



## Evidence-Based Series 8-2 IN REVIEW

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

### Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities

*F. Wright, K. Spithoff, A. Easson, C. Murray, J. Toye, D. McCready, T. Petrella,  
and the Melanoma Disease Site Group*

Report Date: May 17, 2010

An assessment conducted in November 2015 placed Evidence-based Series (EBS) 8-2 IN REVIEW. This means that it is undergoing a review for currency and relevance. The Melanoma Disease Site Group (DSG) has determined that it is still appropriate for this document to continue to be available while this updating process unfolds. The PEBC has a formal and standardize process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

The full Evidence-based Series 8-2 is comprised of 3 sections and is available on the [CCO website](#) on the [PEBC Melanoma DSG page](#).

**Section 1: Guideline Recommendations**

**Section 2: Evidentiary Base**

**Section 3: EBS Development Methods and External Review Process**

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## Evidence-Based Series #8-2: Section 1

# Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities: Guideline Recommendations

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### QUESTIONS

1. What are the optimal primary margins of excision for clinically node-negative cutaneous melanoma that is a) in situ, b) <1 mm, c) 1-2 mm, d) 2-4 mm, or e) >4 mm?
2. Should patients with clinically node-negative cutaneous melanoma that is a) in situ, b) <1 mm, c) 1-2 mm, d) 2-4 mm, or e) >4 mm undergo sentinel lymph node biopsy (SLNB)?

### OUTCOMES OF INTEREST

The outcomes of interest for these guideline recommendations are local and regional recurrence, overall survival, disease-free survival, and morbidity.

### TARGET POPULATION

These recommendations apply to adult patients with truncal or extremity early-stage (clinically node-negative) cutaneous melanoma.

### INTENDED USERS

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

### OVERVIEW

Using systematic review methodology and a targeted search of guideline developers, the Melanoma Disease Site Group (DSG) identified an existing clinical practice guideline, *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008* (1). The scope of this guideline aligned with our objectives, and the guideline was recent and of high quality. The DSG examined the evidence in the Australia and New Zealand guideline along with any new evidence identified in an updated literature search. This

resulted in concordant conclusions between the DSG and the developers of the Australia and New Zealand guideline (1). Therefore, the DSG adopted the relevant sections of this work to the Ontario healthcare setting.

**RECOMMENDATIONS**

The following recommendations are adopted from the *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand* (1).

➤ **Excision Margins**  
 After initial excision biopsy, the radial excision margins, measured clinically from the edge of the melanoma, should be:

MELANOMA DEPTH	MARGIN
pTis melanoma in situ	5 mm
pT1 melanoma <1.0 mm	1 cm
pT2 melanoma 1.0-2.0 mm	1-2 cm
pT3 melanoma 2.0-4.0 mm	1-2 cm
pT4 melanoma >4.0 mm	2 cm

Caution should be exercised for melanomas 2-4 mm thick, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours, depending on tumour site and surgeon/patient preference.

➤ **Sentinel Lymph Nodes**

Patients with a melanoma greater than 1.0 mm in thickness should be given the opportunity to discuss SLNB to provide staging and prognostic information.
SLNB should be performed only, following discussion of the options with the patient, in a unit with access to appropriate surgical, nuclear medicine and pathology services.

**TECHNICAL CONSIDERATIONS**

**Excision Margins**

- The depth of the excision should be down to the fascia.
- Margins (e.g., 1 cm or 2 cm) should be included in the surgical operating room (OR) report.
- Standard synoptic pathology reporting should be used (2-4)
- Excision margins should be 1-2 cm where possible but may involve amputation depending on the anatomical location of the lesion (e.g., fingers and toes). For more complex areas such as anus, vulva, vagina, fingers and toes, or where the primary melanoma involves anatomic areas not amenable to simple wide excision, multidisciplinary input should be sought.

### Sentinel Lymph Node Biopsy

- Lymphoscintigraphy is mandatory to identify sentinel lymph nodes.
- Intradermal injection of radioactive tracer and either patent blue or lymphazurin blue dye is recommended.
- SLNB should be discussed with patients with melanomas <1.0 mm in thickness and with high-risk features such as young age, mitotic rate  $\geq 1 \text{ mm}^2$  (5), ulceration, and diagnosis by shave biopsy if the deep margin is positive and consequently the depth of the lesion may be underestimated. High-risk features within the clinical context should be considered on an individual basis. In the future, the size of micro-metastases may be used to guide whether or not completion lymph node dissection is preformed. However, the data regarding this is still evolving.
- SLNB should include the use of IHC and hematoxylin and eosin (H & E) staining.

### KEY EVIDENCE

Key evidence supporting these recommendations is described below. It is based on the evidence review in the *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008* (1) and the update undertaken by the Melanoma DSG. No new evidence that contradicted the original guideline recommendations was found by the working group since the publication of the Australia and New Zealand guideline.

### Excision Margins

- A meta-analysis published in 2007 by Lens et al. (6) of five randomized controlled trials (RCTs) comparing narrow versus (vs.) wide excision margins did not detect a significant difference in overall survival (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.85-1.17;  $p=0.93$ ), locoregional recurrence (OR, 1.18; 95% CI, 0.98-1.41;  $p=0.08$ ), or local recurrence (OR, 0.93; 95% CI, 0.42-2.08;  $p=0.86$ ). Sixty-six percent (66%) of the patients in these trials had melanomas that were less than 2 mm thick. The authors concluded that further research is required to determine the optimal excision margins for all melanoma thicknesses.

### Sentinel Lymph Node Biopsy

- The MSLT-1 trial by Morton et al. (7) reported no significant difference in melanoma-specific survival between wide excision plus SLNB followed by immediate completion lymphadenectomy (CLND) versus wide excision and postoperative observation with CLND at nodal recurrence (hazard ratio [HR], 0.92; 95% CI, 0.6-1.25;  $p=0.58$ ) in patients with melanoma lesions between 1.2 and 3.5 mm thick. Five-year disease-free survival was significantly higher in the SLNB arm than in the control arm (78.3% [versus] vs. 73.1%; HR, 0.74; 95% CI, 0.59 to 0.93;  $p=0.009$ ). In a planned post-randomization subgroup analysis, patients who underwent immediate lymphadenectomy following positive SLNB had significantly higher five-year survival than did patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm). A greater number of positive lymph nodes was observed in patients who underwent delayed lymphadenectomy compared to patients who underwent immediate lymphadenectomy following positive SLNB (3.3 vs. 1.4  $p<0.001$ ). A multivariate analysis demonstrated that sentinel node status is a significant prognostic factor for disease recurrence and death from melanoma ( $p<0.001$ ) in the MSLT-1 trial (3).
- SLNB is a technically challenging procedure. It requires specific skills and resources (8).

## QUALIFYING STATEMENT

### Sentinel Lymph Node Biopsy

- Although the MSLT-1 data regarding SLNB is limited to patients with melanomas that are 1.2-3.5 mm thick, it was the expert opinion of the working group that the data should be extrapolated to those with melanomas that are  $\geq 1.0$ -1.2 mm thick and to those with melanomas greater than 3.5 mm thick and clinically node negative. The opinion was that SLNB provides good staging and prognostic information and potentially improved locoregional control.

