Advocating Sentinel Node Biopsy in the Management of Cutaneous Melanoma

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Abstract The incidence of melanoma has increased in North America, Europe, Australia, and New Zealand in the past decade. Currently, the mainstay treatment for patients with primary cutaneous melanoma is surgery, as adjuvant systemic therapy has limited efficacy. The role of sentinel node biopsy has been debated since its introduction 20 years ago. A review of the role of this technique in the management of patients with stage I and II melanoma in terms of staging, prognosis, morbidity, therapeutic benefit, and enrollment in clinical trials appears to be timely.

Keywords Melanoma · Sentinel lymph node biopsy · Staging · Lymph node excision

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Introduction

The incidence of melanoma is increasing. The Canadian Cancer Society reports that melanoma is the eighth most common diagnosed malignancy across Canada, with 5,500 new cases and 950 deaths from melanoma estimated for 2011 [1]. For patients with stage I and II melanoma, the mainstay of treatment is surgery including sentinel node biopsy.

Several guidelines have been published worldwide with different recommendations regarding sentinel node biopsy (SNB). North American [2–5], Australian [6•], German [7], and Swiss [8] guidelines recommend SNB for routine use in staging patients, whereas guidelines from France [9] and the United Kingdom [10] do not (only recommended within a clinical trial setting). This reflects the current controversy surrounding this technique since its publication in 1992 [11]. Interestingly, recent publications have shown that even in places where guidelines do not categorically recommend SNB, these are not applied routinely and more than 80 % of the patients involved in the decision-making discussion, elected to undergo SNB [12, 13].

Here we aim to review the role of sentinel lymph node biopsy as part of the management of patients with cutaneous stage I and II melanoma and advocate its use within the University of Toronto practice guidelines (Table 1). We review its role in staging, defining prognosis, optimizing loco-regional control, minimizing surgical morbidity, and providing opportunity for clinical trials enrollment. In addition, we discuss the indications for SNB beyond intermediate thickness (1.0–4.0 mm) melanomas for truncal or extremity locations, the therapeutic impact of improved loco-regional control, and the uncertainty with respect to an overall survival benefit.

Table 1 Management of stage I and II cutaneous melanoma at the University of Toronto

Primary tumour	Management	Special notes
<1 mm Breslow thickness (T1)	<ul style="list-style-type: none"> ■ Wide local excision with 1 cm margins ■ SNB is not indicated in most cases 	<p>When melanoma 0.75–1 mm, we discuss and offer SNB in patients with any of the following features:</p> <ul style="list-style-type: none"> • Ulcerated (T1b) • Mitotic rate $\geq 1/\text{mm}^2$ (T1b) • Young patients (≤ 40 years) • Skin of the head and neck region • Deep margin transected
1–4 mm Breslow thickness (T2,T3)	<ul style="list-style-type: none"> ■ 1–2 mm Melanomas: Wide local excision with 1–2 cm margins ■ 2–4 mm Melanomas: Wide local excision with 2 cm margins ■ Discuss and offer SNB 	The updated available Level I evidence is insufficient to determine optimal excision margins for melanoma including all Breslow thickness.
> 4 mm Breslow thickness (T4)	<ul style="list-style-type: none"> ■ Metastatic work-up: head CT scan or brain MRI, CT scan chest, abdomen and pelvis ■ Wide local excision with 2 cm margins ■ Discuss and offer SNB 	Very limited data supporting routine standard metastatic work-up

SNB sentinel node biopsy

(From Cukier et al. [52].)

Accurate Staging and Defining Prognosis

In Ontario and similar to the rest of North America, the currently recommended staging system for cutaneous melanoma is the American Joint Committee on Cancer (AJCC) 7th edition [14]. In this staging system, metastatic deposits found in the nodal basin are defined as micrometastases (N1a/2a) when there is no clinically palpable regional nodal disease but detected by SNB. Approximately 15 % to 20 % of patients with who present with a clinically negative lymph node examination will have microscopic nodal metastases on SNB [15••].

A recent meta-analysis of all published studies of SNB for staging patients with melanoma included more than 25,000 patients and showed that the average proportion of successfully mapped cases was 98 %. In this study, the reported false-negative rate of this technique was 12.5 % overall (95 % CI, 11–14.2 %) and the estimated risk of nodal recurrence after a negative SNB was ≤ 5 % [15••].

