

Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline

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ABSTRACT

Background For patients who are diagnosed with early-stage cutaneous melanoma, the principal therapy is wide surgical excision of the primary tumour and assessment of lymph nodes. The purpose of the present guideline was to update the 2010 Cancer Care Ontario guideline on wide local excision margins and sentinel lymph node biopsy (SLNB), including treatment of the positive sentinel node, for melanomas of the trunk, extremities, and head and neck.

Methods Using Ovid, the MEDLINE and EMBASE electronic databases were systematically searched for systematic reviews and primary literature evaluating narrow compared with wide excision margins and the use of SLNB for melanoma of the trunk and extremities and of the head and neck. Search timelines ran from 2010 through week 25 of 2017.

Results Four systematic reviews were chosen for inclusion in the evidence base. Where systematic reviews were available, the search of the primary literature was conducted starting from the end date of the search in the reviews. Where systematic reviews were absent, the search for primary literature ran from 2010 forward. Of 1213 primary studies identified, 8 met the inclusion criteria. Two randomized controlled trials were used to inform the recommendation on completion lymph node dissection.

Key updated recommendations include:

- Wide local excision margins should be 2 cm for melanomas of the trunk, extremities, and head and neck that exceed 2 mm in depth.
- SLNB should be offered to patients with melanomas of the trunk, extremities, and head and neck that exceed 0.8 mm in depth.
- Patients with sentinel node metastasis should be considered for nodal observation with ultrasonography rather than for completion lymph node dissection.

Conclusions Recommendations for primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in patients with cutaneous melanoma have been updated based on the current literature.

Key Words Melanoma, sentinel lymph nodes, sentinel lymph node metastases, wide excision margins, practice guidelines, melanoma *in situ*, margins, completion lymph node dissection

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INTRODUCTION

The incidence of melanoma is increasing both worldwide and in Canada. In Canada between 2001 and 2010, the incidence rates of melanoma increased by 2.3% per year in men and by 2.9% per year in women¹. Melanoma is the 7th most common cancer in Canada, and in 2017, 7300 new cases were diagnosed and more than 1250 deaths were recorded¹. For patients who are diagnosed with early-stage cutaneous melanoma [clinically node-negative and <4 mm thickness (pT1–pT3)], the principal therapy is wide surgical excision of the primary tumour and assessment of lymph nodes.

In the past, standard therapy included wide radial excision margins of up to 5 cm; however, that practice is associated with significant morbidity and disfigurement. A series of randomized controlled trials (RCTs) demonstrated that narrower margins have not been associated with higher local recurrence rates or worse overall survival (OS)^{2–7}. However, uncertainty about optimal excision margins for the primary tumour—especially those deeper than 2 mm—remains⁸.

Standard surgical treatment for patients who are clinically node-negative also includes assessment of the regional lymph nodes. The risk for nodal involvement rises with increasing tumour thickness; however, 90% of patients with stage I and II cutaneous melanomas have no clinical evidence of lymphadenopathy at initial presentation, and yet approximately 16% are found to have microscopic involvement upon further examination⁹.

Sentinel lymph node biopsy (SLNB) is a surgical procedure that identifies the sentinel node, the first lymph node or nodes that drain the primary melanoma site. The SLNB is identified by lymphatic mapping with a blue dye (isosulfan or patent blue) and a radioactive tracer (Tc-99). The process allows for the status of a clinically node-negative regional basin to be determined without a complete lymph node dissection. The nodes are serially sectioned and carefully examined pathologically for the presence of melanoma metastases (hematoxylin and eosin stain and immunohistochemistry for HMB-45, S-100, and MART-1). The technique is predicated on the empiric observation that melanoma metastasizes through lymphatics sequentially, preferentially to the sentinel lymph node (SLN) and then to other regional lymph nodes. The Multi-site Lymphadenectomy Trial I (MSLT-I) demonstrated a survival benefit of SLNB at 5 years for patients with an intermediate-thickness melanoma when completion lymphadenectomy was performed after melanoma metastases in the SLNs were identified⁹. However, uncertainty remains about the optimal indications for SLNB, especially for melanomas that are thin (<1 mm) or thick (>4 mm) or that occur on the head and neck.

After the publication of MSLT-I, two key studies assessed the survival benefit of completion lymphadenectomy (CLND) after identification of a positive SLNB by comparing CLND with ultrasound monitoring of the lymph node basin: DECOG-SLT and MSLT-II^{10,11}.

In the present guideline, we also synthesize the literature about whether CLND after identification of a positive SLN improves outcomes. The purpose of the guideline was to update the 2010 Cancer Care Ontario

guideline about wide local excision margins and SLNB, including the positive SLN for trunk, extremities, and head and neck, in the context of recent literature.