## RELATED GUIDELINES

PEBC Evidence-Based Series Reports (EBS):

- EBS #8-1: *Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma* (<http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34373>)
- EBS #8-6: *Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities* - currently under development

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## Evidence-Based Series #8-2: Section 2

# Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities: Evidentiary Base

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### QUESTIONS

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2. Should patients with clinically node-negative cutaneous melanoma that is a) in situ, b) <1 mm, c) 1-2 mm, d) 2-4 mm, or e) >4 mm, undergo sentinel lymph node biopsy (SLNB)?

### INTRODUCTION

Although cutaneous melanoma is an uncommon disease compared with other non-melanoma skin cancers, there is evidence that the incidence of melanoma is increasing. Approximately 2,300 new cases of melanoma will be diagnosed in Ontario in 2009 (1). For patients who are diagnosed with early-stage (clinically node negative, less than 4 mm thickness [T1-T3], and systemically negative) cutaneous melanoma, the principal therapy is surgical excision of the primary tumour and surgical management of nodal metastases. Uncertainty exists regarding the optimal excision margins for the primary tumour and the identification of patients with clinically negative regional nodes who should undergo additional therapy.

In the past, standard therapy has included wide radial excision margins (5 cm); however, this practice is associated with significant morbidity and disfigurement. Use of narrower excision margins (1-3cm) has become more common in practice but the effect of narrow margins on locoregional recurrence, disease-free survival, and overall survival is unclear. Several randomized trials have been conducted that compared different excision margins for various Breslow thicknesses of early-stage melanoma.

Cutaneous melanoma frequently spreads to regional lymph nodes, and the risk for nodal involvement rises with increasing tumour thickness. Ninety percent of stage I and II

patients have no clinical evidence of lymphadenopathy at initial presentation, yet approximately 20% have subclinical involvement. SLNB is a surgical procedure that identifies the sentinel node, the first lymph node(s) that drain the primary melanoma site. The SNLB allows the status of a clinically negative regional basin to be determined without a complete lymph node dissection. The procedure involves lymphatic mapping with a blue dye (lymphazurin or patent blue) and a radioactive tracer and offers a promising way to select the patients who might benefit from nodal dissection and subsequent treatment. The nodes are serially sectioned and carefully examined pathologically (hematoxylin & eosin [H&E] staining and immunohistochemistry) for the presence of melanoma metastases. The technique is predicated on the empiric observation that melanoma metastasizes along lymphatics sequentially, first to the sentinel lymph node and then to other regional lymph nodes.

In order to provide health practitioners with recommendations on optimal primary resection margins and the use of SLNB for adult patients with cutaneous melanoma, development of a systematic review of the evidence and clinical practice guideline was undertaken by the Melanoma Disease Site Group (DSG). Although the issues of resection margins and SLNB in those with head and neck or gynecological melanomas are important, it was decided to limit the scope of the guideline to cutaneous melanoma of the trunk or extremities.

## **METHODS**

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (2). For this project, the core methodology used to develop the evidentiary base was the adaptation of an existing clinical practice guideline located through a systematic search of the literature and the subsequent update of the systematic review used to inform that guideline.

Evidence was selected and reviewed by members of the PEBC Melanoma DSG and a methodologist. The systematic review is a convenient and up-to-date source of the best available evidence on surgical excision margins and SLNB in early stage cutaneous melanoma.

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 Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

### **A. EVIDENCE-BASED GUIDELINES**

#### **METHODS**

##### ***Guideline Literature Search Strategy***

The MEDLINE and EMBASE databases were searched from 2002 to April week 3 2010 to identify evidence-based clinical practice guidelines on excision margins or SLNB for melanoma. In MEDLINE, the Medical Subject Heading (MeSH) terms "exp melanoma" or "exp skin neoplasms" were used and results were limited to the following publication types: consensus development conference, guideline, or practice guideline. In EMBASE, the MeSH terms "exp melanoma" or "exp skin tumours" were combined with "exp practice guidelines" and further limited by title keywords for melanoma and skin tumours to increase specificity. (See Appendix 1 for the complete search strategies.)

The National Guideline Clearinghouse (<http://www.guideline.gov/>) and CMA Infobase ([http://www.cma.ca/index.cfm/ci\\_id/54316/la\\_id/1.htm](http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm)) websites were also searched for relevant guidelines using the keyword "melanoma". In addition, websites for the following guideline development organizations were searched: National Institute for Health and Clinical

Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), National Health and Medical Research Council, New Zealand Guidelines Group, BC Cancer Agency, Alberta Cancer Board, Saskatchewan Cancer Agency, Cancer Care Manitoba, and Cancer Care Nova Scotia.

### ***Guideline Selection Criteria***

Evidence-based guidelines were included if they met the following criteria:

- Provided recommendations on primary excision margins and/or SLNB for adult patients with early-stage cutaneous melanoma.
- Described a systematic literature search process to identify evidence on which to base recommendations.
- Published in English, due to the unavailability of translation services.
- Published in 2002 or later.

### ***Quality Appraisal of Guidelines***

The Melanoma DSG formed a working group (Appendix 2) to review and assess the clinical practice guidelines identified in the systematic search. The working group consisted of five clinicians with expertise in the surgical management of cutaneous melanoma and one methodologist. Working group members assessed the guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument (3). Assessments were collected and collated by one panel member (KS).

The AGREE instrument consists of six domains assessing guideline quality: 1) scope and purpose, 2) stakeholder involvement, 3) rigour of development, 4) clarity of presentation, 5) applicability, and 6) editorial independence. Each domain consists of a number of items addressing that particular aspect of guideline quality. The guideline is rated on each item using a scale from one (strongly disagree) to four (strongly agree). Agreement between reviewers consists of a difference between the highest and lowest scores of no more than one point on the scale, and disagreement exists when scores differ by 2 or more points.

### ***Adoption of Evidence-based Guidelines***

The AGREE domain scores for each evidence-based guideline identified in the systematic search were reviewed by the working group. The domain scores and overall assessment of guideline applicability were used as the basis for selection of a single evidence-based guideline for adoption. The guideline development group of the selected guideline was contacted to obtain additional information, including literature search strategies and study selection criteria.

Following the review of additional primary studies published since the search endpoint of the selected evidence-based guideline (see description below in Section B: Updated Literature Search), the working group discussed each of the relevant recommendations within the guideline to determine whether they were appropriate given the available evidence and whether they should be applied in the context of Ontario. Individual recommendations were adopted as written.

## **RESULTS**

### ***Guideline Literature Search Results***

The search of the MEDLINE and EMBASE databases identified 360 documents, of which 55 were retrieved for full-text review following title and abstract screening. The search of the National Guideline Clearinghouse and websites of guideline development groups yielded an additional four relevant reports for review. Fifty-five documents were subsequently

excluded for the following reasons: they were not practice guidelines, they were published in a language other than English, they were not relevant to the research questions, or they did not describe systematic searches of the literature. Four evidence-based guidelines were identified that met the inclusion criteria: SIGN 2003 (4), NICE 2006 (5), American Society of Plastic Surgeons (ASPS) 2007 (6), and Australian Cancer Network (National Health and Medical Research Council [NHMRC]) in collaboration with the New Zealand Guidelines Group (NZGG) 2008 (7).

