a only).

Impact on Guidelines and Its Recommendations

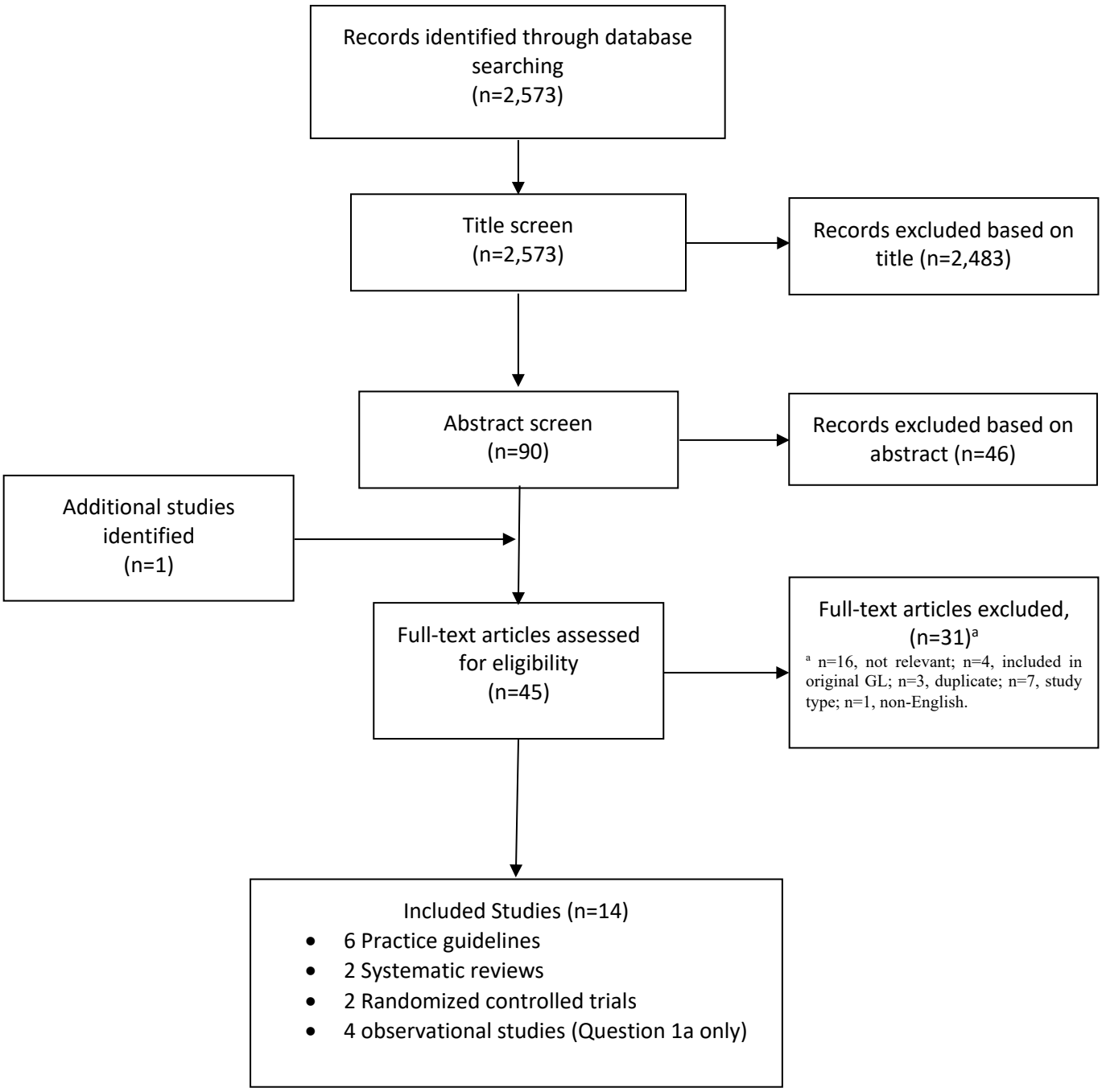
The new evidence in the form of other recent practice guidelines, systematic reviews, randomized controlled trials, and observational studies across the three research questions did not impact the relevancy of the of the 2012 PEBC guideline. Hence, the Melanoma DSG decided to endorse the 2012 PECB guideline recommendations.

With respect to Research Question 1b specifically, it was identified a priori that the ongoing Multicenter Selective Lymphadenectomy Trial II (MSLT-II) is the largest randomized controlled trial to provide direct evidence regarding Question 1b; however, its anticipated completion date is September 2022. Whether the results from MSLT-II will be published in a timely manner post-2022 and whether the MSLT-II trial results will be able to answer our research question is not known at this time. Therefore, MSLT-II was not considered in our decision-making at this time. From our new literature search, there was new evidence identified in the form of a recent randomized controlled trial (DeCOG-SLT) [9]. The DeCOG-SLT trial found no difference in distant metastasis-free survival, overall survival, or recurrence-free survival when SLN positive patients who received CLND were compared to patients who were observed. Although this study indicates no benefit for CLNB, the study was small (n=240 CLNB; n=233 observation) and included a short median follow-up time of 35 months. Additionally, the new literature search identified another related randomized controlled trial, the MSLT-I trial, as well as a Cochrane systematic review, which was based on the MSLT-I trial; however, this evidence was considered to be based on indirect evidence, in that, the randomization scheme did not directly answer our comparative research question regarding lymphadenectomy among melanoma patients already with a positive sentinel lymph node. Given the limitations of the DeCOG-SLT trial, the Melanoma DSG believes that the 2012 PEBC guideline recommendations for Question 1b are still valid. Results from the DeCOG-SLT trial has been added as Key Evidence in Section 1 of this report.

The original recommendations for extent of nodal dissection stated that recommendation would only be altered when good quality randomized data became available.

For this reason, only randomized studies and systematic reviews of randomized studies were included in the new literature search. There was no new evidence identified by the literature search; however, two observational studies [15,16], which were supplied from author files, were discussed by the Melanoma DSG. Both observational studies indicated that level III dissection may be unnecessary. Based on the non-randomized nature of these studies, the results cannot alter the current recommendations, but do point to an essential need for randomized controlled trials to evaluated the extent of nodal dissection in this patient population.

Figure 1. Citation Flow Chart



Document Review Tool

Number and title of document under review	8-6 Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities
Current Report Date	December 5, 2012
Clinical Expert	Alexandra Easson
Research Coordinator/PEBC Methodologist	Jennifer Salerno
Date Assessed	December 11, 2015
Approval Date and Review Outcome (once completed)	October 3, 2016 ENDORSE

Research Questions:

Question 1a. What are the factors predicting non-sentinel lymph node positivity among melanoma patients with positive sentinel lymph nodes?

Question 1b. What is the clinical effectiveness of completion lymph node dissection at the time of sentinel lymph node positivity on outcomes including local and regional recurrence, distant recurrence, overall survival, and disease-free survival compared with observation?

