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

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

WARNING

As of June 2017, recent new evidence indicates that Recommendation 1b in this document is no longer valid and may in fact cause harm. An updated version of this guideline will be made available shortly.
Evidence-Based Series 8-6 Version 2

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

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Evidence-Based Series 8-6 was reviewed and ENDORSED by the Melanoma Disease Site Group (DSG). New evidence was added to Section 1 and recommendations are still current and relevant for decision making. See Section 4: Document Assessment and Review for details.

This EBS consists of 4 sections and is available on the CCO website on the PEBC Melanoma DSG page.

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

October 3, 2016

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Guideline Report History

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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

October 3, 2016

The 2012 guideline recommendations have been ENDORSED. This means that the recommendations are still current and relevant for decision making.

Please see below for Key Evidence added following the review process. Additionally, Section 4 contains a summary of all updated evidence published between 2011 and 2016, as well as 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

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

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

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

- **Completion Lymph Node Dissection (CLND)** - The surgical removal of the remaining lymph nodes within an axillary or inguinal nodal basin after the identification of metastatic melanoma within a previously removed sentinel lymph node (SLN) from that same nodal basin. The axillary nodal basin is divided into three levels: level 1 nodes lie below, level 2 nodes lie behind, and level 3 nodes lie above the pectoralis minor muscle. The inguinal nodal basin includes the nodes from below/superficial to the inguinal ligament to the apex of the femoral triangle. The nodes above the inguinal ligament in the pelvis along the iliac vessels up to the common iliac bifurcation can also be considered a part of the inguinal nodal basin. If they are also removed, this is an ilioinguinal dissection.

- **Therapeutic Lymph Node Dissection (TLND)** - The surgical removal of all lymph nodes within an axillary or inguinal nodal basin in the presence of biopsy-proven clinically palpable, or biopsy-proven radiologically detected lymph nodes.

- **Radiologically Detected Lymph Node** - A node that was not clinically palpable but that was biopsied under radiologic guidance after appearing abnormal on radiologic imaging.

- **Cloquet’s node** - The node medial to the femoral vein at the level of the inguinal ligament.

RECOMMENDATIONS AND KEY EVIDENCE

1. **Patients with a positive sentinel lymph node**
   a. **Prognostic factors for predicting non-sentinel lymph node involvement**

   No consistent set of factors reliably predicts non-sentinel lymph node positivity in those patients with a positive SLN. Hence, it is recommended that all patients where the SLN contains melanoma 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 further nodal positivity at CLND. Therefore, it is not possible to identify a group of patients who can reliably be spared CLND.

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

   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.

   There are three small non-randomized studies that have evaluated the benefit of CLND versus observation [40-42]. That question is currently under study in the randomized Multicentre Selective Lymphadenectomy Trial II (MSLT-II), the results of which are not expected for years. 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].

**Key Evidence added in 2016**

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. 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. Due to the limitations of this study, the current recommendation was not altered.

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.

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

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

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

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

**Extent of nodal dissection**

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

Inguinal dissection is recommended for patients with biopsy-proven clinically or biopsy-proven radiologically detected positive inguinal lymph nodes, pending the emergence of good quality randomized data. Because there is a greater likelihood of positive ilioinguinal nodes in this clinical situation, Cloquet’s node could be examined and ilioinguinal dissection undertaken if the node is positive.
In the small dataset currently available there is no clear advantage to ilioinguinal dissection [53] or the evaluation of Cloquet’s node [54,55] with respect to survival or morbidity. Decisions regarding iliac dissection should be made on a case-by-case basis [56,57]. This recommendation is based on expert opinion.

FUTURE RESEARCH

The development of more consistency among studies of factors to predict additional disease in non-sentinel lymph nodes would be invaluable, not only in the selection of variables, but also in the strict definition of the variables selected. Standardized synoptic reporting of the SLN would help bring consistency to these types of studies.

RELATED GUIDELINES

PEBC Evidence-Based Series Report (EBS):


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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.


