

# Sentinel Node Biopsy in Primary Cutaneous Melanoma

Effective Date: April, 2016



## Background

The incidence of melanoma continues to increase. In Alberta, the age-standardized incidence rate [ASIR] increased 0.8% annually between 1992 and 2012 to an ASIR of 13.9 in 2012.<sup>1</sup> This increase was only observed in males while female melanoma incidence rates remained stable. The five-year survival rate for patients diagnosed with melanoma between 2010 and 2012 is estimated to be 91%. It is also estimated that the incidence of melanoma will continue to increase with 700 new cases and 95 deaths resulting from melanoma expected in 2017.<sup>1</sup>

Some controversy exists regarding the surgical management of the regional lymph nodes in melanoma. For years, elective lymph node dissection was recommended to control metastases. However, this procedure was not shown to provide any survival benefit in randomized trials and was associated with high morbidity.<sup>2</sup> Subsequently, intraoperative lymphatic mapping and sentinel node biopsy were introduced as an alternative that would allow for excision of only the sentinel draining lymph nodes, limiting complete lymph node dissection to patients with metastasis to the sentinel node.<sup>3</sup> This guideline aims to provide recommendations on some of the technical aspects of sentinel node biopsy in melanoma. For American Joint Committee on Cancer melanoma staging,<sup>4,5</sup> please refer to the Appendix.

## Guideline Questions

1. What are indications and contraindications for sentinel node biopsy (SLNB)?
2. How is the sentinel node examined pathologically?
3. If the sentinel node is positive, what are the indications for a therapeutic node dissection and to what extent?
4. What is the role of ultrasound-guided fine-needle aspiration in identifying positive lymph nodes?
5. Should ultrasound be utilized before every SLNB?
6. Is there a role for routine use of ultrasound for follow-up?

## Search Strategy

The MEDLINE, EMBASE, and Cochrane databases were searched (1990 through May 2010) for clinical trials and meta-analyses. Search terms included: “fine needle aspiration” or “lymph node biopsy” or “lymph node dissection” or “complete lymph node dissection” AND “stage III melanoma” or “melanoma lymph node metastasis” with limits of Human and English language. A total of 25 clinical trials were identified by the search.

In addition, the National Guidelines Clearinghouse and individual guideline organizations were searched for practice guidelines relevant to this topic. A total of eight original clinical practice guidelines were identified from the following organizations: the Australian Cancer Network, the National Comprehensive Cancer Network, the BC Cancer Agency, the European Dermatology Forum, the Scottish Intercollegiate Guidelines Network, the German Cancer Society, the American Society of Plastic Surgeons, and the European Society for Medical Oncology.

PubMed was again searched in 2013 for evidence on regional node dissection in cutaneous melanoma. The search term “melanoma” was used and results were limited to clinical trials, published through January 2013. Citations were hand-searched for studies pertaining to regional node dissection, resulting in a total of two prospective cohort studies and seven retrospective studies, as well as one updated clinical practice guideline from the American Society of Clinical Oncology. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes to the recommendations were made.

Using the same search strategy, four relevant articles published between January 2013 and January 2014 were identified during the 2014 update. Following a review of the evidence by the Alberta Cutaneous Tumour Team, minor changes were made to the recommendation on sentinel lymph node biopsy eligibility criteria and contraindications.

The 2016 update did not necessitate a full literature review; recommendations were modified based on a consensus discussion at the 2016 Alberta Cutaneous Tumour Team Meeting.

## Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with malignant melanoma. Different principles may apply to pediatric patients.

## Recommendations

An initial biopsy should first be performed according to recommendations outlined in the CancerControl Alberta guideline, [\*Biopsy of a Suspicious Pigmented Lesion\*](#).

1. For the purposes of staging, a sentinel node biopsy (SLNB) should be considered for the following:<sup>6-12</sup>

- Primary melanoma >1.0 mm thick with any characteristic
- Primary melanoma >0.75 mm thick with mitotic rate  $\geq 1$  per  $\text{mm}^2$
- Primary melanoma <1mm if ulcerated
- Desmoplastic melanomas and pigmented epithelial melanocytomas can be discussed.