### **Quality Appraisal Results and Selection of Guideline for Adoption**

The quality of the four evidence-based guidelines was appraised using the AGREE instrument (3). Results are reported in Table 1. The working group reviewed the suitability of each guideline for adaptation, with consideration of the AGREE ratings, the currency of the evidence review, and the applicability of the guideline for the purpose of answering the research questions. Working group members agreed that the Australia and New Zealand (AUS/NZ) (7) guideline was most suitable for adoption.

**Table 1. AGREE ratings for evidence-based practice guidelines.**

AGREE Domain	SIGN 2003 (4) (%)	NICE 2006 (5) (%)	ASPS 2007 (6) (%)	AUS/NZ 2008 (7) (%)
Scope and Purpose	75.0	83.3	50.0	83.3
Stakeholder Involvement	68.8	66.7	12.5	89.6
Rigor of Development	72.6	67.9	34.5	88.1
Clarity and Presentation	81.2	50.0	41.7	81.2
Applicability	61.1	52.8	0	41.7
Editorial Independence	58.3	29.0	16.7	70.8
Would you recommend these guidelines for use in practice?	Recommend	Recommend	Would not recommend	Strongly recommend

## **B. UPDATED LITERATURE SEARCH**

### **METHODS**

#### **Updated Literature Search Strategy**

The literature search strategies for excision margins and SLNB used by the AUS/NZ guideline (7) were modified where necessary and updated to April, week 3, 2010. The following databases were searched: MEDLINE, EMBASE, Cochrane Library, and ASCO Annual Meeting Proceedings. (See Appendix 1 for the search strategies.)

#### **Updated Literature Search Selection Criteria**

##### **Excision Margins**

Studies were included if they met the following criteria:

- Randomized controlled trials (RCTs) of adult patients with cutaneous melanoma comparing wide vs. narrow excision margins. Syntheses of evidence from RCTs in the form of systematic reviews or meta-analyses were also included. Abstract reports of RCTs or meta-analyses were included unless they reported results from preliminary analyses.
- Reported on at least one of the following outcomes: local or regional recurrence, overall survival, disease-free survival, morbidity, quality of life.
- Published in English, due to unavailability of translation services.
- Published in April 2006 or later.

### *Sentinel Lymph Node Biopsy*

Studies were included if they met the following criteria:

- Comparative studies (randomized or non-randomized) comparing outcomes of interest for patients undergoing SLNB versus patients not undergoing SLNB, or non-comparative prospective or retrospective studies including  $\geq 50$  patients who underwent SLNB.
- Reported on at least one of the following outcomes: local or regional recurrence, overall survival, disease-free survival, morbidity, quality of life.
- Published in English, due to unavailability of translation services.
- Published in May 2008 or later.

### ***Quality Appraisal of Articles Identified in Literature Search Update***

The quality of systematic reviews identified in the updated literature search was appraised using the AMSTAR tool (8). The risk of bias for primary studies was assessed by extracting data for the following methodological and quality characteristics: patient allocation, blinding of patients and outcome assessors, completeness of outcome reporting, and other sources of bias.

## **RESULTS**

### ***Updated Literature Search Results***

#### ***Excision Margins***

The updated literature search of the MEDLINE and EMBASE databases for primary excision margins identified 869 articles, 15 of which were retrieved for full-text review. One report of an updated meta-analysis (9) and one other meta-analysis (10) were identified that met the inclusion criteria. The remaining citations were excluded because they were not published in English or they were not reports of systematic reviews, meta-analyses, or randomized trials. No additional relevant reports were identified in the search of the Cochrane Library or ASCO meeting proceedings.

### *Sentinel Lymph Node Biopsy*

The updated literature search of the MEDLINE and EMBASE databases for SLNB identified 878 articles, 98 of which were retrieved for full-text review. One article (11) met the inclusion criteria and all other articles were excluded because they were duplicates, were not published in English, were not relevant to the research question, or did not report outcomes of interest. Four abstract reports from the ASCO annual meeting proceedings were retrieved for review. One abstract report of a SEER registry study comparing patients with versus without SLNB (12) was initially selected for inclusion. However, the authors of this abstract subsequently discovered a coding problem in the SEER data they used and published a short paper stating that the results reported in their ASCO abstract were invalid (13). Therefore, this abstract was withdrawn from the evidence retrieved regarding SLNB.

### ***Quality Appraisal of Articles Identified in Literature Search Update***

The meta-analyses by Lens (9) and Sladden et al. (10) that were retained were deemed to be of good quality based on the AMSTAR tool (see Appendix 3). These meta-analyses scored 10 and 11 AMSTAR points, respectively. The only other study retained in the literature search update was a retrospective study of SLNB versus no SLNB. Retrospective studies suffer from the limitation of these types of studies in general, namely, lack of randomization. Lack of randomization makes it unclear whether selection bias (either self-selection by patients or selection by physicians) affected the results of a given study.

## C. EVIDENCE SUMMARY

### *Primary Margins of Excision*

#### **a) Evidence from the Australia/New Zealand Guideline (7)**

Two systematic reviews with meta-analyses (14,15) and five RCTs (16-20) comparing narrow versus wide excision margins were included in the evidence review of the AUS/NZ guideline (7). A protocol of a systematic review was also included (20). No RCTs were available that assessed in situ melanoma.

No RCTs specifically assessed melanomas that were less than 1 mm thick. Three RCTs (16,18,19) investigated melanomas less than 2 mm that also included some melanomas less than 1 mm thick. Two of these RCTs (18,19) compared 2 cm excision margins to 5 cm margins, and one RCT (16) compared 1 cm margins to 3 cm margins. No difference in mortality was found for wider excision compared with narrower excision.

Three RCTs (16, 18,19) assessed melanomas less than 2mm, and one RCT (17) assessed melanomas between 1 mm and 2 mm thick. This latter study compared 2 cm excision margins to 4 cm excision margins. No statistically significant difference in overall survival was demonstrated between the groups treated with narrow or wide excision.

Balch et al. (17) and Thomas et al. (20) included melanomas between 2 mm and 4 mm thick. There was no statistically significant difference in overall survival between the two groups treated with narrow or wide excision margins. However, the numbers of patients and events were relatively small for statistical comparison.

Only Thomas et al. (20) evaluated melanomas greater than 4 mm thick, but patient numbers were too small to permit statistical analysis (approximately 207 evaluable patients).

No consistent definition of local recurrence was utilized in these studies, and consequently, it is difficult to interpret this data. No RCT demonstrated that a margin greater than 2 cm further improved survival or further decreased local recurrence. Two RCTs (16,20) described no survival detriment for excision margins of 1cm in melanomas  $\leq$  2 mm. However, an excision margin of 1cm had an unclear effect on local recurrence (16,20).