Question 1c. What is the extent of nodal dissection for melanoma patients with positive sentinel lymph nodes? (including biopsy-proven or radiologically detected positive nodes) in the following:

(c) Axilla?
(d) Groin?

Target Population: Adult patients (≥18 years of age) with truncal or extremity cutaneous melanoma with nodal metastases.

Study Section Criteria:

Inclusion criteria

- English-language reports published between Jan 1, 2011 to April 14, 2016*.
- Studies related to the surgical management of node-positive cutaneous melanoma.
- Clinical practice guidelines and systematic reviews (with or without meta-analyses).
- Primary studies that are phase II or III randomized controlled trials.
- Other non-randomized comparative studies and single-arm observational studies (Question 1a only).

*Note: the systematic literature search was conducted in planned stages: performed on April 14, 2016 to identify systematic reviews, on April 21, 2016 to identify clinical studies and randomized controlled trials, on April 29, 2016 to identify practice guidelines, and on May 10, 2016 to identify observational studies (Question 1a only).

Exclusion criteria

- Letters, editorials, notes, case reports, commentaries, and general reviews.

Search Details: Using MEDLINE and EMBASE, years: Jan 1, 2011-April 14, 2016* (earliest, see explanation above).

See above Figure 1 for the citation flow chart and see below for the detailed literature search strategies.

Brief Summary/Discussion of New Evidence:

The literature search identified 2,573 citations, of which six practice guidelines, two systematic reviews, two randomized controlled trials, and four observational studies (Question 1a only) were eligible for inclusion.

With regards to Question 1a, the new evidence showed a number of different factors associated with non-sentinel lymph node positivity. The largest synthesis of the evidence came from a systematic review which included 54 observational studies. The 2012 PEBC guideline had identified 39 observational studies at that time, and the new search identified four additional observational studies. However, taken together, there was a lack of new evidence with advanced statistical methods that could show whether a 'nomogram' (i.e., a synthesis of relevant predictive factors) was associated with non-sentinel lymph node positivity. Therefore, there was a lack of new evidence in the form of higher quality evidence and consequently, the prior 2012 PECB guideline recommendations for Question 1a are still valid.

A priori, it was identified that the ongoing Multicenter Selective Lymphadenectomy Trial II (MSLT-II) (www.clinicaltrials.gov) is the largest randomized controlled trial to provide direct evidence regarding Question 1b however its anticipated completion date is September 2022. Whether the results from MSLT-II will be published in a timely manner post-2022 and whether the MSLT-II trial results will be able to answer our research question is not known at this time. Therefore, MSLT-II was not considered in our decision-making at this time. From our new literature search, there was new evidence identified in the form of a recent randomized controlled trial (DeCOG-SLT). The DeCOG-SLT trial found no difference in distant metastasis-free survival, overall survival, or recurrence-free survival when SLN positive patients who received CLND were compared to patients who were observed. Although this study indicates no benefit for CLNB, the study was small (n=240 CLNB; n=233 observation) and included a short median follow-up time of 35 months. Additionally, the new literature search identified another related randomized controlled trial, the MSLT-I trial, as well as a Cochrane systematic review, which was based on the MSLT-I trial; however, this evidence was considered to be based on indirect evidence, in that, the randomization scheme did not directly answer our comparative research question regarding lymphadenectomy among melanoma patients already with a positive sentinel lymph node. Given the limitations of the DeCOG-SLT trial, the Melanoma DSG believes that the 2012 PEBC guideline recommendations for Question 1b are still valid. Results from the DeCOG-SLT trial has been added as Key Evidence in Section 1 of this report.

The original recommendations for extent of nodal dissection stated that recommendation would only be altered when good quality randomized data became available. For this reason, only randomized studies and systematic reviews of randomized studies were included in the new literature search. There was no new evidence identified by the literature search; however, two observational studies, which were supplied from author files, were discussed by the Melanoma DSG. Both observational studies indicated that level III dissection may be unnecessary. Based on the non-randomized nature of these

studies, the results cannot alter the current recommendations, but do point to an essential need for randomized controlled trials to evaluated the extent of nodal dissection in this patient population. The original 2012 recommendations for this Research Questions are still valid. Clinical Expert Interest Declaration: No conflicts of interest to declare.	
Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.	
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes Yes
3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
4. Do the PEBC and the DSG/GDG responsible for this document have the	Not applicable.

resources available to write a full update of this document within the next year?		
Review Outcome	ENDORSE	
DSG/GDG Approval Date	October 3, 2016	
DSG/GDG Commentary		

Appendix 1.

Table 1. Summary of New Evidence from Updated Literature Searches

Study [Ref]	Study Type	*Applicable Question(s) (1a, 1b or 1c)
Dummer et al, 2016 [1]	Practice Guideline	b
Berrocal et al, 2015 [2]	Practice Guideline	b
Pflugfelder et al, 2013 [3]	Practice Guideline	a, b, c
Wong et al, 2012 [4]	Practice Guideline	b
Dummer et al, 2012 [5]	Practice Guideline	b
Coit et al, 2012 [6]	Practice Guideline	b, c
Kyrgidis et al, 2015 [7]	Systematic Review	b
Nagaraja and Eslick, 2013 [8]	Systematic Review	a
Leiter et al, 2016 [9]	Randomized Controlled Trial	b
Morton et al, 2014 [10]	Randomized Controlled Trial	b
Damude et al, 2016 [11]	Observational Study	a
Bertolli et al, 2016 [12]	Observational Study	a
Kibrite et al, 2016 [13]	Observational Study	a
Wevers et al, 2013 [14]	Observational Study	a

*Applicable Questions:
Question 1a. What are the factors predicting non-sentinel lymph node positivity among melanoma patients with positive sentinel lymph nodes?

Question 1b. What is the clinical effectiveness of completion lymph node dissection at the time of sentinel lymph node positivity on outcomes including local and regional recurrence, distant recurrence, overall survival, and disease-free survival compared with observation?

Question 1c. What is the extent of nodal dissection for melanoma patients with positive sentinel lymph nodes? (including biopsy-proven or radiologically detected positive nodes) in the following: a. Axilla? b. Groin?

Appendix 2.

For each above stated research questions (a, b, c), the following data abstraction summary tables are presented by 'type of study':

Tables 1.X Recommendations from Practice Guidelines

Tables 2.X Results from Systematic Reviews

Tables 3.X Results from Clinical Studies or Randomized Controlled Trials

Tables 4.X Results from Observational Studies

Note: shaded rows indicate the findings from the 2012 PEBC guideline.

Question 1a: What are the factors predicting non-sentinel lymph node positivity among melanoma patients with positive sentinel lymph nodes?