A positive SNB has been consistently found to be one of the strongest prognostic factors in melanoma patients, followed by Breslow thickness, ulceration status [16, 17] and, recently proposed, mitotic rate [18]. In Balch et al.'s [19•] recent study, nodal status as well as the extent of regional metastatic involvement [one positive sentinel node (N1a) compared to two or three sentinel nodes (N2a)] was shown to have significant prognostic value. In this multivariate analysis the authors stress the fact that, despite observation, there was substantial heterogeneity in survival among patients with nodal micrometastases; the number of nodal metastases was

the most significant independent predictor of survival. The relevance of these findings is reflected by their inclusion in the current AJCC melanoma staging and classification.

An additional prognostic factor associated with lymph node involvement is the presence of metastases in non-sentinel nodes when the completion lymphadenectomy (LND) is performed. This is addressed in two studies analyzing the prognosis in patients who have undergone a completion lymphadenectomy after a positive SNB [20, 21]. Both reviewed their institutional databases to assess prognosis and outcomes in patients that have non-sentinel nodes positive for metastatic nodal deposits that were identified in the completion nodal dissection. They concluded that non-sentinel node involvement is a significant negative predictive factor for survival.

The primary purpose of SNB is to reliably diagnose occult nodal metastases and to accurately stage patients. The identification of subclinical nodal metastases by SNB allows for the better stratification of melanoma patients by selecting a subgroup with more aggressive disease [22].

The role of ultrasound (US) and US-guided fine needle aspiration in the assessment of regional lymph nodes in patients with cutaneous melanoma has been reported [23, 24]. The consistent failure to detect metastatic deposits under 2 to 3 mm suggests that this modality is inferior to SNB for accurate nodal staging.

As we delve into the future of personalized medicine and clinical trials of targeted treatments, accurate staging, and thus prognostic categorization, will be paramount in patient selection for the assessment of these interventions.

Providing Loco-Regional Control

Because this discussion is focused on advocating for SNB in patients with cutaneous melanoma, we have to keep in mind that we are comparing it with no regional nodal surgery. The Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) [25•], the largest prospective randomized trial to date (1,269 patients) but with long-term 10-year follow up data still pending, reported that 16 % of the patients undergoing SNB had positive nodes (micrometastases) and an additional 3 % presented clinically palpable nodal recurrence at 59.8 months of median follow-up compared to 15.6 % of the patients in the observation group (no regional surgery group) diagnosed with clinically palpable regional nodal disease during the same follow-up period. The fourth interim analysis of the MSLT-1 trial [26] shows that immediate or early completion LND has less morbidity than therapeutic or delayed LND (wound dehiscence 3.1 % vs 6.1 %, seroma 3.1 % vs 6.1 %, lymphedema 12.4 % vs 20.4 %) and fewer nodes with metastasis (1.5 vs 3.3 nodes). Furthermore, rates of regional recurrence are at least 17 % for patients who have four or more metastatic nodes in their regional lymph node basin [27]. We believe that the majority of the micrometastases will eventually become macroscopic, and thus SNB provides a better opportunity of loco-regional control compared to observation.

There are only two ways of pathologically staging the regional nodes: SNB and elective lymphadenectomy. In terms of morbidity, the SNB has clear advantages and also can accurately pick the patients who should undergo dissection for regional control.

Until the results from the Multicenter Selective Lymphadenectomy Trial II (MSLT-II, a prospective, multicenter clinical trial assessing if completion LND provides a survival advantage in positive SNB patients compared to observation and close follow-up) or the European Organisation for Research and Treatment of Cancer (EORTC) MINITUB study (a prospective multicenter single-arm registration study evaluating the efficacy of not performing a completion lymph node dissection [CLND] for minimal sentinel node [SN] tumor burden) are available, the standard of care in patients with regional nodal metastatic disease detected by SNB is to perform completion LND.

Complications associated with SNB include seroma and hematoma (1–5 %), lymphedema (<1–9 %), wound infection (1–4 %), and allergic reactions to blue dye (1 %). When compared to complete LND, SNB is associated with fewer complications. Two large prospective studies, the Sunbelt Melanoma Trial [28] and the MSLT-1 [29•], have reported complications rates of 4.6 % and 10 %, respectively, in patients with SNB alone, as opposed to those undergoing completion LND (23.2 % and 37.2 %). Recent institutional series with long-term follow-up are consistent with earlier studies, showing complications rates of 6.9 % for SNB [16].

By diagnosing nodal-positive patients earlier and potentially with less nodal basin involvement, the likelihood of undergoing radiotherapy is reduced. In our institutions, patients with non-metastatic primary melanoma are referred to radiation oncology to discuss radiotherapy when there are more than three positive LN, presence of extracapsular extension, or LN>3 cm. The morbidity from this intervention is not negligible, being one of the major risk factors for lymphedema after inguinal LND [30].