2. The contraindications for SLNB are as follows:<sup>13,14</sup>

- Absolute contraindications: pathologically positive (N1) lymphadenopathy based on a positive fine-needle aspiration cytology and/or core biopsy of palpable lymph nodes.
- Relative contraindications (due to the disruption of the lymphatics): Prior wide excision of the primary tumour with a flap closure or skin graft, prior extensive surgery (e.g., dissection of the neck), previous radiation to the head and the neck, allergy to blue dye and radiocolloid. While SLNB is not contraindicated in pregnancy, it should be noted that vital dyes have not been proven safe for use during pregnancy. Radiocolloid should be used alone if SLNB is undertaken.<sup>15-17</sup>

3. The treating centre and clinician must be experienced in SLNB.

4. In accordance with the College of American Pathologists' Protocol for the Examination of Specimens from Patients with Melanoma of the Skin,<sup>18</sup> pathological examination of the sentinel node should include:

- Review of sentinel node specimens of multiple permanent sections examined by H&E and immunohistochemical staining for markers (i.e. S-100, HMB-45, MART-1, or Melan-A).
- Reporting of the following features:
  - Number of sentinel nodes examined (total number of nodes examined: sentinel and nonsentinel)
  - Number of lymph nodes with metastases
  - Extranodal tumor extension (present, not identified, indeterminate)
  - Size of largest metastatic focus (mm, for sentinel node)
  - Location of metastatic tumor (subcapsular, intramedullary, subcapsular and intramedullary, for sentinel node)

5. The indications for a therapeutic node dissection and recommended extent of dissection are:<sup>6,8,19-26</sup>

- Positive sentinel node biopsy (i.e. any malignant cells in the lymph node, regardless of size, is considered positive).<sup>4</sup> Observation alone may be considered for select patients with positive sentinel node biopsy who are at low risk of recurrence and at high risk of operative morbidity. The latter patients should be followed up more closely.
- Evidence of metastatic nodal disease.
- A therapeutic node dissection includes full levels (I to III) clearance in the axilla.
- A therapeutic neck dissection may include a superficial parotidectomy as clinically indicated.
- For inguinal node metastases, clearance of the intra-pelvic iliac and obturator nodes should be considered when the staging investigation demonstrates evidence of involvement.

6. Use of fine-needle aspiration (FNA) biopsy, with ultrasound (US) or CT scan radiological guidance when required, is recommended for the identification of positive lymph nodes in patients suspected of having lymph node *metastasis* from cutaneous melanoma.<sup>6,27</sup>

- The use of US examination alone is more accurate than palpation for the detection of lymph node metastases, as metastases >4.5 mm in size can be detected. However, SLNB is superior to ultrasound alone in the detection of occult regional lymph node metastases.<sup>6,12</sup>
- Note: The sensitivity of US-guided FNA biopsy was 65%; the specificity was 99%; the positive predictive value was 93% and the negative predictive value was 92%. Sensitivity varied with tumour size (40% for pT1a/b; 79% for pT4a/b).<sup>27</sup>

7. For follow-up, the routine use of US of the nodal basin is not recommended.

- Ultrasound may be used in conjunction with clinical examination in the follow-up of patients with more advanced primary disease or following treatment of metastases.<sup>6,8</sup>

- Patients with positive SLNB who do not undergo complete lymph node dissection should undergo more intensive follow-up for two years post SLNB. Ultrasound of the nodal basin every 3-6 months should be considered.<sup>5,28</sup>
- Patients with a thin primary melanoma have only a small risk of relapse; imaging techniques are not necessary.<sup>8,12</sup>

