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

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. All other recommendations have been ENDORSED and are still relevant for decision making.

This EBS consists of 4 sections and is available on the CCO Skin Cancer page.

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

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

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<td>Version 2 June 2016</td>
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<td>New evidence added to Section 1 and new data found in Section 4</td>
<td>Updated web publication</td>
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<td>NA</td>
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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 oringuinal 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. Theinguinal 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 oringuinal 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:
  o patients with extensive sentinel node metastasis in which CLND would be the only option for local control
  o 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

<table>
<thead>
<tr>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

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):

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Updating
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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgt@mcmaster.ca
References

16. van Akkooi ACJ, de Wilt JHW, Verhoef C, Schmitz PIM, van Geel AN, Eggermont AMM, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Annals of Oncology. 2006;17(10):1578-85.


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: 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
Section 2: Evidentiary Base

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>
<thead>
<tr>
<th>Database</th>
<th>Dates Searched</th>
<th>Hits</th>
<th>Fully reviewed</th>
<th>Retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>1980 - Sep (week 1) 2011</td>
<td>2516</td>
<td>194</td>
<td>51</td>
</tr>
<tr>
<td>EMBASE</td>
<td>1980 - Week 37 2011</td>
<td>3243</td>
<td>57</td>
<td>3</td>
</tr>
<tr>
<td>ASCO</td>
<td>Up to 2011</td>
<td>82</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SSO</td>
<td>Up to 2011</td>
<td>59</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reference Mining</td>
<td>NA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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.

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

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>H &amp; E</th>
<th>IHC</th>
<th>Sectioning Technique</th>
<th>Number of Nodes Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Star2 2001 [11]</td>
<td>Yes</td>
<td>Anti-S100 HMB-45</td>
<td>Specimens formalin fixed and cut into slices a few mm thick, 1-mm slices then paraffin embedded</td>
<td>Evaluable Nodes: Neck - 2 Axillary - 22 Inguinoiliac - 12 Inguinal - 4</td>
</tr>
<tr>
<td>Reeves 2003 [5]</td>
<td>Yes</td>
<td>No</td>
<td>Bivalved</td>
<td>Mean &gt;20</td>
</tr>
<tr>
<td>Salti 2003 [12]</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dewar 2004 [14]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Elias 2004 [15]</td>
<td>Yes</td>
<td>S-100, HMB-45, NKIC3, MART-1</td>
<td>Serial sectioning</td>
<td>NR</td>
</tr>
<tr>
<td>Lee 2004 [6]</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Scolyer 2004 [16]</td>
<td>Yes</td>
<td>No</td>
<td>Whole nodes embedded in paraffin, sliced if &gt;3mm diameter</td>
<td>Median - 14</td>
</tr>
<tr>
<td>Starz 2004 [17]</td>
<td>Yes</td>
<td>S-100</td>
<td>Specimen formalin fixed, cut into thin slices</td>
<td>Mean - 29</td>
</tr>
<tr>
<td>Fink 2005 [18]</td>
<td>Yes</td>
<td>No</td>
<td>Specimen formalin fixed, cut into thin slices</td>
<td>NR</td>
</tr>
<tr>
<td>Sabel 2005 [19]</td>
<td>Yes</td>
<td>No</td>
<td>Bivalved</td>
<td>Mean number of nodes removed: Axillary - 18 Inguinal - 10 Neck - 33</td>
</tr>
<tr>
<td>Vuylsteke 2005 [20]</td>
<td>Yes</td>
<td>No</td>
<td>LNs lamellated and embedded in paraffin. LN &lt;0.5 cm - embedded whole LN 0.5-1.0 cm - halved LN &gt;1.0 cm - lamellated into sections approximately 0.5 cm in size</td>
<td>Median - 11.5 nodes</td>
</tr>
<tr>
<td>Pearlman 2006 [21]</td>
<td>Yes</td>
<td>No</td>
<td>Bivalved</td>
<td>NR</td>
</tr>
<tr>
<td>van Akkooi 2006 [22]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Govindarajan 2007 [23]</td>
<td>Yes</td>
<td>For confirmation only</td>
<td>Bisected or trisected depending on size</td>
<td>Mean - 18.5 nodes</td>
</tr>
<tr>
<td>Debarbieux 2007 [24]</td>
<td>Yes</td>
<td>For confirmation only</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Page 2007 [25]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Frankel 2008 [26]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Glumace 2008 [27]</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Guggenheim 2008 [28]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Roka 2008 [29]</td>
<td>Yes</td>
<td>No</td>
<td>Bivalved</td>
<td>NR</td>
</tr>
<tr>
<td>Rossi 2008 [30]</td>
<td>Yes</td>
<td>For confirmation only</td>
<td>LN diameter ≤4 mm - embedded whole in paraffin LN diameter &gt;4 mm - cut into 3-4-mm thick slices, which were each embedded in paraffin</td>
<td>Median - 18.5</td>
</tr>
<tr>
<td>Satzger 2008 [31]</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van Akkooi 2008 [32]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of SLNB Positive Patients</th>
<th>Number (%) of Patients Undergoing CLND</th>
<th>Number (%) of Patients with Positive CLND</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joseph 1998 [10]</td>
<td>83</td>
<td>64(77.1)</td>
<td>5(7.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Starz 2001 [11]</td>
<td>62</td>
<td>39(62.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>McMasters 2002 [4]</td>
<td>274</td>
<td>274(100.0)</td>
<td>45(16.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Reeves 2003 [5]</td>
<td>98</td>
<td>98(100.0)</td>
<td>16(16.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Salti 2003 [12]</td>
<td>56</td>
<td>56(100.0)</td>
<td>8(14.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Cochran 2004 [13]</td>
<td>90</td>
<td>90(100.0)</td>
<td>19(21.1)</td>
<td>-</td>
</tr>
<tr>
<td>Dewar 2004 [14]</td>
<td>146</td>
<td>146(100.0)</td>
<td>24(16.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Elias 2004 [15]</td>
<td>87</td>
<td>80(92.0)</td>
<td>12(15.0)</td>
<td>-</td>
</tr>
<tr>
<td>Lee 2004 [6]</td>
<td>191</td>
<td>191(100.0)</td>
<td>46(24.1)</td>
<td>0.025</td>
</tr>
<tr>
<td>Scolyer 2004 [16]</td>
<td>175</td>
<td>140(80.0)</td>
<td>24(17.1)</td>
<td>-</td>
</tr>
<tr>
<td>Starz 2004 [17]</td>
<td>65</td>
<td>45(69.2)</td>
<td>12(26.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Fink 2005 [18]</td>
<td>26</td>
<td>26(100.0)</td>
<td>4(15.4)</td>
<td>-</td>
</tr>
</tbody>
</table>

