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

Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

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

Guideline 8-2 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/51116

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PUBLICATIONS RELATED TO THIS REPORT

The original clinical practice guideline from 2010 was published in the peer-reviewed journal *Clinical Oncology*:

1. Wright F, Spithoff K, Easson A, Murray C, Toye J, McCready D, et al. Primary excision margins and sentinel lymph node biopsy in clinically node-negative melanoma of the trunk or extremities. Clin Oncol. 2011;23:572-578.

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Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To provide guidance on the optimal surgical excision margins and use of sentinel lymph node biopsy (SLNB) in adults diagnosed with cutaneous melanoma located on the trunk, extremities, and head and neck.

TARGET POPULATION

These recommendations apply to adults (>18 years) diagnosed with truncal, extremity, or head and neck non-metastatic cutaneous melanoma.

INTENDED USERS

Intended users of this guideline include general surgeons, otolaryngologists, head and neck surgeons, surgical oncologists, dermatologists, and plastic surgeons that provide care for patients with melanoma. Additionally, all clinicians and healthcare providers who are involved in the management or referral of patients with cutaneous melanoma are intended users of these recommendations.

UPDATES FROM 2010

In 2010, the Melanoma Disease Site Group developed a systematic review and clinical practice guideline to provide healthcare providers with guidance on optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk or extremities [Appendix 6: Evidence Base from 2010 Guideline]. As this guideline is now six years old and new evidence has emerged in the field, the Working Group of the Surgical Management of Melanoma Guideline Development Group developed this evidentiary base to update the recommendations of the clinical practice guideline. The following are key differences between the 2010 and current guideline:

- Recommendations specific to patients with head and neck melanoma have been added. This patient population was not included in the 2010 Guideline.
- Surgical margins for in situ melanomas of the trunk and extremities have been increased from 5 mm to a range of 5 mm to 1 cm.
- Surgical margins for pT2 melanomas of the trunk and extremities remain at 1 to 2 cm but a 2 cm margin, when possible, is suggested.
- Surgical margins for pT3 melanomas of the trunk and extremities have been increased from a range of 1 to 2 cm to 2 cm.
- The recommendations for SLNB have been significantly updated based on new evidence.

It should be noted that the studies used to inform the 2010 recommendations are included in two systematic reviews [1,2] and, therefore, have been included in this 2017 update of the 2010 Guideline.

RECOMMENDATIONS

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 be:

Melanoma Depth/Thickness	Margin
pTis melanoma in situ	5 mm–1 cm
pT1 melanoma ≤1.0 mm	1 cm
pT2 melanoma 1.01-2.0 mm	1–2 cm
pT3 melanoma 2.01-4.0 mm	2 cm
pT4 melanoma >4.01 mm	2 cm

Qualifying Statements for Recommendation 1

- For melanoma in situ, there are no randomized controlled trials evaluating 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 melanoma in situ were completely excised with a 9 mm surgical margin [3]. Consequently, some patients may require wider surgical margins of 1 cm to achieve clear pathologic margins.
- Where possible, for pT2 lesions, it may be desirable to take a wider margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference, because evidence concerning optimal excision margins is unclear.

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 be:

Melanoma Depth/Thickness	Margin
pTis melanoma in situ	5 mm–1 cm
pT1 melanoma ≤1.0 mm	1 cm
pT2 melanoma 1.01-2.0 mm	1–2 cm
pT3 melanoma 2.01-4.0 mm	2 cm
pT4 melanoma >4.01 mm	2 cm

Qualifying Statements for Recommendation 2

- For melanoma in situ, margin-controlled excision may provide tissue sparing and improved tumour clearance in challenging locations such as near the eye, nose, lips, and ears.
    - In this context, margin-controlled excision refers to assessment of margins prior to reconstruction so that surgeons may perform further resection until clear margins are achieved. This can be achieved via Mohs surgery or other forms of en face margin control prior to reconstruction; however, the superiority of one technique over the other is outside of the scope of this Guideline.
- For pT2 melanomas, where possible, it may be desirable to take a wider surgical margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference, because evidence concerning optimal excision margins is unclear.

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

Recommendation 3 – SLNB for Melanoma located on the Trunk and Extremities

Patients with a clinically node negative, stage I or II melanoma, >1.0 mm in thickness and located on the trunk and extremities should be given the opportunity to discuss SLNB to provide staging and prognostic information.

Melanoma Depth/Thickness	Use of SLNB
pTis melanoma in situ	Not recommended
pT1 melanoma ≤1.0 mm	If melanoma is ≥0.75 mm, has a Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, or microsatellites, physicians should discuss SLNB with these patients. If the results of SLNB indicate these patients have melanoma metastases in their sentinel node, they may benefit from adjuvant therapy and/or entry into adjuvant clinical trials and therefore may have an improved melanoma-specific survival (MSS).
pT2 melanoma 1.01-2.0 mm and pT3 melanoma 2.01-4.0 mm	SLNB is recommended for these patients to provide locoregional control and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB does provide an MSS benefit if the sentinel node contains melanoma metastases.
pT4 melanoma >4.01 mm	Physicians should discuss SLNB with these patients and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB will provide prognostic information and may provide locoregional control but not MSS benefit.

Qualifying Statements for Recommendation 3

- SLNB should be performed only following discussion of the options with the patient, in a high-volume unit (>50 cases) with access to appropriate surgical, nuclear medicine, and pathology services.
    - The false-negative rate of SLNB is lowest when >50 cases have been performed at the institution [4].
    - A double dye technique with Tc99 and blue dye (isosulfan or patent blue) increases the identification rate of the sentinel lymph nodes (SLNs) [5]
- For patients with intermediate-thickness melanomas diagnosed with nodal metastases on pathology of the sentinel node(s), there is a 10-year MSS benefit for SLNB; however, overall survival was not reported.
- SLNB should be discussed with patients to identify those eligible for adjuvant therapy and for enrollment into clinical trials.
- Ideally, for best accuracy, SLNB is performed at the same time as the wide local excision of the primary melanoma. SLNB is less reliable or may fail when performed as a separate operation for a patient having already had their wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft.

Recommendation 4 – SLNB for Cutaneous Melanoma located on the Head and Neck

Patients with a clinically node-negative, stage I or II cutaneous melanoma >1.0 mm in thickness and located on the head and neck should be given the opportunity to discuss SLNB to provide staging and prognostic information.

Melanoma Depth/Thickness	Use of SLNB
pTis melanoma in situ	Not recommended
pT1 melanoma ≤1.0 mm	If melanoma is ≥0.75 mm thickness, has a Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, or microsatellites, physicians should discuss SLNB with these patients. If the results of SLNB indicate these patients have melanoma metastases in their sentinel node they may benefit from adjuvant therapy and/or entry into adjuvant clinical trials and therefore may have an improved MSS.
pT2 melanoma 1.01-2.0 mm and pT3 melanoma 2.01-4. 0mm	SLNB is recommended for these patients to provide locoregional control and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB does provide a MSS benefit if the sentinel node contains melanoma metastases.
pT4 melanoma >4.01 mm	Physicians should discuss SLNB with these patients. SLNB will provide prognostic information and may provide locoregional control but not MSS benefit.

Qualifying Statements for Recommendation 4

- 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.
  - The false-negative rate of SLNB is lowest when >50 cases have been performed at an institution [4].
  - A double dye technique with Tc99 and blue dye (isosulfan or patent blue) increases the identification rate of the SLNs [5]
- SLNB should be discussed with patients to identify those eligible for adjuvant therapy and for enrollment into clinical trials.
- Ideally, for greatest accuracy, SLNB should be performed at the same time as the wide local excision of the primary melanoma. SLNB is less reliable or may fail when performed as a separate operation for a patient having already had a wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft.

Technical Considerations

These considerations have been transcribed from the original 2010 guideline and any changes have been italicized. As such, the technical considerations are based on evidence identified in the original systematic review [Appendix 6: Evidence Base from 2010 Guideline].

Excision Margins

- The depth of the excision should be down to, *but not including*, the fascia.
- Margins (e.g., 1 cm or 2 cm) should be included in the surgical operating room *report and are clinically measured with a ruler at the time of surgery from the visible edge of the melanoma or previous biopsy scar*.

- Standard synoptic pathology reporting should be used *for both the primary melanoma and the sentinel node biopsy*.
- Excision margins should be 1 to 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 fingers and toes, or where the primary melanoma involves anatomic areas not amenable to simple wide excision, multidisciplinary input should be sought.
- *Total radial margin excision may include margins from biopsy as well as wide local excision, as clinically appropriate*.

Sentinel Lymph Node Biopsy

- Lymphoscintography after *intradermal injection of radioactive tracer* is mandatory to identify SLNs.
- Either patent blue or isosulfan blue dye is recommended *in addition to the radioactive tracer*.
- SLNB assessment should include the use of immunohistochemistry and hematoxylin & eosin staining.
- *Size of melanoma metastases should be noted in the pathology report as should extranodal extension for each positive node*.

FURTHER QUALIFYING STATEMENTS

- Physicians should discuss the feasibility of enrollment into clinical trials with all patients.

IMPLEMENTATION CONSIDERATIONS

These recommendations are best implemented in the context of a multidisciplinary team and with involvement of a pathologist with expertise in dermatopathology.

Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

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UPDATES FROM 2010

In 2010, the Melanoma Disease Site Group (DSG) developed a systematic review and clinical practice guideline to provide healthcare providers with guidance on optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk or extremities [Appendix 6: Evidence Base from 2010 Guideline]. As this guideline is now six years old and new evidence has emerged in the field, the Working Group of the Surgical Management of Melanoma Guideline Development Group (GDG) developed this evidentiary base to update the recommendations of the clinical practice guideline. The following are key differences between the 2010 and current guideline:

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RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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 be:

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pT3 melanoma 2.01-4.0 mm	2 cm
pT4 melanoma >4.01 mm	2 cm

Qualifying Statements for Recommendation 1

- For melanoma in situ, there are no randomized controlled trials (RCTs) evaluating 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 melanoma in situ were completely excised with a 9 mm surgical margin [3]. Consequently, some patients may require wider surgical margins of 1 cm to achieve clear pathologic margins.
- Where possible, for pT2 lesions, it may be desirable to take a wider margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference, because evidence concerning optimal excision margins is unclear.

Key Evidence for Recommendation 1

A systematic review with meta-analysis that pooled six RCTs, published in 2016, compared narrow (1-2 cm) and wide (3-5 cm) margins for thin (≤2 mm) and thick (>2 mm) melanoma [1]. The Wheatley et al. meta-analysis found that for **all** patients, overall survival (OS) and recurrence-free survival (RFS) were not different when narrow margins were compared with wide; however, melanoma-specific survival (MSS) was improved with wide margins (3-5 cm) compared with narrow margins (1-2 cm) [1]. Subgroup analysis for thin and thick melanoma found no difference in OS, MSS, RFS, or locoregional recurrence (LR) when assessing ≤2 mm and >2 mm melanoma depths separately [1]. Furthermore, nodal status of these patients was unknown in most studies, thus potentially affecting MSS results.

A new RCT not included in the Wheatley et al. meta-analysis, which enrolled patients with thick (≥2 mm) melanomas, found no difference in OS when comparing 1 cm with 3 cm margins but there was a trend in reduction of MSS; however, this did not reach statistical significance [6]. An additional case-control study that enrolled patients with thin (≤1 mm) melanoma who had experienced local recurrence found that median time to recurrence was significantly shorter for patients with margins <1 cm, but no difference when margins >2 cm were compared with <2 cm margins [7].

Interpretation of Evidence for Recommendation 1

Key evidence identified by the 2016 search was compiled with the evidence identified in the 2010 guideline [Appendix 6: Evidence Base from 2010 Guideline] and refinements to the Recommendations were made when appropriate. Data from the Wheatley et al. systematic review with meta-analysis [1] are contrary to previously published data and the Working Group members interpreted the overall MSS benefit with caution. MSS was improved when all patients were pooled. However, MSS was not different when a subset analysis for patients with ≤2 mm melanoma or >2 mm melanoma was completed and nodal status was not known for all patients; thus, different stages of melanoma were potentially compared. Although the meta-analysis reported no heterogeneity for the pooling of all patients, when the six individual RCTs are examined (Section 4, Table 4-6), the Working Group noted that of

Recommendation 1 – Surgical Margins for Melanoma located on the Trunk and Extremities

the approximately 4000 patients pooled, there were few patients with melanoma depths of <1 mm (n=518) and, few patients in the RCTs received 1 cm margins (n=758). In most of the studies, the narrow margin was 2 cm (Section 4, Table 4-6). When performing wide local excision with 2 cm margins, primary closure is usually possible and low morbidity is generally achieved; however, if the recommended margin was increased to 3 cm, this would result in many more patients requiring more complex closures such as skin grafts or flaps, which could lead to higher morbidity. In addition, for stage I and II melanoma, local recurrence after wide local excision with clear margins is less than 5% [8].

The Working Group weighed the meta-analysis data, including patient numbers within each depth range (for example, few patients with melanomas <1.0 mm) against the morbidity of larger margins, the lack of benefit for OS, and the low rates of local recurrence against the reported MSS benefit with 3 to 5 cm margins for patients with all melanoma depths and chose to retain the original margin recommendations from the 2010 guideline for pT1, pT2, and pT4. After using the previous recommendations for six years, based on clinical experience with the recommendations, for thick melanoma of 2.0 to 4.0 mm, the Working Group has decided to increase the margin recommendation from 1 to 2 cm to 2 cm.

Similarly, for melanoma in situ, consensus resulted in the Working Group agreeing to increase the surgical margin recommendation from 5 mm to a range of 5 mm to 1 cm. This consensus opinion can be backed with evidence from a prospective study that used Mohs micrographic surgery for 1120 patients with melanoma in situ (42% of the lesions were on the trunk and extremities) [3]. The minimum surgical margin in this study was 6 mm and 86% of in situ melanomas were successfully excised with a 6 mm margin; 98.9% of melanoma in situ were completely excised with a 9 mm surgical margin and 100% were excised with a 12 mm margin on the trunk and extremities. The superiority of 9 mm compared with 6 mm margins was significant (P<0.001). Sex, location, and diameter did not affect results. Recurrence rate for this set of patients treated with Mohs micrographic surgery was 0.3% [3].

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 be:

Melanoma Depth/Thickness	Margin
pTis melanoma in situ	5 mm–1 cm
pT1 melanoma ≤1.0 mm	1 cm
pT2 melanoma 1.01-2.0 mm	1–2 cm
pT3 melanoma 2.01-4.0 mm	2 cm
pT4 melanoma >4.01 mm	2 cm

Qualifying Statements for Recommendation 2

- For melanoma in situ, margin-controlled excision may provide tissue sparing and improved tumour clearance in challenging locations such as near the eye, nose, lips, and ears.
    - In this context, margin-controlled excision refers to assessment of margins prior to reconstruction so that surgeons may perform further resection until clear margins are achieved. This can be achieved via Mohs surgery or other forms of en face margin control prior to reconstruction; however, the

superiority of one technique over the other is outside of the scope of this Guideline.

- For pT2 melanomas, where possible, it may be desirable to take a wider surgical margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference, because evidence concerning optimal excision margins is unclear.
- It is recognized that wide margins may not always be possible based on the location of melanoma in relation to facial structures. When possible, wide margins should be employed; however, they may be difficult to achieve when melanoma is located on the eyelid, nose, lip, or ear.

Key Evidence for Recommendation 2

Three low-quality retrospective cohort studies were identified to directly inform this recommendation for invasive (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 [9-11] or recurrence rates [9,10] when margins of different sizes were compared.

