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# Sentinel Lymph Node Biopsy in Head and Neck Melanoma: A Review

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## Abstract

The incidence of melanoma in the United States continues to rise. Head and neck melanomas comprise approximately 20% of all primary cutaneous melanomas. Sentinel lymph node (SLN) biopsy (SLNB) has become the standard of care for staging in melanoma. It has a number of advantages, including the addition of prognostic information, accurate staging, and the potential to add completion lymph node dissection (CLND) or adjuvant therapy when indicated. Furthermore, it may allow for the identification of patients who would benefit from inclusion in clinical trials; this advantage may be amplified based on the introduction of novel targeted therapies.

SLNB does have some disadvantages in head and neck melanomas. The complex lymphatic drainage and anatomy of the head and neck can result in some technical challenges. SLN positivity rates in head and neck melanoma are lower than for trunk or extremity melanoma; despite this, overall and disease free survival rates are lower in head and neck melanoma.

This review examines the literature evidence for the efficacy of SLNB in head and neck melanoma, and in particular attempts to estimate five variables: the likelihood of finding a SLN, the number of SLNs found, the likelihood of a positive SLN, the likelihood of identifying positive non-sentinel lymph nodes on CLND, and the likelihood of recurrence in the neck despite a negative SLNB.

Overall, despite the technical challenges inherent in SLNB when applied to head and neck melanoma, it remains a technically feasible and effective procedure in this anatomic site. (*J Patient-Centered Res Rev.* 2014;1(1):27-32.)

## Keywords

melanoma, head and neck, sentinel lymph node biopsy

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## Introduction

The incidence of melanoma in the United States continues to rise, with an estimated 76,690 new cases and 9,480 deaths in 2013 alone.<sup>1</sup> Although the incidence is increasing, survival is also improving over time, likely due to earlier detection. Head and neck melanoma represents 20% of all primary cutaneous melanomas.<sup>2</sup> Prognostic factors for head and neck melanoma include a patient's age,<sup>3</sup> sex,<sup>4</sup> depth of tumor,<sup>5</sup> ulceration,<sup>6</sup> number of mitotic factors per high power field,<sup>7</sup> specific location of tumor site<sup>8,9</sup> and most importantly the sentinel lymph node (SLN) status.

First introduced in 1992 by Morton,<sup>10</sup> sentinel lymph node biopsy (SLNB) has become the standard of care for staging in head and neck melanoma patients. This technique of lymph node mapping was created as a minimally invasive alternative to elective lymph node dissection for nodal staging. It allows for detection of patients with occult nodal metastases who may benefit from a completion lymph node dissection (CLND). The procedure can be performed in one of two ways (or as a combination): preoperatively using a radiotracer (usually technetium 99m (Tc99)), or intraoperatively using Isosulfan blue dye. Several studies have shown that using a combination of the two methods improves results.<sup>11,12</sup> The idea is that either technique will identify the first echelon lymph node(s) draining the tumor site.<sup>13</sup> Many centers also use preoperative mapping with the addition of single photon emission CT (SPECT) to determine the location of the lymph node prior to surgery.

Intraoperatively, four injections are made using Isosulfan blue dye around the primary tumor. Next, wide local excision of the primary tumor is performed. At this point the surgeon makes an incision over the area identified preoperatively by lymphoscintigraphy and dissection is performed to identify the blue-stained lymph node(s). The handheld gamma probe is used to confirm the SLN by its high counts and the subsequent presence of only background radiation once the node or nodes have been removed.<sup>13</sup> Pathologic analysis is performed and if metastatic melanoma is present in the lymph node(s) the patient is a candidate for a CLND of the adjacent nodal basins in the ipsilateral neck.

Unfortunately, SLNB in the head and neck does have some limitations. Many of these are related to the more complex lymphatic drainage in the head and neck, compared to the extremities or trunk. This complexity has raised concerns about the reliability of SLNB in the setting of head and neck melanoma to accurately reflect the status of the entire nodal basin. Cervical lymphatic drainage is interlacing and can be watershed in nature; at least one-third of primary melanomas of the head and neck will show drainage to nodal basins outside the parotid bed and/or neck levels that are usually dissected when performing elective nodal dissections. O'Brien et al.<sup>14</sup> demonstrated this complexity of lymphatic drainage in the head and neck by reporting a 34% discordance between the clinical prediction of lymphatic drainage and lymphoscintigraphy findings in 97 cases of head and neck cutaneous melanoma.