METHODS

This practice guideline was developed by the Melanoma Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) using the methods of the practice guidelines development cycle¹². For this guideline, the core method used to develop the evidentiary base was an update of a systematic review from a previous version of the guideline, together with the addition of a systematic review evaluating excision margins and the use of SLNB in patients with head-and-neck melanoma. Evidence was selected and reviewed by 2 members of the Melanoma DSG and 1 research methodologist.

This practice guideline is an up-to-date source of the best available evidence about optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk, extremities, or head and neck. It was developed by systematic review, data synthesis, internal review by a clinician and a methodologist, and external review by clinical experts and Ontario practitioners. The systematic review evidence forms the basis of the recommendations developed by the Melanoma DSG. This practice guideline is intended to promote evidence-based practice in Ontario. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Questions

The Melanoma DSG determined that these questions would guide the literature review:

- In patients with nonmetastatic cutaneous melanoma with clinically node-negative or node-positive disease of the trunk or extremities, what are the optimal primary clinical margins of excision?
- In patients with a diagnosis of melanoma of the trunk or extremities and concurrent distant metastases at presentation, what are the optimal primary clinical margins of excision for the cutaneous disease?
- Which patients with clinically node-negative cutaneous melanoma of the trunk and extremities should undergo SLNB?
- In patients with nonmetastatic cutaneous melanoma with clinically node-negative or node-positive disease of the head and neck, what are the optimal primary margins of excision?
- In patients with a diagnosis of melanoma of the head and neck and concurrent distant metastases at presentation, what are the optimal primary margins of excision for the cutaneous disease?
- Which patients with clinically node-negative cutaneous melanoma of the head and neck should undergo SLNB?
- What is the optimal surgical management of patients with positive SLNs from cutaneous melanoma of the trunk or extremities with respect to CLND compared with observation at the time of SLN positivity.

It should be noted that, for all research questions (with the exception of CLND), these categories of melanoma thickness were addressed: *in situ*, less than 1 mm, 1.01–2 mm, 2.01–4 mm, and 4.01 mm or more.

Target Population

The guideline recommendations apply to adults (>18 years of age) diagnosed with truncal, extremity, or head-and-neck cutaneous melanoma.

Systematic Review

A search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To that end, these sources were searched for existing guidelines addressing the research questions:

- Practice guideline databases
The SAGE Directory of Cancer Guidelines, the U.S. Agency for Healthcare Research and Quality's National Guideline Clearinghouse, and the Canadian Medical Association's CPG Infobase
- Guideline developer Web sites
The U.K. National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, the American Society of Clinical Oncology, and Australia's National Health and Medical Research Council

These criteria were used to select potentially relevant guidelines:

- Published after the year 2010 (because the original PEBC guideline was published in 2010)
- Included a systematic review of the literature that covered at least 1 of the outcomes of interest

Using Ovid, the MEDLINE and EMBASE electronic databases were systematically searched for systematic reviews and primary literature evaluating narrow compared with wide excision margins and the use of SLNB. For melanoma of the trunk and extremities, the Ovid search ran from 2010 to week 25 of 2017, and for melanoma of the head and neck, the Ovid search ran from 2002 to week 25 of 2017. For both searches, these keywords were used: "melanoma," "head and neck" (for the head-and-neck search only), "excision margin," "SLNB," and "sentinel node." In addition, Web sites and databases of specific guideline developers that used systematic reviews as their evidentiary base and of producers of systematic reviews were also searched, using the same keywords and the same time periods.

Using Ovid, the MEDLINE and EMBASE electronic databases were systematically searched for primary studies evaluating optimal excision margins and use of SLNB in adults diagnosed with melanoma. The search ran from 2002 for head-and-neck populations, and from 2010 for trunk and extremity populations, through week 25 of 2017. The literature search strategy included keywords for identification of excision margins, SLNB, head-and-neck melanoma populations, and trunk and extremity melanoma populations. In addition to the MEDLINE and EMBASE database searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

The titles and abstracts that resulted from the search were reviewed by one reviewer (LHS) and verified by a second (FCW). For items that warranted full-text review, 1 reviewer determined whether the inclusion and exclusion criteria were met. The list of proposed studies was verified by the Melanoma DSG.

Development of Recommendations

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle^{12,13}. That process includes a systematic review; interpretation of the evidence by a Working Group, with production of draft recommendations; an internal review by content and methodology experts; and external reviews by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework¹⁴ as its methodologic strategy for guideline development. The 23-item validated AGREE II tool is designed to assess the methodologic rigour and transparency of guideline development.