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.
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 predictive 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.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of SLNB Positive Patients</th>
<th>Number (%) of Patients Undergoing CLND</th>
<th>Number (%) of Patients with Positive CLND</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabel 2005 [19]</td>
<td>232</td>
<td>221(95.3)</td>
<td>34(15.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Vuylsteke 2005 [20]</td>
<td>71</td>
<td>71(100.0)</td>
<td>19(26.8)</td>
<td>-</td>
</tr>
<tr>
<td>Pearman 2006 [21]</td>
<td>90</td>
<td>80(88.9)</td>
<td>17(21.3)</td>
<td>ns</td>
</tr>
<tr>
<td>van Akkooi 2006 [22]</td>
<td>77</td>
<td>67(87.0)</td>
<td>10(14.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Govindarajan 2007 [23]</td>
<td>127</td>
<td>127(100.0)</td>
<td>20(15.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Debarbieux 2007 [24]</td>
<td>98</td>
<td>98(100.0)</td>
<td>-</td>
<td>0.001</td>
</tr>
<tr>
<td>Page 2007 [25]</td>
<td>70</td>
<td>70(100.0)</td>
<td>19(27.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Frankel 2008 [26]</td>
<td>136</td>
<td>136(100.0)</td>
<td>29(21.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Glumac 2008 [27]</td>
<td>74</td>
<td>73(98.6)</td>
<td>16(21.9)</td>
<td>-</td>
</tr>
<tr>
<td>Gugenheim 2008 [28]</td>
<td>107</td>
<td>100(93.5)</td>
<td>22(22.0)</td>
<td>-</td>
</tr>
<tr>
<td>Roka 2008 [29]</td>
<td>85</td>
<td>85(100.0)</td>
<td>18(21.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Rossi 2008 [30]</td>
<td>101</td>
<td>96(95.0)</td>
<td>20(20.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Satzger 2008 [31]</td>
<td>180</td>
<td>180(100.0)</td>
<td>28(16.0)</td>
<td>-</td>
</tr>
<tr>
<td>van Akkooi 2008 [32]</td>
<td>388</td>
<td>360(92.8)</td>
<td>92(25.6)</td>
<td>-</td>
</tr>
<tr>
<td>Cadili 2009 [33]</td>
<td>92</td>
<td>68(73.9)</td>
<td>12(17.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gershenwald 2008 [34]</td>
<td>359</td>
<td>343(95.5)</td>
<td>48(14.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ollila 2009 [35]</td>
<td>90</td>
<td>86(95.6)</td>
<td>18(20.9)</td>
<td>-</td>
</tr>
<tr>
<td>Santinami 2009 [36]</td>
<td>150</td>
<td>150(100.0)</td>
<td>36(24.0)</td>
<td>-</td>
</tr>
<tr>
<td>Cadili 2010 [37]</td>
<td>606</td>
<td>606(100.0)</td>
<td>-</td>
<td>0.0046</td>
</tr>
<tr>
<td>Cadili 2010 [38]</td>
<td>144</td>
<td>140(97.2)</td>
<td>19(17)</td>
<td>ns</td>
</tr>
<tr>
<td>Murali 2010 [39]</td>
<td>409</td>
<td>309(75.6)</td>
<td>53(17.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Wiener 2010 [40]</td>
<td>501</td>
<td>323(65)</td>
<td>61(18.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Younan 2010 [41]</td>
<td>82</td>
<td>82(100)</td>
<td>10(12.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Bogenrieder 2011 [42]</td>
<td>70</td>
<td>70(100)</td>
<td>18(25.7)</td>
<td>ns</td>
</tr>
<tr>
<td>Fink 2011 [43]</td>
<td>124a</td>
<td>124(100)a</td>
<td>30(24.2)a</td>
<td>-</td>
</tr>
<tr>
<td>Kunte 2011 [44]</td>
<td>213</td>
<td>176(82.6)</td>
<td>26(14.8)</td>
<td>ns</td>
</tr>
<tr>
<td>van der Ploeg 2011 [45]</td>
<td>1080</td>
<td>1009(93.4)</td>
<td>212(21.0)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