Table 1a. Recommendations from Practice Guidelines

Author (Year)	Population	Methods	Outcomes	Recommendations
Pflugfelder et al, 2013 [3] **German Guidelines**	Pts with CM (excluding mucosal and uveal)	Systematic literature	Diagnosis, therapy and follow-up of melanoma	Weighted scores including several histologic and/or clinical risk factors *may be* employed to assess the risk of metastases in non-sentinel lymph nodes, but require further clinical validation before a general recommendation [Grade of Recommendation n/a, Level of Evidence 2b, according to the Oxford level of evidence hierarchy]

Table 2a. Results from Systematic Reviews

Author (Year)	Population	Methods	Outcomes	Brief Results
Nagaraja and Eslick, 2013 [8]	Pts with CM with SLN(+) who had CLND	Systematic review and meta-analysis, +2 databases, literature searched up to March 2013	Risk factors for NSLN metastases: 1. Ulceration 2. Satellitosis 3. Neurotropism 4. >1 positive SLN 5. Starz 3 (old) 6. Angiolymphatic invasion 7. Extensive location 8. Macrometastases >2 mm 9. Extranodal extension 10. Capsular involvement 11. Subcapsular location 12. Rotterdam Criteria <0.1 mm 13. Starz I (new) 14. Gender 15. Regression 16. Histologic type 17. Breslow thickness less than 2 mm and 2-4 mm 18. Primary site 19. Sentinel-node location 20. Parenchymal and Combined anatomic locations 21. Rotterdam criteria 0.1-1 mm 22. Starz 2 (old and new) 23. Micrometastases <2 mm	54 retrospective studies were included: Risk factors #1-10 were associated with NSLN metastases, e.g., OR > 1 (all but one factor was statistically significant at the 95% CI) Risk factors #11-13 were associated with a low risk of NSLN metastases, e.g. OR < 1 (all were statistically significant at the 95% CI) Risk factors #14-23 were shown to be equivocal

Table 3a. No clinical studies or randomized controlled trials were identified for this question.

Table 4a. Results from Observational Studies

Author (Year)	Population	Methods	Intervention/Outcomes	Results

Bertolli et al, 2016 [12]	SLN(+) CM pts + CLND, 2000-2010	Retrospective cohort	Metastatic area ratio: metastatic tumor area divided by the total lymph node area Outcome: NSN positivity	N=146 pts, positive NSN in 23 pts (15.8%) Tumor ratio showed a statistically significant association with NSN positivity in a model with perinodal vascular invasion
Damude et al, 2016 [11]	SLN(+) CM pts + CLND, 2004-2015	Prospective cohort	Biomarkers: serum S-100B and LDH Outcome: NSN positivity	N=107 pts, positive NSN in 22 pts (20.6%) Only S-100B showed a statistically significant association with NSN positivity in multivariable models
Kibrite et al, 2016 [13]	SLN(+) CM pts + CLND, 1996-2010	Retrospective cohort (review of a prospectively maintained database)	'Identify significant factors associated with subsequent lymph node status' Outcome: NSN positivity	N=171 pts with CLND, positive 'lymph nodes' in 33 pts (19.3%) Breslow thickness ≥ 2 mm or SLN with macroscopic burden ≥ 2 mm were reported to be statistically significant predictors of CLND lymph node status
Wevers et al, 2013 [14]	SLN(+) CM pts + CLND, 1995-2010	Retrospective cohort	N-SNORE (non-sentinel node risk score) Outcome: NSN positivity	N=130 pts, positive NSN in 30 pts (23.1%) Presence of regression showed a statistically significant association with NSN positivity in multivariable models, no other N-SNORE was associated (sex, regression in primary melanoma, proportion of harvested NS containing metastatic melanoma, maximum size of largest tumor deposit in SN, excluded: perinodal lymphatic invasion in SN) N-SNORE showed 'reasonable' model fit, r^2 = 0.21

Question 1b: What is the clinical effectiveness of completion lymph node dissection at the time of sentinel lymph node positivity on outcomes including local and regional recurrence, distant recurrence, overall survival, and disease-free survival compared with observation?

Table 1b. Recommendations from Practice Guidelines

Author (Year)	Population	Methods	Outcomes	Recommendations
Dummer et al, 2016 [1] **Swiss Guidelines**	Pts with CM	Literature review and graded recommendations according to CMA 1998 Levels of Evidence Hierarchy	Management and treatment	**For isolated tumor cells** detected on SLNB, *we do not recommend* CLND in patients who present only isolated tumor cells in their sentinel node until the presence of this pathological feature has shown clear prognostic implications. The benefits and shortcomings of CLND should be discussed carefully with patients having SLN with isolated tumor cells and stage N1a with low tumor load, until MSLT-II has clarified the issue.
Berrocal et al, 2015 [2] **SEOM Guidelines**	Malignant melanoma	Review of all phase III clinical trials and other main guidelines	Treatment, surgical management and follow-up	Complete lymph node dissection consists of anatomically thorough dissection of the involved nodal basin. It *must be performed* if sentinel node is positive or there are clinically positive nodes (stages IIB or IIIC). [Grade recommendation A; Level of Evidence 2a]
Pflugfelder et al, 2013 [3] **German Guidelines**	Pts with CM (excluding mucosal and uveal)	Systematic literature	Diagnosis, therapy and follow-up	When micrometastases are present in the sentinel lymph node a complete lymph node dissection *should be offered*. The decision for complete lymph node dissection in sentinel lymph nodes with a minimal tumor burden and/or subcapsular location must be made together with the patient and should take further risk factors such as tumor thickness, ulceration, tumor mitosis rate, number of positive sentinel lymph nodes and anatomic site of the primary tumor into consideration [Grade of recommendation B, Level of Evidence 2b, according to the Oxford level of evidence hierarchy]
Dummer et al, 2012 [5] **ESMO Guidelines**	Pts with CM	Not specified.	Guidelines for the diagnosis, treatment and follow-up	SLNB *should be followed by* a complete lymphadenectomy of regional lymph nodes, if the sentinel node was found positive for metastases [III, C]. Surgical removal of locoregional recurrence or single distant metastasis *should be* considered in fit patients as a therapeutic option offering potential for long-term disease control [*III, C].*
Wong et al, 2012 [4] **ASCO Guideline**	Pts with newly dx CM	Systematic review, 2 databases, Jan 1990 to Aug 2011	Primary outcomes were measures of test performance Secondary outcomes were results of CLND and measures of test performance	Completion lymph node dissection *is recommended* for all patients with a positive SLN biopsy.
Coit et al, 2012 [6] **NCCN Guidelines**	Pts with CM	Consensus-based with review of the literature, otherwise not specified	Staging, workup, primary treatment, adjuvant therapy, recurrence, metastatic disease	Patients with stage III disease based on a positive SLN *should be offered* a complete lymph node dissection of the involved nodal basin, either as standard care or in the context of a clinical trial evaluating alternative strategies (such as close monitoring with nodal basin ultrasound).