Another potential pitfall with the use of SLNB for head and neck melanoma is the possibility of a "false-negative" result. Patients with negative SLNs are considered unlikely to have nodal metastatic disease, and therefore may not be offered follow-up CLND or adjuvant therapy. Various authors have described "false-negatives" for SLNB in the head and neck in different ways; some report any nodal recurrence after a negative SLNB as a "false-negative," while others report only "in-basin" nodal recurrence. Still others exclude nodal recurrence as a "false-negative" if it occurs in conjunction with local or distant recurrence. This makes the reporting of "false-negatives" difficult to compare across studies. What is agreed upon is that SLNB in the head and neck has lower rates of positive SLNs than SLNB used for trunk or extremity melanoma.<sup>15</sup> In addition, despite the fact that SLN positivity is a strong negative prognostic factor for survival in melanoma, head and neck melanomas have lower rates of disease-free and overall survival.<sup>15,16</sup> This implies a higher rate of "false-negatives" for head and neck melanoma than melanomas in other anatomical sites.

The head and neck is a relatively small area of the body that contains arguably the most complex anatomy. The potential for damage to important anatomic structures is a real and serious concern in the setting of all procedures in the head and neck, but perhaps more so in the setting of SLNB due to limited surgical exposure. If the SLN is contained within the parotid bed, a superficial parotidectomy may be required in order to adequately expose and preserve the facial nerve, which adds to the risk of the procedure and operative time.

Perhaps the most important limitation of SLNB is the fact that CLND following detection of a positive SLN has not

been proven to improve survival. Several studies have shown that there is no significant difference in disease-free or disease-specific survival between patients with melanoma who undergo SLNB alone compared with those that have a CLND.<sup>17,18</sup> In fact, Bilimora et al. used the National Cancer Data Base in the United States and found that only 50% of patients in the United States who have a positive SLNB undergo a CLND.<sup>19</sup> Arguments for CLND include regional disease control and accurate staging.

Despite the above limitations, most clinicians agree that SLNB in the setting of head and neck cutaneous melanoma remains the standard of care. It is well established that the status of the SLN is the most important predictor of survival in patients with melanoma.<sup>20</sup> Thus, SLNB acts as an important diagnostic staging procedure to facilitate further treatment for patients with head and neck melanoma. In particular, it allows for early CLND for management of neck metastasis. As a staging procedure SLNB allows clinicians to stratify patients when reporting treatment outcomes and/or when grouping patients within clinical trials. Finally, the approval by the Federal Drug Administration (FDA) in the United States of targeted therapies for melanoma represents the most important advancement in melanoma treatment in decades. Currently, the anti-CLA4 blocking antibody ipilimumab and the BRAF inhibitor vemurafenib are FDA-approved, with other molecularly targeted antibodies such as dabrafenib (BRAF), trametinib (anti-MEK), and salmetinib (anti-MEK) potentially available in the near future.<sup>21</sup> The exact role for these targeted therapies in the adjuvant setting is the subject of current clinical trials; stratification of patients to identify those at high risk for recurrence (as SLNB does) is critical for their appropriate inclusion in these trials. With further development of these exciting treatments SLNB may well play a critical role in personalized treatment for patients with melanoma.

In 2011, de Rosa et al. published a systematic review of the use of SLNB in head and neck melanoma.<sup>22</sup> This paper reported on the published literature up to and including 2009, and reported a number of important variables that could be used to evaluate the benefits of SLNB in head and neck melanoma, including the likelihood of identification of a SLN, the median number of SLNs identified, the rate of SLN positivity, the incidence of positive non-sentinel lymph nodes (NSLNs) found during CLND, and the incidence of recurrence in the neck despite a negative SLNB. They identified a trend toward an increased SLN identification rate (a key component to successful use of SLNB in melanoma) in studies published in later years. The purpose

of this current review is to update the results of the de Rosa systematic review using publications since 2009, as part of an ongoing assessment of the efficacy of SLNB for head and neck melanoma.

## Methods

### Search Strategy

A computerized literature search was performed using Ovid, Medline, Embase, and PubMed databases using the terms “melanoma,” “head and neck neoplasms,” “head and neck cancer,” “sentinel lymph node” and “sentinel lymph node biopsy.” The results were limited to English publications from 2010 to September 13, 2013. Once duplicates were identified and removed, the retrieved articles were then reviewed to ensure their relevance for our review. Once all articles to be included were identified, the references of all included articles were reviewed to identify any additional applicable publications that may have been missed by our original search.