#### **b) Evidence from updated literature search**

An update of a meta-analysis by Lens et al. (14) included in the AUS/NZ guideline was identified in the updated literature search. The 2007 meta-analysis by Lens et al. (9) pooled published overall mortality, locoregional recurrence, and local recurrence data for 3,313 subjects from the five available RCTs comparing wider vs. narrower excision margins. In this study, 66.4% of the patients pooled from these trials had melanomas that were less than 2 mm thick. The results indicated no significant difference between wide vs. narrow margins for overall mortality (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.85 to 1.17;  $p=0.93$ ), locoregional recurrence (OR, 1.18; 95% CI, 0.98 to 1.41;  $p=0.08$ ), or local recurrence (OR, 0.93; 95% CI, 0.42 to 2.08;  $p=0.86$ ). Chi-square tests for heterogeneity did not indicate statistically significant heterogeneity between trial results for any of the three outcomes; however, there was considerable clinical heterogeneity between trials. It was noted that disease stage, length of follow-up, definition of wide and narrow excisions, and definition of local recurrence differed between the five RCTs. The authors concluded that the available evidence remains insufficient to determine optimal excision margins for all types of melanoma and further research is required. Sladden et al. (10) report no significant difference in overall survival (HR, 1.04; 95% CI, 0.95 to 1.15;  $p=0.40$ ) or recurrence free survival (HR, 1.13; 95% CI, 0.99 to 1.28;  $p=0.06$ ) in their meta-analysis and also conclude that there is insufficient evidence to determine optimal excision margins for primary cutaneous melanoma.

## **Sentinel Lymph Node Biopsy**

### **a) Evidence from Australia/New Zealand guideline (7)**

An analysis of 17,600 melanoma patients demonstrated that SLNB is a reliable indicator of the presence of micrometastases in that node field and is an accurate prognostic factor in primary melanoma (7,22).

One RCT was identified that compared wide excision plus delayed completion lymph node dissection for clinically detectable nodal recurrence versus wide excision plus SLNB with immediate completion lymph node dissection for patients with positive sentinel nodes (23). MSLT-1 is a superiority trial that randomized 1,347 patients with intermediate thickness melanoma (1.2 to 3.5 mm), of whom 1,269 were evaluable. The data and safety monitoring committee (DSMC) of this trial recommended publication of these interim analysis results. At the third of five planned analyses, the primary outcome of five-year melanoma-specific survival did not differ significantly between the SLNB and the control arms (87.1% vs. 86.6%; hazard ratio [HR], 0.92; 95% CI, 0.67 to 1.25;  $p=0.58$ ). Five-year disease-free survival was significantly higher in the SLNB arm than in the control arm (78.3% vs. 73.1%; HR, 0.74; 95% CI, 0.59 to 0.93;  $p=0.009$ ). In a planned post-randomization subgroup analysis, patients who underwent immediate lymphadenectomy following positive SLNB had significantly higher five-year survival than patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm). With respect to regional disease, there was a greater number of positive lymph nodes in patients who underwent delayed lymphadenectomy compared to patients who underwent immediate lymphadenectomy following positive SLNB (3.3 vs. 1.4,  $p<0.001$ ). In the SLNB arm, the five-year survival rate was significantly lower for patients with positive sentinel nodes than for those with negative sentinel nodes (72.3% vs. 90.2%; HR, 2.48; 95% CI, 1.54 to 3.98;  $p<0.001$ ).

### **b) Evidence from updated literature search**

One retrospective study (11) was identified that compared a group of patients who had received SLNB ( $n=439$ ) with a group who had not received SLNB ( $n=440$ ). All of these patients had primary cutaneous melanoma with tumour thickness of 1.00 mm or more. The authors report that those receiving SLNB had a significantly better five-year disease-free survival (76.9%; 95% CI, 72.6-81.2) than those who had not had a SLNB (67.8%; 95% CI, 63.1-75.2;  $p=0.003$ ). However, there was no significant difference in five-year overall survival (RR=0.74; 95% CI, 0.52-1.05;  $p=0.09$ ).

## **ONGOING TRIALS**

The National Cancer Institute (NCI) clinical trials database was searched on May 3, 2010 ([www.cancer.gov/search/clinical\\_trials/](http://www.cancer.gov/search/clinical_trials/)) for reports of new or ongoing trials that met the inclusion criteria for this review. No trials were identified that investigated surgical resection margins or that compared SLNB vs. no SLNB for patients with early-stage cutaneous melanoma.

## **DISCUSSION**

### **Primary Excision Margins**

Standard therapy for primary cutaneous melanoma has historically been wide excision with radial margins up to 5 cm or greater; however, this practice is not evidence-based and recent randomized trials have challenged the need for such radical surgery. Five trials have been published to date that compared wide vs. narrow excision margins (16-20). Three trials included patients with T1 and T2 melanomas (<2.0 mm thick), and all three trials concluded that narrower margins of 1 or 2 cm were safe (16,18,19). Two trials included patients with thicker lesions (17,20). Balch et al. (17) compared 2 cm vs. 4 cm margins in patients with T2

and T3 lesions (1.0-4.0 mm thick) (17), and Thomas et al. (20) compared 1 cm vs. 3 cm margins in patients with T3 and T4 lesions (>2.0 mm thick) (20). The Balch et al. (17) trial demonstrated that a 2 cm margin is safe with respect to locoregional recurrences and overall survival; however, the Thomas et al. (20) trial reported lower disease-free survival in patients with 1 cm margins compared with 3 cm margins, although overall survival was not significantly different between groups. As the evidence concerning optimal excision margins is unclear for T3 lesions, consideration may be given to 1 cm margins in cosmetically sensitive areas and a multidisciplinary (e.g., Ear, Nose, Throat [ENT], plastics) opinion should be sought.

Meta-analyses of published data from the five available randomized trials did not demonstrate a significant difference in overall survival, locoregional recurrence, or local recurrence between wide and narrow excision margins (9, 10). Lens et al. (9) noted that the effect of excision margin width on local recurrence is somewhat unclear, given that long-term follow-up is required to assess this outcome and definitions of local recurrence vary between trials. The majority of patients in the meta-analysis (66.4%) had lesions less than 2.0 mm thick; therefore, although the results provide reasonably strong evidence that excision margins greater than 1 cm for melanomas up to 2 mm thick do not affect overall survival, the data supporting the safety of 1 cm margins for melanomas greater than 2 mm thick remains weak. None of the five available trials reported data on quality of life, and no trials were identified that included patients with melanoma in situ.

Based on the available evidence, the Melanoma DSG agreed with the recommendations provided in the AUS/NZ 2008 guideline (7). The only new evidence that was published after the literature review conducted by the AUS/NZ group was the updated meta-analysis by Lens et al. (9) and the meta-analysis by Sladden et al. (10). These results were consistent with the evidence contained in the AUS/NZ guideline.

### *Sentinel Lymph Node Biopsy*

SLNB is a surgical procedure for primary cutaneous melanoma that can identify patients who may benefit from additional treatment such as adjuvant therapy, radiation to the regional lymph nodes basin, or completion lymphadenectomy. In addition, it provides staging and prognostic information, locoregional control, and a possible disease-free survival benefit.