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.

**Section 2: Evidentiary Base**

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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 predictive 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Breslow Thickness</th>
<th>Ulceration</th>
<th>Primary Site</th>
<th>Clark Level</th>
<th>Mitotic Rate</th>
<th>Satellitosis</th>
<th>Angio-lymphatic Invasion</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starz 2004 [17]</td>
<td>ns</td>
<td>-</td>
<td>0.039</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sabel 2005 [19]</td>
<td>0.03</td>
<td>0.005</td>
<td>ns</td>
<td>0.02</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Vuylsteke 2005 [20]</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peariman 2006 [21]</td>
<td>0.003</td>
<td>-</td>
<td>0.027</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>van Akkooi 2006 [22]</td>
<td>ns</td>
<td>0.05*</td>
<td>-</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Govindarajan 2007 [23]</td>
<td>ns</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Debarbieux 2007 [24]</td>
<td>ns</td>
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<td>-</td>
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<td>Page 2007 [25]</td>
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<td>ns</td>
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<td>-</td>
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<tr>
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<td>0.0013</td>
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<td>&lt;0.02</td>
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<td>&lt;0.001</td>
<td>ns</td>
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</tr>
<tr>
<td>Roko 2008 [29]</td>
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<td>ns</td>
<td>ns</td>
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<td>Rossi 2008 [30]</td>
<td>ns</td>
<td>-</td>
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<td>0.05</td>
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<td>Gershenwald 2008 [34]</td>
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<td>Santinami 2009 [36]</td>
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<td>ns</td>
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</tr>
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<td>Younan 2010 [41]</td>
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<td>Bogenrieder 2011 [42]</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kunte 2011 [44]</td>
<td>0.022</td>
<td>†</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>†</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Note: Dash(−), not evaluated; NR, not reported; ns, not significant.

*Absence of ulceration

†significant but study authors report that the p-value is questionable
### Table 6b: Factors predictive of a positive CLND from univariate analysis: Other SLN features

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumour Size in SLN</th>
<th>Size of largest tumour deposit in SLN</th>
<th>Diameter of SLN metastasis</th>
<th>SLN tumour burden (Rotterdam Criteria)</th>
<th>Area of tumour</th>
<th>Relative area of tumour</th>
<th>No. Of SLN metastatic foci</th>
<th>Depth of SLN metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochran 2004 [13]</td>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>Dewar 2004 [14]</td>
<td>-</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Scolyer 2004 [16]</td>
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<td>ns</td>
<td>&lt;0.01</td>
<td>ns</td>
<td>ns</td>
<td>0.05</td>
<td>-</td>
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<td>-</td>
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<td>van Akkooi 2006 [22]</td>
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</tr>
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<td>Glumac 2008 [27]</td>
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<td>-</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guggenheim 2008 [28]</td>
<td>-</td>
<td>-</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Roka 2008 [29]</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rossi 2008 [30]</td>
<td>ns</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.009</td>
</tr>
<tr>
<td>Satzger 2008 [31]</td>
<td>-</td>
<td>0.001</td>
<td>-</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>van Akkooi 2008 [32]</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cadili 2009 [33]</td>
<td>0.01</td>
<td>-</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gershenwald 2008 [34]</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>-</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>0.004</td>
<td>-</td>
</tr>
<tr>
<td>Santinami 2009 [36]</td>
<td>-</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cadili 2010 [37]</td>
<td>0.0293</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cadili 2010 [38]</td>
<td>0.0023</td>
<td>0.045</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Murali 2010 [39]</td>
<td>-</td>
<td>0.049</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ns</td>
<td>0.02</td>
</tr>
<tr>
<td>Bogenrieder 2011 [42]</td>
<td>-</td>
<td>0.021</td>
<td>0.007</td>
<td>0.014</td>
<td>-</td>
<td>-</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>van der Ploeg 2011 [45]</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ns</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Dash(-), not evaluated; NR, not reported; ns, not significant; SLN, sentinel lymph node.  

- Diameter 2: shortest diameter of the largest metastasis observed in serial sections  
- 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 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.

