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Evidence-Based Series 8-6 Version 2

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

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

The Melanoma Disease Site Group

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

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

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

August 31, 2018

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

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

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

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

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

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

Original Report Date: December 5, 2012

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

QUESTIONS

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

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

OUTCOMES OF INTEREST

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

TARGET POPULATION

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

INTENDED USERS

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

DEFINITIONS

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

RECOMMENDATIONS AND KEY EVIDENCE

1. Patients with a positive sentinel lymph node

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

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

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

New 2018

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

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

Qualifying Statements for Recommendation 1b

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

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

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

Key Evidence Added in the 2018 Update of Recommendation 1b

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

Key Evidence added in the 2016 Endorsement

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

Original Key Evidence from 2012

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

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

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

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

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

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

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

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

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

Extent of nodal dissection

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

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

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

FUTURE RESEARCH

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

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

RELATED GUIDELINES

PEBC Evidence-Based Series Report (EBS):

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

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Updating

All PEBC documents are maintained and updated
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https://www.cancercareontario.ca/en/cancer-care-ontario/programs/data-research/evidence-based-care

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

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