Table 2b. Results from Systematic Reviews

Author (Year)	Population	Methods	Outcomes	Brief Results
Kyrgidis et al, 2015 [7]	Pts with localized CM	Systematic review and meta-analysis, +2 databases, up to Feb 2015	Primary outcomes • Overall survival • Rate of treatment complications and side effects Secondary outcomes • Disease-specific survival • Disease-free survival • Local and regional recurrence • Distant metastases	MSLT-I trial comparing: excision + SLNB + 'early' CLND [experimental arm] vs. excision ('observation' and then 'delayed' LND for clinical relapse) [control arm] • *No survival benefit* for experimental arm, HR (ITT): 0.99, 95% CI: 0.82-1.19 o Intermediate-thickness, HR: 0.92, 95% CI: 0.73-1.16 o Thick, HR: 1.15, 95% CI: 0.82-1.61 • *No disease-specific survival* for experimental arm, HR: 0.92, 95% CI: 0.74-1.14 o Intermediate-thickness, HR: 0.84, 95% CI: 0.65-1.09 o Thick, HR: 1.12, 95% CI: 0.77-1.64 • *Beneficial effect* of experimental arm on disease-free survival, HR: 0.75, 95% CI: 0.63-0.89 [Author's note of *lead time bias* thus favouring the experimental arm] o Intermediate-thickness, HR: 0.77, 95% CI: 0.63-0.95 o Thick, HR: 0.70, 95% CI: 0.50-0.97 • *Beneficial effect* of experimental arm local and regional recurrence, RR: 0.56, 95% CI: 0.45-0.69 o Intermediate-thickness, HR: 0.57, 95% CI: 0.44-0.74 o Thick, HR: 0.52, 95% CI: 0.36-0.75 • *Reverse effect* of experimental arm on distant metastases as site of first recurrence, HR: 1.33, 95% CI: 1.03-1.72 [Author's note of increased regional immunity in the observational group thus favouring the observational group] o Intermediate-thickness, HR: 1.25, 95% CI: 0.92-1.70 o Thick, HR: 1.56, 95% CI: 0.95-2.54 • Author's conclusions are **low quality of evidence** since evidence was limited to a single RCT and the risk of bias was 'high' or 'unclear' in components.

Table 3b. Results from Clinical Studies or Randomized Controlled Trials

Author (Year)	Population	Methods	Outcomes	Brief Results
Leiter et al, 2016 [9]	Pts with CM + SLN	Phase III clinical trial	Primary outcome • Distant metastasis-free survival	Intervention, N=240; Control, N=233 Median follow-up: 35 months

DeCOG-SLT Trial	biopsy positive	Intervention: CLND Control: observation	Secondary outcome • Recurrence-free survival • Overall survival • Recurrence of regional lymph node metastasis • Side effects (CLND arm)	*No differences in primary or secondary survival outcomes:* Distant metastasis-free survival, HR: 1.19, 95% CI: 0.83-1.69 Overall survival, HR: 1.02, 95% CI: 0.68-1.52 Recurrence-free survival, HR: 0.96, 95% CI: 0.70-1.31

Morton et al, 2014 [10]
 	
MSLT-I Trial
	Pts with localized CM	Phase III clinical trial
		
		Intervention: WE + SLNB. CLND if metastases detected in SLN
		
		Control: WE + nodal observation. Delayed LND for nodal metastases occurring during observation.
			Primary outcome
			• Melanoma-specific survival
			
			Secondary outcomes
			• Disease-free survival
			• Survival based on SLN status
			• Incidence of nodal metastases
				Primary outcome
				• No significant effect on 10yr melanoma-specific survival, HR: 0.84, 95% CI: 0.64-1.09
				
				Secondary outcomes
				• *Beneficial effect* of intervention on 10yr disease-free survival
				  ○ Intermediate-thickness, HR: 0.76, 95% CI: 0.62-0.94
				  ○ Thick, HR: 0.70, 95% CI: 0.50-0.96
				• Among intervention arm, there was an *increased hazard* of SLN(+) vs SLN(-) on 10yr melanoma-specific survival
				  ○ Intermediate-thickness, HR: 3.09, 95% CI: 2.12-4.49
				  ○ Thick, HR: 1.75, 95% CI: 1.07-2.87
				• No difference in the 10yr cumulative incidence of nodal metastases between invention and control
				  ○ Intermediate-thickness, 21.9% vs. 19.5%
				  ○ Thick, 42.0% vs. 41.4%
				• For the subgroup of patients with nodal metastases, the 10 yr melanoma-specific survival *favoured the intervention* group [SLNB(+) vs. OBS]
				  ○ Intermediate-thickness, HR: 0.56, 95% CI: 0.37-0.84
				  ○ Thick, HR: 0.92, 95% CI: 0.53-1.60
				• No difference on melanoma-specific survival among SLNB(-) patients who then developed metastases (false-negatives) and SLNB(-) patients who then did not develop metastases for intermediate-thickness and thick melanomas
				• *Beneficial effect* of the intervention on distant-disease free survival (i.e. regional node metastases) but only among intermediate-thickness melanomas [SLNB(+) vs. OBS and clinical relapse]
				  ○ Intermediate-thickness, HR: 0.62, 95% CI: 0.42-0.91
				  ○ Thick, HR: 0.96, 95% CI: 0.56-1.64

	• Latent subgroup statistical methods showed *increased survival for treatment effect* of biopsy followed by immediate LND in patients with nodal metastases on disease-free survival (3.2), distant disease-free survival (2.1) and melanoma-specific survival (2.0)

Table 4b. No observational studies were considered for this question

Question 1c. What is the extent of nodal dissection for melanoma patients with positive sentinel lymph nodes? (including biopsy-proven or radiologically detected positive nodes) in the following: (a) Axilla? (b) Groin?

Table 1c. Recommendations from Practice Guidelines

Author (Year)	Population	Methods	Outcomes	Recommendations
Pflugfelder et al, 2013 [3] **German Guidelines**	Pts with CM (excluding mucosal and uveal)	Systematic literature	Diagnosis, therapy and follow-up of melanoma	Before a lymph node dissection staging imaging diagnostics and/or histologic confirmation of the lymph node metastasis e.g. with fine needle puncture should have been performed. Preoperatively, if indicated, lymphoscintigraphy may be performed for surgical planning. Due to the considerable risk of local lymph node recurrences, *a radical lymph node dissection shall be performed*. This applies to the femoral triangle lymph nodes in the **inguinal region (lower extremities and trunk)** [Extension includes Iliacal and obturator lymph nodes]. In the **axillary region (upper extremities and trunk)** the dissection of the typical lymph node stations *Level I-III is only recommended for primary tumors whose lymphatic drainage is to this site* [Based on 'good clinical practice' non-evidence based recommedations]
Coit et al, 2012 [6] **NCCN Guidelines**	Pts with CM	Consensus-based with review of the literature, otherwise not specified	Staging, workup, primary treatment, adjuvant therapy, recurrence, metastatic disease	In the groin, *consider* elective iliac and obturator lymph node dissection if clinically positive superficial nodes or ≥ 3 superficial nodes positive (category 2B). Iliac and obturator lymph node dissection indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).