<table>
<thead>
<tr>
<th>Study</th>
<th>All SLNs positive</th>
<th>Proportion of positive SLNs</th>
<th>Area of dendritic cells</th>
<th>Density of dendritic cells/mm²</th>
<th>Pattern of SLN involvement</th>
<th>Capsular involvement</th>
<th>SLN sub-capsular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reeves 2003 [9]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.01</td>
</tr>
<tr>
<td>Cochran 2004 [13]</td>
<td>-</td>
<td>-</td>
<td>0.0245</td>
<td>0.008</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Elias 2004 [15]</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rossi 2008 [30]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.015</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Satzger 2008 [31]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Murali 2010 [39]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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.

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

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.
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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Recurrence</th>
<th>Type of Recurrence</th>
<th>Median Relapse-Free Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong, 2006(^2) [46]</td>
<td>134/164</td>
<td>49(37)/85(52)</td>
<td>LR Only: 7(5)/29(18); Nodal Only: 14(10)/12(7); Nodal +/- LR: 17(13)/14(9)</td>
<td>NR/20(15)/17(10)/NR/25(19)/42(26)</td>
</tr>
<tr>
<td>Kingham, 2010(^2) [47]</td>
<td>42/271</td>
<td>20(48)/146(54)</td>
<td>LR Only: 7(17)/48(18); Nodal Only: 2(5)/15(6); Nodal +/- LR: 7(17)/45(17)</td>
<td>NR/3(7)/17(6)/9(21)/73(27)/11(26)/78(29)/NR</td>
</tr>
<tr>
<td>van der Ploeg, 2009 [48]</td>
<td>20/50</td>
<td>NR/0(0)</td>
<td>LR Only: 1(2); Nodal Only: 0(0)</td>
<td>NR/0(0)/NR/0(0)</td>
</tr>
</tbody>
</table>

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)
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

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

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
*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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Arm</th>
<th>Nodal Status of Pts Included</th>
<th>No. of Pts</th>
<th>DFS</th>
<th>5-year Survival</th>
<th>Recurrence</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes 1999 [52]</td>
<td>SR</td>
<td>Ilioinguinal LND Inguinal LND</td>
<td>Some studies included: Clinically Palpable Nodes or Clinically Negative Nodes or Mixture</td>
<td>34 studies</td>
<td>NR</td>
<td>NR</td>
<td>&lt;5%</td>
<td>Report no difference in morbidity in the two arms</td>
</tr>
<tr>
<td>Zoltie 1991 [53]</td>
<td>Retro</td>
<td>Ilioinguinal LND Inguinal LND</td>
<td>NR</td>
<td>20 22</td>
<td>NR</td>
<td>24 mos, 18 mos, p=ns</td>
<td>40%</td>
<td>Wound Complication s (Ilioinguinal vs. Inguinal LND) 65 vs. 50%, p=ns</td>
</tr>
<tr>
<td>Karakousis 1994 [54]</td>
<td>Retro</td>
<td>Ilioinguinal LND Inguinal LND</td>
<td>Ilioinguinal Arm - Palpable Nodes Inguinal Arm - Clinically Positive Nodes</td>
<td>104 94</td>
<td>NR</td>
<td>Pts with Histologically Positive Nodes 28%</td>
<td>NR</td>
<td>Lymphedema (Ilioinguinal vs. Inguinal LND) 35 vs. 18%, p=ns</td>
</tr>
<tr>
<td>van der Ploeg 2008 [55]</td>
<td>Retro</td>
<td>Ilioinguinal LND Inguinal LND</td>
<td>Positive SLNs</td>
<td>24 18</td>
<td>NR</td>
<td>5-yr DFS 61% (95%CI: 31-90)</td>
<td>80% (95%CI: 61-100), p=ns</td>
<td>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</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essner 2006</td>
<td>Retrospective</td>
<td>93</td>
<td>NR</td>
<td>NR</td>
<td>66</td>
<td>97</td>
</tr>
<tr>
<td>Chu 2010</td>
<td>Retrospective</td>
<td>53</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Nodal Status of Included Patients</th>
<th>Number of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen 2000 [59]</td>
<td>Retro</td>
<td>Palpable nodes - 81% Non-palpable nodes - 17% Metastatic - 2%</td>
<td>68</td>
<td>71</td>
<td>73</td>
<td>67</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Strobbe 2001 [60]</td>
<td>Retro &amp; prosp</td>
<td>Palpable nodes - 91% Non-palpable nodes - 6% Positive SLN - 4%</td>
<td>194</td>
<td>54</td>
<td>90</td>
<td>69</td>
<td>82</td>
</tr>
</tbody>
</table>

NPV=negative-predictive value; PPV=positive-predictive value, prosp=prospective; retro=retrospective

<sup>a</sup>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.