Interpretation of Evidence for Recommendation 2

There were no RCTs identified to inform a recommendation for melanoma in situ in the head and neck. Consensus from the Working Group led to an agreement to increase the surgical margin recommendation from 5 mm to a range of 5 mm to 1 cm. The studies that informed this decision included a retrospective study by Felton et al. [12] that evaluated 343 in situ melanomas of the head and neck. In this study, 65% percent of melanoma in situ were cleared by a 5 mm surgical margin, 75% with an 8 mm margin, 92% with a 10 mm margin, and 97% with a 15 mm margin. The increased clearance with the additional margin was significant ($p<0.0001$). Patient age, lesion site, and preoperative size did not predict a clear margin. The Working Group applied knowledge from the Mohs micrographic surgery literature, which indicate that margins of 9 to 10 mm may be needed to achieve a complete clearance rate in **some** patients with melanoma in situ [3,12]. However, for the majority of patients, a 5 mm surgical margin will lead to clear pathologic margins.

The evidence identified to inform a recommendation on appropriate surgical margins for invasive melanoma (pT1-pT4) located on the head and neck was low quality. Based on the biological similarities between melanoma located on the head and neck and melanoma located on the trunk and extremities, the Working Group felt comfortable adopting the higher quality key evidence and resultant Recommendations from melanoma on the trunk and extremities, with a few exceptions. It is recognized that wide margins are not always possible with these patients and, thus, wide margins should be employed whenever possible, but may be unachievable when melanoma is located on the eyelid, nose, lip, or ear.

Recommendation 3 – SLNB for Melanoma located on the Trunk and Extremities

Patients with a clinically node-negative, stage I or II melanoma, >1.0 mm in thickness and located on the trunk and extremities should be given the opportunity to discuss SLNB to provide staging and prognostic information.

Melanoma Depth/Thickness	Use of SLNB
pTis melanoma in situ	Not recommended
pT1 melanoma ≤1.0 mm	If melanoma is ≥0.75 mm, has a Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, or microsatellites, physicians should discuss SLNB with these patients. If the results of SLNB indicate these patients have melanoma metastases in their sentinel node, they may benefit from adjuvant therapy and/or entry into

	adjuvant clinical trials and therefore may have an improved MSS.
pT2 melanoma 1.01-2.0 mm and pT3 melanoma 2.01-4.0 mm	SLNB is recommended for these patients to provide locoregional control and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB does provide an MSS benefit if the sentinel node contains melanoma metastases.
pT4 melanoma >4.01 mm	Physicians should discuss SLNB with these patients and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB will provide prognostic information and may provide locoregional control but not MSS benefit.

Qualifying Statements for Recommendation 3

- SLNB should be performed only following discussion of the options with the patient, in a high-volume unit (>50 cases) with access to appropriate surgical, nuclear medicine, and pathology services.
  - The false-negative rate of SLNB is lowest when >50 cases have been performed at the institution [4].
  - A double dye technique with Tc99 and blue dye (isosulfan or patent blue) increases the identification rate of the sentinel lymph nodes (SLNs) [5]
- For patients with intermediate-thickness melanomas diagnosed with nodal metastases on pathology of the sentinel node(s), there is a 10-year MSS benefit for SLNB; however, OS was not reported.
- SLNB should be discussed with patients to identify those eligible for adjuvant therapy and for enrollment into clinical trials.
- Ideally, for best accuracy, SLNB is performed at the same time as the wide local excision of the primary melanoma. SLNB is less reliable or may fail when performed as a separate operation for a patient having already had their wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft.

Key Evidence for Recommendation 3

The 10-year follow-up of the Multicenter Selective Lymphadenectomy Trial (MSLT-I trial) [13] has been published since the 2010 guideline [Appendix 6: Evidence Base from 2010 Guideline]. The 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 only reported 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) [13]. For those in the sentinel node biopsy group, patients with positive SLNB had immediate lymphadenectomy, while patients in the observation group had nodal observation and only lymphadenectomy if patients later presented with nodal relapse [13]. The MSLT-I trial reported on disease-free survival (DFS) and MSS, but not OS. Ten-year DFS was significantly higher in the SLNB group compared with the observation group for patients with both intermediate and thick melanomas (p=0.01 and p=0.03, respectively) [13]. Overall, the 10-year MSS was not different between groups for either intermediate or thick melanomas [13]. However, for *patients with nodal metastases*, 10-year MSS was significantly higher in patients with intermediate-thickness melanoma in the SLNB group compared with the observation group (62.1±4.8% vs. 41.5±5.6%) [13]; this was not the case for the patients with thick melanomas.

A meta-analysis that included studies of multiple Breslow thicknesses, but due to missing data could only pool data for the thick melanoma (>4.01 mm) group, found that OS was reduced in patients with positive SLNs when compared with patients with negative SLNs

[2]. A second meta-analysis included only studies involving patients diagnosed with thin melanoma (≤1 mm) and found that, overall, 4.5% of these patients had positive SLNs at biopsy [14]. Melanoma thickness of ≥0.75 mm, Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, and microsatellites were predictors of sentinel node metastases, with the rates of SLN positivity being 8.8%, 7.3%, 8.8%, 5.8%, and 26.6%, respectively, for each predictor [14].

Interpretation of Evidence for Recommendation 3

All patients with a melanoma >1.0 mm in thickness should be given the opportunity to discuss SLNB. SLNB is performed to provide information on staging and prognosis, and to identify patients who may benefit from adjuvant therapy/clinical trials. Although the MSLT-I trial did not report on OS at 10 years, it reported a MSS benefit in the SLNB group for patients with intermediate-thickness melanomas with nodal metastases, and improved locoregional control benefit for patients with melanoma of 1.2 mm through >3.5 mm thickness. Based on the MSLT-I results and the expertise and clinical experiences of the Working Group, the majority of the Working Group feels confident in recommending SLNB for patients with 1.01 to 4.0 mm-thick melanoma to provide locoregional control, staging, and prognosis, as well as determining eligibility for clinical trials, but note that there is not OS benefit for all patients. For patients with a melanoma thicker than 4.0 mm, SLNB provides locoregional control and prognostic information, but does not improve MSS. Patients should thus still be given the opportunity to discuss the role of SLNB for prognostic information and locoregional control.

Lastly, based on the Cordeiro et al. systematic review with meta-analysis [14], in patients with thin melanoma, a melanoma of ≥0.75 mm, Clark level IV/V, high mitotic rates, ulceration, and/or microsatellites indicate a higher chance for SLN positivity, and therefore physicians should discuss SLNB with these patients.

Recommendation 4 – SLNB for Cutaneous Melanoma located on the Head and Neck

Patients with a clinically node-negative, stage I or II cutaneous melanoma >1.0 mm in thickness and located on the head and neck should be given the opportunity to discuss SLNB to provide staging and prognostic information.

Melanoma Depth/Thickness	Use of SLNB
pTis melanoma in situ	Not recommended
pT1 melanoma ≤1.0 mm	If melanoma is ≥0.75 mm thickness, has a Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, or microsatellites, physicians should discuss SLNB with these patients. If the results of SLNB indicate these patients have melanoma metastases in their sentinel node they may benefit from adjuvant therapy and/or entry into adjuvant clinical trials and therefore may have an improved MSS.
pT2 melanoma 1.01-2.0 mm and pT3 melanoma 2.01-4. 0mm	SLNB is recommended for these patients to provide locoregional control and to identify patients who may benefit from adjuvant therapy and/or entry into adjuvant clinical trials. SLNB does provide a MSS benefit if the sentinel node contains melanoma metastases.
pT4 melanoma >4.01 mm	Physicians should discuss SLNB with these patients. SLNB will provide prognostic information and may provide locoregional control but not MSS benefit.

Qualifying Statements for Recommendation 4

- 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.
  - The false-negative rate of SLNB is lowest when >50 cases have been performed at an institution [4].
  - A double dye technique with Tc99 and blue dye (isosulfan or patent blue) increases the identification rate of the SLNs [5]
- SLNB should be discussed with patients to identify those eligible for adjuvant therapy and for enrollment into clinical trials.
- Ideally, for greatest accuracy, SLNB should be performed at the same time as the wide local excision of the primary melanoma. SLNB is less reliable or may fail when performed as a separate operation for a patient having already had a wide local excision and repair with any flap (with the exception of an advancement flap) or skin graft.

Key Evidence for Recommendation 4

One systematic review [15] and one diagnostic cohort study [16] assessed the diagnostic performance of SLNB for melanoma located on the head and neck and reported high false-negative rates of 20.4% and 4.8%, respectively.

It is now known that the MSLT-I trial [13] included 334 patients with primary melanomas located on the head and neck [M. Faries, personal communication, June 2, 2016]. Although head and neck patients were not separately analyzed, for all enrolled patients, 10-year DFS was significantly higher in the SLNB group compared with the observation group for patients with both intermediate and thick melanomas [13]. Additionally, in patients with intermediate-thickness melanomas with nodal metastases, 10-year MSS was significantly higher in the SLNB group compared with the observation group [13]. However, MSS was not improved for patients with thick melanomas.

Interpretation of Evidence for Recommendation 4

Due to the MSLT-I trial enrolling head and neck patients, we report the same DFS and MSS benefit in the head and neck population as in the trunk and extremity population. However, data indicate that there is a higher chance of false negatives when using SLNB patients with melanoma of the head and neck. To help minimize the number of false negatives, SLNB should be performed in high-volume centres (>50 cases) [4]. Furthermore, a dual tracer technique with Tc99 and blue dye increases the detection rate of SLNs [5].

Technical Considerations

These considerations have been transcribed from the original 2010 guideline and any changes have been italicised. As such, the technical considerations are based on evidence identified in the original systematic review [Appendix 6: Evidence Base from 2010 Guideline].

Excision Margins

- The depth of the excision should be down to, *but not including*, the fascia.
- Margins (e.g., 1 cm or 2 cm) should be included in the surgical operating room *report and are clinically measured with a ruler at the time of surgery from the visible edge of the melanoma or previous biopsy scar*.
- Standard synoptic pathology reporting should be used *for both the primary melanoma and the sentinel node biopsy*.
- Excision margins should be 1 to 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 fingers and toes, or where the primary melanoma involves anatomic areas not amenable to simple wide excision, multidisciplinary input should be sought.

- *Total radial margin excision may include margins from biopsy as well as wide local excision, as clinically appropriate.*

Sentinel Lymph Node Biopsy

- Lymphoscintography after *intradermal injection of radioactive tracer* is mandatory to identify SLNs.
- Either patent blue or isosulfan blue dye is recommended *in addition to the radioactive tracer*.
- SLNB assessment should include the use of immunohistochemistry (IHC) and hematoxylin & eosin (H&E) staining.
- *Size of melanoma metastases should be noted in the pathology report as should extranodal extension for each positive node.*

FURTHER QUALIFYING STATEMENTS

- Physicians should discuss the feasibility of enrollment into clinical trials with all patients.

IMPLEMENTATION CONSIDERATIONS

These recommendations are best implemented in the context of a multidisciplinary team and with involvement of a pathologist with expertise in dermatopathology.

Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

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). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of GDGs in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

In 2010 the Melanoma DSG developed a systematic review and clinical practice guideline to provide healthcare providers with guidance on optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk or extremities. Since completion of this guideline, new evidence has emerged, prompting the Melanoma DSG to update the systematic review and subsequent recommendations.

GUIDELINE DEVELOPERS

This guideline was developed by the Surgical Management of Melanoma GDG (Appendix 1), which was convened at the request of the Melanoma DSG.

The project was led by a small Working Group of the Surgical Management of Melanoma GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in surgical oncology, head and neck surgery, plastic surgery, dermatology, pathology, medical oncology, and health research methodology. Other members of the Surgical Management of Melanoma GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [17,18]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [19] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

The following criteria were used to select potentially relevant guidelines:

- Guidelines published after the year 2010.
- Guidelines that included a systematic review of the literature that covered at least one of the outcomes of interest.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [19].

- A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4).
- One guideline, developed by NICE, was identified and considered for inclusion [20]. The NICE guideline covered all assessment and management for melanoma and had a search date of September 2014. As such, it was not considered appropriate for adaption or endorsement.
- The Australia/New Zealand guideline [21], which the original version of this clinical practice guideline was based upon, is in the process of being updated by Cancer Council Australia's Clinical Guidelines Network and was not considered for adaptation since only the 2008 version is available currently.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with

methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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- Sara Miller for copy editing.

Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

Section 4: Systematic Review

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. In Canada, the incidence rates of melanoma have increased by 2.3% per year in men between 2001 and 2010, and by 2.9% per year for woman within the same time frame [22]. In 2015, it was estimated that 3250 new cases of melanoma would be diagnosed in Ontario out of 6500 new diagnoses in Canada [22]. For patients who are diagnosed with early-stage (clinically node negative and <4 mm thickness [pT1-pT3]) cutaneous melanoma, the principal therapy is surgical excision of the primary tumour and assessment of lymph nodes. 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 surgical 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 (1-3 cm) has become more common in practice but the effect of narrow margins on LR, DFS, and OS remains 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 patients with stage I and II cutaneous melanoma have no clinical evidence of lymphadenopathy at initial presentation, yet approximately 16% have subclinical involvement [13]. SLNB is a surgical procedure that identifies the sentinel node, the first lymph node(s) that drain the primary melanoma site. The SLNB allows the status of a clinically node-negative regional basin to be determined without a complete lymph node dissection. The procedure involves lymphatic mapping with a blue dye (isosulfan or patent blue) and a radioactive tracer (Tc99) and offers a way to select the patients who might benefit from nodal dissection and subsequent treatment. The nodes are serially sectioned and carefully examined pathologically (H&E staining and IHC for HMB-45, S-100, and MART-1) for the presence of melanoma metastases. The technique is predicated on the empiric observation that melanoma metastasizes along lymphatics sequentially, preferentially to the SLN and then to other regional lymph nodes.

In 2010, the Melanoma DSG developed a systematic review and clinical practice guideline to provide healthcare providers with guidance on optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk or extremities [Appendix 6: Evidence Base from 2010 Guideline]. As this guideline is now six years old and new evidence has emerged in the field, the Working Group of the Surgical Management of Melanoma GDG developed this evidentiary base to update the recommendations of the clinical practice guideline. Patients with melanoma located on the head and neck have been added to the target population in this guideline update.

RESEARCH QUESTIONS

Please note: for all research questions, the categories of melanoma thickness that are of interest are: in situ, <1 mm, 1.01-2 mm, 2.01-4 mm, and >4.01 mm.

1. In patients with non-metastatic cutaneous melanoma with clinically node-negative or node-positive disease of the trunk or extremities, what are the optimal primary clinical margins of excision for melanoma?
2. In patients with distant metastases following a diagnosis of melanoma of the trunk or extremities, what are the optimal primary clinical margins of excision for cutaneous melanoma?
3. Should patients with clinically node-negative cutaneous melanoma of the trunk and extremities undergo SLNB for melanoma?
4. In patients with non-metastatic cutaneous melanoma with clinically node-negative or node-positive disease of the head and neck, what are the optimal primary margins of excision for melanoma?
5. In patients with distant metastases following a diagnosis of melanoma of the head and neck, what are the optimal primary margins of excision for cutaneous melanoma?
6. Should patients with clinically node-negative cutaneous melanoma of the head and neck undergo SLNB for melanoma?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections. Since the original guideline included a literature search up to 2010 for melanoma located on the trunk and extremities, the current update focused on systematic reviews and studies published after 2010. For melanoma located on the head and neck, the literature search started in 2002, which was the original start search date for the 2010 guideline.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews evaluating narrow compared with wide excision margins and the use of SLNB. For melanoma of the trunk and extremities, OVID was searched from 2010 to week 25 of 2016, and for melanoma of the head and neck, OVID was searched from 2002 to week 25 of 2016. For both searches, the following keywords were used: “melanoma”, “head and neck” (for head and neck search only), “excision margin”, “SLNB”, and “sentinel node”. In addition, websites/databases of specific guideline developers that used systematic reviews as their evidentiary base, as well as systematic review producers, were also searched, using the same keywords and for the same period.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [23] tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

Below are methods for locating and evaluating primary literature if no existing systematic reviews were identified, or if identified reviews were incomplete in some fashion. If the identified systematic reviews are incomplete, then the primary literature review might be reduced in scope (e.g., subject areas covered, time frames covered).

Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles evaluating the optimal excision margins and use of SLNB in adults diagnosed with melanoma, published from 2002 for head and neck populations, and from 2010 for trunk and extremity populations through week 25 of 2016. The literature searches were then updated to week 25 of 2017 prior to project completion. The literature search strategy included keywords for identification of excision margins, SLNB, head and neck melanoma populations, and trunk and extremity melanoma populations. The complete literature search strategy can be found in Appendix 2. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Based on the known evidence *a priori*, different study types were included for each research question. For studies that evaluated excision margins in patients with melanoma located on the trunk and extremities, it was believed *a priori* that no RCTs would be identified, so the search was designed to identify RCT and prospective cohort studies, with a plan to exclude cohort studies if RCTs were identified. For head and neck patients, due to a known lack of published studies, retrospective cohort studies were also considered. It was known *a priori* that the 10-year MSLT-1 trial results had been recently published; thus, only RCTs were considered when choosing studies that evaluated SLNB in patients with melanoma on the trunk and extremities. As no RCT that evaluated SLNB solely in a head and neck melanoma population was known, for the head and neck search both RCTs and prospective cohort studies were considered. For all cohort studies, the study had to compare a narrow margin with a wide margin, or the use of SLNB compared with observation, and the study had to enrol at least 30 patients to be considered for inclusion in the evidence base. Case series, letters, editorials, and studies not published in English were excluded from the entire evidence base for all Research Questions.

All hits from the OVID literature search were input into reference management software (EndNote X6), where duplicate citations were removed. A review of the titles and abstracts that resulted from the search was performed by one reviewer (LS) and verified by a second (FW). For those items that warranted full-text review, one reviewer (LS) determined whether the inclusion and exclusion criteria were met. The list of proposed studies was verified by the Working Group. The literature search flow diagram can be found in Appendix 3.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by one reviewer (LS). Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating reduced risk for recurrence or death, unless otherwise indicated. All extracted data and information were audited by an independent auditor.

Important quality features, such as study design, comparison type, power calculation reporting, sources of bias, and sources of funding were extracted for each study. To evaluate the risk of bias within the identified studies, the Cochrane Risk of Bias Tool [24] was used for randomized studies, A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) [25] was used for cohort studies, and QUADAS-2 [26] was used for diagnostic studies.

Synthesizing the Evidence

Due to the anticipated lack of evidence and anticipated variation in reported comparisons and outcomes measured, a meta-analysis was not planned.

RESULTS

Search for Existing Systematic Reviews

The search for existing systematic reviews identified 126 possible reviews on optimal resection margins and use of SLNB in melanoma patients. Four systematic reviews [1,2,14,15] were chosen for inclusion in the evidence base. One evaluated narrow versus wide excision margins in patients with melanoma on the trunk and extremities [1], while the remaining three assessed the use of SLNB in melanoma on the trunk and extremities [2,14] and in melanoma on the head and neck [15]. Although there is some overlap in the studies included in the Cordeiro et al. [14] and the Freeman et al. [2] systematic reviews, the Cordeiro et al. [14] review is newer, thus includes some additional studies, and focuses on thin melanomas only, while the Freeman et al. [2] review included studies with melanoma of various Breslow thickness categories. All included systematic reviews scored highly when evaluated with the AMSTAR tool (Appendix 4). In an exception of note, all four did not use the status of publication as an inclusion criterion for the systematic review, and only Wheatley et al. [1] included a list of all included and excluded studies (Appendix 4). The likelihood of publication bias was assessed in the Freeman et al. [2] and Wheatley et al. [1] reviews, but not in the Codeiro et al. [14] or de Rosa et al. [15] reviews. Finally, the Freeman et al. [2] review did not include details on conflict of interest.

Search for Primary Literature

The primary literature systematic review was used to address outcomes of interest and Breslow thicknesses not covered by the included systematic reviews. Where systematic reviews existed, a search of the primary literature was conducted from the end date of the search in the reviews.

Literature Search Results

Eight studies were identified that met inclusion criteria (Appendix 3). Table 4-1 summarizes the number of studies identified per research question, melanoma location, and Breslow thickness. Since many of the identified studies included patients with various melanoma thicknesses, studies may be included multiple times in the table (Table 4-1). When the studies have defined Breslow thickness differently than the ranges used in the research questions, a detailed note has been provided below the table (Table 4-1).

Table 4-1. Studies selected for inclusion.

Topic	Melanoma Location	Breslow Thickness	Studies [ref]
Primary excision margins	Trunk and extremity	In situ	No studies identified
		≤1 mm	1 SR with meta-analysis [1][a] 1 case-control study [7]
		1.01–2 mm	1 SR with meta-analysis [1][a]
		2.01–4 mm	1 SR with meta-analysis [1][a] 1 RCT [6][b]
		>4.01 mm	1 meta-analysis [1][a] 1 RCT [6][b]
	Head and neck	In situ	1 retrospective cohort [11][e]
		≤1 mm	2 retrospective cohorts [11][e][9]
		1.01–2 mm	2 retrospective cohorts [11][e][9]
		2.01–4 mm	2 retrospective cohorts [11][e][9]

Topic	Melanoma Location	Breslow Thickness	Studies [ref]
		>4.01 mm	3 retrospective cohorts [11][e][9,10]
SLNB	Trunk and extremity	In situ	No studies identified
		≤1 mm	2 SRs with meta-analyses [2,14] 1 RCT [13][c]
		1.01–2 mm	1 SR with meta-analysis [2] 2 RCTs [13][c][27][d]
		2.01–4 mm	1 SR with meta-analysis [2] 1 RCT [13][c]
		>4.01 mm	1 SR with meta-analysis [2] 1 RCT [13][c]
	Head and neck	In situ	No studies identified
		≤1 mm	1 SR without meta-analysis [15][f] 1 RCT [13][c] 1 diagnostic cohort [16][g]
		1.01–2 mm	1 SR without meta-analysis [15][f] 1 RCT [13][c] 1 diagnostic cohort [16][g]
		2.01–4 mm	1 SR without meta-analysis [15][f] 1 RCT [13][c] 1 diagnostic cohort [16]
		>4.01 mm	1 SR without meta-analysis [15][f] 1 RCT [13][c] 1 diagnostic cohort [16]

Abbreviations: RCT, randomized controlled trial; SR, systematic review

[a] Study compared ≤2.0 mm thick to >2.0 mm thick [1].

[b] UK trial included patients with Breslow thickness of at least 2.0 mm [6].

[c] MSLT-I trial defined thin melanoma as <1.2 mm, intermediate as 1.2-3.5 mm, and thick melanoma as >3.5 mm [13].

[d] Study enrolled patients with Breslow thickness of ≥1.0 mm; median thickness was 1.55 mm [27].

[e] Study classified patients by disease stage and included patients with Tis through T4 [11].

[f] Systematic review included studies that enrolled patients of all Breslow thicknesses [15].

[g] Thin melanoma defined as ≤2.0 mm with the lowest limit not reported [16].

Study Design and Quality

The primary literature in the 2016 evidentiary base was comprised of three RCTs [6,13,27], one case-control study [7], three retrospective cohort studies [9-11], and one diagnostic cohort study [16]. A description of the study design and risk of bias assessment for all studies can be found in Appendix 5.

The 10-year follow-up for the MSLT-I trial [13] was assessed as high quality. There was unclear risk for selection bias as the study reported that patients were randomly assigned in a 60:40 ratio, but there was no detail provided on the sequence generation process or allocation concealment (Appendix 5). Additionally, concerns had been raised after publication of the original study surrounding ascertainment bias based on the known sentinel node status in the biopsy group while sentinel node status was not known in the observation group. This bias was addressed by a latent-subgroup analysis in this 10-year follow-up publication. The Hayes et al. [6] RCT was also assessed as high quality. The study did not blind participants or outcome assessors, but outcomes are not likely to be influenced by a lack of blinding (Appendix 5). Additionally, SLNB was not routinely performed in this study and that could affect survival rates, but lack of SLNB was across both comparisons groups, so considered to be balanced (Appendix 5). The final RCT [27] was a reanalysis of the original Sunbelt Melanoma Trial [28], and the original trial was used to assess the first five domains of the Cochrane Risk of Bias Tool.

This study was assessed as moderate quality due to an unclear risk to selection bias, high risk of attrition bias, and lack of blinding (Appendix 5).

The one case-control study [7] and three retrospective studies [9-11] were all assessed as low quality and suffered from bias due to confounding [7,9], bias in selection of participants [9-11], bias in classification of interventions [7,10,11], and bias in selection of the reported results [7] (Appendix 5). The diagnostic cohort study [16] was also assessed as low quality based on a lack of universal reference standard [16] and differences in timing between index test and reference standard and patient flow [16] (Appendix 5).

Outcomes

The results are organized by research question and, where appropriate, subdivided into specific melanoma patient populations based on Breslow thickness. All included studies are summarized in the text with more complete details found in tables. The two main outcomes of interest were recurrence rate and survival rate. Recurrence rates included local, locoregional, and regional recurrence rates. Survival within the studies was reported as OS, MSS, and DFS. Secondary outcomes included morbidity, when reported, and rate of SLN positivity. Additionally, for the head and neck population, accuracy of SLNB was extracted. When studies inform multiple research questions, only details appropriate for the specific research question are included for that question.

Surgical Margins for Melanoma of the Trunk and Extremities

The literature search identified one systematic review with meta-analysis [1], one RCT [6], and one case-control study [7] to inform this research question. It should be noted that the systematic review with meta-analysis [1] included the studies that were used to inform the recommendations from the previous version of the Guideline [Appendix 6: Evidence Base from 2010 Guideline]. The case-control study was included despite the presence of a systematic review with meta-analysis because outcomes were specific to patients with thin melanomas (<1 mm thickness). Outcomes for these patients were not differentiated in the systematic review with meta-analysis; therefore, the case-control study was retained. The meta-analysis by Wheatley et al. included both thick melanoma, defined as melanoma >2.0 mm thick, and thin melanoma, defined as ≤2 mm thick, and defined narrow margins as 1 to 2 cm and wide margins as 3 to 5 cm. When all patients were pooled, OS was not different when comparing narrow with wide margins (Table 4-2) [1]. However, MSS was improved with wide margins (Table 4-2) [1]. The meta-analysis conducted two sets of subgroup analysis to determine whether survival differed by the size of margin or Breslow thickness. When comparing ranges of excision margins in all patients, there was no significant difference in OS, or LR for subgroups of 1 cm vs. 3 cm, 2 cm vs. 4 cm, or 2 cm vs. 5 cm margins (Table 4-2) [1]. When only melanomas <2 mm were assessed, there was no significant difference in OS for narrow (1–2 cm) compared with wide (3-5 cm) margins (Table 4-2). When only melanomas ≥2 mm in thickness were assessed, there was also no significant difference in OS for narrow compared with wide margins. These subgroup analyses led the study conductors to conclude that there was no evidence that treatment effects differed by Breslow thickness or margin size. The meta-analysis then used Bayesian likelihood plots to evaluate the probability of worse OS, MSS, RFS, and LR and found a high chance for worse endpoints in all measures with narrow margins (Table 4-2) [1].

The identified RCT focused on thick melanomas of at least 2 mm and randomized patients to narrow excision margins (1 cm) or wide margins (3 cm) [6]. When comparing the groups with a median follow-up of 8.8 years, there was no difference in OS, while MSS was improved with the wide margin (Table 4-2) [6]. It should be noted that patients in this RCT did not routinely receive SLNB. The case-control study focused on thin melanoma (≤1 mm) and enrolled cases that had experienced local recurrence arising <5 cm from the edge of the primary

[7]. Using 1 cm surgical margin as a cut-off, the study found that median time to recurrence was significantly shorter for patients with margins <1 cm, while there was no difference when margins greater than and less than 2 cm were compared (Table 4-2) [7]. The study also conducted multivariate regression and found that melanoma subtype, cell type, Breslow thickness, Clark level, ulceration, mitotic rate, and lymphovascular invasion were all not associated with local recurrence [7].

Table 4-2. Studies evaluating surgical margins for patients with melanoma of the trunk or extremities.

Study Details	Primary Melanoma	Margins	Results Summary
Meta-Analyses			
Wheatley et al, 2016 [1] • Search: 2009 – 2015 • 6 RCTs included • 4249 patients total	• ≤2.0 mm thick ○ 3 studies • >2.0 mm thick ○ 2 studies • 1.0–4.0 mm ○ 1 study ○ Data for >2 mm and ≤2 mm subgroups included in meta-analysis	Narrow (1-2 cm) vs. wide (3-5 cm) • Subgroups: ○ 1 cm vs. 3 cm ○ 2 cm vs. 4 cm ○ 2 cm vs. 5 cm	• HR >1 indicates a wide margin is better • All patients: overall survival not significantly different for narrow margins compared with wide margins (HR, 1.09; 95%CI, 0.98-1.22; p=0.1) • All patients: melanoma-specific survival significantly improved with wide margins compared with narrow margins (HR, 1.17; 95%CI, 1.03-1.34; p=0.02) • All patients: OS ○ 1 cm vs. 3 cm: HR, 1.13; 95%CI, 0.96-1.33; p=0.1 ○ 2 cm vs. 4 cm: HR, 1.11; 95%CI, 0.93-1.34; p=0.3 ○ 2 cm vs. 5 cm: HR, 1.00; 95%CI, 0.80-1.25; p=1.0 • All patients: risk of locoregional recurrence ○ 1 cm vs. 3 cm: HR, 1.22; 95%CI, 0.99-1.51; p=0.06 ○ 2 cm vs. 4 cm: HR, 0.99; 95%CI, 0.81-1.22; p=0.9 ○ 2 cm vs. 5 cm: HR, 1.11; 95%CI, 0.82-1.50; p=0.5 • Thin melanomas (melanoma <2 mm thick) ○ OS - narrow vs. wide: HR,1.05; 95%CI, 0.87-1.27; p=0.6 • Thick melanomas (melanoma ≥2mm thick) ○ OS - narrow vs. wide: HR, 1.12; 95%CI, 0.98-1.27; p=0.09 • By Bayesian likelihood plot ○ 94% probability that OS is worse with a narrow margin ○ 99% probability that melanoma-specific survival is worse with narrow margins ○ 92% probability that recurrence-free survival is worse with narrow margins

Study Details	Primary Melanoma	Margins	Results Summary
			○ 92% probability that locoregional recurrence is worse with a narrow margin
Randomized Controlled Trials			
Hayes et al, 2016 [6] • n=900 • Thick melanoma (≥2 mm) • Median follow-up: 8.8 years	• Single primary localized melanoma greater than 2 mm in Breslow thickness • SLNB not routinely done	• 1 cm excision margin (n=453) • 3 cm excision margin (n=447)	• HR >1 indicates advantage with wide margin • OS: HR, 1.14; 95%CI, 0.96-1.36; p=0.14 • Melanoma specific survival: HR, 1.24; 95%CI, 1.01-1.53; p=0.041 • Surgical complications: ○ 8% (n=35/453) in 1 cm group ○ 15% (n=65/447) in 3 cm group • Sites of local recurrences not reported
Observational Studies			
MacKenzie Ross et al, 2016 [7] • Case-control • Cases: n=176 • Controls: n=172 • Thin melanomas (≤1 mm) • Median follow-up: Cases: 93 months; controls: 128 months	• Localized T1 • Cases had experienced local recurrence arising <5 cm from edge of the primary tumour margin • Controls did not experience local recurrence	• Subgroup: <8 mm vs. ≥8 mm HEM • HEM corresponds to 1 cm surgical margin after accounting for 20% tissue shrinkage due to fixation and processing	• Using 8 mm as cut-off, HEM significantly influenced time to local recurrence (p=0.004) ○ Median time to recurrence for patients with <8 mm HEM: 110.6 months (95%CI, 70.7-150.4) ○ Median time to recurrence for patients with ≥8 mm HEM: not reached • No significant difference found for ≥16 mm HEM (~2 cm surgical margin) compared with <16 mm HEM (p=0.223)

Abbreviations: CI, confidence interval; HEM, histopathologic excision margin; HR, hazard ratio; OS, overall survival; RCT, randomized controlled trial; SLNB, sentinel lymph node biopsy

Sentinel Lymph Node Biopsy for Melanoma of the Trunk and Extremities

The literature search identified two systematic reviews with meta-analyses [2,14], and two RCTs [13,27] to inform this research question. It should be noted that these systematic reviews included the studies that were used to inform the original recommendations for the previous version of this Guideline [Appendix 6: Evidence Base from 2010 Guideline]. The first systematic review included studies of multiple Breslow thicknesses (Table 4-3) and reported on five-year OS for patients that were positive for SLN metastases and patients that were negative [2]. Due to missing data, a meta-analysis was only completed for the thick melanoma (>4 mm) group and showed that SLN positivity leads to a higher risk of death (Table 4-3) [2]. The systematic review reported on five-year OS for the other thickness categories based on SLN positivity, but rates were not statistically compared (Table 4-3). The second systematic review included only studies involving patients diagnosed with thin melanoma (≤1 mm) and found by meta-analysis that 4.5% of these patients had positive sentinel nodes at biopsy (Table 4-3) [14]. Thickness of ≥0.75 mm, Clark level IV/V, high mitotic rate (≥1 mitosis/mm^2), ulceration, and microsatellites were predictors of sentinel node metastases, with the rates of SLN positivity being 8.8%, 7.3%, 8.8%, 5.8%, and 26.6%, respectively, for each predictor (Table 4-3) [14].