#### *I. Survival Benefit*

Evidence comparing clinical outcomes for patients who underwent SLNB vs. patients who did not undergo SLNB is limited to the MSLT-1 trial described in the AUS/NZ guideline (7). Interim results of the MSLT-1 trial have not shown an overall survival benefit for SLNB in patients with melanomas that are 1.2 to 3.5 mm thick. However, a significant overall five-year disease-free survival benefit for SLNB was demonstrated (78.3±1.6% in the SLNB group and 73.1±2.1% in the observation group; HR, 0.74; 95% CI, 0.59-0.93; p=0.009). Morton et al. (23) also reported that survival was significantly improved for a subgroup of patients with positive SLNB who underwent immediate lymphadenectomy compared with patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases. As the patients in this subsequent subgroup analysis were selected after randomization, the validity of these results has been challenged (24). Others have criticized the subgroup analysis because it is based on the assumption that all metastases detected by SLNB would go on to become clinically relevant (25). This assumption has not been proven. Other limitations of the MSLT-1 trial include low power, because of the small number of patients who could benefit from CLND (26), and lack of information regarding allocation concealment (27).

#### *II. Prognosis*

The MSLT-1 trial reported that SLNB provides valuable prognostic information for patients with intermediate thickness melanomas (23). This is in concordance with the results of the analysis by Balch et al. (22) of 17,600 melanoma patients that indicated that SLN status is the most accurate predictor of outcome after consideration of prognostic information obtained from the primary lesion.

### *III. Loco-regional Recurrence*

In terms of regional recurrence, patients in the observation arm of MSLT-1 (23) who developed clinically detectable lymph nodes did so at a median 16 months after randomization. There were a greater number of positive lymph nodes in the observation arm compared to the SLNB arm (3.3 vs. 1.4,  $p < 0.001$ ) at surgery. The implications of this are very important. Rates of regional recurrence increase significantly with increasing numbers of lymph node metastases in the nodal basin removed at the initial surgery (22, 28). Indeed, rates of regional recurrence are 17% and above for patients who have four or more metastatic nodes in their regional lymph node basin (28). In addition, in some centres, patients with clinically detected lymph nodes are offered radiation as it appears to improve locoregional control (29).

### *IV. Technical Issues*

Methods for the identification of sentinel nodes and examination of nodes to detect metastases vary in clinical practice and in the available clinical studies. No standard techniques for nodal examination have been established, although H&E and immunohistochemical analysis are routinely used; however, the available data do not support the routine use of reverse transcriptase–polymerase chain reaction (RT-PCR) techniques. There are data to suggest that patients with micrometastatic sentinel nodes have similar prognosis to SLN-negative nodes (30,31), although not all study results are in agreement (32). Based on the majority of evidence, the routine administration of additional therapy based on RT-PCR positive results in the absence of metastases detected using standard pathologic techniques may not be appropriate.

The mean number of sentinel lymph nodes per lymph node basin ranges from 1.3-2.3 (33-35). Seven to 32% of patients will have sentinel lymph nodes in more than one lymph node basin (33-38). All sentinel nodes in all basins should be removed during the procedure. The false-negative rate for the sentinel node for melanoma ranges between 5% and 38% depending on how it is calculated (39). Importantly, the sentinel node false-negative rate decreases with an increasing number of cases completed (40).

Morbidities associated with SLNB include seroma and hematoma (<1-5.5%), lymphedema (<1-9.2%), wound infection (1-4.8%), neurapraxia ( $\leq 1.0\%$ ), and allergic reactions to blue dye (<1-1.2%)(33-35,40-43).

### *V. Patient Selection*

The question regarding which criteria should be used to select patients for SLNB remains unclear due to limited data. Tumour thickness is commonly believed to be one of the most significant predictors of SLN positivity. Other potential predictors include tumour location and presence of ulceration. While it is generally accepted that patients with primary cutaneous melanoma lesions greater than 1 mm in thickness should be offered SLNB, there is much debate regarding the use of SLNB for patients with lesions less than 1 mm thick (44). A meta-analysis of 3,651 patients with tumours  $\leq 1$  mm thick from 34 studies indicated a pooled SLNB positive rate of 5.6% (44). Of 10 studies included in this meta-analysis that examined predictors of SLN positivity for patients with thin melanomas, five studies were not able to identify significant predictors, and five reported the following significant predictors based on

univariate analyses: tumour thickness, Clarks level, ulceration, mitotic rate, vertical growth phase, regression, and lack of regression. The conclusion was that the available data are inconsistent and inadequate for determining which patients with thin melanomas  $\leq 1$  mm should be considered for SLNB. Due to the low SLNB-positive rate in these patients, the Melanoma DSG does not recommend the routine use of SLNB for patients with melanoma lesions less than 1 mm thick. However, high-risk features within the clinical context should be considered on an individual basis. In the future, the size of micro-metastases may be used to guide whether or not completion lymph node dissection is performed. However, the data regarding this is still evolving.

#### VI. Positive sentinel lymph node

At the current time a positive sentinel node for melanoma mandates a discussion with the patient about a completion lymphadenectomy and a referral to a medical oncologist for consideration of interferon (45,46). This is the topic of an upcoming guideline currently in development by the Melanoma DSG.

#### CONCLUSIONS

The use of wide radial excision margins does not confer an overall survival advantage in patients with clinically node-negative cutaneous melanoma of the trunk or extremities. Margins ranging from 5 mm to 2 cm, depending of the thickness of the melanoma, are sufficient (see Section 1). SNLB provides staging and prognostic information and should be discussed with all patients with melanomas  $\geq 1.0$  mm in thickness and where clinically indicated in melanomas  $< 1$  mm in thickness, including those with high-risk features.

#### CONFLICT OF INTEREST

All authors declared no conflicts of interest.

#### JOURNAL REFERENCE

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For a complete list of the Melanoma DSG members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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## Appendix 1. Literature search strategies.

### **MEDLINE: Clinical Practice 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 yr="2002 - 2009"

### **EMBASE: Clinical Practice 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="2002 - 2009"
- 7 (melanoma: or (skin and (tumor: or tumour: or neoplasm: or cancer:))).ti.
- 8 6 and 7

### **MEDLINE: Systematic Reviews**

- 1 exp melanoma/
- 2 exp skin neoplasms/
- 3 1 or 2
- 4 Meta-Analysis as topic/
- 5 meta analy\$.tw.
- 6 metaanaly\$.tw.
- 7 meta analysis.pt.
- 8 (systematic adj (review\$1 or overview\$1)).tw.
- 9 exp Review Literature as topic/
- 10 or/4-9
- 11 cochrane.ab.
- 12 embase.ab.
- 13 (psychlit or psyclit).ab.
- 14 (psychinfo or psycinfo).ab.
- 15 (cinahl or cinhal).ab.
- 16 science citation index.ab.
- 17 bids.ab.
- 18 cancerlit.ab.
- 19 or/11-18
- 20 reference list\$.ab.
- 21 bibliograph\$.ab.
- 22 hand-search\$.ab.
- 23 relevant journals.ab.
- 24 manual search\$.ab.
- 25 or/20-24
- 26 selection criteria.ab.
- 27 data extraction.ab.
- 28 26 or 27
- 29 review.pt.

