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

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

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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).

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#### Excision Margins

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

<table>
<thead>
<tr>
<th>MELANOMA DEPTH</th>
<th>MARGIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTis melanoma in situ</td>
<td>5 mm</td>
</tr>
<tr>
<td>pT1 melanoma &lt;1.0 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>pT2 melanoma 1.0-2.0 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>pT3 melanoma 2.0-4.0 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>pT4 melanoma &gt;4.0 mm</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

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.

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#### 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.

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**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
- Lymphoscintography 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 ≥ 1 mm² (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 performed. 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 ≥ 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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REFERENCES