The first RCT was a reanalysis of data from the Sunbelt Melanoma Trial and was designed to evaluate the prognostic value of polymerase chain reaction (PCR) for staging of SLN biopsy specimens in an effort to identify high-risk patients with histologically negative SLN [27]. All patients in the Sunbelt Melanoma Trial who had negative nodes by IHC underwent molecular staging with PCR and patients positive by PCR were randomized to observation, complete lymph node dissection, or complete lymph node dissection plus high-dose interferon [27]. Patients with positive SLN by PCR who were randomized to observation showed decreased DFS when compared with patients who were PCR-negative and patients who were PCR-positive and received complete lymph node dissection (Table 4-3) [27]. There was no difference in OS across the groups (Table 4-3).

The second RCT reported on 10-year follow-up of the MSLT-I trial [13]. The RCT enrolled patients with thin (<1.2 mm), intermediate (1.2–3.5 mm), and thick (>3.5 mm) melanomas, but this publication only reported on the patients with intermediate and thick melanoma. Enrolled patients had melanomas located on the trunk, extremities, head, and neck. Patients were randomized to a SLN biopsy group, which included wide excision (2-3 cm) and SLNB, followed by immediate lymphadenectomy for patients positive for nodal metastases, or observation, which included wide excision (2-3 cm) and nodal observation and only lymphadenectomy if patients presented with nodal relapse [13]. The MSLT-I trial reports on DFS and MSS, but not OS. Ten-year DFS was significantly higher in the biopsy group compared with the observation group for intermediate and thick melanomas (Table 4-3) [13]. However, 10-year MSS was not different between groups for either intermediate or thick melanoma (Table 4-3) [13]. When looking at only patients with nodal metastases, 10-year MSS was significantly higher in patients with intermediate-thickness melanomas in the biopsy group compared with the observation group (Table 4-3) [13]. This association was not seen in patients with thick melanomas (Table 4-3).

Table 4-3. Studies evaluating SLNB for patients with melanoma of the trunk or extremities.

Study Details	Primary Melanoma	SLNB details	Results Summary
Systematic Reviews and Meta-Analyses			
Freeman et al, 2013 [2] • Systematic review (29 studies) and meta-analysis (6 studies) • Search: April 2011	• Included studies of <1 mm, 1-2 mm, 2-4 mm, or ≥4 mm Breslow thickness melanomas	• Studies evaluated risk of OS according to SLN status	• 5y OS - <1 mm Breslow (1 study) ○ SLN-pos patients: 100% ○ SLN-neg patients: 100% • 5y OS - 1-2 mm Breslow ○ SLN-pos patients: 76%; 95%CI, 58-87% ○ SLN-neg patients: 94%; 95%CI, 88-96% • 5y OS - 2-4 mm Breslow ○ SLN-pos patients: 40%; 95%CI, 22-55% ○ SLN-neg patients: 82%; 95%CI, 76-90% • 5y OS - ≥4 mm Breslow ○ SLN-pos patients: 46%; 95%CI, 19-67% ○ SLN-neg patients: 68%; 95%CI, 40-89.5% • Meta-analysis – only performed for 4 mm category due to missing data ○ OS: HR, 2.42; 95%CI, 2.00-2.92 indicating higher risk of death in

Study Details	Primary Melanoma	SLNB details	Results Summary
			SLN-pos patients compared with SLN-neg
Cordeiro et al, 2016 [14] • Systematic review(n=60) and meta-analysis (n=60) • Search: 1980 – May 2015	• Included studies enrolling patients with thin melanomas (Breslow thickness ≥0.75 mm)	• Outcomes were proportion of SLN positivity, and proportion of patients with high-risk features – NOT our outcomes of interest	• Proportion of positive SLNs within the patients (n=10,928): 4.5%; 95%CI, 3.8-5.2%; I2=61% • Predictors of SLN positivity: ○ Thickness ≥0.75 mm: 8.8%; 95%CI, 6.4-11.2% ○ Clark level IV/V: 7.3%; 95%CI, 6.2-8.4% ○ ≥1 mitosis/mm^2: 8.8%; 95%CI, 6.2-11.4% ○ Ulceration: 5.8%; 95%CI, 3.1-8.5% ○ Microsatellites: 26.6%; 95%CI, 4.3-48.9%
Randomized Controlled Trials			
Morton et al, 2014 [13] • 10y MSLT-I • n=2001	• Localized cutaneous melanoma of Clark level III and Breslow thickness of ≥1 mm • OR melanoma of Clark level IV or V and any Breslow thickness • n=340 thin melanomas (<1.2 mm; outcomes not reported) • n=1347 intermediate thickness melanomas (1.2-3.5 mm) ○ n=814 biopsy group ○ n=533 observation • n=314 thick melanomas (>3.5 mm) ○ n=186 biopsy ○ n=128 observation	• Biopsy group: wide excision and SLNB and immediate lymphadenec-tomy for nodal metastases detected by SLNB • Observation group: wide excision and nodal observation and lymphadenec-tomy for nodal relapse • Margins of 2-3 cm recommended	• 10y melanoma-specific survival not significantly different between groups with intermediate-thickness melanoma (HR, 0.84; 95%CI, 0.64-1.09; p=0.18) ○ SLNB: 81.4 ± 1.5% ○ Observation: 78.3 ± 2.0% • 10 y melanoma-specific survival not significantly different between groups with thick melanoma • 10 yr DFS significantly higher in biopsy group with intermediate-thickness melanoma (HR, 0.76; 95%CI, 0.62-0.94; p=0.01) ○ SLNB: 71.3 ± 1.8% ○ Observation: 64.7 ± 2.3% • 10 y DFS significantly higher in biopsy group with thick melanomas (HR, 0.70; 95%CI, 0.50-0.96; p=0.03) ○ SLNB: 50.7 ± 4.0% ○ Observation: 40.5 ± 4.7% • In biopsy group, patients with SLN metastases had poorer outcomes than patients with tumour-free SLNs (intermediate thickness, p<0.001; thick, p=0.03) • Among intermediate-thickness melanoma patients with nodal metastases, 10y melanoma-specific survival was significantly higher in biopsy group (HR, 0.56; 95%CI, 0.37-0.84; p=0.006) • Among thick melanoma patients with nodal metastases, 10y melanoma-specific survival not significantly different between treatment groups (p=0.78)

Study Details	Primary Melanoma	SLNB details	Results Summary
Kimbrough et al, 2016 [27] • Reanalysis of data from Sunbelt Melanoma Trial • n=1464 ○ PCR- obs, n=908 ○ PCR+ obs, n=180 ○ PCR+ CLND or CLND+HDI, n=376	• Stage I and II melanoma patients • ≥1mm Breslow thickness • No clinical evidence of regional or distant metastasis • Wide local excision with SLN biopsy	• Serial sectioning (≥5 sections/block) with H&E • IHC for S-100 • SLN-negative by H&E and IHC underwent molecular staging • PCR for tyrosinase, MART1, MAGE3, GP-100, followed by Southern blot	• Ultra-staging with PCR used to identify high-risk patients with histologically negative SLNs • PCR-pos patients randomized to observation, CLND, or CLND and high-dose interferon • No difference in OS (p=0.792) between groups • Compared to PCR-obs and PCR+CLND, PCR+obs group showed decreased DFS (p=0.024) ○ PCR+obs vs. PCR-obs, p=0.008 ○ PCR+obs vs. PCR+CLND, p=0.022 • No significant difference in DFS for PCR+CLND and PCR-obs patients (p=0.904)

Abbreviations: CI, confidence interval; CLND, complete lymph node dissection; DFS, disease-free survival; H&E, hematoxylin & eosin; HDI, high-dose interferon; HR, hazard ratio; IHC, immunohistochemistry; MSLT-I, Multicenter Selective Lymphadenectomy Trial; neg, negative; obs, observation; OS, overall survival; PCR, polymerase chain reaction; pos, positive; SLN, sentinal lymph node; SLNB, sentinal lymph node biopsy; y, year

Surgical Margins for Melanoma of the Head and Neck

The literature search identified three small retrospective cohort studies that evaluated excision margins in patients with melanoma of the head and neck. The first study compared a wide local excision cohort to a reduced margin cohort and had a total of 79 patients in the study (Table 4-4). Patients in the reduced margin cohort were unable to receive wide local excision due to proximity of the lesion to the eyelid, nose, mouth, or auricle [9]. At 60 months of follow-up, local recurrence rates and OS were not significantly different for the wide local excision cohort compared with the reduced margin cohort (Table 4-4) [9]. This study enrolled patients with Breslow depth melanomas of <1.0 mm through >4.0 mm, but no subgroup analysis was conducted. The second retrospective study reviewed the records of 108 patients diagnosed with thick melanoma (>4.0 mm Breslow thickness) who had received complete local excision [10]. Study conductors grouped the patients into excision margins groups of 0 to 1 cm, 1 to 2 cm, and 2 to 3.5 cm and found that LR and MSS were not significantly different when the three groups were compared (Table 4-4) [10]. The final retrospective study reported on disease stage instead of Breslow thickness and reviewed the medical records of 353 patients diagnosed with stage Tis through T4 [11]. Using a histopathologic margin of ≥4 mm as the reference standard, OS was not significantly different when compared with margin groups of <1 mm, ≥1 to <2 mm, or ≥2 mm to <4 mm (Table 4-4) [11]. By Cox multivariate analysis, both ulceration and depth of invasion were predictive for reduced survival (Table 4-4) [11].

Table 4-4. Studies evaluating surgical margins for patients with melanoma of the head and neck.

Study Details	Primary Melanoma	Margins	Results Summary
Observational Studies			
Rawlani et al, 2015 [9] • Retrospective cohort • n=79	• Stage I (n=51), stage II (n=21), stage III (n=7) patients • Breslow depth: <1.0 mm (n=38),	• WLE cohort (n=42): 1 cm margins for lesions <1.0 mm thick, 1-2 cm margin for	• Compared WLE cohort to reduced margin cohort • Reduced margins used for cases where melanoma was located on or near eyelid, nose, mouth, or auricle

Study Details	Primary Melanoma	Margins	Results Summary
• Mean F/U time: 71.3 months	1.01-2 mm (n=21), 2.01-4 mm (n=12), >4.0 mm (n=8) • Melanoma located on eye (n=7), nose (n=9), ear (n=11), cheek (n=26), forehead (n=8), neck (n=11), scalp (n=7)	lesions 1.01-2.0 mm thick, 2 cm margin for lesions >2.01 mm thick • Reduced margin cohort (n=37): 0.5 cm margin for lesions ≤1 mm thick, 0.5-1.0 cm margin for lesions 1.01-2.0 mm thick, 1.0 cm margin for lesions >2.0 mm thick	• 46 patients received SLNB, with 7 positive for nodal disease • At 60-month follow-up, local recurrence rates not significantly different for WLE cohort compared with reduced margin cohort at any Breslow depth • At 60-month follow-up, overall recurrence rates not significantly different for WLE cohort compared with reduced margin cohort at any Breslow depth
Ruskin et al, 2016 [10] • Retrospective cohort • n=108 • Median F/U: 40 months	• Patients with thick (Breslow thickness >4 mm) melanoma • Median Breslow thickness: 6.0 mm • Melanoma located on scalp (n=30), face (n=48), neck (n=19)	• Patients received complete local excision • 59 patients received SLNB	• Excision margins reviewed from patient records and grouped ○ 0-1 cm, n=27 ○ 1-2 cm, n=61 ○ 2-3.5 cm, n=20 • Locoregional recurrence rates not significantly different when comparing margin groups (p=0.17) • Melanoma-specific survival not significantly different when comparing margin groups (p=0.58)
Teng et al, 2015 [11] • Retrospective cohort • n=353	• Stage Tis (n=88), T1a (n=92), T1b (n=71), T2a (n=42), T2b (n=25), T2c (n=9), T3 (n=22), T4 (n=4) patients • Melanoma located on the scalp (n=60), ear (n=66) or other head and neck location (n=227)	• Histopathologic margins of <1 mm (n=12), ≥1 mm to <2 mm (n=14), ≥2 mm to <4 mm (n=18), ≥4 mm (n=309)	• Margins ≥4 mm used as reference for OS comparison • Overall survival - HR>1 indicates worse OS compared with ≥4 mm margin group ○ Margins <1 mm: HR, 1.251; 95%CI, 0.44-3.58; p=0.677 ○ Margins ≥1 mm to <2 mm: 1.686; 95%CI, 0.69-4.13; p=0.254 ○ Margins ≥2 mm to <4 mm: 1.230; 95%CI, 0.38-3.96 • Presence of ulceration significantly increased risk of death (HR, 0.449; 95%CI, 0.26-0.77; p=0.004) • Thicker depth of melanoma invasion predicted for worse overall survival (HR, 1.313; 95%CI, 1.19-1.45; p=0.000)

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio; OS, overall survival; SLNB, sentinal lymph node biopsy; WLE, wide local excision

Sentinel Lymph Node Biopsy for Melanoma of the Head and Neck

The literature search identified one systematic review without meta-analysis, one RCT, and two diagnostic cohort studies that assessed the use of SLNB in patients with melanoma of the head and neck. The systematic review included 32 studies that tested the diagnostic

performance of SLNB [15]. The review reported a positive predictive value of 13.1% for SLNB (Table 4-5) and a false-negative rate for nodal recurrence of 20.4% (Table 4-5) [15].

The MSLT-I trial [13] included 334 patients with primary melanomas located on the head and neck [M. Faries, personal communication, June 2, 2016]. Although head and neck patients were not separately analyzed, for all enrolled patients 10-year DFS was significantly higher in the biopsy group compared with the observation group for both intermediate and thick melanomas (Table 4-5) [13], while MSS was not different between groups for either intermediate or thick melanomas (Table 4-5) [13]. For patients with intermediate-thickness melanomas with nodal metastases, 10-year MSS was significantly higher in SLNB group compared with the observation group (Table 4-5) [13]. This association was not seen in patients with thick melanomas (Table 4-5).

The identified diagnostic cohort study assessed the accuracy of SLNB in patients with head and neck melanoma. The study included any lesion located above a horizontal line passing through the superior margin of the clavicles and the 7th cervical vertebra and found that 26.3% of enrolled patients were positive for a SLN metastases, with a false-negative rate of 4.8% (Table 4-5) [16].