RESULTS

Literature Search Results

The search for existing systematic reviews identified 126 possible reviews on optimal resection margins and use of SLNB in melanoma patients. Four systematic reviews^{15–18} were chosen for inclusion in the evidence base. One review evaluated narrow compared with wide excision margins in patients with melanoma of the trunk and extremities¹⁸; the remaining three reviews assessed the use of SLNB in melanoma of the trunk and extremities^{15,16} and in melanoma of the head and neck¹⁷.

The systematic review of the primary literature addressed outcomes of interest not covered by the four systematic reviews included in the evidence base. Where one or more systematic reviews were available, the search of the primary literature started from the end date of the search in the review or reviews. Of 1213 studies identified, 8 studies met the inclusion criteria. Table 1 summarizes the number of studies identified per research question, the melanoma location, and the Breslow thickness.

Details about the methodologic characteristics and clinical outcomes of the included trials can be found in the full guideline report at the Cancer Care Ontario Web site²⁶.

It should be noted that the present guideline focuses on patients with clinically node-negative disease. The reason for that decision was that no data were available concerning the extent of wide local excision in patients who were node-positive or who had metastatic disease. The current standard of practice for patients with node-positive disease is a standard wide local excision. No data were found for patients with metastatic disease, and the extent of wide local excision should be discussed in a multidisciplinary team cancer conference on a case-by-case basis.

Recommendation 1—Surgical Margins for Melanoma Located on the Trunk and Extremities

After initial excision or biopsy for melanoma located on the trunk and extremities, the radial excision margins, measured clinically from the edge of the melanoma or biopsy scar, should accord with the recommendations in Table II.

TABLE I Literature identified

Topic	Melanoma location	Breslow thickness	Studies
Primary excision margins	Trunk and extremities	<i>In situ</i>	None identified
		≤1 mm	1 SR with meta-analysis ^{18,a} 1 Case-control study ¹⁹
		1.01–2 mm	1 SR with meta-analysis ^{18,a}
		2.01–4 mm	1 SR with meta-analysis ^{18,a} 1 Randomized controlled trial ^{20,b}
		≥4.01 mm	1 SR with meta-analysis ^{18,a} 1 Randomized controlled trial ^{20,b}
	Head and neck	<i>In situ</i>	1 Retrospective cohort ^{21,c}
		≤1 mm	2 Retrospective cohorts ^{21,22,c}
		1.01–2 mm	2 Retrospective cohorts ^{21,22,c}
		2.01–4 mm	2 Retrospective cohorts ^{21,22,c}
		≥4.01 mm	3 Retrospective cohorts ^{21,22,23,c}
Sentinal lymph node biopsy	Trunk and extremities	<i>In situ</i>	No studies identified
		≤1 mm	2 SRs with meta-analyses ^{15,16} 1 Randomized controlled trial ^{9,d}
		1.01–2 mm	1 SR with meta-analysis ¹⁵ 2 Randomized controlled trials ^{9,24,d,e}
		2.01–4 mm	1 SR with meta-analysis ¹⁵ 1 Randomized controlled trial ^{9,d}
		≥4.01 mm	1 SR with meta-analysis ¹⁵ 1 Randomized controlled trial ^{9,d}
	Head and neck	<i>In situ</i>	None identified
		≤1 mm	1 SR without meta-analysis ^{17,f} 1 Randomized controlled trial ^{9,d} 1 Diagnostic cohort ^{25,g}
		1.01–2 mm	1 SR without meta-analysis ^{17,f} 1 Randomized controlled trial ^{9,d} 1 Diagnostic cohort ^{25,g}
		2.01–4 mm	1 SR without meta-analysis ^{17,f} 1 Randomized controlled trial ^{9,d} 1 Diagnostic cohort ²⁵
		≥4.01 mm	1 SR without meta-analysis ^{17,f} 1 Randomized controlled trial ^{9,d} 1 Diagnostic cohort ²⁵

^a Compared tumours 2.0 mm or less thick with those more than 2.0 mm thick.
^b U.K. trial including patients with a Breslow thickness of at least 2.0 mm.
^c MSLT-I (Multi-site Lymphadenectomy Trial I) defined thin melanomas as those less than 1.2 mm, intermediate as 1.2–3.5 mm, and thick melanomas as those greater than 3.5 mm.
^d Enrolled patients with a Breslow thickness of 1.0 mm or greater; median thickness was 1.55 mm.
^e Patients were classified by disease stage and included those with Tis through T4 tumours.
^f Included studies that enrolled patients of all Breslow thicknesses.
^g “Thin melanoma” defined as 2.0 mm or less; lowest limit not reported.
 SR = systematic review.