Table 2c. No systematic reviews were identified for this question.
Table 3c. No clinical studies or randomized controlled trials were identified for this question.
Table 4c. No observational studies were considered for this question.

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Abbreviations: CI, confidence interval; CLND, complete lymph node dissection; CM, cutaneous melanoma; CMA, Canadian Medical Association; CT, computed tomography; HR, hazard ratio; ITT, intent-to-treat; LDH, lactate dehydrogenase; MSLT, Multicentre Selective Lymphadenectomy Trial; NSLN, non-sentinel lymph node; NSN, non-sentinel node; OBS, observation; OR, odds ratio; RCT, randomized controlled trial; RR, SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SN, sentinel node; TLND, therapeutic lymph node dissection; WE, wide excision.

New References Identified:

1. Dummer R, Siano M, Hunger RE, Lindenblatt N, Braun R, Michielin O, et al. The updated Swiss guidelines 2016 for the treatment and follow-up of cutaneous melanoma. Swiss Med Wkly. 2016;146:w14279.
2. Berrocal A, Arance A, Espinosa E, Castano AG, Cao MG, Larriba JLG, et al. SEOM guidelines for the management of Malignant Melanoma 2015. Clinical and Translational Oncology. 2015;17(12):1030-5.
3. Pflugfelder A, Kochs C, Blum A, Capellaro M, Czeschik C, Dettenborn T, et al. Malignant melanoma S3-guideline "Diagnosis, therapy and follow-up of melanoma". J Dtsch Dermatol Ges. 2013;11(SUPPL. 6):1-126.
4. Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, Cochran A, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. Annals of Surgical Oncology. 2012;19(11):3313-24.
5. Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G, Group EGW. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2012;23 Suppl 7:vii86-91.
6. Coit DG, Andtbacka R, Anker CJ, Bichakjian CK, Carson WE, 3rd, Daud A, et al. Melanoma. Journal of the National Comprehensive Cancer Network. 2012;10(3):366-400.
7. Kyrgidis A, Tzellos T, Mocellin S, Apalla Z, Lallas A, Pilati P, et al. Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma. Cochrane Database of Systematic Reviews. 2015;5:CD010307.
8. Nagaraja V, Eslick GD. Is complete lymph node dissection after a positive sentinel lymph node biopsy for cutaneous melanoma always necessary? A meta-analysis. European Journal of Surgical Oncology. 2013;39(7):669-80.
9. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer N, Berking C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. 2016.
10. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. New England Journal of Medicine. 2014;370(7):599-609.
11. Damude S, Hoekstra HJ, Bastiaannet E, Muller Kobold AC, Kruijff S, Wevers KP. The predictive power of serum S-100B for non-sentinel node positivity in melanoma patients. European Journal of Surgical Oncology. 2016;42(4):545-51.
12. Bertolli E, Macedo MP, Pinto CA, Damascena AS, Molina AS, Duprat Neto JP. Metastatic area ratio can help predict nonsentinel node positivity in melanoma patients. Melanoma Research. 2016;26(1):42-5.
13. Kibrite A, Milot H, Douville P, Gagne EJ, Labonte S, Friede J, et al. Predictive factors for sentinel lymph nodes and non-sentinel lymph nodes metastatic involvement: a database study of 1,041 melanoma patients. American Journal of Surgery. 2016;211(1):89-94.
14. Wevers KP, Murali R, Bastiaannet E, Scolyer RA, Suurmeijer AJ, Thompson JF, et al. Assessment of a new scoring system for predicting non-sentinel node positivity in sentinel node-positive melanoma patients. European Journal of Surgical Oncology. 2013;39(2):179-84.
15. Nessim C, Law C, McConnell Y, Shachar S, McKinnon G, Wright F. How often do level III nodes bear melanoma metastases and does it affect patient outcomes? Annals of Surgical Oncology. 2013;20(6):2056-64.

16. Tsutsumida A, Takahashi A, Namikawa K, Yamazaki N, Uhara H, Teramoto Y, et al. Frequency of level II and III axillary nodes metastases in patients with positive sentinel lymph nodes in melanoma: a multi-institutional study in Japan. Int J Clin Oncol. 2016;21(4):796-800.

Search Strategy:

Practice Guidelines

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Searched on April 29, 2016.

1 exp melanoma/
2 exp skin neoplasms/
3 1 or 2
4 (guideline or practice guideline).pt.
5 exp consensus development conference/
6 consensus/
7 (guideline: or recommend: or consensus or standards).ti.
8 4 or 5 or 6 or 7
9 3 and 8
10 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
11 exp animal/ not humans/
12 10 or 11
13 9 not 12
14 limit 13 to yr="2011 -Current"

Embase 1974 to 2016 Week 17. Searched on April 29, 2016.

1 exp melanoma/
2 exp skin cancer/
3 1 or 2
4 consensus development conference/
5 practice guideline/
6 *consensus development/ or *consensus/
7 *standard/
8 (guideline: or recommend: or consensus or standards).kw.
9 (guideline: or recommend: or consensus or standards).ti.
10 or/4-9
11 3 and 10
12 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
13 exp animal/ not humans/
14 12 or 13
15 11 not 14
16 limit 15 to yr="2011 -Current"

Systematic Reviews
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Searched on April 14, 2016.

1 exp Melanoma/
2 melanoma.mp. or Melanoma/
3 (maligna: adj2 lentigo).mp.
4 (malignant adj1 (nev: or naev:)).mp.
5 (malignan: adj5 melanoma:).mp.
6 or/1-5
7 exp Sentinel Lymph Node Biopsy/
8 (sentinel adj3 biops:).mp.
9 exp Lymph Node Excision/
10 (lymph adj2 excision).mp.
11 (lymph adj2 biops:).mp.
12 (lymph adj2 dissection).mp.
13 (lymph node adj2 surgery).mp.
14 (SLNB or SNB).mp.
15 completion lymph node dissection.mp.
16 (complet: adj1 lymph node dissection).mp.
17 completion lymphadenectomy.mp.
18 therapeutic lymph node dissection.mp.
19 (therap: adj1 lymph node dissection).mp.
20 therapeutic lymphadenectomy.mp.
21 extent of dissection.mp.
22 extent of excision.mp.
23 deep inguinal node dissection.mp.
24 deep inguinal node.mp.
25 superficial inguinal node dissection.mp.
26 superficial inguinal node.mp.
27 level 3 axillary dissection.mp.
28 level 3 axillary node.mp.
29 cloquet's node dissection.mp.
30 cloquet's node.mp.
31 iliac node dissection.mp.
32 iliac node.mp.
33 obturator node dissection.mp.
34 obturator node.mp.