Table 4-5. Studies evaluating SLNB for patients with melanoma of the head and neck.

Study Details	Primary Melanoma	SLNB Details	Results Summary
Systematic Reviews			
de Rosa et al, 2011 [15] • Systematic review without meta-analysis (32 studies) • Search dates: 1990 – 2009	• Mean Breslow thickness: 2.53 mm (range, 0.02-20 mm)	• Median SLNB identification rate: 95.2% (range, 64.8-100%) • All enrolled patients underwent SLNB as a staging procedure	• Median false-negative rate for nodal recurrence: 20.4% (range, 3.3-44%) • Predictive value positive (PVP) of SLNB: 13.1% (range, 3.3-42.9%)
Randomized Controlled Trials			
Morton et al, 2014 [13] • 10 yr MSLT-I • n=2001	• Localized cutaneous melanoma of Clark level III and Breslow thickness of ≥1 mm • OR melanoma of Clark level IV or V and any Breslow thickness • n=340 thin melanomas (<1.2 mm; outcomes not reported) • n=1347 intermediate-thickness melanomas (1.2-3.5 mm)	• Biopsy group: wide excision and SLNB and immediate lymphadenec-tomy for nodal metastases detected by SLNB ○ n=193 head and neck patients • Observation group: wide excision and nodal observation and lymphadenec-tomy for nodal relapse	• 10 y melanoma-specific survival not significantly different between groups with intermediate thickness melanoma (HR, 0.84; 95%CI, 0.64-1.09; p=0.18) ○ SLNB: 81.4 ± 1.5% ○ Observation: 78.3 ± 2.0% • 10 y melanoma-specific survival not significantly different between groups with thick melanoma • 10 y DFS significantly higher in biopsy group with intermediate-thickness melanoma (HR, 0.76; 95%CI, 0.62-0.94; p=0.01) ○ SLNB: 71.3 ± 1.8% ○ Observation: 64.7 ± 2.3% • 10 y DFS significantly higher in biopsy group with thick melanomas (HR, 0.70; 95%CI, 0.50-0.96; p=0.03) ○ SLNB: 50.7 ± 4.0% ○ Observation: 40.5 ± 4.7%

Study Details	Primary Melanoma	SLNB Details	Results Summary
	○ n=814 biopsy group ○ n=533 observation • n=314 thick melanomas (>3.5 mm) ○ n=186 biopsy ○ n=128 observation • n=334 primaries located on the head and neck	○ n=141 head and neck patients • Margins of 2-3 cm recommended	• In biopsy group, patients with SLN metastases had poorer outcomes than patients with tumour-free SLNs (intermediate thickness, p<0.001; thick, p=0.03) • Among intermediate-thickness melanoma patients with nodal metastases, 10 y melanoma-specific survival was significantly higher in biopsy group (HR, 0.56; 95%CI, 0.37-0.84; p=0.006) • Among thick melanoma patients with nodal metastases, 10 y melanoma-specific survival not significantly different between treatment groups (p=0.78)
Observational Studies			
Giudice et al, 2014 [16] • Prospective cohort study (n=84) • Median follow-up: 46.4months, range 1.2-179.6 months	• ≥0.75 mm thick or with a Clark level IV or V, or a thinner melanoma with adverse prognostic features	• Lymphoscinti-graphy performed in 57 patients • Positive SLN in 15 (26.3%)	• Objective: accuracy of SLNB in head and neck melanomas • False-negative rate of 4.8% (n=4/84)

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; PPV, positive predictive value; SLN, sentinal lymph node; SLNB, sentinel lymph node biopsy; y: year

Ongoing, Unpublished, or Incomplete Studies

A search of https://clinicaltrials.gov identified one study. The MelMarT RCT (NCT02385214) is currently recruiting patients and will randomize patients with melanoma of ≥1 mm Breslow thickness to either 1 cm or 2 cm excision margins. The trial aims to recruit 9684 patients, including 6968 in the intermediate-risk group and 2896 patients in the high-risk group (MelMarT Trial website).

DISCUSSION

In 2010, the Melanoma DSG developed a systematic review and clinical practice guideline to provide healthcare providers with guidance on optimal primary resection margins and the use of SLNB in patients with cutaneous melanoma located on the trunk or extremities. The current systematic review sought to update the original evidentiary base and determine whether refinements to the original recommendations were appropriate. Due to a lack of evidence, patients with head and neck melanomas were outside the scope of the original 2010 guideline. These patients have been added in this guideline update.

Primary Excision Margins

Historically, standard therapy for primary cutaneous melanoma involved wide excision with radial margins up to 5 cm or greater without evidence to support the practice. The 2010 guideline concluded that wide margins did not confer an OS benefit in patients with clinically

node-negative melanoma on the trunk and extremities and recommended margins ranging from 5 mm to 2 cm, depending on the thickness of the melanoma.

Data identified in this update from a systematic review and meta-analysis [1] could potentially change practice and the Working Group members interpreted the data with extreme caution. The meta-analysis found that for all patients, OS and RFS were not different when narrow margins were compared with wide margins, but MSS was improved with wide margins [1]. By Bayesian likelihood plots, the systematic review reported a high probability that narrow margins were worse than wide margins for OS, MSS, RFS, and LR [1]. A Cochrane Systematic Review [29], which the Wheatley et al. systematic review with meta-analysis [1] updated, similarly reported no difference in OS or RFS for narrow (1-2 cm) compared with wide (3-5 cm) margins. In the knowledge of the Working Group, the Wheatley meta-analysis [1] provides the first data ever published that indicated narrow margins are not safe and refutes clinical practice guidelines from worldwide organizations. Local recurrence rates around the primary lesion are approximately 5% [8].

When comparing ranges of excision margins across all melanoma depths, the meta-analysis reported no significant difference in OS or LR when comparing margin subgroups of 1 cm vs. 3 cm, 2 cm vs. 4 cm, or 2 cm vs. 5 cm [1]. However, when the six individual RCTs are examined (Table 4-6), of the approximately 4000 patients included across the six studies, few patients (n=758) received 1 cm margins. In most of the studies, the narrow margin was 2 cm. When performing wide local excision with 2 cm margins, primary closure is usually possible and low morbidity is generally achieved; however, if the recommended margin was increased to 3 cm, this would result in many more patients requiring more complex closures such as skin grafts or flaps and could lead to higher morbidity. In fact, the Hayes et al. RCT, which compared 1 cm with 3 cm margins, reported an 8% complication rate following excision with 1 cm margins and a 15% complication rate following excision with 3 cm margins [6]. National guidelines from Australia [21], Germany [30], and Switzerland [31] all recommend margins of 1 to 2 cm based on the Breslow thickness. The 2010 United Kingdom guideline extends margins to 2 to 3 cm for melanoma of 2.01 to 4.0 mm thickness and 3 cm for melanoma of >4.0 mm thickness [32].

The meta-analysis also conducted subgroup analysis for thin melanoma (<2 mm) and thick melanoma (≥2 mm) and compared narrow margins of 1 to 2 cm with wide margins of 3 to 5 cm [1]. For both thin and thick melanoma, the meta-analysis found no significant difference in OS for narrow compared with wide margins and concluded that there is no evidence that treatment effects differed by Breslow thickness [1]. However, when patients enrolled in the six RCTs are examined (Table 4-6), of the approximately 4000 patients pooled, there were few patients with melanoma depths of <1 mm (n=518). These considerations make it difficult to consider the need for 3 cm margins in patients with melanomas <1 mm.

The Working Group weighed the meta-analysis data [1], including patient numbers within each depth range, against the morbidity of larger margins and believed that more confirmatory data are needed before practice change can be recommended. Confirmatory data would preferentially be in the form of an RCT designed to compare 1 cm, 2 cm, and 3 cm margins.

For melanoma in situ and thick melanoma of 2.01 to 4.0 mm, the Working Group, in addition to reviewing the literature, discussed their experience using the previous recommendations for six years, and through a consensus-based process decided to refine the recommendations. For melanoma in situ, the original recommendation of 5 mm was based on consensus of the Australia/New Zealand guideline developers and adopted. Experience with a 5 mm margin led the Working Group to increase the recommended margin to a range of 5 mm to 1 cm. This consensus opinion can be backed with evidence from Mohs micrographic surgery, which included 1072 patients with 1120 lesions. Of the 1120 lesions, 451 (40.2%) lesions were located on the truck, extremities, hands, feet, and palms; and 668 (59.6%) were located on the

scalp, face, and neck. A 9 mm margin resulted in complete clearance of 99% for melanoma in situ located on multiple locations of the body, including the in situ lesions located on the trunk and extremities [3]. Similarly, for melanoma of 2.0 to 4.0 mm thickness, the margin recommendation has been increased from 1 to 2 cm to 2 cm.

In the current version of the guideline, the Working Group has added the head and neck population. The evidence identified to inform a recommendation on appropriate margins for melanoma located on the head and neck specifically was of low quality. Based on the biological similarities between melanoma located on the head and neck and melanoma located on the trunk and extremities, the Working Group felt comfortable adopting the key evidence and resultant recommendation for the melanoma on the trunk and extremities, with an exception. It is recognized that wide margins are not always possible with these patients and, thus, wide margins should be employed whenever possible, but may be unachievable when melanoma is located on the eyelid, nose, lips, or ear. There were no studies identified to inform a recommendation for melanoma in situ; however, based on the clinical experience of the Working Group members, the original recommendation of 5 mm does not lead to complete clearance. The Working Group borrowed knowledge from Mohs micrographic surgery, which has studies indicating that margins of 1.5 to 2.1 cm are required to achieve complete clearance in 100% of melanoma in situ patients [3,12], and through a consensus process, increased the recommended margin from 5 mm, up to a range of 5 mm to 1 cm.

Table 4-6. Studies included in the Wheatley et al. [1] meta-analysis.

Study	Margins	Breslow Thickness	Sample Size
WHO melanoma trial	Narrow: 1 cm Wide: 3 cm	≤1 mm	n=359 (narrow margin, n=186; wide margin, n=173)
		1-2 mm	n=253 (narrow margin, n=119; wide margin, n=134)
Swedish I	Narrow: 2 cm Wide: 5 cm	0.8 mm – 2.0 mm	All patients (n=989) with median thickness of 1.2 mm; n=476 narrow margin and n=513 wide margin
Intergroup melanoma trial	Narrow: 2 cm Wide: 4 cm	1-4 mm	n=740 total patients with individual thickness characteristics not reported
European /French trial	Narrow: 2 cm Wide: 5 cm	≤0.5 mm	n=18 (narrow margin, n=8; wide margin, n=10)
		0.51 - 1.0 mm	n=141 (narrow margin, n=72; wide margin, n=69)
		1.01 – 1.5 mm	n=106 (narrow margin, n=51; wide margin, n=55)
		≥1.51 mm	n=61 (narrow margin, n=30; wide margin, n=31)
UK trial BAPS/MSG	Narrow: 1 cm Wide: 3 cm	<2.0 mm	n=3 (narrow margin, n=1; wide margin, n=2)
		2.0 - 2.5 mm	n=305 (narrow margin, n=160; wide margin, n=145)
		2.6 - 3.0 mm	n=159 (narrow margin, n=83; wide margin, n=76)
		3.1 – 4.0 mm	n=192 (narrow margin, n=93; wide margin, n=99)
		>4.0 mm	n=242 (narrow margin, n=116; wide margin, n=126)
Swedish II	Narrow: 2 cm Wide: 4 cm	2.0 – 3.0 mm	n=460 (narrow margin, n=230; wide margin, n=230)
		>3.0 mm	n=474 (narrow margin, n=233; wide margin, n=241)

Abbreviations: BAPS, British Association of Plastic Surgeons; MSG, Melanoma Study Group; WHO, World Health Organization

Sentinel Lymph Node Biopsy

All patients with melanoma >1.0 mm in thickness and with no clinical evidence of nodal metastasis should be given the opportunity to discuss SLNB. SLNB is performed to provide information on staging and prognosis, and to identify patients who may benefit from adjuvant

therapy or clinical trials. This conclusion has not changed since the 2010 guideline. Although the MSLT-I trial did not report on OS at 10 years, it reported a MSS benefit for patients with intermediate–thickness melanomas with nodal metastases and improved locoregional control for patients with melanomas 1.2 mm through greater than 3.5 mm thickness on the trunk and extremity or head and neck. Based on the MSLT-I results, the Working Group feels confident recommending SLNB for patients with 1.0 to 4.0 mm-thick melanoma to provide locoregional control, but again note that there is no OS benefit reported. For patients with 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. Lastly, based on the Cordeiro systematic review with meta-analysis [14], in patients with thin melanomas (thickness ≥0.75 mm), Clark level IV/V, high mitotic rates, ulceration, and microsatellites indicate a higher chance for SLN positivity and, thus, physicians may discuss SLNB with these patients. When discussing melanoma located on the head and neck alone, the available data indicate a higher chance for false negatives [15,16] when using SLNB in head and neck patients. Thus, caution should be used when using SLNB in these patients. To help minimize the number of false negatives, the Working Group suggested the following: performing SLNB in high-volume centres (>50 cases) [4]; the utilization of a dual tracer technique with Tc99 and blue dye to improve the detection rate of SLN [5]; and the use of single-photon emission computed tomography/computed tomography, which may improve the identification of SLNs in head and neck areas [33].

CONCLUSIONS

There is still insufficient evidence to indicate that use of wide radial excision margins of >3 cm confers an OS advantage in patients with clinically node-negative cutaneous melanoma of the trunk and extremities, or head and neck. Margins ranging from 5 mm to 1 cm for melanoma in situ and from 1 to 2 cm, depending on the thickness of the melanoma, are sufficient. SLNB provides staging and prognostic information and should be discussed with all patients with melanomas of ≥1.0 mm thickness and when features indicate a high risk for SLN positivity for patients with melanoma <1.0 mm in thickness. SLNB is indicated for locoregional control and improved MSS as well as prognostication in patients with melanoma located on the trunk and extremities, and the head and neck; however, SLNB does carry a high false-negative rate when used in the head and neck areas.