## Discussion

The recommendation that SLNB is indicated for primary melanomas >1.0 mm thick with any characteristic or >0.75 mm thick with mitotic rate  $\geq 1$  per  $\text{mm}^2$  was derived from existing guidelines as well as evidence showing that, among patients with primary melanoma and a positive SLNB (n=88), mitotic rate, tumour infiltrating lymphocytes, and Breslow thickness were found to be independent prognostic factors for SLN positivity. In lesions with a depth less than 2.0 mm, mitotic rate was important in risk-stratifying patients.<sup>9</sup> Literature looking at the positivity rate for melanomas with a mitotic index  $\geq 1$  and Breslow <0.75 versus >0.75 mm have shown that these thin melanomas are rarely SLNB positive in the more shallow group.<sup>29-32</sup> In tumours  $\leq 1.0$  mm thick with ulceration, the rate of SLN positivity was 5.4%; in tumours  $\leq 1.0$  mm thick with a mitotic rate of 0.1 to 5  $\text{mm}^2$ , the rate of SLN positivity was 8.9%.<sup>9</sup> The false-negative rate for SLNB decreases to 5.2% after 25 cases.<sup>3,11</sup> There is limited data on the usefulness of SLNB in larger ( $\geq 4$  mm) melanomas; however, a recent retrospective review of 195 patients with thick melanomas revealed a positivity rate of 33% among 66 eligible patients and that positive SLNB positivity was not significantly related to Breslow thickness, Clark level, mitotic rate, or ulceration in this group. Furthermore, DFS and OS were governed by tumour thickness.<sup>33</sup> A retrospective review of 21 patients with atypical spitzoid tumours who underwent SLNB revealed a SLN metastasis rate of 29% (6 patients); tumours with a positive SLN were more likely to have a greater mean tumour thickness (3.38 mm vs. 2.04 mm;  $p < 0.05$ ).<sup>34</sup> A study in which patients with desmoplastic melanoma  $\geq 1.0$  mm Breslow thickness who underwent SLNB in a prospective clinical trial were combined with a single institution melanoma database demonstrated a positive SLN rate of 17.0% (8 of 47). Breslow thickness  $\geq 2.6$  mm (HR 8.17, 95% CI 1.26 to 160.1;  $p = 0.026$ ) and an interaction between SLN status and ulceration ( $p = 0.001$ ) were independent risk factors for worse OS.<sup>35</sup> In contrast, a retrospective series reported a rate of SLN positivity rate of 0% among patients with head and neck desmoplastic melanoma. The same study summarized the literature describing a total of 148 patients and found that only 5 patients (3.4%) had positive SLNB.<sup>36</sup>

A therapeutic node dissection can be performed when the sentinel node biopsy is positive or there is clinically palpable nodal disease and should include full levels (I to III) clearance in the axilla. There is some data to suggest that the rate of level III axillary node metastasis is low (3%) in patients with a positive SLNB and no palpable disease.<sup>37</sup> In patients with cervical nodal metastasis, a superficial parotidectomy should be performed as clinically indicated. In the case of inguinal node involvement, clearance of the intra-pelvic iliac and obturator nodes can be considered but is controversial.<sup>6,8,19-21</sup> It should be noted that for every one positive superficial node, the number of deep positive nodes is increased by 0.55.<sup>26</sup> The ongoing MSLT-II phase III trial will compare immediate complete lymph node dissection (CLND) with observation in patients with a positive SLNB to determine the

therapeutic benefit of CLND, however, results are not expected until 2022 and until then there is a lack of strong evidence to base clinical decisions on.<sup>38</sup> The MSLT-I trial found a relapse-free survival benefit and no overall survival benefit with SLNB and immediate CLND compared to observation alone without SLNB.<sup>5</sup> Wong, et al. (2006)<sup>25</sup> showed that, among patients with a median tumour thickness of 2.6 mm, 77% of which had tumours with invasion to Clark level IV/V, nodal recurrence-free survival was insignificantly worse than that seen in a contemporary cohort of patients who underwent complete lymphadenectomy. Kingham, et al. (2010)<sup>22</sup> also showed that patients who had a positive SLN but did not undergo a complete lymphadenectomy had similar rates and patterns of recurrence and similar recurrence-free and disease-specific survival as those who did undergo a complete lymphadenectomy. Of note, patients in the no-CLND group were older (median age 70 vs. 56 years,  $p < 0.01$ ), had a trend toward thicker melanomas (3.5 vs. 2.8 mm,  $p < 0.06$ ), and more often had lower-extremity melanomas (40% vs. 13% CLND;  $p < 0.01$ ). Preliminary results of the DECOG multicentre randomized trial found no significant treatment related differences in 5-year recurrence-free survival, distant metastases-free survival and melanoma specific survival between patients with cutaneous melanoma of the trunk and extremities and positive SLNB who received immediate CLND versus observation.<sup>28</sup> Should the course of treatment following a positive SLNB preclude a complete node dissection in favor of observation alone, the patient can expect similar recurrence odds as patients who do undergo the procedure? Patients who undergo observation alone require intensive follow-up.