Qualifying Statements

The total wide local excision margin can be a composite margin from the biopsy and from the wide local excision.

For melanoma *in situ*, no RCTs have evaluated appropriate surgical margins. In a single prospective study of pathologic margins for melanoma *in situ*, 86% of patients had clear pathologic margins with a 6 mm wide excision margin, and 98.9% of melanomas *in situ* were completely excised with a 9 mm surgical margin²⁷. Consequently, some patients might require wider surgical margins of 1 cm to achieve clear pathologic margins; however, a 5 mm margin is suggested as the initial wider margin, especially in areas in which obtaining wider margins is challenging or in which wider margins would have an unacceptable effect on form or function.

Where possible, it might be desirable to take a wider margin (2 cm) for pT2 lesions, depending on tumour site and surgeon or patient preference, because the evidence concerning optimal excision margins in those cases (1 cm vs. 2 cm) is unclear.

Key Evidence and Interpretation

A 2016 systematic review with meta-analysis that pooled six RCTs compared narrow (1–2 cm) with wide (3–5 cm) excision margins for thin (≤ 2 mm) and thick (> 2 mm) melanomas¹⁸. That meta-analysis by Wheatley *et al.* found that, for all patients (≤ 2 mm and > 2 mm alike), OS and recurrence-free survival (RFS) were not different when narrow compared with wide margins were used; however, melanoma-specific survival (MSS) was improved with wide margins (3–5 cm) compared with narrow margins (1–2 cm)¹⁸. Subgroup analysis for thin and thick melanomas found no difference in OS, MSS, RFS, or locoregional recurrence when the melanoma depths (≤ 2 mm and > 2 mm) were separately assessed¹⁸. Furthermore, the nodal status of the patients was unknown in most studies, thus potentially affecting MSS results.

A new RCT that was not included in the Wheatley *et al.* meta-analysis and that enrolled patients with thick melanomas (≥ 2 mm), found no difference in OS when comparing 1 cm with 3 cm margins; however, a trend toward a reduction in MSS was seen that did not reach statistical significance²⁰. The nodal status of the patients in this new study was unknown, thus potentially affecting the results.

The Working Group considered both the Wheatley meta-analysis, previous margin studies, and the potential morbidity associated with a 3–5 cm margin for all melanomas

when making its recommendations. In particular, for the meta-analysis data¹⁸, several factors were considered: patient numbers within each depth range; the fact that this analysis was the first to suggest that narrow margins were associated with worse MSS; and the morbidity of larger margins, with the likelihood of more complex closures using skin grafts and flaps. The Working Group believes that more confirmatory data are needed before such a significant practice change (a > 3 cm excision margin for all melanomas) can be recommended.

An additional case-control study that enrolled patients with thin melanomas (≤ 1 mm) who had experienced local recurrence found that median time to recurrence was significantly shorter for patients with margins less than 1 cm, but was not different when margins greater than 2 cm were compared with margins less than 2 cm¹⁹.

Recommendation 2—Surgical Margins for Cutaneous Melanoma Located on the Head and Neck

After initial excision or biopsy for cutaneous melanoma located on the head and neck, the radial excision margins, measured clinically from the edge of the melanoma or biopsy scar, should accord with the recommendations in Table III.

Qualifying Statements

For pT2 melanomas, it could be desirable, where possible, to take a wider surgical margin (2 cm) depending on tumour site and surgeon or patient preference, because evidence concerning optimal excision margins is unclear.

The total wide local excision margin can be a composite margin from the biopsy and the wide local excision.

It is recognized, however, that wide margins might not always be possible, based on the location of the melanoma in relation to facial structures. When possible, wide margins should be used; however, they could be difficult to achieve when the melanoma is located on the eyelid, nose, lip, or ear.

For melanoma *in situ*, margin-controlled excision might provide tissue-sparing and improved tumour clearance in challenging locations such as near the eye, nose, lips, and ears.

Key Evidence and Interpretation

Three low-quality retrospective cohort studies were identified to directly inform this recommendation for invasive

TABLE II Surgical margins for cutaneous melanoma located on the trunk and extremities

TNM classification	Thickness	Total margin
pTis	<i>In situ</i>	5 mm–1 cm
pT1	≤ 1.0 mm	1 cm
pT2	1.01–2.0 mm	1–2 cm
pT3	2.01–4.0 mm	2 cm
pT4	≥ 4.01 mm	2 cm

TABLE III Surgical margins for cutaneous melanoma located on the head and neck

TNM classification	Thickness	Total margin
pTis	<i>In situ</i>	5 mm–1 cm
pT1	≤ 1.0 mm	1 cm
pT2	1.01–2.0 mm	1–2 cm
pT3	2.01–4.0 mm	2 cm
pT4	≥ 4.01 mm	2 cm

(pT1–pT4) melanoma. All three reviewed the medical records of patients diagnosed with melanoma located on the head and neck and found no difference in survival rates^{21–23} or recurrence rates^{22,23} when margins of different sizes were compared.