30 28 and 29  
31 comment.pt.  
32 letter.pt.  
33 editorial.pt.  
34 animal/  
35 human/  
36 34 not (34 and 35)  
37 or/31-33,36  
38 10 or 19 or 25 or 30  
39 38 not 37  
40 3 and 39

**EMBASE: Systematic Reviews**

1 exp melanoma/  
2 exp skin cancer/  
3 1 or 2  
4 exp Meta Analysis/  
5 ((meta adj analy\$) or metaanalys\$.tw.  
6 (systematic adj (review\$1 or overview\$1)).tw.  
7 or/4-6  
8 cancerlit.ab.  
9 cochrane.ab.  
10 embase.ab.  
11 (psychlit or psyclit).ab.  
12 (psychinfo or psycinfo).ab.  
13 (cinahl or cinhal).ab.  
14 science citation index.ab.  
15 bids.ab.  
16 or/8-15  
17 reference lists.ab.  
18 bibliograph\$.ab.  
19 hand-search\$.ab.  
20 manual search\$.ab.  
21 relevant journals.ab.  
22 or/17-21  
23 data extraction.ab.  
24 selection criteria.ab.  
25 23 or 24  
26 review.pt.  
27 25 and 26  
28 letter.pt.  
29 editorial.pt.  
30 animal/  
31 human/  
32 30 not (30 and 31)  
33 or/28-29,32  
34 7 or 16 or 22 or 27  
35 34 not 33  
36 3 and 35

**MEDLINE: Primary Studies (Excision Margins)**

1 melanoma.mp.  
2 exp Melanoma/  
3 1 or 2  
4 (surg: or resect: or excision: or margin:).mp.  
5 3 and 4  
6 5 and (2006: or 2007: or 2008: or 2009:).ed.  
7 Meta-Analysis as topic/  
8 meta analy\$.tw.  
9 metaanaly\$.tw.  
10 meta analysis.pt.  
11 (systematic adj (review\$1 or overview\$1)).tw.  
12 exp Review Literature as topic/  
13 or/7-12  
14 cochrane.ab.  
15 embase.ab.  
16 (psychlit or psyclit).ab.  
17 (psychinfo or psycinfo).ab.  
18 (cinahl or cinhal).ab.  
19 science citation index.ab.  
20 bids.ab.  
21 cancerlit.ab.  
22 or/14-21  
23 reference list\$.ab.  
24 bibliograph\$.ab.  
25 hand-search\$.ab.  
26 relevant journals.ab.  
27 manual search\$.ab.  
28 or/23-27  
29 selection criteria.ab.  
30 data extraction.ab.  
31 29 or 30  
32 review.pt.  
33 31 and 32  
34 comment.pt.  
35 letter.pt.  
36 editorial.pt.  
37 animal/  
38 human/  
39 37 not (37 and 38)  
40 or/34-36,39  
41 13 or 22 or 28 or 33  
42 41 not 40  
43 Randomized controlled trials as topic/  
44 randomized controlled trial.pt.  
45 random allocation/  
46 Double blind method/  
47 Single blind method/  
48 clinical trial.pt.  
49 exp clinical trials as topic/

50 or/43-49  
51 (clinic\$ adj trial\$1).tw.  
52 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.  
53 Placebos/  
54 Placebo\$.tw.  
55 Randomly allocated.tw.  
56 (allocated adj2 random).tw.  
57 or/51-56  
58 50 or 57  
59 Case report.tw.  
60 Letter.pt.  
61 Historical article.pt.  
62 or/59-61  
63 58 not 62  
64 63 or 42  
65 6 and 64

**EMBASE: Primary Studies (Excision Margins)**

1 melano:.mp.)  
2 exp melanoma/  
3 1 or 2  
4 (surg: or resect: or excision: or margin:).mp.  
5 3 and 4  
6 5 and (2006: or 2007: or 2008: or 2009:).ew.  
7 exp Meta Analysis/  
8 ((meta adj analy\$) or metaanalys\$).tw.  
9 (systematic adj (review\$1 or overview\$1)).tw.  
10 or/7-9  
11 cancerlit.ab.  
12 cochrane.ab.  
13 embase.ab.  
14 (psychlit or psyclit).ab.  
15 (psychinfo or psycinfo).ab.  
16 (cinahl or cinhal).ab.  
17 science citation index.ab.  
18 bids.ab.  
19 or/11-18  
20 reference lists.ab.  
21 bibliograph\$.ab.  
22 hand-search\$.ab.  
23 manual search\$.ab.  
24 relevant journals.ab.  
25 or/20-24  
26 data extraction.ab.  
27 selection criteria.ab.  
28 26 or 27  
29 review.pt.  
30 28 and 29  
31 letter.pt.  
32 editorial.pt.

33 animal/  
34 human/  
35 33 not (33 and 34)  
36 or/31-32,35  
37 10 or 19 or 25 or 30  
38 37 not 36  
39 clinical trial/  
40 randomized controlled trial/  
41 randomization/  
42 single blind procedure/  
43 double blind procedure/  
44 crossover procedure/  
45 placebo/  
46 randomi?ed controlled trial\$.tw.  
47 rct.tw.  
48 random allocation.tw.  
49 randomly allocated.tw.  
50 allocated randomly.tw.  
51 (allocated adj2 random).tw.  
52 single blind\$.tw.  
53 double blind\$.tw.  
54 ((treble or triple) adj blind\$).tw.  
55 placebo\$.tw.  
56 Prospective study/  
57 or/39-56  
58 Case study/  
59 case report.tw.  
60 abstract report/ or letter/  
61 or/58-60  
62 57 not 61  
63 6 and (38 or 62)

***Cochrane Library: Primary Studies (Excision Margins)- strategy from AUS/NZ 2008***

1 (melanoma\*):ti,ab,kw  
2 MeSH descriptor Melanoma explode all trees  
3 (surgical):ti,ab,kw  
4 MeSH descriptor Surgery explode all trees  
5 MeSH descriptor Surgical Procedures, Elective explode all trees  
6 MeSH descriptor Surgical Procedures, Minor explode all trees  
7 (excision\*):ti,ab,kw or (excised):ti,ab,kw  
8 (#1 or #2)  
9 (#3 or #4 or #5 or #6)  
10 (#8 and #9)  
11 (#10 and #7)  
12 (margin\*):ti,ab,kw  
13 (resection\*):ti,ab,kw  
14 (#7 or #12 or #13)  
15 (#8 and #9 and #14)  
16 (#15), from 2006 to 2009

**MEDLINE: Primary Studies (Sentinel Lymph Node Biopsy)**

- 1 exp melanoma/
- 2 melanoma:.mp.
- 3 (maligna: adj2 lentigo).tw.
- 4 (malignant adj1 (nev: or naev:)).tw.
- 5 (malignan: adj5 melanoma:).tw.
- 6 exp sentinel lymph node biopsy/
- 7 (sentinel adj3 biops:).tw.
- 8 exp lymph node excision/
- 9 (lymph adj2 excision).tw.
- 10 (lymph adj2 biops:).tw.
- 11 (lymph adj2 dissection).tw.
- 12 (lymph node adj2 surgery).tw.
- 13 (SLNB or SNB).tw.
- 14 or/6-13
- 15 or/1-5
- 16 and/14-15
- 17 (200805: or 200806: or 200807: or 200808: or 200809: or 20081: or 2009:).ed.
- 18 16 and 17