Primary Excision Margins and Sentinel Lymph Node Biopsy in Cutaneous Melanoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the nine members of the GDG Expert Panel, seven members cast votes and two abstained, for a total of 78% response in January 2017. Of those that cast votes, seven approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. I found the recommendations for the in situ margins vague and somewhat nebulous. We are providing a range of 5 mm to 1 cm and I do not see anything to distinguish 5 vs. 1 cm. Wouldn't we rather say the recommendation is for 9 mm to 1 cm, unless prohibited by the location of the lesion, in which case the recommendation is for a minimum of 5 mm? I think it would be more precise. "There were no studies identified to inform a recommendation for melanoma in situ; however, based on the clinical experience of Working Group members, the original 2010 recommendation of 5 mm does not always lead to complete clearance. The Working Group borrowed knowledge from Mohs micrographic surgery literature, which has studies indicating that margins of 9-10 mm achieve a complete clearance rate of 92-99% in melanoma in situ patients [5,9], and through a consensus process, increased the recommended margin from 5 mm, up to a range of 5 mm-1 cm"	The margin for in situ melanoma was based on version 1 of this Guideline, which endorsed the recommendations of the Australia/New Zealand guideline, which was a margin of 5 mm. This margin continues to be endorsed; however, based on recent evidence from pathologic case studies [3,12] and a consensus among Working Group members, it was increased to a range of 5 mm to 10 mm. It is understood that wider margins may not be possible, particularly in areas on the head and neck, because of this a qualifying statement was added: *"It is recognized that wide margins may not always be possible based on the location of melanoma in relation to facial structures. When possible, wide margins should be employed; however, they may be difficult to achieve when melanoma is located on the eyelid, nose, lip, or ear."*
2. Recommendation 3: Should DFS be mentioned in T3 and T4 category as this is improved by SLNB?	DFS was not significantly improved for thick melanomas, only intermediate. This has been clarified in the text.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in December 2016. The RAP Approved (n=2) and Conditionally Approved (n=1) the document in December 2016. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. In the table below (Table 4-1; page 15) you refer to studies as meta-analysis – here you refer to them as systematic reviews. Please be consistent. You could say systematic reviews with meta-analyses, or something similar.	We have updated the table for clarity.
2. Regarding surgical margins of melanoma of the truck and extremities: does the case-control study matter given your systematic review with meta-analysis and your RCT?	The case-control study referred to deals with melanomas <1 mm thickness. Outcomes for this thickness were not defined in the systematic review with meta-analysis [1], so therefore the case-control study was retained.
3. Where is the old PEBC systematic review in all of this?	The studies that were used as the evidentiary base for version 1 of this Guideline were included in the systematic reviews that were included in the present update. Therefore, through these systematic reviews, the older studies have been included in the current report and we have not disregarded them. Where possible, we have tried to make this association clearer in the text.
4. It is a little confusing to me as to how the evidentiary basis for the 2010 guideline is being integrated into the 2016 guideline. I have the 2010 document as a separate document. Is it to be inserted into the 2016 document via a link in the technical considerations and in the systematic review section? If that is what will occur then I am fine with that.	Please see above. We have made this clearer in the text. The original (version 1) will be hyperlinked to the present Guideline.
5. Agree but wonder whether, in the absence of explicit evidence for the melanoma 1-2 mm thickness, whether the consensus should have been for a 2 cm margin whenever possible, especially as it is stated that most studies use as the narrowest margin of 2 cm.	The original 1-2 cm margin was from the previous version of the guideline and we continue to endorse this; however, we recognise that there is a lack of evidence regarding the optimal margin. To help remedy this we have the following qualifying statement: *Where possible, it may be desirable to take a wider margin (2 cm) for these tumours depending on tumour site and surgeon/patient preference, because evidence concerning optimal excision margins is unclear.*
6. Because of the multiple numbers related to depth of lesion and width of resection margin, it would be helpful to be very explicit as to when the document is referring to thickness.	We have updated the Guideline for clarity where appropriate.
7. I would like more clarity about how the recommendation for melanomas 1-2 mm thickness and a resection margin of 1-2 cm was made. What were the factors that lead to a consensus of a recommendation for 1-2 cm as opposed	Please see response to Comment 5.

Comments	Responses
to a 2 cm recommendation in the absence of evidence that a narrower margin is sufficient and leads to an equivalent outcomes? Would it not be more appropriate to err on the side of the wider resection margin until data show that a narrower margin is adequate?	
8. Why were gynecological melanomas excluded? Most gynecological melanomas are vulvar and they do have a node basin.	Due to the unavailability of evidence and the unique nature of these melanomas (type, treatment modality), we have determined them to be outside the scope of this Guideline.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

5 targeted peer reviewers from Ontario, 1 from Alberta, 1 from the U.K, 1 from Australia and 1 from the USA who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. 6 agreed to be the reviewers (Appendix 1). 6 responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=6)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	1	3	2
2. Rate the guideline presentation.	0	0	0	3	3
3. Rate the guideline recommendations.	0	0	1	4	1
4. Rate the completeness of reporting.	0	0	1	3	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	5	1
6. Rate the overall quality of the guideline report.	0	0	1	4	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	1	2	2
8. I would recommend this guideline for use in practice.	0	0	1	2	2
9. What are the barriers or enablers to the implementation of this guideline report?	*Barriers*: • OR time				

	• Melanoma Quality-Based Procedure implementation • Access to single-photon emission computed tomography/computed tomography (SPECT/CT) as a component of lymphscintigraphy (very valuable to improve accuracy of SLN identification) • Limited volumes of SLNB cases or the lack of a clinical mentorship program to facilitate the goal of 50 SLNB per clinician. • Penetration of guideline use may be hampered by the inability to assess compliance with guidelines in certain clinical settings (e.g., dermatology offices). At least, those types of facilities are not well monitored in the United States. Conditions may be different in Ontario. *Enablers*: • These guidelines should be widely disseminated to the non-academic centres to ensure greater standardization in approach. • Easily accessible guidelines, clearly written and detailed systematic review.

Table 5-4. Responses to comments from targeted peer reviewers.

COMMENTS	RESPONSES
Reviewer 1 (Greg McKinnon – general surgeon)	
Regarding the qualifying statements for recommendations 3 and 4:"a double dye technique increases the identification rate of SLN's" and cites ref 12, a report on the Sunbelt trial. This study compared the number of hot nodes removed with false negative rate but did not compare gamma counter versus gamma counter plus blue dye. The downside of blue dye use is a .17% allergy rate (MSLT-1), unsafe in pregnancy and possible tattoing of non-resected tissue, particularly in the head and neck. Most studies recommending it come from early in the experience of using SNB in melanoma. Furthermore, only 59% of all SN's inI the head and neck were stained blue. Visible dye adds little to the procedure, particularly in the head and neck.	We acknowledge the shortcomings of blue dye (allergy rate, unknown safety in pregnancy, and tattooing of non-resected tissues); however, the Working Group based this qualifying statement on data from the utilization of blue dye in breast cancer where it increases accuracy. (The Expert Panel on SLNB in Breast Cancer. Sentinel lymph node biopsy in early-stage breast cancer. George R, Kennedy E, reviewers. Toronto (ON): Cancer Care Ontario; 2009 Jul 14 [Ed & Info 2016 August]. Program in Evidence-based Care Evidence-based Series No.: 17-5 Education and Information 2016). It is felt that the utilization would be similar in melanoma and increase accuracy, particularly in the head and neck and with low volumes.
Re interpretation of evidence for Recommendations 1 and 2, the document states that the Working Group "applied knowledge from the Mohs micrographic surgery literature" to determine margin of excision guidelines. I am uncertain why Mohs surgery is not explicitly stated in the recommendations as an acceptable method of primary tumor control, particularly in the head and neck. Under "qualifying statements for Recommendation 2", it does refer to "margin-controlled" excision. Is this the same thing? If so clarification would be helpful.	The PEBC is currently developing a Guideline for the use of Mohs micrographic surgery in skin cancer. This document will provide evidence-based recommendations pertaining to the utilization of Mohs in melanoma. Recommending a particular mode to achieve narrow margins is outside of the scope of this Guideline; however, we have updated the guideline to clarify what is meant by "margin-controlled" surgery.
Reviewer 2 (Kevin Higgins)	
No additional comments (identified barriers to implementation, see Table 5-3, above).	-
Reviewer 3 (Kathryn Roth)	
A small recommendation: Should specify that the Head & Neck recommendations are for Cutaneous Melanoma (as opposed to Mucosal)	Thank you. This has been added for clarification.
Should a caveat be written regarding the sentinel node biopsy rationale? This is currently bolstered by the results arising from the MSLT-I trial. We are awaiting the publication of interim results reporting from MSLT-II regarding randomized patients with positive sentinel node biopsy to either completion lymphadectomy vs. observation.	The MSLT-II trial is outside the scope of this Guideline. We are currently updating PEBC Guideline 8-6 which pertains to the surgical management of patients with lymph node metastases from cutaneous melanoma in the trunk or extremities.

COMMENTS	RESPONSES
There is some conflicting evidence as to whether completion lymph node dissection is necessary if a positive sentinel node is identified. It is felt that the results from MSLT-II could be change practice significantly if no survival benefit is shown. (see below). *This could also be listed in Section 4, Page 14 Research Questions in order to highlight this area of persistent controversy. Similarly, the Wheatley study discussed in Section 4, Page 27 could also be placed in the Research questions category. Survival of SLNB-positive melanoma patients with and without complete lymph node dissection: A multicenter, randomized DECOG trial. Meeting: 2015 ASCO Annual Meeting Abstract Number: LBA9002 Leiter, U et al. J Clin Oncol 33, 2015 (suppl; abstr LBA9002)	Please see above.
Recommendation 4 – SLNB of Melanoma located on the Head and Neck (bottom of page 7): Last bullet. Is there a way to further emphasize this particular recommendation? As a surgeon who sees a high volume of revision cases, it strikes me that this may not be a well known recommendation among our community practice colleagues. * I suggest a more strongly worded statement regarding SLNB at the time of the WLE and to have it placed among the primary recommendations.	The Working Group does agree that the SLNB should be performed at the same time as wide local excision; however, due to the lack of evidence to support this and because it is outside the scope of the recommendations we do not feel that it should be placed among the primary recommendations.
Regarding the Concluding statements (Section 4: page 29): Should emphasize the SLNB technique as being critical to the success of SLNB in the head and neck region. May wish to edit "however, SLNB does carry a higher false-negative rate when used in the head and neck areas.	We agree, and feel that this is effectively communicated in the Guideline.
It may be valuable to provide some additional evidence for the Page 8 Technical Considerations (which will likely appear as a hyperlink). *In particular, the depth of excision recommendations "down to, but not including, the fascia." This should be brought forward into the Margin Recommendations section with supporting evidence highlighting this; as nowhere else in the guidelines are	These technical considerations (with minor Working Group revisions) were carried over from the 2010 guidelines, which were adapted from the Australian Guidelines on Melanoma.

COMMENTS	RESPONSES
the Deep Margins discussed in any detail. This can frequently be the source of recurrence and the need for revision surgery and affects the ability to accurately stage.	
Section 2: Guideline – Apr 20, 2017 Page 6, Recommendation 3. Qualifying statements. 2nd bullet. Please clarify was is meant by the statement "……MSS benefit for SLNB (OS) not reported	This was an error and has been corrected.
Reviewer 4 (David Gyorki)	
The guideline development process appears comprehensive. The European guidelines from 2012 as well as the updated Australian guidelines (2016) provide a similar framework to the CCO guideline process. It is unclear why "a search of existing guidelines for adaptation failed to identify a source document (pg 14)". It is unclear from the document whether relevant consumer groups were consulted for the guideline process or whether a separate consumer document will be prepared. As key stakeholders in the guideline process, the views of stakeholders would be essential.	Australian guidelines were not publically available at the time of this guideline development; however, upon review the Working Group is confident that the recommendations within this Guideline are in line with the recommendations from the Australian Guideline: Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the Diagnosis and Management of Melanoma. Sydney: Cancer Council Australia. [Version URL: http://wiki.cancer.org.au/australiawiki/index.php?oldid=159263, cited 2017 Jun 29]. Available from: http://wiki.cancer.org.au/australia/Guidelines:Melanoma. A patient representative (Annette Cyr) was part of the Expert Panel, which is responsible for reviewing the final draft of the Guideline prior to it being released for External Review.
The layout of the recommendations is somewhat confusing. The heading 'recommendation' and then subsequent subheadings 'qualifying statements' and 'key evidence' are in places contradictory. For example for recommendation 3, the main recommendation states that "patients should be given the opportunity to discuss SLNB". The subsequent qualifying statement for pT2 and pT3 melanoma says "SLNB is recommended". In the "interpretation of evidence for recommendation 3", the authors write that they are "confident in recommending SLNB for patients with melanoma 1.0-4.0mm thick". These are fundamentally different strengths of recommendation and therefore the main recommendation should	This layout is standard in all PEBC Guideline documents.

COMMENTS	RESPONSES
be changed to be consistent with the interpretation and include the word "recommended".	
There are some areas where the guidelines are unclear. eg: pg4 qualifying statement for recommendation 2. Does 'margin controlled excision' refer to Moh's surgery? The evidence for this is poor and including this in the guidelines to be performed outside of selected expert centres has inherent risks for patient care. pg 5/6 - recommendation 3: pT2 and pT3 - "identify patients who may benefit from adjuvant therapy or enrolment in clinical trials". The same recommendation should be extended to pT4 patients as they may also be excluded from clinical trials without appropriate staging using SLNB. pg 6 qualifying statement for recommendation 3. "For patients with intermediate thickness melanomas with nodal metastasis... there is a MSS benefit..." It is unclear what this sentence is referring to. Does it mean compared to not having SLNB?	Pg 4 – The guideline deals with excision margins only, not the method used to achieve this margin. Evidence is not sufficient to declare the superiority of one method over the other; however, we have clarified what it meant by "margin-controlled surgery". Page 5/6 – We agree with this and have changed the Guideline accordingly. Page 6 – Thank you, we have corrected this for clarity.
Key evidence for Recommendation 3 refers to a meta-analysis demonstrating that OS was reduced in patients with positive SLNB. This was also demonstrated in a separate meta-analysis (not discussed - Gyorki et al. Ann Surg Oncol 2016). Some mention of the use of SPECT/CT in the 'technical considerations section on page 8 would be useful. Reference should be made to the updated AJCC VIIIth edition, in particular the revision of cut point for stage IA melanoma at 0.8 mm.	We are pleased that this meta-analysis arrived at the same conclusions as this Guideline. This paper would be included in any subsequent update, provided it meets the inclusion criteria. The use of SPECT/CT is discussed in the Discussion in Section 4 as a way of reducing false negatives. Because the technical considerations are carried over from the 2010 review with some minor changes, the evaluation of the use of SPECT/CT was not within the scope of the current literature review. At the time of publication, the new AJCC VIIIth edition was not publically available to the Working Group. Once published, if the Working Group feels that the new cut-offs would make the recommendations incorrect, the Guideline will be updated.
When discussing the Wheatley et al. paper (page 3), it is also important to note that no difference seen in RFS between narrow and wide margins, therefore raising questions about the validity of MSS result.	We agree and this is reflected in the interpretation of evidence.

COMMENTS	RESPONSES
Page 16 Introduction - "approximately 20% (of patients with stage I and II melanoma) have subclinical involvement." This is a major overstatement. In MSLT-1, 16% of patients with melanoma 1.2 to 3.5 mm had subclinical nodal involvement. This population represents this highest risk, approximately one-third of patients with stage I and II melanoma; therefore, the total fraction would be well under this.	Thank you, we reviewed the MLST-I information and have corrected page 16.
Reviewer 5 (Mark Faries)	
This was a good job of creating sensible recommendations where the data can be incomplete. There is some concern in prominently citing the Freeman "meta-analysis" in dermatologic surgery, which appears to be highly biased and with exclusion of numerous large studies based on unclear criteria. The data and conclusions of that paper are generally well outside generally accepted conclusions on the same subjects.	Thank you, we agree with your comments and have outlined our confidence in the studies as best as possible in Appendix 4 and 5.
The process was clearly documented and transparent. One area that might be considered in the determination of indications for SLNB in thin melanoma are series that use nodal recurrence in patients who do not undergo initial surgical staging of regional nodes. There are numerous such series with relatively large sample sizes. These series are also not troubled by the inherent selection bias of SLNB series (i.e., those patients in the series were already selected for SLNB for one reason or another, and may not be representative of the overall thin melanoma population.)	Thank you, and we agree with your comments.
One area that is not dealt with in the selection of patients for SLNB is the issue of age. This appears to be related to the absence of an age-related analysis in the systematic review that was cited. However, both for thin melanomas and for other primary tumor groups, age has a strong effect on the likelihood of nodal metastasis. The panel might consider mentioning this.	Sub-analysis of different age groups was not within the scope of this guideline; however, the SLNB studies included in the Guideline enrolled patients 75 years and younger.
The distinction between clinical margins and pathologic margins is accurately noted in the guideline, but might be emphasized. There are very limited data on adequate pathologic margins.	We agree and have emphasized that we are referring to clinical margins when possible.