No RCTs were identified to inform a recommendation for melanoma *in situ* in the head and neck. The Working Group applied knowledge from the Mohs micrographic surgery literature, which indicates that margins of 9–10 mm might be needed to achieve a complete clearance rate in some patients with melanoma *in situ*, but that a 5 mm margin is suggested as the initial surgical margin^{27,28}.

Recommendation 3—SLNB for Melanoma Located on the Trunk and Extremities

Patients with a clinically node-negative stage I or II melanoma 0.8 mm in thickness and located on the trunk or extremities should be given the opportunity to discuss SLNB to provide staging and prognostic information (Table IV).

Qualifying Statements

Sentinel lymph node biopsy should be performed only after a discussion of the options with the patient, when access to appropriate surgical, nuclear medicine, and pathology services is available.

The false-negative rate of SLNB is lowest when more than 50 cases have been performed at the institution²⁹.

A double dye technique with Tc-99 and blue dye (isosulfan or patent blue) increases the identification rate of the SLNs³⁰.

It should be noted that, in MSLT-I²⁹, the subgroup for intermediate-thickness melanoma was 1.2–3.5 mm. We applied the MSLT-I data to all intermediate-thickness melanomas 1–4 mm.

For patients with intermediate-thickness melanomas diagnosed with nodal metastases on pathology of the sentinel node or nodes, a 10-year MSS benefit for SLNB was reported on a planned subset analysis; however, OS was not reported.

Sentinel lymph node biopsy should be discussed with patients to identify those eligible for adjuvant therapy and for enrolment into clinical trials.

Ideally, for best accuracy, SLNB is performed at the same time as the wide local excision of the primary melanoma. Sentinel lymph node biopsy is less reliable or might fail when performed as a separate operation for a patient already having had wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft.

Key Evidence and Interpretation

The 10-year follow-up of MSLT-I⁹ was published after the 2010 guideline. That RCT enrolled patients with thin (<1.2 mm), intermediate (1.2–3.5 mm), and thick (>3.5 mm) melanomas, but the 10-year follow-up publication reported only on the patients with intermediate and thick melanomas. Patients were randomized to a wide excision (2–3 cm) alone (observation group) or wide excision (2–3 cm) plus SLNB (biopsy group)⁹. Patients in the biopsy group with a positive SLNB underwent immediate lymphadenectomy; patients in the observation group received nodal observation and lymphadenectomy only if they later presented with nodal relapse⁹. The MSLT-I update reported on disease-free survival (DFS) and MSS, but not OS. The 10-year DFS was significantly higher in the SLNB group than in the observation group whether patients had intermediate or thick melanomas ($p = 0.01$ and $p = 0.03$ respectively)⁹. Overall, the 10-year MSS was not different between the groups with either intermediate or thick melanomas⁹. However, for patients with nodal metastases, the 10-year MSS on a planned subset analysis was significantly higher for patients with intermediate-thickness melanomas in the SLNB group than for those in the observation group ($62.1\% \pm 4.8\%$ vs. $41.5\% \pm 5.6\%$)⁹; the same case did not hold for the patients with thick melanomas.

Other studies reviewed for recommendation 3 included a meta-analysis that considered studies of multiple Breslow thicknesses, but because of missing data, could pool data only for thick melanomas (>4.01 mm), finding that OS was reduced in patients having positive SLNs compared with patients having negative SLNs¹⁵. A second meta-analysis included only studies involving patients diagnosed with thin melanomas (≤ 1 mm), finding that, overall, 4.5% of those patients had positive SLNs¹⁶. Melanoma thickness of 0.75 mm

TABLE IV Sentinel lymph node biopsy (SLNB) for cutaneous melanoma located on the trunk and extremities

TNM classification	Thickness	Use of sentinel lymph node biopsy
pTis	<i>In situ</i>	Not recommended
pT1	≤ 1.0 mm	If melanoma is ≥ 0.8 mm in thickness, is Clark level 4 or 5, or has a high mitotic rate (≥ 1 mitosis/mm ²), ulceration, or microsattellites, the physician should discuss SLNB with the patient. Biopsy might provide a melanoma-specific survival benefit if the sentinel node contains melanoma metastases. Such patients might also benefit from adjuvant therapy or entry into adjuvant clinical trials (or both).
pT2 and pT3	1.01–2.0 mm 2.01–4.0 mm	For these patients, SLNB is recommended to provide locoregional control and to identify individuals who might benefit from adjuvant therapy or entry into adjuvant clinical trials (or both). Biopsy might provide a melanoma-specific survival benefit if the sentinel node contains melanoma metastases.
pT4	≥ 4.01 mm	Physicians should discuss SLNB with these patients to identify patients who might benefit from adjuvant therapy or entry into adjuvant clinical trials (or both). Biopsy will provide prognostic information. If the sentinel node contains metastases, removing it might provide locoregional control, but not a melanoma-specific survival benefit.