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Date last modified</th>
<th>Type of trial</th>
<th>Comparison</th>
<th>Primary endpoint</th>
<th>Accrual</th>
<th>Sponsorship</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00297895; NIH P01 CA029605</td>
<td>August 09, 2011</td>
<td>Phase III RCT, open-label, active control</td>
<td>CLND vs US observation + delayed CLND if recurrence detected</td>
<td>Melanoma-specific survival</td>
<td>Target enrolment 1925</td>
<td>John Wayne Cancer Institute; National Institutes of Health</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
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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- Targeted Peer Reviewers: Rona Cheifetz, Greg McKinnon, Geoff Porter
- Report Approval Panel Members: Gail Darling, Marko Simunovic, Melissa Brouwers

For a complete list of the Melanoma Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca/
References

16. Sculley RA, Li L-XL, McCarthy SW, Shaw HM, Stretch JR, Sharma R, et al. Micromorphometric features of positive sentinel lymph nodes predict involvement of


22. van Akkooi ACJ, de Wilt JHW, Verhoef C, Schmitz PIM, van Geel AN, Eggermont AMM, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Annals of Oncology. 2006;17(10):1578-85.


45. van der Ploeg APT, van Akkooi ACJ, Rutkowski P, Nowecki ZI, Michej W, Mitra A, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the


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

**Chair:**
Alexandra Easson  
Surgeon  
Princess Margaret Hospital, Toronto, ON

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  Methodologist  
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- David McCready  
  Surgeon  
  Princess Margaret Hospital, Toronto, ON
- Teresa Petrella  
  Medical Oncologist  
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- Claire Temple  
  Plastic Surgeon  
  Tom Baker Cancer Centre, Calgary, AB
- Frances Wright  
  Surgeon  
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- Frances Wright, Surgical Oncologist

Members:
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- 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/
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/
11. (lymph adj2 biops:).tw.
12. (lymph adj2 dissection).tw.
14. (SLNB or SNB).tw.
15. completion lymph node dissection.mp.
17. completion lymphadenectomy.mp.
18. therapeutic 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.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.
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/
11. (lymph adj2 biops:).tw.
12. (lymph adj2 dissection).tw.
14. (SLNB or SNB).tw.
15. completion lymph node dissection.mp.
17. completion lymphadenectomy.mp.
18. therapeutic 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.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.

- Literature
  - MEDLINE
    - Hits = 2516
      - Excluded on Abstract Review 2322
        - Full Paper Review 194
          - Excluded 143
            - Retained 51
      - Excluded 143
        - Retained 51
  - EMBASE
    - Hits = 3243
      - Excluded on Abstract Review 3186
        - Full Paper Review 57
          - Excluded 54
            - Retained 3
  - ASCO
    - Hits = 82
      - Excluded 0
        - Retained 0
  - SSO
    - Hits = 59
      - Excluded 0
        - Retained 0
  - Reference Mining
    - Full Paper Review 0
      - Excluded 0
        - Retained 0
**Appendix 5. Quality attributes of studies used to inform each of the topics addressed in this guidance report.**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Study</th>
<th>Design</th>
<th>N Undergoing CLND</th>
<th>Funding Reported</th>
<th>Control Details</th>
<th>Blinded Assessment</th>
<th>Power Calc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicting NSLN Positivity</td>
<td>Joseph, 1998</td>
<td>Prospective cohort</td>
<td>64</td>
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<td>McMasters 2002</td>
<td>Subgroup analysis of an RCT</td>
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<tr>
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<td>Retrospective cohort</td>
<td>176</td>
<td>Yes</td>
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<td>van der Ploeg</td>
<td>Retrospective cohort</td>
<td>1009</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>CLND vs O</td>
<td>Wong 2006</td>
<td>Retrospective cohorts - comparison</td>
<td>298</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Kingham 2010</td>
<td>Retrospective cohorts - comparison</td>
<td>313</td>
<td>No</td>
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<td>van der Ploeg 2009</td>
<td>Prospective cohorts - comparison</td>
<td>70</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
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<td>CLND vs TLND</td>
<td>Pasquali 2010</td>
<td>Meta-analysis</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Rutkowski 2006</td>
<td>Prospective cohorts - comparison</td>
<td>530</td>
<td>No</td>
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<td>Veenstra 2010</td>
<td>Retrospective cohorts - comparison</td>
<td>319</td>
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<td>Hughes 1999</td>
<td>Systematic review</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Zoltie 1991</td>
<td>Retrospective cohorts - comparison</td>
<td>42</td>
<td>No</td>
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<td>Karakousis 1994</td>
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<td>Topic</td>
<td>Study</td>
<td>Design</td>
<td>N Undergoing CLND</td>
<td>Funding Reported</td>
<td>Control Details</td>
<td>Blinded Assessment</td>
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<tr>
<td>Nodal Dissection (Cloquet)</td>
<td>van der Ploeg 2008</td>
<td>Retrospective cohorts - comparison</td>
<td>42</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>NA</td>
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<tr>
<td>Nodal Dissection (Cloquet)</td>
<td>Essner 2006</td>
<td>Retrospective cohort</td>
<td>93</td>
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<td>Nodal Dissection (Cingual)</td>
<td>Chu 2010</td>
<td>Retrospective cohort</td>
<td>53</td>
<td>Yes</td>
<td>NA</td>
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<tr>
<td>Nodal Dissection (Cloquet)</td>
<td>Kretschmer 2001</td>
<td>Retrospective cohorts - comparison</td>
<td>104</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>NA</td>
</tr>
<tr>
<td>Nodal Dissection (Cingual)</td>
<td>Shen 2000</td>
<td>Retrospective cohort</td>
<td>65</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Nodal Dissection (Cingual)</td>
<td>Strobbe 2001</td>
<td>Retrospective &amp; Prospective cohorts</td>
<td>195</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

*Quality of the meta-analysis and systematic review evaluated by AMSTAR tool. See page 4 of Evidentiary Base.
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 PEB 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.