Ultrasound (US) can be used to guide a fine-needle aspiration (FNA) biopsy, but should not be used alone, in substitution of a diagnostic biopsy. The sensitivity and specificity of US-guided FNA biopsy have been reported as 65% (sensitivity increasing with tumour size) and 99%, respectively, while the positive and negative predictive values have been reported as 93% and 92%, respectively.<sup>27</sup> The use of ultrasound alone to detect SLN metastases is more accurate than palpation, but still considered experimental. Furthermore, this application of US may not be cost effective: Starritt, et al. (2005)<sup>39</sup> showed that among 304 patients with primary cutaneous melanoma who had SLNs examined with high-resolution US and then removed and assessed histologically, US was able to detect SLN metastases in seven of 31 (22.6%) cases and missed cases with metastases  $< 4.5$  mm in diameter, which represent the majority of cases at the time of initial staging.



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## Appendix:

### AJCC 2009 (7th Edition) Anatomic Stage Groupings for Cutaneous Melanoma <sup>4</sup>

	Clinical Staging <sup>a</sup>				Pathologic Staging <sup>b</sup>			5-year Survival (%)	
	T	N	M		T	N	M		
0	Tis	N0	M0	0	Tis	N0	M0	100%	
IA	T1a	N0	M0	IA	T1a	N0	M0	95%	
IB	T1b T2a	N0	M0	IB	T1b T2a	N0	M0	90%	
IIA	T2b T3a	N0	M0	IIA	T2b T3a	N0	M0	78%	
IIB	T3b T4a	N0	M0	IIB	T3b T4a	N0	M0	65%	
IIC	T4b	N0	M0	IIC	T4b	N0	M0	45%	
III	Any T	N > N0	M0	IIIA	T1-4a	N1a	M0	66%	
					T1-4a	N2a			
				IIIB	T1-4b	N1a			50%
					T1-4b	N2a			
	T1-4a	N1b	27%						
	T1-4a	N2b							
	T1-4a	N2c							
				IIIC	T1-4b	N1b			
					T1-4b	N2b			
					T1-4b	N2c			
					Any T	N3			
IV	Any T	Any N	M1	IV	Any T	Any N	M1	13%	

<sup>a</sup> Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

<sup>b</sup> Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

### AJCC 2009 (7<sup>th</sup> Edition) TNM Staging Categories for Cutaneous Melanoma <sup>4</sup>

T	Thickness (mm)	Ulceration Status/Mitoses
Tis	NA	NA
T1	≤ 1.00	a: without ulceration and mitosis < 1/mm <sup>2</sup> b: with ulceration or mitoses ≥ 1/mm <sup>2</sup>
T2	1.01-2.00	a: without ulceration b: with ulceration
T3	2.01-4.00	a: without ulceration b: with ulceration
T4	> 4.00	a: without ulceration b: with ulceration
N	Number of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	a: micrometastasis <sup>a</sup> b: macrometastasis <sup>b</sup>
N2	2-3	a: micrometastasis <sup>a</sup> b: macrometastasis <sup>b</sup> c: in transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	Site	Serum LDH (lactate dehydrogenase)
M0	No distant metastases	not applicable
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

<sup>a</sup> Micrometastases are diagnosed after sentinel lymph node biopsy.

<sup>b</sup> Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

### Development and Revision History

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

This guideline was originally developed in February 2011. This guideline was revised in March 2012, February 2013, February 2014 and April 2016.

### Maintenance

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2018. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

### Abbreviations

ASIR	age-standardized incidence rate
CLND	complete lymph node dissection
FNA	fine needle aspiration
GyE	Gray equivalents
H&E	hematoxylin and eosin
pT	primary tumour
SLNB	sentinel node biopsy
US	ultrasound

### Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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### Funding Source

Financial support for the development of CancerControl Alberta's evidence-based clinical practice guidelines and supporting materials comes from the CancerControl Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).