It has been suggested that SNB could increase the risk of in-transit metastasis and recurrence rates [31, 32]; however the current available evidence, including a randomized controlled trial, has demonstrated that this is not a genuine concern [33–36], with an explanation leading towards a more aggressive tumor biology in these patients than attributable to the SNB.

Unclear Survival Benefit

The ultimate goal for every intervention in cancer treatment is to improve overall survival. In this aspect, sentinel node biopsy for melanoma remains a topic of much debate. Proponents [37–39] and detractors [40, 41] analyzing the current trials available have valid arguments in favor and against. The well known and not less controversial MSLT-1 trial [25•], failed to demonstrate definitive overall survival improvement (primary endpoint) in patients with intermediate thickness melanoma undergoing SNB. Disease-free survival and subgroup analyses appear to show a tendency towards benefiting the SNB approach [42] but with statistical caveats and potential misinterpretations.

Even though some authors have stated that micrometastases in the sentinel node are destined to be destroyed [43], from the tumor biology perspective, the rationale for suggesting that patients undergoing SNB could improve survival is that some proportion of positive sentinel nodes, no matter what the size of the metastatic deposit, will progress to clinical nodal disease. It is our opinion that although there is not yet a clear understanding of the behavior of these micrometastases, there is no evidence that these malignant deposits provide clinical benefit and these metastases with the potential to progress are better removed for the patient than left intact.

Opportunity for Adjuvant Treatment and Clinical Trials Enrollment

To date, no standard effective adjuvant systemic treatment exists for melanoma. Some authors have suggested that, in the absence of effective adjuvant therapy for melanoma, the role of SNB as a staging procedure is minimal. However, recent publications have changed the panorama in melanoma

treatment, with new reports showing improved survival in patients with distant metastatic melanoma [44, 45]. The drugs ipilimumab and vemurafenib are now approved by the US Food and Drug Administration (FDA) to be used in patients with metastatic melanoma. Whether this will translate to the adjuvant setting is pending, but certainly encouraging.

Currently, and more than ever before, accurate nodal staging information is crucial in order to stratify patients according to prognosis and be able to appropriately offer patients enrollment in ongoing clinical trials. SNB also remains useful in counselling patients regarding available adjuvant therapies such as interferon (IFN- α).

Beyond Intermediate Thickness and Trunk and Extremities

If the role of SNB in the management of malignant melanoma is embraced, we might acknowledge that majority of the evidence is for patients with intermediate thickness (1.01–4.00 mm) melanoma and mostly located in the trunk or extremities.

Some authors have reported 58 % to 65 % 5-year survival of patients with node-negative T4 or thick (>4 mm) melanoma, suggesting that in this subgroup of patients, SNB may have the same role as in intermediate thickness patients [46, 47]. A population-based study performed by our institution supports this practice; furthermore, we found that 90 % of the patients with thick melanoma that were analyzed presented with no metastatic disease at diagnosis [48].

In a recent large single-institutional series of primary melanomas with head and neck location [49], SNB demonstrated to be accurate and a prognostic tool in the management of these patients, challenging earlier reports that stated the opposite [50, 51]. In our institution, we discuss and offer SNB to patients with melanomas ≥ 0.75 mm located in the head and neck region. We previously published the technical difficulties of performing SNB in the head and neck: the anatomic complexity of the area, the potential for injury to cranial nerves, variable lymphatic drainage patterns (frequently bilateral), the frequency of intraparotid sentinel lymph nodes, as well as the incision planning for cosmetic outcomes and inclusion in potential further therapeutic dissections [22].

Conclusions

In the absence of effective treatment options for patients diagnosed with malignant melanoma, physicians have explored different options to offer optimal care with limited tools. The SNB technique was developed with the goal of identifying patients with subclinical regional nodal metastases without undergoing a full regional nodal basin dissection.

Compelling evidence has demonstrated the staging value of SNB with minimal morbidity. This staging information is one of the strongest prognostic factors that can be incorporated into the overall treatment algorithm, whether it includes regional surgery, systemic treatment, research-related eligibility, or individualized survival estimates.

However, with the advent of personalized medicine and the promise of new and efficacious targeted therapy, now and more than ever it is paramount to accurately stage patients to be enrolled in current and future trials.

The surgical literature supports that SNB has high accuracy and low morbidity when completed by skilled teams dedicated to the management of melanoma patients. We strongly advocate that this procedure should be offered in a multidisciplinary setting in a high-volume referral center.

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