or greater, Clark level 4 or 5, high mitotic rate (≥ 1 mitosis/mm²), ulceration, and microsatellites were predictors of SLN metastases, with the rates of SLN positivity being 8.8%, 7.3%, 8.8%, 5.8%, and 26.6% for each predictor respectively¹⁶.

Lastly, based on the systematic review with meta-analysis from Cordeiro *et al.*¹⁶ in patients with thin melanomas, any or some combination of a melanoma thickness of 0.75 mm or greater, Clark level 4 or 5, a high mitotic rate, ulceration, or microsatellites indicated a higher chance for SLN positivity, and physicians should therefore discuss SLNB with affected patients. For guideline recommendation 3, the 8th edition of the American Joint Committee on Cancer staging manual for melanoma was used³¹.

Recommendation 4—SLNB for Cutaneous Melanoma Located on the Head and Neck

Patients with a clinically node-negative stage I or II cutaneous melanoma more than 0.8 mm in thickness and located on the head and neck should be given the opportunity to discuss SLNB to provide staging and prognostic information (Table v).

Qualifying Statements

Sentinel lymph node biopsy should be performed only after a discussion of the options with the patient, when access to appropriate surgical, nuclear medicine, and pathology services is available.

The false-negative rate of SLNB is lowest when more than 50 cases have been performed at an institution²⁹.

A double dye technique with Tc-99 and blue dye (isosulfan or patent blue) increases the identification rate of the SLNs³⁰.

Sentinel lymph node biopsy should be discussed with patients to identify those eligible for adjuvant therapy and for enrolment into clinical trials.

Ideally, for greatest accuracy, SLNB should be performed at the same time as the wide local excision of the primary melanoma. Sentinel lymph node biopsy is less reliable or might fail when performed as a separate operation for a patient already having had a wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft^{32,33}.

Key Evidence and Interpretation

One systematic review¹⁷ and one diagnostic cohort study²⁵ assessed the diagnostic performance of SLNB for melanoma located on the head and neck and reported high false-negative rates: 20.4% and 4.8% respectively.

It is now known that MSLT-I⁹ included 334 patients with primary melanomas located on the head and neck (Faries M. Personal communication. 2 June 2016). Although head-and-neck patients were not separately analyzed, 10-year DFS for all enrolled patients was significantly higher in the SLNB group than in the observation group for patients with intermediate or thick melanomas⁹. Additionally, in patients with intermediate-thickness melanomas and nodal metastases, a planned subset analysis found that 10-year MSS was significantly higher in the SLNB group than in the observation group⁹. However, MSS was not improved for patients with thick melanomas.

Recommendation 5—CLND Compared with Observation at the Time of SLN Positivity

Patients with SLN metastasis should be considered for nodal observation with ultrasonography rather than for CLND. Monitoring of the affected nodal basin with ultrasonography and clinical exam will be required, at a minimum, every 4–6 months for the first 2 years and every 6 months from year 3 to year 5. Suspicion of a nodal recurrence in a lymph node basin includes any 2 of these observations: lymph node length-to-depth ratio less than 2; hypochoic centre; and failure to identify a nodal hilar vessel or focal rounded area of low-level echoes with increased vascularity in that area, or both. Suspicion of a nodal recurrence by ultrasonography should be confirmed with a biopsy of the suspicious lymph node. If the biopsy shows melanoma, the patient should be re-staged before any further surgery. For certain patients with a positive SLN, a CLND rather than ultrasound monitoring might still be the best option for local control, but the choice should be discussed by a multidisciplinary team.