**EMBASE: Primary Studies (Sentinel Lymph Node Biopsy)**

- 1 exp melanoma/
- 2 melanoma:.mp.
- 3 (maligna: adj2 lentigo).tw.
- 4 (malignant adj1 (nev: or naev:)).tw.
- 5 (malignan: adj5 melanoma:).tw.
- 6 exp sentinel lymph node biopsy/
- 7 (sentinel adj3 biops:).tw.
- 8 exp lymph node excision/
- 9 (lymph adj2 excision).tw.
- 10 (lymph adj2 biops:).tw.
- 11 (lymph adj2 dissection).tw.
- 12 (lymph node adj2 surgery).tw.
- 13 (SLNB or SNB).tw.
- 14 or/6-13
- 15 or/1-5
- 16 and/14-15
- 17 (200819: or 20082: or 20083: or 20084: or 20085: or 2009:).ew.
- 18 and/16-17

**Cochrane Library: Primary Studies (Sentinel Lymph Node Biopsy)**

- 1 (melanoma\*):ti,ab,kw
- 2 MeSH descriptor Melanoma explode all trees
- 3 (#1 or #2)
- 4 MeSH descriptor Sentinel Lymph Node Biopsy explode all trees
- 5 (sentinel):ti,ab,kw
- 6 (lymph or node or nodal):ti,ab,kw and (excision or biops\* or dissection or surgery):ti,ab,kw
- 7 (SLNB):ti,ab,kw or (SNB):ti,ab,kw
- 8 (#4 or #5 or #6 or #7)
- 9 (#3 and #8)
- 10 (#9), from 2008 to 2009

**Appendix 2. Members of the Working Group.**

Chair: Frances Wright      Surgeon

Panel Members:

Alexandra Easson	Surgeon
David McCreedy	Surgeon
Christian Murray	Dermatologist
Teresa Petrella	Medical Oncologist
Karen Spithoff	Metholologist
John Toye	Plastic Surgeon

IN REVIEW

### Appendix 3. Evaluation of included systematic reviews/meta-analyses using AMSTAR.

ITEM	Lens et al., 2009 (ref)	Sladden et al., 2010 (ref)
1. Was an 'a priori' design provided?	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y
3. Was a comprehensive literature search performed?	Y	Y
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Y	Y
5. Was a list of studies (included and excluded) provided?	N	Y
6. Were the characteristics of the included studies provided?	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y
10. Was the likelihood of publication bias assessed?	Y	Y
11. Was the conflict of interest stated?	Y	Y
TOTAL AMSTAR POINTS	10	11

Abbreviations: N = no; Y = yes

## Evidence-Based Series #8-2: Section 3

# Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-Negative Cutaneous Melanoma of the Trunk or Extremities: EBS Development Methods and External Review Process

*F. Wright, K. Spithoff, A. Easson, C. Murray, J. Toye, D. McCready, T. Petrella,  
and the Melanoma Disease Site Group*

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

Report Date: May 17, 2010

### 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) (1). 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 healthcare 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 DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on surgical excision margins and sentinel lymph node biopsy in early stage cutaneous melanoma, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Canada.

### 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, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel and their resolution by the working group (*italicized*) included:

- concern about the use of GRADE and specifically how the grades were assigned by the developers of the Australia/New Zealand guideline. *It was decided to remove the GRADE evaluation. The PEBC historically does not use the GRADE system to evaluate recommendations. The rationale has been that it is not advantageous to create hierarchies of recommendations that imply that some are better than others. The recommendations are to be considered in their totality and the reader can then decide on their 'importance' based on the readers own needs/priorities, the qualifying statements (if included) and the key evidence sections.*
- a comment that the guideline was not a strict endorsement of the Australia/New Zealand guideline but rather a re-appraisal of the data from the Australia/New Zealand guideline along with any other data published subsequently with concordance conclusions. *The working group agreed that this was indeed the case, and this was clarified in the document.*
- a comment that some of the recommendations are not based on the evidence, but a consensus process and that this should be stated. *All the recommendations are based on some level of evidence. Appropriate references were added in as needed.*
- clarifying whether the MSLT-1 trial was a superiority or non-inferiority trial. *It was clarified in the document that the MSLT-1 trial was a superiority trial.*
- a comment that there was some confusion regarding the way disease free survival was reported in the Key Evidence of Section 1 and in the Discussion of Section 2. *This was corrected.*

- a question regarding what the parameters were for releasing the interim results of MSLT-1. *It was clarified in the document that publication of the interim results was recommended by the data safety and management committee.*

### 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:**

DRAFT RECOMMENDATIONS (approved for external review February 9, 2010)

#### **QUESTIONS**

1. What are the optimal primary margins of excision for clinically node-negative cutaneous melanoma that is a) in situ, b) <1 mm, c) 1-2 mm, d) 2-4 mm, or e) >4 mm?
2. Should patients with clinically node-negative cutaneous melanoma that is a) in situ, b) <1 mm, c) 1-2 mm, d) 2-4 mm, or e) >4 mm undergo sentinel lymph node biopsy (SLNB)?

#### **OUTCOMES OF INTEREST**

The outcomes of interest for these guideline recommendations are local and regional recurrence, overall survival, disease-free survival, and morbidity.

#### **TARGET POPULATION**

These recommendations apply to adult patients with truncal or extremity early-stage (clinically node-negative) cutaneous melanoma.

#### **INTENDED USERS**

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

#### **OVERVIEW**

Using systematic review methodology and a targeted search of guideline developers, the Melanoma Disease Site Group (DSG) identified an existing clinical practice guideline, *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008* (1). The scope of this guideline aligned with our objectives, and the guideline was recent and of high quality. The DSG examined the evidence in the Australia and New Zealand guideline along with any new evidence identified in an updated literature search. This resulted in concordant conclusions between the DSG and the developers of the Australia and New Zealand guideline (1). Therefore, the DSG adopted the relevant sections of this work to the Ontario healthcare setting.

## RECOMMENDATIONS

The following recommendations are adopted from the *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand* (1).

### ➤ Excision Margins

After initial excision biopsy, the radial excision margins, measure clinically from the edge of the melanoma, should be:

MELANOMA DEPTH	MARGIN
pTis melanoma in situ	5 mm
pT1 melanoma <1.0 mm	1 cm
pT2 melanoma 1.0-2.0 mm	1-2 cm
pT3 melanoma 2.0-4.0 mm	1-2 cm
pT4 melanoma >4.0 mm	2 cm

Caution should be exercised for melanomas 2-4 cm thick, because evidence concerning optimal excision margins is unclear. Where possible, it may be desirable to take a wider margin (2 cm) for these tumours, depending on tumour site and surgeon/patient preferences.

### ➤ Sentinel Lymph Nodes

Patients with a melanoma greater than 1.0 mm in thickness should be given the opportunity to discuss SLNB to provide staging and prognostic information.

SLNB should be performed only, following discussion of the options with the patient, in a unit with access to appropriate surgical, nuclear medicine and pathology services.

## TECHNICAL CONSIDERATIONS

### Excision Margins

- The depth of the excision should be down to the fascia.
- Margins (e.g., 1 cm or 2 cm) should be included in the surgical operating room (OR) report.
- Standard synoptic pathology reporting should be used (2-4)
- Excision margins should be 1-2 cm where possible but may involve amputation depending on the anatomical location of the lesion (e.g., fingers and toes). More complex areas should be discussed at a multidisciplinary cancer conference (MCC).