COMMENTS	RESPONSES
Confusion on this issue may lead some to re-excise sites based on pathology measures, which is probably not generally appropriate.	
Regarding melanoma in situ margins, the guideline has now expanded the margin from 5 mm to 5 to 10 mm. The supporting data seem to relate to the amount of clinical margin needed to achieve negative pathologic margins. While wider clinical margins will be more likely to result in an initial negative pathologic margin, they will also engender additional morbidity, often in patients who did not need the wider clinical margin taken. I think this may suggest that the critical recommendation would be for thorough pathologic assessment of margins, rather than wide clinical margins from the outset.	This has been emphasized in the guideline.
There is also no comment about appropriate pathologic assessment technique (e.g., does the panel recommend frozen section as acceptable?) The issue is often difficult in heavily sun-damaged, head and neck, and lentigo maligna cases. This may be more critical for avoiding local recurrence than the clinical margin measured by the surgeon. I am not sure whether pathology is out of scope for this guideline, but I would consider it an important point to note in the margins discussion.	We agree, however, this is outside of the scope of the Guideline. Many of the included studies refer to having expert pathologic analysis. We advocate the need for an expert pathologist to examine clinical margins, especially in complex cases.
Reviewer 6 (An-Wen Chan)	
Pages 5 and 28: "Based on the biological similarities between melanoma located on the head and neck and melanoma located on the trunk and extremities…" Should a reference be provided for this statement? There is evidence that head and neck melanomas have poorer prognosis.	This statement is based on the expert opinion of the Working Group, which included three surgeons with expertise on head and neck melanoma.
Page 5 and 7, Recommendations 3 and 4 for intermediate-thickness melanoma: "SLNB does provide an MSS benefit if the sentinel node contains melanoma metastases" This assertion is strongly stated as fact but is based on flawed data from MSLT-I. The methodological problems with this conclusion have been detailed in the literature, but essentially there are two major biases that persist in the latest paper: a) The cut-offs defining intermediate thickness (1.2-3.5 mm) are odd, having never been used in staging or other studies. This led to one-third of the randomized patients being excluded from the MSLT-I papers	We have outlined our confidence in the included RCTs in Appendix 5 and the potential weaknesses in the evidence have been outlined in the body of the Guideline. The subgroup analysis was planned and the study also includes a Supplementary appendix which includes a comparison of 1.2 to 3.5 mm thicknesses versus patients with 1.4 to 4.0 mm thicknesses; the results were similar.

COMMENTS	RESPONSES
(their melanoma thickness was not between 1.2-3.5 mm). The entire paper is thus a subgroup analysis and raises suspicion of data mining (i.e., testing various cut-offs until a significant result is found). b) This result for intermediate-thickness melanoma with nodal metatastases is a subgroup analysis of a subgroup, which is highly prone to bias. It is also telling that MSLT-I did not report 10-year OS. The guideline's statement about this MSLT-I result needs to be qualified with recognition that a subgroup analysis cannot provide definitive answers. The recommendation for intermediate-thickness melanomas should thus mirror the other thicknesses – i.e., physicians should discuss SLNB. The evidence does not support the current wording that SLNB is recommended for these patients with intermediate thickness. Recommendation 4 is particularly problematic, as the uncertainty of SLNB on the head and neck is even greater. This is recognized on page 29 ("caution should be used when using SLNB in these patients") but is not translated to a cautious recommendation for intermediate-thickness head and neck melanomas.	
The guideline lacks any discussion of the potential complications of SLNB, particularly when it leads to lymphadenectomy. The harms and benefits should be weighed, particularly given the lack of benefit of SLNB in terms of OS.	PEBC has a guideline that specifically pertains to lymphadenectomy (PEBC Guideline 8-6: Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities). It is currently undergoing an rapid update to include the data from the recent publication of the MSLT-II trial.
Page 26, Ongoing Studies: Is MSLT-II relevant?	Please see above.
Page 46, Risk of Bias assessment for Morton 2014: Given that OS is not reported in the paper, the Selective Reporting domain cannot be rated as 'low risk.' Also, in terms of 'Other bias', major concerns remain (see my comment #2 above).	See above regarding confidence in MSLT-I trial.
The depths defining pT1-3 stages are incorrect in the recommendation tables and Page 14. pT1 should include 1 mm, pT2 should start at 1.01 mm, and pT3 should start at 2.01 mm.	We have clarified this in the Guideline.
Page 4: "For melanoma in situ, margin-controlled excision may provide tissue sparing and improved tumour clearance in challenging locations such as near the eye, nose, lips, and ears."	Recommending one type of margin-controlled excision technique is outside the scope of this Guideline. We have tried to provide clarification on the different types of margin-controlled excision where applicable.

COMMENTS	RESPONSES
Margin control only leads to tissue sparing if a smaller initial margin size is used (i.e., <5 mm), and only improves tumour clearance if circumferential margin control is performed (i.e., en face histologic sectioning of peripheral margins rather than standard breadloafing). In terms of preserving normal anatomy and function, the main advantage of margin control is that it allows for optimal reconstruction by avoiding situations where a complex immediate reconstruction is performed with subsequently positive margin status. I suggest re-wording as follows: "For melanoma in situ, margin-controlled excision may facilitate optimal reconstruction with clear margins in challenging locations such as near the eye, nose, lips, and ears. Circumferential margin control with en face tissue sectioning may provide improved tumour clearance."	
Pages 5 and 7: Please clarify that Recommendations 3 and 4 applies only to localized melanoma (stage I or II) but not stage III or IV.	We have clarified this. These recommendations apply only to clinical stage I and II when clinically node negative.
Pages 6 and 8, Recommendations 3 and 4: "SLNB is less reliable or may fail when performed as a separate operation for a patient having already had their wide local excision and repair with rotation flap or skin graft". Isn't this a problem with any flap (e.g., transposition) rather than just rotation flaps?	The Working Group feels that anything but an advancement flap is safe, and transposition flaps are used commonly in the face. We have clarified this in the qualifying statements for Recommendations 3 and 4.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All surgical oncologists, surgeons, dermatologists, and plastic surgeons specializing in melanoma and/or head and neck cancers or with an interest in melanoma in the PEBC database were contacted by email to inform them of the survey. In total, 71 professionals were contacted. Seven (9.8%) responses were received. The results of the feedback survey from seven people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 7 (9.8%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	5	2
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	1	6
3. I would recommend this guideline for use in practice.	0	0	0	2	5
4. What are the barriers or enablers to the implementation of this guideline report?	**Barriers:** • Some centres probably do not reach the 50 case threshold for SLN biopsy. If these centres stop doing SLN biopsy, this will increase the demand on larger centres and could affect patient wait times. • Ability to primarily close wider defects. • Its dissemination to all the physicians and surgical disciplines listed at the beginning of the guideline that is critical to its implementation. Is there a way of having them acknowledge reading the report? I would also add pathologists to your list of readers. • I do not anticipate any barriers to the implementation of this guideline. It is straightforward and the modifications are fairly minor and are somewhat flexible. As always, these guidelines are to be incorporated In discussions with individual patients to guide their management. • I do not see any barriers--just getting the word out. I think surgeons will be very happy to adopt these guidelines.				

	• NO significant barriers. Easy web access would continue to be helpful.

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Comments on nail bed melanomas or melanoma in situ for amputation	These cases should be assessed by a multidisciplinary team.
2. Updates on changing information would be helpful as they occur, i.e., is there really any survival benefit to sentinel biopsy in patients with node-negative intermediate-thickness melanoma who go on to have completion lymphadenectomy.....	We have a system in place at PEBC where documents are updated as new and practice-changing evidence becomes available.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Working Group Members

Name and Expertise	Affiliation	Conflict of Interest
Frances Wright, Surgical Oncologist	Sunnybrook Cancer Centre Toronto, ON	No conflict declared
Alexandra Easson, Surgical Oncologist	Princess Margaret Hospital Toronto, ON	No conflict declared
Christian Murray, Dermatologist	Skin Surgery Centre, University of Toronto Toronto, ON	No conflict declared
John Toye, Plastic Surgeon	Plastic Surgery Practice Orillia, ON	No conflict declared
David McCready, Surgical Oncologist	Princess Margaret Hospital Toronto, ON	Has provided guidance on SLNB as standard of care
Carolyn Nessim, Surgical Oncologist	Ottawa Hospital Ottawa, ON	No conflict declared
Danny Ghazarian, Pathologist	Toronto General Hospital Toronto, ON	No conflict declared
Nicole Look Hong, Surgical Oncologist	Sunnybrook Cancer Centre Toronto, ON	No conflict declared
Stephanie Johnson, Surgeon (H&N expertise)	Ottawa Hospital, Toronto, ON	No conflict declared
David Goldstein, Surgeon (H&N expertise)	University Hospital Network Toronto, ON	No conflict declared
Teresa Petrella, Medical Oncologist	Odette Cancer Centre Toronto, ON	No conflict declared
Lesley Souter, PEBC Methodologist	Juravinski Hospital, Hamilton, ON	No conflict declared
Sarah Kellett PEBC Methodologist	Juravinski Hospital, Hamilton, ON	No conflict declared

Report Approval Panel Members

Name and Expertise	Affiliation	Conflict of Interest
Dr. Melissa Brouwers	Program in Evidence Based Care, CCO Hamilton, ON	No conflict declared
Dr. Lorraine Elit	Juravinski Hospital, Hamilton, ON	No conflict declared
Dr. William Evans	Department of Oncology, McMaster University, Hamilton, ON	No conflict declared

Expert Panel Members

Name	Affiliation	Conflict of Interest
Timothy Hanna	Cancer Research Institute at Queen's University Kingston, ON	No conflict declared
Xinni Song	The Ottawa Hospital Ottawa, ON	No conflict declared
Annetter Cyr	Melanoma Network of Canada Toronto, ON	No conflict declared
Tara Baetz	Cancer Center of Southeastern Ontario Kingston, ON	No conflict declared
Gregory Knight	Grand River Regional Cancer Centre Kitchener, ON	Declared financial and/or material support of $5000 or more in a single year.

Name	Affiliation	Conflict of Interest
Alexander Sun	Princess Margaret Hospital Toronto, ON	No conflict declared
Caroline Hamm	Windsor Regional Cancer Centre (WRH) Windsor, ON	No conflict declared
Pablo Cano	Sudbury Regional Hospital Sudbury, ON	No conflict declared
Sudha Rajgopal	Trillium Health Partners - Credit Valley Hospital Site Toronto, ON	No conflict declared

Targeted Peer Reviewers

Name	Affiliation	Conflict of Interest
Greg McKinnon	Division Head of Surgical Oncology University of Calgary Calgary, Alberta, Canada	Co-investigator (not PI) of MSLT-I and MSLT-II trials
Kevin Higgins	Head and Neck surgeon Sunnybrook Health Sciences Center Toronto, Ontario, Canada	No conflict declared
Kathryn Roth	Head and Neck surgeon St. Josephs Health Care Center London, Ontario, Canada	Hoffmann-La Roche for Advanced Cell Basal Cell Carcinoma Treatment with Vismodegib – Not used in melanoma treatment. Travel support, speaker honorarium. Three separate engagements ($6000) Business Entity – Kathryn Roth Medicine Professional Corporation Rogers Daytime television segment: melanoma identification an awareness of skin surveillance Hoffmann-La Roche educational grant support ($5000) to the department of Otolaryngology – Head and Neck Surgery, Western University for booth and rep at the Annual Resident Research Day. K. Roth is current continuing professional development director – Department of Otolaryngology – Head and Neck Surgery
David Gyorki	Surgeon Peter MacCallum Cancer Center Victoria, Australia	No conflict declared
Mark Faries	Surgeon – Melanoma John Wayne Cancer Center Santa Monica, California, USA	No conflict declared
An-Wen Chan	Clinical Epidemiologist Women's College Research Institute Toronto, Ontario, Canada	No conflict declared

Appendix 2: Literature Search Strategy

Search Strategy: Excision Margins for Melanoma of the Trunk and Extremities
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Terms (hits)	Search Term Description
1. exp melanoma/ (82028)	Melanoma terms
2. melanoma$.mp. (109582)	
3. (maligna$ adj2 lentigo).mp. (959)	
4. (maligna$ adj5 melanoma$).mp. (27301)	
5. (maligna$ adj1 (nev$ or naevi$)).mp. (211)	
6. or/1-5 (109907)	
7. (surg$ adj2 margin$).mp. (9207)	Excision margin terms
8. (resect$ adj2 margin$).mp. (7101)	
9. (excision adj2 margin).mp. (388)	
10. or/7-9 (15647)	
11. (mito$ adj2 rate).mp. (3200)	Mitotic rate terms
12. mitotic rate.mp. (1794)	
13. 11 or 12 (3200)	
14. (6 and 10) or (6 and 13) (834)	Combining of terms
15. exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (825497)	Study type terms
16. prospective study/ (421184)	
17. retrospective study/ (588926)	
18. cohort study/ (198272)	
19. (case adj control).mp. (251183)	
20. or/15-19 (2024329)	
21. 14 and 20 (265)	Combining of terms
22. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1993888)	Exclusions and limits
23. 21 not 22 (261)	
24. animal/ not (exp human/ or humans/) (4230832)	
25. 23 not 24 (261)	
26. limit 25 to english (248)	
27. limit 26 to yr="2010-2016" (116)	

Search Strategy: Excision Margins for Melanoma of the Trunk and Extremities
Database: Embase <1996 to 2016 Week 25>

Search Terms (hits)	Search Term Description
1. melanoma.mp. (115273)	Melanoma terms
2. melanoma:.mp. (116161)	
3. exp melanoma/ (90201)	
4. (maligna$ adj2 lentigo).mp. (1505)	
5. (maligna$ adj1 (nev$ or naevi$)).mp. (191)	
6. or/1-5 (116578)	
7. (surg$ adj2 margin$).mp. (14213)	Excision margins terms
8. (resect$ adj2 margin$).mp. (10230)	
9. (excision adj2 margin).mp. (598)	
10. or/7-9 (23468)	
11. mitotic rate/ (5163)	Mitotic rate terms
12. (mito$ adj2 rate).mp. (6899)	
13. 11 or 12 (6899)	
14. (6 and 10) or (6 and 13) (1425)	Combining of terms
15. exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (905120)	Study type terms
16. prospective study/ (317593)	
17. retrospective study/ (441284)	
18. cohort study/ (213325)	
19. (case adj control).mp. (151906)	
20. or/15-19 (1833688)	
21. 14 and 20 (290)	Combining of terms
22. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1882146)	Exclusions and limits
23. 21 not 22 (275)	
24. animal/ not (exp human/ or humans/) (566239)	
25. 23 not 24 (275)	
26. limit 25 to english (254)	
27. limit 26 to yr="2010-2016" (181)	
28. limit 27 to exclude medline journals (10)	

Search Strategy: Excision Margins for Melanoma of the Head and Neck
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Terms (hits)	Search Term Description
1. exp "head and neck neoplasms"/ (267100)	Head and neck melanoma terms
2. "head and neck neoplasms"/su (9791)	
3. "head and neck neoplasms"/th (5887)	
4. (head and neck).mp. (93488)	
5. (1 or 2 or 3 or 4) and melanoma.mp. (7046)	
6. ((head or neck) adj5 cutaneous).mp. (739)	
7. ((head or neck) adj5 melanoma).mp. (995)	
8. ("head and neck" adj5 cutaneous).mp. (504)	
9. ("head and neck" adj5 melanoma).mp. (785)	
10. (parotid adj5 melanoma).mp. (94)	
11. or/5-10 (7698)	
12. (surg$ adj2 margin$).mp. (9202)	Excision margin terms
13. (resect$ adj2 margin$).mp. (7099)	
14. (excision adj2 margin).mp. (388)	
15. margin?.mp. (70287)	
16. or/12-15 (70856)	
17. 11 and 16 (370)	Combining of terms
18. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1993649)	Exclusions and limits
19. 17 not 18 (359)	
20. animal/ not (exp human/ or humans/) (4230832)	
21. 19 not 20 (354)	
22. limit 21 to english (300)	
23. limit 22 to yr="2002-2016" (207)	

Search Strategy: Excision Margins for Melanoma of the Head and Neck
Database: Embase <1996 to 2016 Week 25>