Qualifying Statements

In MSLT-II¹¹, one third of the patients had melanoma metastases greater than 1 mm in diameter, and 72% of

TABLE V Sentinel lymph node biopsy (SLNB) for cutaneous melanoma located on the head and neck

TNM classification	Thickness	Use of sentinel lymph node biopsy
pTis	<i>In situ</i>	Not recommended
pT1	≤ 1.0 mm	If melanoma is ≥ 0.8 mm in thickness, is Clark level 4 or 5, has a high mitotic rate (≥ 1 mitosis/mm ²), ulceration, or microsatellites, the physician should discuss SLNB with the patient. Biopsy might provide a melanoma-specific survival benefit if the sentinel node contains melanoma metastases. Such patients might also benefit from adjuvant therapy or entry into adjuvant clinical trials (or both).
pT2 and pT3	1.01–2.0 mm 2.01–4.0 mm	For these patients, SLNB is recommended to provide locoregional control and to identify individuals who might benefit from adjuvant therapy or entry into adjuvant clinical trials (or both). Biopsy might provide a melanoma-specific survival benefit if the sentinel node contains melanoma metastases.
pT4	≥ 4.01 mm	Physicians should discuss SLNB with these patients. Biopsy will provide prognostic information. If the sentinel node contains melanoma metastases, removal might provide locoregional control, but not a melanoma-specific survival benefit. These patients might also benefit from adjuvant therapy or entry into adjuvant clinical trials (or both).

the patients had 1 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 CLND was more likely in high-risk groups (>1 mm) than in low-risk groups (≤ 1 mm)¹¹.

Patients for whom CLND might be a better option than nodal observation with ultrasonography are

- those with extensive sNL metastasis in which CLND would provide regional control.
- those unlikely to comply with an intensive surveillance protocol.
- those treated at centres in which radiologists are not comfortable performing serial surveillance ultrasonography examinations.

Although guideline 5 is specific to the trunk and extremities, the same recommendation can be applied to melanomas of the head and neck and their respective drainage basins.

Key Evidence and Interpretation

Two randomized trials, MSLT-II¹¹ and DECOG-SLT¹⁰, evaluated the utility of CLND compared with observation through frequent nodal ultrasonography, with dissection only in melanoma patients with progression of nodal disease. In MSLT-II¹¹, patients with melanoma metastases in a SLN were randomized to either nodal observation (every 4 months for 3 years and then every 6 months for 2 years for a total of 5 years of nodal observation) or to immediate CLND. Patients with biopsy-proven isolated nodal recurrence underwent a therapeutic lymph node dissection. Median follow-up was 43 months. In a planned subset analysis, no patients were found to benefit from immediate CLND. Most patients had low-volume nodal tumour burden (1 positive SLN; mean diameter of nodal metastasis: 1.1 mm). The 3-year mss was 86% \pm 1.3% in the CLND group and 86% \pm 1.2% the observation group ($p = 0.42$). The 3-year DFS rate was slightly higher in the CLND group ($p = 0.05$), but the investigators suggested caution about the significance of that result based on the lack of significance of the mss, which was the primary outcome. Overall, some regional control and prognostic value can be derived from CLND, but at the expense of increased adverse events—in particular, lymphedema and a potential delay to adjuvant therapy. The nonsignificant difference in mss and the increase in adverse events in the CLND group indicate that CLND is not recommended for low-volume nodal tumour burden and does not offer a survival benefit. Whether a CLND should or should not be recommended with larger-volume disease in the SLNs is unclear; however, on subset analysis, no patients (including those with a higher volume of melanoma metastases) benefited from CLND, which led to recommendation 5. Similarly, the DECOG-SLT trial¹⁰ found no difference in distant metastasis-free survival, OS, or RFS when patients with positive SLNs who received CLND were compared with patients who were observed with nodal ultrasonography and computed tomography imaging of the affected basin. Median follow-up for the trial was 35 months¹⁰.

DISCUSSION

In this systematic review, we summarize the last 8 years of surgical melanoma trials for patients with head-and-neck, truncal, and extremity primaries. In particular, we focus on the extent of wide local excision for the primary melanoma, which patients should be offered a SLNB, and which patients with melanoma metastases in their SLN should undergo CLND.

One of the most discussed papers identified during this update was the Wheatley *et al.* systematic review and meta-analysis¹⁸. The findings from that study could substantially change practice with respect to wide local excision margins for patients with melanoma. The Working Group members interpreted those data with extreme caution. The meta-analysis found that, for all patients with melanoma, OS, locoregional recurrence, and RFS were not different when narrow margins (1–2 cm) were compared with wide margins (3–5 cm), but that mss was improved with wide margins¹⁸. Using Bayesian likelihood plots, the systematic review reported a high probability that narrow margins were worse than wide margins for OS, mss, RFS, and locoregional recurrence¹⁸, providing the first-ever published data indicating that narrow margins are not safe and refuting clinical practice guidelines from worldwide organizations. When making its recommendations, the Working Group considered the Wheatley meta-analysis, prior margin studies, and the potential morbidity associated with a 3–5 cm margin for all melanomas. In particular, for the meta-analysis data¹⁸, we considered patient numbers within each depth range; the fact that the Wheatley analysis is the first to suggest that mss is worse with narrow margins; and the morbidity of larger margins, with the likelihood of more complex closures requiring skin grafts and flaps. The Working Group believes that more confirmatory data are needed before such a significant practice change (a >3 cm excision margin for all melanomas) can be recommended. The main change that was made to the original guideline was to increase the margin recommendation for melanomas of 2.0–4.0 mm thickness to 2 cm from 1–2 cm. The Working Group strongly supports a RCT comparing margins of 1 cm, 2 cm, and 3 cm.