### Inclusion & Exclusion Criteria

Inclusion criteria consisted of studies:

- a. completed in 2010 or later
- b. with 100 or more patients
- c. that report clearly the following outcomes of SLNB for cutaneous malignant melanoma of the head and neck:
  - i. likelihood of identifying a SLN
  - ii. number of SLNs identified
  - iii. odds of detecting a positive SLN
  - iv. identification of positive non-sentinel nodes during completion neck dissection
  - v. risk of nodal recurrence after negative SLNB

Studies were excluded if they did not meet the above inclusion criteria resulting in a total of 12 included studies. See Figure 1 for Consort diagram.

## Results

### 1. Likelihood of identifying a sentinel lymph node

In a meta-analysis of 3,442 patients from 32 studies up to 2009, de Rosa et al. reported the identification of at least one SLN in 95% of cases.<sup>22</sup> Several other authors have published individual institution reviews since 2009 (Table 1). The range of SLN identification rates for head and neck melanoma in these more recent reports, when averaged together, showed a 98% rate in 1,575 patients. These reports confirm the fact that, despite the complex lymphatic drainage in the head and neck, in the vast majority of cases at least one SLN is identified during SNLB for head and neck melanomas.

**Table 1.** Rate of identification of a sentinel lymph node (SLN).

Author	Year	Patients	SLN identification rate
de Rosa <sup>22*</sup>	2011	3,442	95%

Author	Year	Patients	SLN identification rate
Patuzzo <sup>23</sup>	2013	331	98%
Saltman <sup>24</sup>	2010	236	92%
Parrett <sup>25</sup>	2012	365	99%
Erman <sup>26</sup>	2012	353	100%
Miller <sup>27</sup>	2011	153	98%
Jensen <sup>28</sup>	2013	137	97%
Total/ Weighted Average		1,575	98%

\*de Rosa is a meta-analysis of 32 studies. The others are single institution studies.

### 2. Number of sentinel lymph nodes identified

A number of authors have reported on the average number of SLNs identified during SLNB for head and neck melanoma (Table 2). de Rosa reported a median of 2.6 SNs per patient in her 2009 systematic review. Three subsequent individual series have published mean SLN harvest rates ranging from a low of 1.6 to a high of 3.7; the weighted average of these subsequent series was 2.5 in 1,070 patients. Thus, there is evidence that roughly 2-3 sentinel nodes are obtained on average during SLNB for head and neck melanoma.

**Table 2.** Number of sentinel lymph nodes identified.

Author	Number of Patients	Median or Mean	SLNs per patient
de Rosa <sup>22</sup>	3,442	Median	2.6

Author	Number of Patients	Median or Mean	SLNs per patient
Patuzzo <sup>23</sup>	331	Mean	1.6
Parrett <sup>25</sup>	365	Mean	3.7
Jensen <sup>28</sup>	137	Mean	2.6
Al Ghazal <sup>29</sup>	237	Mean	1.9
Total/Weighted Average	1,070	Mean	2.5

### 3. Odds of detecting a positive sentinel node

In her 2009 systematic review, de Rosa published a 15% rate of identifying at least one positive SLN during SLNB for head and neck melanomas. A number of authors have added their single institution reports to this literature since 2009 (Table 3). The odds of a positive sentinel node in these reports ranged from 9–20%, and the weighted average was 14% in a total of 2,450 patients.

**Table 3.** Odds of detecting a positive SLN

Author	Number of Patients	Rate of + SLN
de Rosa <sup>22</sup>	3,442	15%

Author	Number of Patients	Rate of + SLN
Patuzzo <sup>23</sup>	331	18%
Saltman <sup>24</sup>	216	13%
Parrett <sup>25</sup>	365	11%
Martin <sup>30</sup>	339	14%
Fadaki <sup>16</sup>	360	11%
Jensen <sup>28</sup>	137	9%
Al Ghazal <sup>29</sup>	237	20%
McDonald <sup>31</sup>	315	15%
Miller <sup>27</sup>	150	12%
Total/Weighted Average	2,450	14%

### 4. Identification of positive non-sentinel nodes during completion neck dissection

In the presence of a positive SLN, the standard treatment is to perform an ipsilateral CLND. Recent literature has questioned the necessity for a CND in this scenario; an important consideration in this decision is the probability that other NSLNs are found to contain cancer during this dissection. In her systematic review, de Rosa reported that in 12 evaluable studies, 14% of cases contained positive NSLNs; the total number of evaluable cases was not reported. We identified six subsequent papers in which the rate of positive non-sentinel nodes in CLND was evaluable (Table 4); the rate ranged from 21–39%, and the weighted average was 27% in 249 neck dissections. This was the only variable which showed a significant discrepancy between de Rosa’s meta-analysis and the subsequent cases series published in the literature.