35 or/7-34

36 6 and 35

37 (systematic adj (review: or overview:)).mp.

38 (meta-analy: or metaanaly:).mp.

39 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.

40 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.

41 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.

42 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.

43 or/37-42

44 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.

45 (stud: adj1 select:).ab.

46 (44 or 45) and review.pt.

47 43 or 46

48 36 and 47

49 limit 48 to yr="2011-Current"

Embase 1974 to 2016 Week 15. Searched on April 14, 2016.

1 exp Melanoma/

2 melanoma.mp.

3 (maligna: adj2 lentigo).mp.

4 (malignant adj1 (nev: or naev:)).mp.

5 (malignan: adj5 melanoma:).mp.

6 or/1-5

7 exp Sentinel Lymph Node Biopsy/

8 (sentinel adj3 biops:).mp.

9 lymph node excision.mp. or exp lymphadenectomy/

10 (lymph adj2 excision).mp.

11 (lymph adj2 biops:).mp.

12 (lymph adj2 dissection).mp.

13 (lymph node adj2 surgery).mp.

14 (SLNB or SNB).mp.

15 completion lymph node dissection.mp.

16 (complet: adj1 lymph node dissection).mp.

17 completion lymphadenectomy.mp.

18 therapeutic lymph node dissection.mp.
19 (therap: adj1 lymph node dissection).mp.
20 therapeutic lymphadenectomy.mp.
21 extent of dissection.mp.
22 extent of excision.mp.
23 deep inguinal node dissection.mp.
24 deep inguinal node.mp.
25 inguinal lymph node/
26 superficial inguinal node dissection.mp.
27 superficial inguinal node.mp.
28 level 3 axillary dissection.mp.
29 level 3 axillary node.mp.
30 axillary lymph node/
31 cloquet's node dissection.mp.
32 cloquet's node.mp.
33 iliac node dissection.mp.
34 iliac node.mp.
35 obturator node dissection.mp.
36 obturator node.mp.
37 or/7-36
38 6 and 37
39 (systematic adj (review: or overview:)).mp.
40 (meta-analy: or metaanaly:).mp.
41 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
42 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
43 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
44 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
45 or/39-44
46 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
47 (stud: adj1 select:).ab.
48 (46 or 47) and review.pt.
49 45 or 48
50 38 and 49

51 limit 50 to yr="2011-Current"

Clinical Studies and Randomized Controlled Trials
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Searched on April 21, 2016.

1 exp Melanoma/
2 melanoma.mp. or Melanoma/
3 (maligna: adj2 lentigo).mp.
4 (malignant adj1 (nev: or naev:)).mp.
5 (malignan: adj5 melanoma:).mp.
6 or/1-5
7 exp Sentinel Lymph Node Biopsy/
8 (sentinel adj3 biops:).mp.
9 exp Lymph Node Excision/
10 (lymph adj2 excision).mp.
11 (lymph adj2 biops:).mp.
12 (lymph adj2 dissection).mp.
13 (lymph node adj2 surgery).mp.
14 (SLNB or SNB).mp.
15 completion lymph node dissection.mp.
16 (complet: adj1 lymph node dissection).mp.
17 completion lymphadenectomy.mp.
18 therapeutic lymph node dissection.mp.
19 (therap: adj1 lymph node dissection).mp.
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21 extent of dissection.mp.
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27 level 3 axillary dissection.mp.
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29 cloquet's node dissection.mp.
30 cloquet's node.mp.
31 iliac node dissection.mp.
32 iliac node.mp.
33 obturator node dissection.mp.

34 obturator node.mp.

35 or/7-34

36 6 and 35

37 exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/

38 (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.

39 random allocation/ or double blind method/ or single blind method/

40 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).mp.

41 or/37-40

42 (phase II or phase 2).mp. or exp clinical trial/ or exp clinical trial as topic/

43 (clinical trial or clinical trial, phase II or controlled clinical trial).pt.

44 (42 or 43) and random$.mp.

45 (clinic$ adj trial$1).mp.

46 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).mp.

47 placebos/

48 (placebo? or random allocation or randomly allocated or allocated randomly).mp.

49 (allocated adj2 random).mp.

50 or/45-49

51 41 or 44 or 49

52 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.

53 exp animal/ not humans/

54 52 or 53

55 36 and 51

56 55 not 54

57 limit 56 to yr="2011-Current"

Embase 1974 to 2016 Week 16. Searched on April 21, 2016.

1 exp Melanoma/

2 melanoma.mp.

3 (maligna: adj2 lentigo).mp.

4 (malignant adj1 (nev: or naev:)).mp.

5 (malignan: adj5 melanoma:).mp.

6 or/1-5

7 exp Sentinel Lymph Node Biopsy/

8 (sentinel adj3 biops:).mp.

9 lymph node excision.mp. or exp lymphadenectomy/

10 (lymph adj2 excision).mp.

11 (lymph adj2 biops:).mp.
12 (lymph adj2 dissection).mp.
13 (lymph node adj2 surgery).mp.
14 (SLNB or SNB).mp.
15 completion lymph node dissection.mp.
16 (complet: adj1 lymph node dissection).mp.
17 completion lymphadenectomy.mp.
18 therapeutic lymph node dissection.mp.
19 (therap: adj1 lymph node dissection).mp.
20 therapeutic lymphadenectomy.mp.
21 extent of dissection.mp.
22 extent of excision.mp.
23 deep inguinal node dissection.mp.
24 deep inguinal node.mp.
25 inguinal lymph node/
26 superficial inguinal node dissection.mp.
27 superficial inguinal node.mp.
28 level 3 axillary dissection.mp.
29 level 3 axillary node.mp.
30 axillary lymph node/
31 cloquet's node dissection.mp.
32 cloquet's node.mp.
33 iliac node dissection.mp.
34 iliac node.mp.
35 obturator node dissection.mp.
36 obturator node.mp.
37 or/7-36
38 6 and 37
39 exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
40 randomization/ or single blind procedure/ or double blind procedure/
41 (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).mp.
42 or/39-41
43 (phase II or phase 2).mp. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
44 43 and random$.mp.
45 (clinic$ adj trial$1).mp.
46 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).mp.

47 placebo/

48 (placebo? or random allocation or randomly allocated or allocated randomly).mp.

49 (allocated adj2 random).mp.

50 or/45-49

51 42 or 44 or 50

52 38 and 51

53 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.

54 exp animal/ not humans/

55 53 or 54

56 52 not 55

57 limit 56 to yr="2011-Current"

Observational Studies

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present. Searched on May 10, 2016.

1 exp Melanoma/

2 melanoma.mp. or Melanoma/

3 (maligna: adj2 lentigo).mp.