Search Terms (hit)	Search Term Description
1. exp "head and neck cancer"/ (95719)	Head and neck melanoma terms
2. *neck/ (6340)	
3. "head and neck neoplasms"/su (1132)	
4. (1 or 2 or 3) and melanoma.mp. (10188)	
5. ((head or neck) adj5 cutaneous).mp. (806)	
6. ((head or neck) adj5 melanoma).mp. (1272)	
7. ("head and neck" adj5 cutaneous).mp. (574)	
8. ("head and neck" adj5 melanoma).mp. (967)	
9. (parotid adj5 melanoma).mp. (96)	
10. or/4-9 (11464)	
11. (surg$ adj2 margin$).mp. (14213)	Excision margin terms
12. (resect$ adj2 margin$).mp. (10230)	
13. (excision adj2 margin).mp. (598)	
14. margin?.mp. (84895)	
15. or/11-14 (85454)	
16. 10 and 15 (402)	Combining of terms
17. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1882146)	Exclusions and limits
18. 16 not 17 (388)	
19. animal/ not (exp human/ or humans/) (566239)	

20. 18 not 19 (387)	
21. limit 20 to english (357)	
22. limit 21 to yr="2002-2016" (311)	
23. limit 22 to exclude medline journals (18)	

Search Strategy: SLNB for Melanoma of the Trunk and Extremities
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Terms (hits)	Search Term Description
1. exp melanoma/ (82028)	Melanoma terms
2. melanoma$.mp. (109582)	
3. (maligna$ adj2 lentigo).mp. (959)	
4. (maligna$ adj5 melanoma$).mp. (27301)	
5. (maligna$ adj1 (nev$ or naevi$)).mp. (211)	
6. or/1-5 (109907)	
7. exp sentinel lymph node biopsy/ (9023)	SLNB terms
8. (sentinel adj3 biops$).mp. (10874)	
9. exp lymph node excision/ (39674)	
10. (lymph adj2 excision).mp. (27907)	
11. (lymph adj2 biops$).mp. (13546)	
12. (lymph adj2 dissection).mp. (13774)	
13. (lymph node adj2 surgery).mp. (507)	
14. (SLNB or SNB).mp. (2703)	
15. or/7-14 (51424)	
16. (mito$ adj2 rate).mp. (3200)	Mitotic rate terms
17. mitotic rate.mp. (1794)	
18. 16 or 17 (3200)	
19. (6 and 15) or (6 and 18) (4977)	Combining of terms
20. exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (825461)	Study type terms
21. prospective study/ (421184)	
22. cohort study/ (198272)	
23. (case adj control).mp. (251183)	
24. retrospective study/ (588926)	
25. or/20-24 (2024305)	

26. 19 and 25 (1256)	Combining of terms
27. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1993888)	Exclusions and limits
28. 26 not 27 (1229)	
29. limit 28 to english (1136)	
30. animal/ not (exp human/ or humans/) (4230832)	
31. 29 not 30 (1134)	
32. limit 31 to yr="2010-2016" (458)	

Search Strategy: SLNB for Melanoma of the Trunk and Extremities
Database: Embase <1996 to 2016 Week 25>

Search Terms (hits)	Search Term Description
1 melanoma.mp. (115273)	Melanoma terms
2 melanoma:.mp. (116161)	
3 exp melanoma/ (90201)	
4 (maligna$ adj2 lentigo).mp. (1505)	
5 (maligna$ adj1 (nev$ or naevi$)).mp. (191)	
6 or/1-5 (116578)	
7 exp sentinel lymph node biopsy/ (11821)	SLNB terms
8 (sentinel adj3 biops$).mp. (14664)	
9 exp lymph node excision/ (36701)	
10 (lymph adj2 biops$).mp. (23953)	
11 (lymph adj2 dissection).mp. (38038)	
12 (lymph adj2 excision).mp. (1066)	
13 (lymph node adj2 surgery).mp. (706)	
14 (SLNB or SNB).mp. (4230)	
15 or/7-14 (62584)	
16 mitotic rate/ (5163)	Mitotic rate terms
17 (mito$ adj2 rate).mp. (6899)	
18 16 or 17 (6899)	
19 (6 and 15) or (6 and 18) (6583)	Combining of terms
20 exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp. (905120)	Study type terms
21 prospective study/ (317593)	
22 retrospective study/ (441284)	
23 cohort study/ (213325)	

24 (case adj control).mp. (151906)	
25 or/20-24 (1833688)	
26 19 and 25 (1153)	Combining of terms
27 (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1882146)	Exclusions and limits
28 26 not 27 (1082)	
29 limit 28 to english (1009)	
30 animal/ not (exp human/ or humans/) (566239)	
31 29 not 30 (1007)	
32 limit 31 to yr="2010-2016" (673)	
33 limit 32 to exclude medline journals (48)	

Search Strategy: SLNB for Melanoma of the Head and Neck
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

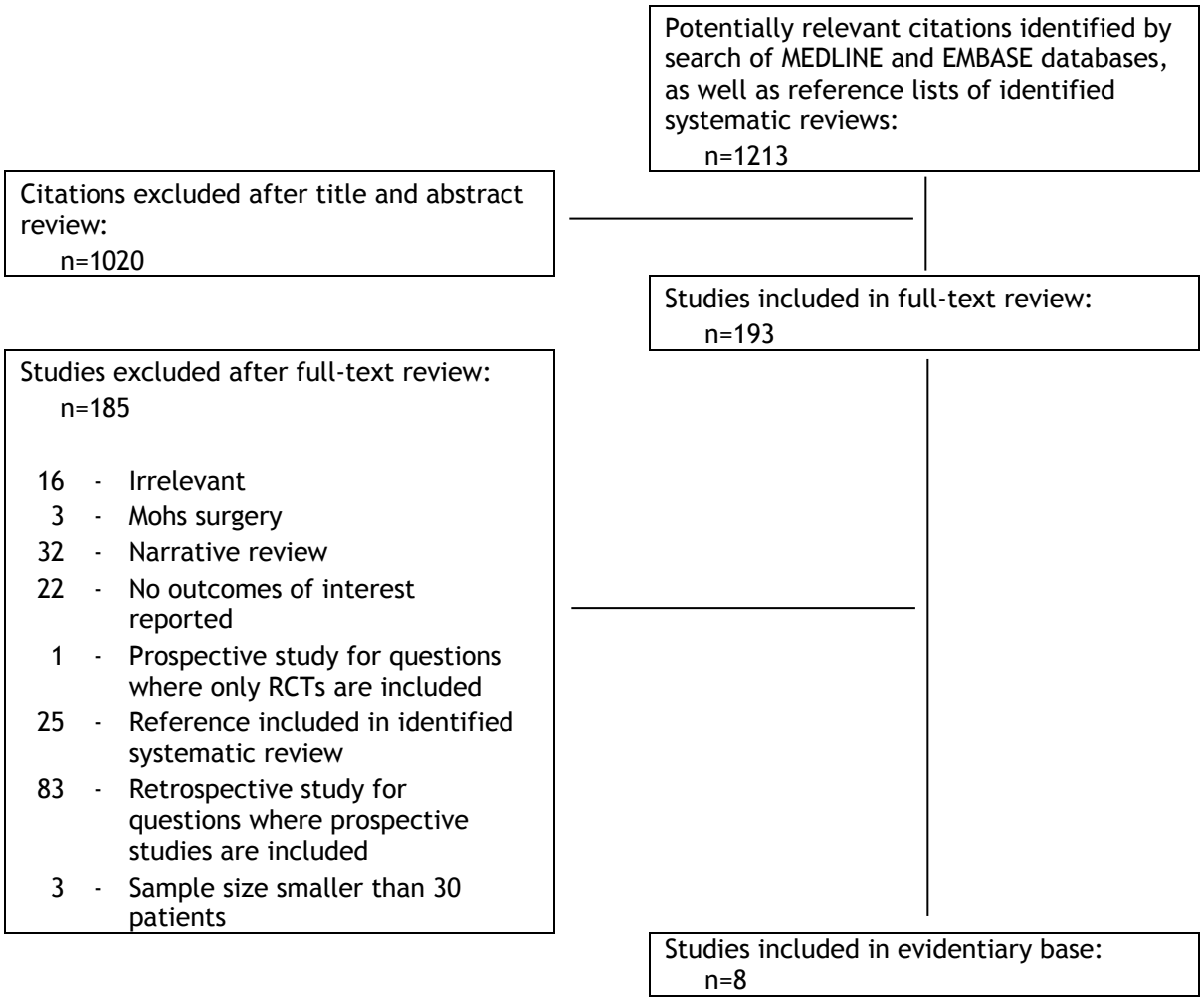
Search Terms (hits)	Search Term Description
1. exp "head and neck neoplasms"/ (267100)	Head and neck melanoma terms
2. "head and neck neoplasms"/su (9791)	
3. "head and neck neoplasms"/th (5887)	
4. (head and neck).mp. (93488)	
5. (1 or 2 or 3 or 4) and melanoma.mp. (7046)	
6. ((head or neck) adj5 cutaneous).mp. (739)	
7. ((head or neck) adj5 melanoma).mp. (995)	
8. ("head and neck" adj5 cutaneous).mp. (504)	
9. ("head and neck" adj5 melanoma).mp. (785)	
10. (parotid adj5 melanoma).mp. (94)	
11. or/5-10 (7698)	
12. exp sentinel lymph node biopsy/ (9023)	SLNB terms
13. *sentinel lymph node/ (5914)	
14. lymphatic metastasis/ (77158)	
15. (sentinel adj3 biops$).mp. (10874)	
16. exp lymph node excision/ (39674)	
17. (lymph adj2 biops$).mp. (13545)	
18. (lymph adj2 dissection).mp. (13772)	
19. (lymph adj2 excision).mp. (27907)	
20. (lymph node adj2 surgery).mp. (507)	
21. sentinel node.mp. (5034)	
22. (SLNB or SNB).mp. (2703)	
23. or/12-22 (109424)	
24. 11 and 23 (1241)	Combining of terms
25. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1993649)	Exclusions and limits
26. 24 not 25 (1212)	
27. animal/ not (exp human/ or humans/) (4230832)	
28. 26 not 27 (1202)	
29. limit 28 to english (988)	
30. limit 29 to yr="2002-2016" (575)	

Search Strategy: SLNB for Melanoma of the Head and Neck
Database: Embase <1996 to 2016 Week 25>

Search Terms (hits)	Search Term Description
1. exp "head and neck cancer"/ (95719)	

2. *neck/ (6340)	Head and neck melanoma terms
3. "head and neck neoplasms"/su (1132)	
4. (1 or 2 or 3) and melanoma.mp. (10188)	
5. ((head or neck) adj5 cutaneous).mp. (806)	
6. ((head or neck) adj5 melanoma).mp. (1272)	
7. ("head and neck" adj5 cutaneous).mp. (574)	
8. ("head and neck" adj5 melanoma).mp. (967)	
9. (parotid adj5 melanoma).mp. (96)	
10. or/4-9 (11464)	
11. *sentinel lymph node/ (3361)	SLNB terms
12. exp sentinel lymph node biopsy/ (11821)	
13. *sentinel lymph node dissection/ (39)	
14. lymphatic metastasis/ (42935)	
15. (sentinel adj3 biops$).mp. (14664)	
16. exp lymph node excision/ (36701)	
17. (lymph adj2 biops$).mp. (23953)	
18. (lymph adj2 excision).mp. (1066)	
19. (lymph adj2 dissection).mp. (38038)	
20. (lymph node adj2 surgery).mp. (706)	
21. (SLNB or SNB).mp. (4230)	
22. or/11-21 (98051)	
23. 10 and 22 (856)	Combining of terms
24. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/ (1882146)	Exclusions and limits
25. 23 not 24 (801)	
26. animal/ not (exp human/ or humans/) (566239)	
27. 25 not 26 (801)	
28. limit 27 to english (744)	
29. limit 28 to yr="2002-2016" (676)	
30. limit 29 to exclude medline journals (53)	

Appendix 3: Primary Literature Search Flow Diagram



Appendix 4: Quality Assessment for Included Systematic Reviews

AMSTAR Assessment Criteria	Cordeiro et al, 2016 [14]	de Rosa et al, 2011 [15]	Freeman et al, 2013 [2]	Wheatley et al, 2016 [1]
1. Was an 'a priori' design provided?	Yes	Yes	Yes	Yes
2. Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes
3. Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	No	No	No
5. Was a list of studies (included and excluded) provided?	No	No	No	Yes
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Yes
9. Were the methods used to combine the finding of studies appropriate?	Yes	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	No	No	Yes	Yes
11. Was the conflict of interest included?	Yes	Yes	No	Yes

Appendix 5: Quality Assessment for Included Studies

RCTs

Cochrane Risk of Bias Domain	Hayes et al, 2016 [6]	Kimbrough et al, 2016 [27][3]	Morton et al, 2014 [13]
Random sequence generation (selection bias)	Low risk	Unclear risk	Unclear risk[6]
Allocation concealment (selection bias)	Low risk	Unclear risk	Unclear risk[6]
Blinding of participants and personnel (performance bias)	Low risk[1]	Low risk[1]	Low risk[1]
Blinding of outcome assessment (detection bias)	Low risk[1]	Low risk[1]	Low risk[1]
Incomplete outcome data (attrition bias)	High risk	High risk[4]	Low risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk
Other bias	High risk[2]	High risk[5]	Low risk[7]

[1] No blinding but study outcomes are not likely to be influenced by a lack of blinding
[2] SLNB was not routinely performed in this study, likely affecting survival rates
[3] First five bias domains assessed based on Sunbelt Melanoma Trial [28] as the Kimbrough study is a reassessment of trial results that lacks complete methodology for the original RCT
[4] Imbalance in missing data across arms; more patients in arm 6 lost to follow-up than any other group, likely related to true outcome
[5] Accrual goal for Protocol A not met
[6] Study reports that patients were randomly assigned in a 60:40 ratio without detail on the sequence generation process or allocation concealment (methods from original RCT also checked [34])
[7] Concerns raised after publication of the original study surrounding ascertainment bias were addressed by a latent-subgroup analysis in this 10-year follow-up. Ascertainment bias concerns were based on the known sentinel node status in the biopsy group while sentinel node status was not known in the observation group

Observational Studies

ROBINs Domain	MacKenzie Ross et al, 2016 [7]	Rawlani et al, 2015 [9]	Ruskin et al, 2016 [10]	Teng et al, 2015 [11]
Study design	Case-control	Retrospective cohort	Retrospective cohort	Retrospective cohort
Bias due to confounding	Moderate risk	Critical risk	Low risk	Low risk
Bias in selection of participants into the study	Low risk	Serious risk	Serious risk	Critical risk
Bias in classification of interventions	Moderate risk	Low risk	Moderate risk	Moderate risk
Bias due to departures from intended interventions	Low risk	Low risk	Low risk	Low risk
Bias due to missing data	Low risk	Low risk	Low risk	Low risk
Bias in measurement of outcomes	Low risk	Low risk	Low risk	Low risk
Bias in selection of the reported result	Serious risk	Low risk	Low risk	Low risk

Diagnostic Studies

QUADAS-2 Domain	Giudice et al, 2014 [16]
DOMAIN 1: PATIENT SELECTION	
Risk of bias	Low risk
Concerns regarding applicability to the research question(s) of the review	Low concern
DOMAIN 2: INDEX TEST(S)	

Risk of bias	Low risk
Concerns regarding applicability to the research question(s) of the review	Low concern
DOMAIN 3: REFERENCE STANDARD	
Risk of bias	High risk
Concerns regarding applicability to the research question(s) of the review	Low concern
DOMAIN 4: FLOW AND TIMING	
Risk of bias	High risk

Appendix 6: Evidence Base from 2010 Guideline

Guideline Literature Search Results

A 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 ≥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 ≤ 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/) 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 (≤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 ≤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 ≤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 ≥1.0 mm in thickness and where clinically indicated in melanomas < 1 mm in thickness, including those with high-risk features.

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Appendix 7 : Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2010	2002 - 2010	Full report	Peer review publication. Web publication.	Not applicable
Version 2 2017	2010 - 2017	New version replaced old	Updated web publication.	Head and neck population added. Literature search for this population 2002 – 2017.