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

<table>
<thead>
<tr>
<th>General Questions: Overall Guideline Assessment</th>
<th>Lowest Quality (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>Highest Quality (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate the overall quality of the guideline report.</td>
<td>1 (6%)</td>
<td>2 (12%)</td>
<td>8 (47%)</td>
<td>6 (35%)</td>
<td></td>
</tr>
<tr>
<td>2. I would make use of this guideline in my professional decisions.</td>
<td>1 (6%)</td>
<td>8 (47%)</td>
<td>8 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I would recommend this guideline for use in practice.</td>
<td>1 (6%)</td>
<td>8 (47%)</td>
<td>8 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. What are the barriers or enablers to the implementation of this guideline report?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| • 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


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 PEBC 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

Records identified through database searching (n=2,573)

Title screen (n=2,573)

Abstract screen (n=90)

Full-text articles assessed for eligibility (n=45)

Records excluded based on title (n=2,483)

Records excluded based on abstract (n=46)

Additional studies identified (n=1)

Full-text articles excluded, (n=31)*

* n=16, not relevant; n=4, included in original GL; n=3, duplicate; n=7, study type; n=1, non-English.

Included Studies (n=14)
- 6 Practice guidelines
- 2 Systematic reviews
- 2 Randomized controlled trials
- 4 observational studies (Question 1a only)
**Document Review Tool**

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

**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.

<table>
<thead>
<tr>
<th>Brief Summary/Discussion of New Evidence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>A priori, it was identified that the ongoing Multicenter Selective Lymphadenectomy Trial II (MSLT-II) (<a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>) 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 PEBB 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.</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td>No</td>
</tr>
<tr>
<td>2. On initial review,</td>
<td></td>
</tr>
<tr>
<td>a. Does the newly identified evidence support the existing recommendations?</td>
<td>Yes</td>
</tr>
<tr>
<td>b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?</td>
<td>Yes</td>
</tr>
<tr>
<td>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:</td>
<td>No</td>
</tr>
<tr>
<td>4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Year?</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--</td>
</tr>
<tr>
<td>Review Outcome</td>
<td>ENDORSE</td>
</tr>
<tr>
<td>DSG/GDG Approval Date</td>
<td>October 3, 2016</td>
</tr>
<tr>
<td>DSG/GDG Commentary</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Summary of New Evidence from Updated Literature Searches