4 (malignant adj1 (nev: or naev:)).mp.

5 (malignan: adj5 melanoma:).mp.

6 or/1-5

7 exp Sentinel Lymph Node Biopsy/

8 (sentinel adj3 biops:).mp.

9 exp Lymph Node Excision/

10 (lymph adj2 excision).mp.

11 (lymph adj2 biops:).mp.

12 (lymph adj2 dissection).mp.

13 (lymph node adj2 surgery).mp.

14 (SLNB or SNB).mp.

15 completion lymph node dissection.mp.

16 (complet: adj1 lymph node dissection).mp.

17 completion lymphadenectomy.mp.

18 therapeutic lymph node dissection.mp.

19 (therap: adj1 lymph node dissection).mp.

20 therapeutic lymphadenectomy.mp.

21 extent of dissection.mp.

22 extent of excision.mp.

23 deep inguinal node dissection.mp.
24 deep inguinal node.mp.
25 superficial inguinal node dissection.mp.
26 superficial inguinal node.mp.
27 level 3 axillary dissection.mp.
28 level 3 axillary node.mp.
29 cloquet's node dissection.mp.
30 cloquet's node.mp.
31 iliac node dissection.mp.
32 iliac node.mp.
33 obturator node dissection.mp.
34 obturator node.mp.
35 or/7-34
36 6 and 35
37 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
38 exp animal/ not humans/
39 37 or 38
40 36 not 39
41 limit 40 to yr="2011 -Current"

Embase 1974 to 2016 Week 19. Searched on May 10, 2016.
1 exp Melanoma/
2 melanoma.mp.
3 (maligna: adj2 lentigo).mp.
4 (malignant adj1 (nev: or naev:)).mp.
5 (malignan: adj5 melanoma:).mp.
6 or/1-5
7 exp Sentinel Lymph Node Biopsy/
8 (sentinel adj3 biops:).mp.
9 lymph node excision.mp. or exp lymphadenectomy/
10 (lymph adj2 excision).mp.
11 (lymph adj2 biops:).mp.
12 (lymph adj2 dissection).mp.
13 (lymph node adj2 surgery).mp.
14 (SLNB or SNB).mp.
15 completion lymph node dissection.mp.
16 (complet: adj1 lymph node dissection).mp.

17 completion lymphadenectomy.mp.
18 therapeutic lymph node dissection.mp.
19 (therap: adj1 lymph node dissection).mp.
20 therapeutic lymphadenectomy.mp.
21 extent of dissection.mp.
22 extent of excision.mp.
23 deep inguinal node dissection.mp.
24 deep inguinal node.mp.
25 inguinal lymph node/
26 superficial inguinal node dissection.mp.
27 superficial inguinal node.mp.
28 level 3 axillary dissection.mp.
29 level 3 axillary node.mp.
30 axillary lymph node/
31 cloquet's node dissection.mp.
32 cloquet's node.mp.
33 iliac node dissection.mp.
34 iliac node.mp.
35 obturator node dissection.mp.
36 obturator node.mp.
37 or/7-36
38 6 and 37
39 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
40 exp animal/ not humans/
41 39 or 40
42 38 not 41
43 limit 42 to yr="2011-Current"

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** –ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.

Appendix 3: 2018 Update of Recommendation 1b

In June 2017, the Melanoma disease site group was advised that the randomized controlled trial MSLT-II was published in the New England Journal of Medicine (1). As this was a practice changing study, the recommendations were reviewed by the Melanoma DSG co-chairs (FW and TP) and it was determined that recommendation 1b would require updating based on the study conclusions. The original recommendation was as follows: *"All patients with a positive SLN should be offered CLND of the appropriate nodal basin or be offered enrolment in a relevant clinical trial pending the emergence of good quality randomized data."* To facilitate this update, the DSG co-chairs evaluated the current recommendation and made edits in concert with the original working group members and DSG members.

New Evidence added in 2018

MSLT-II [58] evaluated the utility of CLND compared to observation with frequent nodal ultrasonography and dissection only in melanoma patients with positive sentinel lymph node metastasis. The majority of patients in MSLT-II had low-volume nodal tumour burden (1 positive sentinel lymph node, longest diameter of the largest tumor deposit measured and the mean diameter of nodal metastasis 1.1mm). Three year MSS for the CLND and the observation group was the same, 86±1.3% and 86±1.2% (p=0.42), respectively. The 3-year DFS rate was slightly higher in the CLND group (p=0.05) but the investigators caution the significance of this result based on the lack of significance of the MSS, which was the primary outcome. The DFS rate may be explained by the lower rate of nodal failure in the CLND group as compared to the observation group at 3 years (92±1% vs. 77±1.5%; p=0.001). Adverse events occurred with more frequency among the CLND patients than the observation group with lymphedema being the most common (24.1% of patients vs. 6.3% at last follow-up, p<0.001). Non sentinel-node metastases, which was identified in 11.5% of the patients in the CLND group was found to be an independent prognostic factor for melanoma related death. Overall, some regional control and prognostic value can be derived from CLND; however, this is at the expense of increased adverse events. The non-significant difference in MSS and increase in adverse events of the CLND group indicates that CLND may not be optimal for patients and does not offer a survival benefit. Although the majority of patients had low volume tumor metastases, sub set analysis did not demonstrate a benefit for any groups of patient receiving CLND. As a result of the publication of the MSLT-II trial, the original recommendation has been altered to reflect this new high-quality evidence.

Draft recommendation based on new evidence

The following is the recommendation that was drafted by the Melanoma DSG co-chairs along with the Melanoma DSG.

"Patients with sentinel nodal tumour burden should be considered for ultrasonographic monitoring rather than CLND. Monitoring with ultrasonography of the affected nodal basin and clinical exam will be required, at minimum, every 4 to 6 months for the first 2 years, every 6 months from 3-5 years and then annually up to 10 years until more data is available. Suspicions of a nodal recurrence in a lymph node basin include any two of the following: lymph node length:depth ratio <2, hypoechoic centre, failure to identify a nodal hilar vessel and/or focal rounded area of low level echoes with increased vascularity in that area. Suspicions of nodal recurrence via ultrasound should be confirmed with a biopsy of the basin. For certain patients, a CLND may still be the best option for local control but should be discussed by a multi-disciplinary team (MDT)."

External Review

The draft recommendation was sent to three surgeons, specializing in melanoma (MF, DG and GM). These specialists were given a questionnaire with 7 questions along with free-form commenting boxes. Their comments and the responses made by the working group are in Table and 2.

Table A3.1. Responses to seven items on the targeted peer reviewer questionnaire.