### Sentinel Lymph Node Biopsy

- Lymphoscintigraphy is mandatory to identify sentinel lymph nodes.
- Intradermal injection of radioactive tracer and either patent blue or lymphazurin blue dye is recommended.
- SLNB should be discussed with all patients with melanomas <1.0 mm in thickness and with high-risk features such as mitotic rate  $\geq 1 \text{ mm}^2$  (5), ulceration, age < 40 years and diagnosis by shave biopsy.
- SLNB should include the use of IHC and hematoxylin and eosin (H & E) staining.

## KEY EVIDENCE

Key evidence supporting these recommendations is described below. It is based on the evidence review in the *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand 2008* (1) and the update undertaken by the Melanoma DSG. No new evidence that contradicted the original guideline recommendations was found by the working group since the publication of the Australia and New Zealand guideline.

### Excision Margins

- A meta-analysis published in 2007 by Lens et al. (6) of five randomized controlled trials (RCTs) comparing narrow versus (vs.) wide excision margins did not detect a significant difference in overall survival (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.85-1.17;  $p=0.93$ ), locoregional recurrence (OR, 1.18; 95% CI, 0.98-1.41;  $p=0.08$ ), or local recurrence (OR, 0.93; 95% CI, 0.42-2.08;  $p=0.86$ ). Sixty-six percent (66%) of the patients in these trials had melanomas that were less than 2 mm thick. The authors concluded that further research is required to determine the optimal excision margins for all melanoma thicknesses.

### Sentinel Lymph Node Biopsy

- The MSLT-1 trial by Morton et al. (7) reported no significant difference in melanoma-specific survival between wide excision plus SLNB followed by immediate completion lymphadenectomy (CLND) vs. wide excision and postoperative observation with CLND at nodal recurrence (hazard ratio [HR], 0.92; 95% CI, 0.6-1.25;  $p=0.58$ ) in patients with melanoma lesions between 1.2 and 3.5 mm thick. Five-year disease-free survival was significantly higher in the SLNB arm than in the control arm (78.3% vs. 73.1%; HR, 0.74; 95% CI, 0.59 to 0.93;  $p=0.009$ ). In a planned post-randomization subgroup analysis, patients who underwent immediate lymphadenectomy following positive SLNB had significantly higher five-year survival than did patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm). A greater number of metastatic lymph nodes was observed in patients who underwent delayed lymphadenectomy compared to patients who underwent immediate lymphadenectomy following positive SLNB (3.3 vs. 1.4  $p<0.001$ ). A multivariate analysis demonstrated that sentinel node status is a significant prognostic factor for disease recurrence and death from melanoma ( $p<0.001$ ) in the MSLT-1 trial (3).
- SLNB is a technically challenging procedure. It requires specific skills and resources (8).

## QUALIFYING STATEMENT

### Sentinel Lymph Node Biopsy

- Although the MSLT-1 data regarding SLNB is limited to patients with melanomas that are 1.2-3.5 mm thick, it was the expert opinion of the working group that the data should be extrapolated to those with melanomas that are  $\geq 1.0$ -1.2 mm thick and to those with melanomas greater than 3.5 mm thick and clinically node negative. The opinion was that SLNB provides good staging and prognostic information and potentially improved locoregional control.

## Methods

**Targeted Peer Review:** During the guideline development process, three targeted peer reviewers from Ontario and Alberta considered to be clinical and/or methodological experts on the topic were identified by working group. 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 February 9, 2010. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The working group from the Melanoma DSG reviewed the results of the survey.

*Professional Consultation:* Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. All plastic surgeons, general surgeons, head and neck surgeons, gynecological oncologists, and dermatologists in the PEBC database were contacted by email to inform them of the survey. 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 March 2, 2010. The consultation period ended on April 15, 2010. The working group from 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.**

Question	Reviewer Ratings (N=3)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	2
2. Rate the guideline presentation.					3
3. Rate the guideline recommendations.			1	1	1
4. Rate the completeness of reporting.			1	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. Rate the overall quality of the guideline report.				2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	1
8. I would recommend this guideline for use in practice.				2	1

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

The only barrier that was identified was the possibility in having difficulty accessing a sentinel lymph node biopsy.

### Summary of Written Comments

The main points contained in the written comments were:

- i. That the optimal surgical margins for a pT3 melanoma (2-4 mm) is unclear and should therefore be treated with a 2 cm margin with consideration given to a 1 cm margin in cosmetically sensitive areas.
- ii. Concern about the technical consideration statement that anyone under 40 years of age should be referred for a discussion about SLNB.
- iii. Concern about the technical consideration statement that anyone who has had a shave biopsy should be referred for a discussion about SLNB.
- iv. The technical consideration statement that those with melanomas in more complex areas should be discussed at a multidisciplinary cancer conference was too vague.
- v. Non-randomized data should have been included.
- vi. Inclusion of head and neck and anogenital melanomas would be useful.

*Professional Consultation:* Seventeen 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.**

General Questions: Overall Guideline Assessment	Number (%)				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				4(24)	13(75)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				3(18)	14(82)
3. I would recommend this guideline for use in practice.			1(6)	2(12)	14(82)

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

Several reviewers noted that the main barrier to the implementation of this guideline is access and availability to SNLB especially outside of Health Science Centre. There were also comments regarding the volume of referrals that should potentially be made and issue of wait times.

### Summary of Written Comments

The main points contained in the written comments (not already articulated by the targeted peer reviewers) were:

- vii. Whether the depth of excision should be down to the fascia and the evidence for it.
- viii. The guideline should be disseminated to all general surgeons, plastic surgeons, dermatologists and general practitioners in the province.
- ix. The need for a summary guideline in lay terms for patient use.

### ***Modifications/Actions***

- i. The uncertainty regarding the optimal excision margins for pT3 melanomas is articulated in the recommendations as a cautionary statement but it was decided to include a statement in the discussion as well.
- ii. The technical consideration statement concerning who should be referred for discussion of SLNB was changed from '< 40 years of age' to 'young age'.
- iii. The technical consideration statement about shave biopsies was amended.
- iv. The technical consideration statement about melanomas in more complex areas was amended to be more specific.
- v. The PEBC only uses non-randomized data in the development of guidelines when randomized data is not available.
- vi. The inclusion of head and neck and anogenital melanomas was beyond the scope of this guideline. A statement stating this was added to the introduction in Section 2. Head and neck or anogenital melanomas could become guideline topics in the future.
- vii. Surgery to the depth of the fascia is suggested in the Aus/NZ guideline (7) and by Veronesi and Cascinelli (14). In addition, in several randomized controlled trials of excision margins in melanoma the surgical procedure stated that excision was to the depth of the fascia (16-18).
- viii. The working group agrees that this guideline should be extensively disseminated. Guideline dissemination is performed by CCO.
- ix. While the working group acknowledges the utility of a patient version of the guideline, it is beyond the mandate of the PEBC.

### **Conclusion**

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Melanoma DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

#### *Funding*

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: [ccopgi@mcmaster.ca](mailto:ccopgi@mcmaster.ca)

IN REVIEW

## REFERENCES

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

IN REVIEW