<table>
<thead>
<tr>
<th>Study [Ref]</th>
<th>Study Type</th>
<th>*Applicable Question(s) (1a, 1b or 1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dummer et al, 2016 [1]</td>
<td>Practice Guideline</td>
<td>b</td>
</tr>
<tr>
<td>Pflugfelder et al, 2013 [3]</td>
<td>Practice Guideline</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Nagaraja and Estlick, 2013 [8]</td>
<td>Systematic Review</td>
<td>a</td>
</tr>
<tr>
<td>Leiter et al, 2016 [9]</td>
<td>Randomized Controlled Trial</td>
<td>b</td>
</tr>
<tr>
<td>Morton et al, 2014 [10]</td>
<td>Randomized Controlled Trial</td>
<td>b</td>
</tr>
<tr>
<td>Bertolli et al, 2016 [12]</td>
<td>Observational Study</td>
<td>a</td>
</tr>
<tr>
<td>Kibrite et al, 2016 [13]</td>
<td>Observational Study</td>
<td>a</td>
</tr>
<tr>
<td>Wevers et al, 2013 [14]</td>
<td>Observational Study</td>
<td>a</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pflugfelder et al, 2013 [3]</td>
<td>Pts with CM (excluding mucosal and uveal)</td>
<td>Systematic literature</td>
<td>Diagnosis, therapy and follow-up of melanoma</td>
<td>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]</td>
</tr>
<tr>
<td>German Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Methods</th>
<th>Intervention/Otures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertolli et al,</td>
<td>SLN(+) CM pts +</td>
<td>Retrospective cohort</td>
<td>Metastatic area ratio: metastatic</td>
<td>N=146 pts, positive NSN in 23 pts (15.8%)</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Cohort</td>
<td>Methodology</td>
<td>Biomarkers</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>2016</td>
<td>CLND, 2000-2010</td>
<td>Tumor area divided by the total lymph node area</td>
<td>Tumor ratio showed a statistically significant association with NSN positivity in a model with perinodal vascular invasion</td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>SLN(+) CM pts + CLND, 2004-2015</td>
<td>Prospective cohort</td>
<td>Biomarkers: serum S-100B and LDH</td>
<td>N=107 pts, positive NSN in 22 pts (20.6%)</td>
</tr>
<tr>
<td>2016</td>
<td>SLN(+) CM pts + CLND, 1996-2010</td>
<td>Retrospective cohort (review of a prospectively maintained database)</td>
<td>'Identify significant factors associated with subsequent lymph node status'</td>
<td>N=171 pts with CLND, positive 'lymph nodes' in 33 pts (19.3%)</td>
</tr>
<tr>
<td>2013</td>
<td>SLN(+) CM pts + CLND, 1995-2010</td>
<td>Retrospective cohort</td>
<td>N-SNORE (non-sentinel node risk score)</td>
<td>N=130 pts, positive NSN in 30 pts (23.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N-SNORE showed 'reasonable' model fit, $r^2 = 0.21$</td>
</tr>
</tbody>
</table>
**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>
<thead>
<tr>
<th>Author</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dummer et al, 2016 [1]</td>
<td>Pts with CM</td>
<td>Literature review and graded recommendations according to CMA 1998 Levels of Evidence Hierarchy</td>
<td>Management and treatment</td>
<td><strong>For isolated tumor cells</strong> 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.</td>
</tr>
<tr>
<td>Swiss Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berrocal et al, 2015 [2]</td>
<td>Malignant melanoma</td>
<td>Review of all phase III clinical trials and other main guidelines</td>
<td>Treatment, surgical management and follow-up</td>
<td>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]</td>
</tr>
<tr>
<td>SEOM Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pflugfelder et al, 2013 [3]</td>
<td>Pts with CM (excluding mucosal and uveal)</td>
<td>Systematic literature</td>
<td>Diagnosis, therapy and follow-up</td>
<td>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]</td>
</tr>
<tr>
<td>German Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dummer et al, 2012 [5]</td>
<td>Pts with CM</td>
<td>Not specified.</td>
<td>Guidelines for the diagnosis, treatment and follow-up</td>
<td>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].</td>
</tr>
<tr>
<td>ESMO Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong et al, 2012 [4]</td>
<td>Pts with newly dx CM</td>
<td>Systematic review, 2 databases, Jan 1990 to Aug 2011</td>
<td>Primary outcomes were measures of test performance</td>
<td>Completion lymph node dissection is recommended for all patients with a positive SLN biopsy.</td>
</tr>
<tr>
<td>ASCO Guideline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coit et al, 2012 [6]</td>
<td>Pts with CM</td>
<td>Consensus-based with review of the literature, otherwise not specified</td>
<td>Staging, workup, primary treatment, adjuvant therapy, recurrence, metastatic disease</td>
<td>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).</td>
</tr>
<tr>
<td>NCCN Guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2b. Results from Systematic Reviews

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
<th>Brief Results</th>
</tr>
</thead>
</table>
| Kyrgidis et al, 2015  | 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  
  - Intermediate-thickness, HR: 0.92, 95% CI: 0.73-1.16  
  - 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  
  - Intermediate-thickness, HR: 0.84, 95% CI: 0.65-1.09  
  - 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]  
  - Intermediate-thickness, HR: 0.77, 95% CI: 0.63-0.95  
  - Thick, HR: 0.70, 95% CI: 0.50-0.97  
  
- Beneficial effect of experimental arm on local and regional recurrence, RR: 0.56, 95% CI: 0.45-0.69  
  - Intermediate-thickness, HR: 0.57, 95% CI: 0.44-0.74  
  - 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]  
  - Intermediate-thickness, HR: 1.25, 95% CI: 0.92-1.70  
  - 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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
<th>Brief Results</th>
</tr>
</thead>
</table>
| Leiter et al, 2016 [9] | Pts with CM + SLN biopsy positive | Phase III clinical trial | Primary outcome:  
  - Distant metastasis-free survival | Intervention, N=240; Control, N=233  
  Median follow-up: 35 months  
  No differences in primary or secondary survival outcomes:  
  Distant metastasis-free survival, HR: 1.19, |

Section 4: Document Review Summary and Tool
<table>
<thead>
<tr>
<th>Trial</th>
<th>Pts with localized CM</th>
<th>Phase III clinical trial</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morton et al, 2014 [10]</td>
<td>Pts with localized CM</td>
<td>Intervention: WE + SLNB. CLND if metastases detected in SLN</td>
<td>Melanoma-specific survival</td>
<td>Disease-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control: WE + nodal observation. Delayed LND for nodal metastases occurring during observation.</td>
<td></td>
<td>Survival based on SLN status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Incidence of nodal metastases</td>
</tr>
</tbody>
</table>

Primary outcome:
- recurrence-free survival
- overall survival
- recurrence of regional lymph node metastasis
- side effects (CLND arm)

Secondary outcomes:
- disease-free survival
- survival based on SLN status
- incidence of nodal metastases

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

**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 intervention 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

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pflugelder et al, 2013 [3]</td>
<td>Pts with CM (excluding mucosal and uveal) German Guidelines</td>
<td>Systematic literature</td>
<td>Diagnosis, therapy and follow-up of melanoma</td>
<td>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 recommendations]</td>
</tr>
<tr>
<td>Coit et al, 2012 [6]</td>
<td>Pts with CM NCCN Guidelines</td>
<td>Consensus-based with review of the literature, otherwise not specified</td>
<td>Staging, workup, primary treatment, adjuvant therapy, recurrence, metastatic disease</td>
<td>In the groin, consider elective iliac and obturator lymph node dissection if clinically positive superficial nodal stations 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).</td>
</tr>
</tbody>
</table>

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.