Question	Reviewer Ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate guideline recommendation 1b				3	
2. Rate the completeness of reporting				3	
3. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?		1		2	
4. What are the barriers or enablers to the implementation of this guideline report?	The paragraph in "Key Evidence Added in 2017 Update" is worded in a way that suggests a bias towards CLND despite the recommendation being that CLND not be performed. For example the sentence "The Non-significant difference in MSS and increase in adverse events of the CLND group indicates that CLND may not be optimal" Could be replaced with a sentence such as "The lack of difference in MSS and increased rate of adverse events with CLND suggests that close surveillance may be preferable for the majority of patients." Availability of high-quality ultrasound may be an issue.				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
5. Rate the overall quality of recommendation 1b.				2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
6. I would make use of this recommendation in my professional decisions.			1	1	1
7. I would recommend this recommendation for use in practice.			1	1	1

Table A3.2: Comments from the TPR reviewers:

Comment	Response and Action
1. The term "sentinel nodal tumour burden" is somewhat cumbersome. The authors might consider the term "sentinel node metastases".	We have modified the recommendation to "sentinel node metastases"
2. It may be preferable to replace the term ultrasonographic monitoring with "nodal observation with ultrasonography" as used in the MSLT2 study.	We have changed the recommendation in light of this
3. The authors may wish to give more information to support the statement "for certain patients, a CLND may still be the best option" For example in patients who are unlikely to be compliant with an intensive surveillance protocol.	We have added the following qualifying statement: • *Patients in whom CLND would be a better option than nodal observation with ultrasonography are:*

	○ *patients with extensive sentinel node metastasis in which CLND would be the only option for local control* ○ *patients unlikely to be compliant with an intensive surveillance protocol*
4. The recommendation appears clinically sound. The recommendation for ultrasound to be carried through 10 years seems reasonable, but has less data support. This is due to the ending of US in the MSLT-II trial at 5 years, so the addition of US in the later years, while certainly safe, may not add much value	Thank you, we have removed the 10 year monitoring requirement from the recommendation. AGREE
5. The report appears complete. However, it only addresses the axilla and groin. Since there may be drainage to cervical nodes from the trunk, it would be more complete if information about that basin was included	To reflect this we have added a qualifying statement: *"While this guideline is specific to the trunk and extremities, this recommendation can be applied to melanomas of the head and neck and their respective drainage basins. "*
6. There is reasonable evidence that the pathologic information from the CLND is important for complete staging. There may be instances where that staging information is a determining factor for adjuvant therapy decisions. That issue might be mentioned in the discussion.	While this is outside the scope of this guideline, this comment has been taken into consideration for future updates.
7. On p 4, under b. Completion lymph node dissection at the time… "Patients with sentinel nodal tumor burden…" I'm not sure "burden" is the right word here. "metastases"?	This has been changed in the recommendation
8. Under the first bullet point on p5, "the mean burden of disease was 1.1 mm" is correct. However the mean in the study may have been a bit skewed by a few larger metastases at the high end. Perhaps using median diameter (0.59/0.67 mm for the two arms) or stating that only one third of patients had metastases greater than 1 mm in diameter would be more representative of the trial population.	The qualifying statement has been changed to reflect this. This has been corrected.
9. Under "Key Evidence … 2016" CLNB is used as an abbreviation. Should this be CLND?	Noted
10. Though this is now irrelevant, the original key evidence from 2012 states that there were no retrospective series showing an advantage to CLND. Since then there was a series in 2016 that did have better survival for the CLND group (Lee et al, JACS, 2016). Again, this is not relevant anymore.	

11. The recommendation to follow up for 10 years is not supported by the data. Although patients in the trial were followed for this length of time, the vast majority of nodal recurrences occurred within 3 years and the recurrence curves are almost flat after 5 years. Follow up with visits and ultrasounds are a large burden on melanoma clinics and practitioners. Most patients are discharged to the community after five years. A change in this practice should be supported by high quality evidence.	Thank you, we have removed the 10 year monitoring requirement from the recommendation.
12. I see no rationale to limit this guideline to patients with melanoma of the trunk and extremities. The relevant trials, including MSLT-II, include head and neck patients. Although it is not always the same group of surgeons that deal with head and neck patients, other physicians such as dermatologists, medical oncologists, radiation oncologists (and most multidisciplinary clinics) do see these patients and look to these guidelines as well. It is the same disease and the same data. Furthermore, many patients with melanomas on their upper back or lower neck have both neck and axillary basins at risk for recurrence and must be dealt with in the same manner. It is probably better to have one comprehensive guideline (if a guideline exist on management of the neck I cannot find it on the CCO website).	To reflect this we have added a qualifying statement: *"While this guideline is specific to the trunk and extremities, this recommendation can be applied to melanomas of the head and neck and their respective drainage basins. "*

Final Recommendation after External Review

"Patients with sentinel node metastasis should be considered for nodal observation with ultrasonography rather than CLND. Monitoring with ultrasonography of the affected nodal basin and clinical exam will be required, at minimum, every 4 to 6 months for the first 2 years and every 6 months from 3-5 years. Suspicions of a nodal recurrence in a lymph node basin include any two of the following: lymph node length:depth ratio <2, hypoechoic centre, failure to identify a nodal hilar vessel and/or focal rounded area of low level echoes with increased vascularity in that area. Suspicions of nodal recurrence via ultrasound should be confirmed with a biopsy of the basin. For certain patients, a CLND may still be the best option for local control but should be discussed by a multi-disciplinary team (MDT)."

Qualifying Statements

- In MSLT-II [1] one third of patients had metastases greater than 1 mm in diameter and 72% of patients had one sentinel node with metastases. A subgroup evaluation of patients with a greater disease burden (maximal tumour diameter >1 mm) did not indicate that a benefit from completion lymph-node dissection was more likely in high-risk groups than in low-risk groups [1].
- Patients in whom CLND would be a better option than nodal observation with ultrasonography are:

- patients with extensive sentinel node metastasis in which CLND would be the only option for local control
- patients unlikely to be compliant with an intensive surveillance protocol

- While this guideline is specific to the trunk and extremities, this recommendation can be applied to melanomas of the head and neck and their respective drainage basins.

References for Appendix 3

1. Faries M, Thompson J, Cochran A, Andtbacka R et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. New England Journal of Medicine. 2017; 376(23):2211-2222.

Conflict of Interest

Table A3.3 Targeted Peer Reviews

Reviewer	Affiliations	Declarations of Interest
Greg McKinnon	Professor of Surgery and Oncology at the University of Calgary and the Tom Baker Cancer Center, Canada	Been a principal investigator for a clinical trial involving any of the objects of study, regardless of the source of funding? If so, please provide the name of the trial in the comment box. Yes MSLT-II
Mark Faries	Surgical Oncologist and co-director of the Melanoma Program and head of Surgical oncology at the Los Angeles Research Institute, USA	Principal Investigator and Study Chair of MSLT-II
David Gyorki	Surgeon at the Peter MacCallum Cancer Center, Australia	None declared