**Table 4.** Odds of detecting positive NSLNs on CND

Author	Number of Patients	Rate of + NSLN
de Rosa <sup>22</sup>	3,442	14%

Author	Number of Patients	Rate of + NSLN
Gyorki <sup>32</sup>	36	22%
Patuzzo <sup>23</sup>	59	39%
Parrett <sup>25</sup>	37	22%
Erman <sup>26</sup>	68	25%
Al Ghazal <sup>29</sup>	31	21%
Miller <sup>27</sup>	18	22%
Total/Weighted Average	249	27%

### 5. Risk of nodal recurrence after negative SNB

Head and neck melanomas are known to have higher recurrence rates despite a negative SLNB than trunk or extremity melanomas. As described earlier, different authors have reported “false-negative” rates for SLNB in head and neck melanoma differently. We restricted our analysis to the description of nodal recurrence (of any kind, with or without other sites of recurrence) after a negative sentinel node biopsy.

In de Rosa’s systematic review, the overall incidence of nodal recurrence after a negative SNB was 5%; again, the overall number of patients was not reported. In five large series published since then, very similar and quite uniform rates of such nodal recurrence have been identified (Table 5), ranging from 4–7%; the weighted average was 6% in 1,202 patients.

**Table 5.** Rate of nodal recurrence despite a negative SLNB

Author	Number of Patients	Nodal Recurrence
de Rosa <sup>22</sup>	3,442	5%

Author	Number of Patients	Nodal Recurrence
Saltman <sup>24</sup>	190	6%
Parrett <sup>25</sup>	325	5%
Erman <sup>26</sup>	283	7%
Jensen <sup>28</sup>	137	4%
McDonald <sup>31</sup>	267	6%
Total/ Weighted Average	1,202	6%

## Discussion

Sentinel lymph node biopsy has been an important element in the treatment of melanoma since Morton's landmark paper in 1992.<sup>10</sup> While it has not demonstrated improved overall and disease-specific survival, the use of SLNB has a number of advantages over observation alone, including the addition of valuable prognostic information, the ability to restrict CLND to patients likely to benefit from it, the improvement of regional control, and the identification of high-risk patients that may benefit from adjuvant therapy and/or inclusion in clinical trials. The advent of a new generation of targeted therapies may well enhance the therapeutic benefit of SLNB, as studies of the benefit of these therapies in the adjuvant setting become available.

Despite a number of challenges that are unique to the head and neck, including more complex lymphatic drainage patterns and specific anatomic issues (for example, the facial nerve in parotid SLNB), head and neck SLNB as a technical exercise remains extremely feasible. Improvements such as pre-operative localization using SPECT/CT fusions have allowed for the successful intraoperative identification of at least one SLN in nearly 100% of cases, and rates of successful SLN identification seem to be increasing with time. Overall, an average of two to three SLNs are identified in the typical head and neck melanoma case, and at least one positive SLN is identified roughly 15% of the time. While the "false-negative" rate for SLNB in head and neck melanoma is higher than in other anatomical sites, a negative SLNB is associated with later nodal recurrence in the neck only about 5% of the time.

A remaining controversy relates to the utility of CLND in the presence of a positive SLNB. Multiple authors have shown that, in the presence of a positive SLN, other, non-sentinel lymph nodes will be found on CLND in head and neck melanoma roughly 15-25% of the time. Certainly, one would expect to see a benefit from CLND in these cases, but such a benefit has not been conclusively and reproducibly demonstrated in studies. The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) is a randomized Phase III trial of SLNB plus CLND vs. SLNB plus ultrasound observation of the lymph nodes in patients with positive SLNs detected by histopathologic or molecular techniques.<sup>33</sup> MSLT-II's primary outcome is melanoma-specific survival, while the secondary outcomes include overall and disease-free survival, prognostic accuracy of histopathologic, molecular, and immunologic markers, and quality of life. The trial opened in 2005 with an aim to enroll 1,925 subjects. This trial could help to better delineate the situations in which CLND after positive SLNB would be beneficial to the patient.

## Conclusions

Sentinel lymph node biopsy is a technically feasible and safe procedure for head and neck melanoma. It has multiple advantages, including the addition of prognostic information, the potential for adding CLND, and the identification of patients who would benefit from adjuvant therapy and/or inclusion in clinical trials. It remains an important element of treatment for head and neck melanomas.

## Conflicts of Interest

None.

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