***

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; DRB, 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:

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"


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 synth?es? 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 psyinfo 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"

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.
therapeutic lymph node dissection.mp.
(therap: adj1 lymph node dissection).mp.
therapeutic lymphadenectomy.mp.
extent of dissection.mp.
extent of excision.mp.
deep inguinal node dissection.mp.
deep inguinal node.mp.
inguinal lymph node/
superficial inguinal node dissection.mp.
superficial inguinal node.mp.
level 3 axillary dissection.mp.
level 3 axillary node.mp.
axillary lymph node/
cloquet's node dissection.mp.
cloquet's node.mp.
iliac node dissection.mp.
iliac node.mp.
obturator node dissection.mp.
obturator node.mp.
or/7-36
6 and 37
(systematic adj (review: or overview:)).mp.
(meta-analy: or metaanaly:).mp.
(pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
(exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
(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.
(reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
or/39-44
(selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.
(stud: adj1 select:).ab.
(46 or 47) and review.pt.
45 or 48
38 and 49
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.
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 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"


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.
placebo/
(placebo? or random allocation or randomly allocated or allocated randomly).mp.
(allocated adj2 random).mp.
or/45-49
42 or 44 or 50
38 and 51
(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.
exp animal/ not humans/
53 or 54
52 not 55
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.
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 (comple: 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"

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.

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

Table A3.2: Comments from the TPR reviewers:

<table>
<thead>
<tr>
<th>Comment</th>
<th>Response and Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The term “sentinel nodal tumour burden” is somewhat cumbersome. The</td>
<td>We have modified the recommendation to “sentinel node metastases”</td>
</tr>
<tr>
<td>authors might consider the term “sentinel node metastases”.</td>
<td></td>
</tr>
<tr>
<td>2. It may be preferable to replace the term ultrasonographic monitoring</td>
<td>We have changed the recommendation in light of this</td>
</tr>
<tr>
<td>with “nodal observation with ultrasonography” as used in the MSLT2</td>
<td></td>
</tr>
<tr>
<td>study.</td>
<td></td>
</tr>
<tr>
<td>3. The authors may wish to give more information to support the statement</td>
<td>We have added the following qualifying statement:</td>
</tr>
<tr>
<td>“for certain patients, a CLND may still be the best option”.</td>
<td>Patients in whom CLND would be a better option than nodal observation with</td>
</tr>
<tr>
<td></td>
<td>ultrasonography</td>
</tr>
</tbody>
</table>
| **best option**” For example in patients who are unlikely to be compliant with an intensive surveillance protocol. | 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 |
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<td><strong>4.</strong> 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.</td>
<td>Thank you, we have removed the 10 year monitoring requirement from the recommendation. AGREE</td>
</tr>
<tr>
<td><strong>5.</strong> 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.</td>
<td>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.”</td>
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<tr>
<td><strong>6.</strong> 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.</td>
<td>While this is outside the scope of this guideline, this comment has been taken into consideration for future updates.</td>
</tr>
<tr>
<td><strong>7.</strong> On p4, 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”?</td>
<td>This has been changed in the recommendation</td>
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<tr>
<td><strong>8.</strong> 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.</td>
<td>The qualifying statement has been changed to reflect this.</td>
</tr>
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<td><strong>9.</strong> Under “Key Evidence ... 2016” CLNB is used as an abbreviation. Should this be CLND?</td>
<td>This has been corrected.</td>
</tr>
<tr>
<td><strong>10.</strong> 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.</td>
<td>Noted</td>
</tr>
<tr>
<td><strong>11.</strong> The recommendation to follow up for 10 years is not supported by the data. Although patients in the trial were followed</td>
<td>Thank you, we have removed the 10 year monitoring requirement from the recommendation.</td>
</tr>
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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.

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


Conflict of Interest

Table A3.3 Targeted Peer Reviews

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Affiliations</th>
<th>Declarations of Interest</th>
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<tbody>
<tr>
<td>Greg McKinnon</td>
<td>Professor of Surgery and Oncology at the University of Calgary and the Tom Baker Cancer Center, Canada</td>
<td>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</td>
</tr>
<tr>
<td>Mark Faries</td>
<td>Surgical Oncologist and co-director of the Melanoma Program and head of Surgical oncology at the Los Angeles Research Institute, USA</td>
<td>Principal Investigator and Study Chair of MSLT-II</td>
</tr>
<tr>
<td>David Gyorki</td>
<td>Surgeon at the Peter MacCallum Cancer Center, Australia</td>
<td>None declared</td>
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