The Working Group also made changes to the margin recommendations for melanoma *in situ*. The original recommendation of a 5 mm margin was adopted from the Australia–New Zealand guideline developers³⁴. Two factors led to a change in the recommendation: a recent prospective study of pathologic margins for melanoma *in situ*, which found that 86% of patients had clear pathologic margins with a 6 mm wide excision margin and that 98.9% of melanomas *in situ* were completely excised with a 9 mm surgical margin²⁷; and the clinical experience of the group. The Working Group now suggests a 5 mm to 1 cm margin for melanoma *in situ*, although a 5 mm margin is recommended for the initial excision, and a 1 cm margin is recommended only if the margins are positive after the initial excision.

With respect to the recommendations for SLNB, the Working Group recommends that all patients with a melanoma greater than 0.8 mm in thickness and with no clinical evidence of nodal metastasis should be given the opportunity to discuss SLNB. Sentinel lymph node biopsy is performed to provide information for staging and

prognosis, and to identify patients who could benefit from adjuvant therapy or clinical trials. Although the MSLT-I trial did not report on OS at 10 years, it reported a mSS benefit for patients with intermediate-thickness melanomas and nodal metastases, and in a planned subset analysis, improved locoregional control for patients with melanomas of 1.2 mm to more than 3.5 mm thickness on the trunk and extremities or head and neck. Some controversy attends that result because, overall, the trial was negative and no OS was reported. For patients with a melanoma thicker than 4.0 mm, SLNB provides locoregional control, and patients should still be given the opportunity to discuss the role of SLNB for prognostic information, locoregional control, and consideration of adjuvant therapy^{35–37}.

Lastly, based on the Cordeiro systematic review with meta-analysis¹⁶, patients with thin melanomas [≥ 0.75 mm (now 0.8 mm with the new American Joint Committee on Cancer staging)] that are Clark level 4 or 5 or have high mitotic rates, ulceration, or microsatellites have a higher chance of SLN positivity, and thus, physicians should discuss SLNB with them. When discussing melanoma located on the head and neck alone, the available data indicate a higher chance for a false negative from the SLNB^{17,25}. To help minimize the number of false negatives, the Working Group suggests performing the SLNB in a high-volume centre (>50 cases)²⁹; using a dual tracer technique with Tc-99 and blue dye to improve the SLN detection rate³⁰; and using integrated single-photon emission computed tomography–computed tomography, which might improve the localization of SLNs in head and neck areas³⁸.

Until the publication of the MSLT-II trial, the value of CLND in patients with SLN metastasis had been inconclusive and controversial. The MSLT-II trial provided sufficient data to determine that, in patients with SLN metastasis, CLND, compared with nodal observation, provided no statistically significant survival benefit¹¹. The Working Group acknowledges that most patients enrolled in the trial had a low-volume nodal tumour burden; however, a subgroup analysis of patients with a greater disease burden (maximal tumour diameter > 1 mm) did not indicate that a benefit of CLND was more likely to accrue in high-risk groups than in low-risk groups¹¹. Although CLND provided some regional control and improved staging, the Working Group weighed those data against the increased potential for adverse events—in particular, lymphedema and a possible delay to adjuvant therapy—and determined that the regional control and improvements in staging did not outweigh the increased possibility of complications and morbidity associated with CLND. The Working Group consequently recommends that all patients with melanoma metastasis in their SLNs be considered for nodal observation. Those guidelines are similar to the 2017 recommendations from the American Society of Clinical Oncology concerning SLNs and the management of regional lymph nodes in melanoma^{39,40}.

INTERNAL AND EXTERNAL REVIEW OF THE PRACTICE GUIDELINE

The PEBC Report Approval Panel reviewed the draft systematic review and practice guideline and provided feedback.

The draft systematic review and practice guideline were distributed to health care providers in the province of Ontario. The results of those two sources of feedback can be found in the full guideline report at the Cancer Care Ontario Web site²⁶.

REVIEW AND UPDATE

Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit the Cancer Care Ontario Web site (<https://www.cancercareontario.ca/en>) for the full evidence-based series report²⁶ and any subsequent updates.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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