Incidence and location of positive nonsentinel lymph nodes in head and neck melanoma


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Abstract

Background: The complex lymphatic drainage in the head and neck makes sentinel lymph node biopsy (SLNB) for melanomas in this region challenging. This study describes the incidence, and location of additional positive nonsentinel lymph nodes (NSLN) in patients with cutaneous head and neck melanoma following a positive SLNB.

Methods: A retrospective review was performed using a single institution prospective database. Patients with a primary melanoma in the head or neck with a positive cervical SLNB were identified. The lymphadenectomy specimen was divided intraoperatively into lymph node levels I–V, and NSLN status determined for each level.

Results: Of 387 patients with melanoma of the head and neck who underwent cervical SLNB, 54 had a positive SLN identified (14%). Thirty six patients (67%) underwent immediate completion lymph node dissection (CLND) of whom eight patients (22%) had a positive NSLN. The remaining 18 patients (33%) did not undergo CLND and were observed. Half of positive NSLNs (50%) were in the same lymph node level as the SLN and 33% were in an immediately adjacent level; only two patients were found to have NSLNs in non-adjacent levels. The only factor predictive of NSLN involvement was the size of the tumor deposit in the SLN > 0.2 mm (p = 0.05). Superficial parotidectomy at CLND revealed metastatic melanoma only in patients with a positive parotid SLN.

Conclusions: A positive NSLN was identified in 22% of patients undergoing CLND after a positive SLNB. The majority of positive NSLNs are found within or immediately adjacent to the nodal level containing the SLN.

Keywords: Sentinel lymph node biopsy; Melanoma; Non-sentinel lymph node; Neck dissection; Parotidectomy; Completion lymphadenectomy

Introduction

Approximately 20% of primary cutaneous melanomas arise in the head and neck.1 Sentinel lymph node (SLN) biopsy (SLNB) is able to accurately identify early nodal micrometastatic disease, and lymph node status is the strongest prognostic factor for patients with clinically lymph node negative melanoma. For patients with a positive SLNB, the standard of care is completion lymph node dissection (CLND), although a recent meta-analysis reported that only 14% of SLNB positive patients will have additional positive nodes found at CLND.1

Most studies of CLND for patients with positive SLNB have included patients with primary melanoma of all sites.2–5 This information may therefore not be relevant to the head and neck because completion neck dissection has some unique features when compared with CLND in the axilla or groin,6 including the complex anatomy and structures at risk, the frequent proximity of the primary lesion to the lymph node basin as well as the lower rates of long term morbidity, specifically lymphedema. These factors have lead to a lack of consensus on the need for
CLND for patients with a positive SLN in the head and neck, as demonstrated by a recent SEER data analysis which reports that only 60% of patients with a positive SLN in the head and neck underwent CLND. This paper describes a single center experience with positive SLNB for melanoma of the head and neck, and details the incidence and location of positive nonsentinel lymph nodes (NSLN) in these patients.

Materials and methods

Patients

All patients undergoing SLNB at Memorial Sloan-Kettering Cancer Center since January 1996 have been prospectively entered into a comprehensive melanoma database. Follow up data is maintained regularly. All patients with a melanoma in the head and neck region who had a positive sentinel lymph node identified were included in the analysis. Patient records were reviewed for details of the SLNB and CLND pathology specimens. The use of patient records for this study was approved by the institutional review board.

Sentinel lymph node biopsy

SLNB has been offered to most patients with melanoma of Breslow thickness greater than 1.0 mm as standard of care since 1996. The technique has been previously described. The majority of patients had combined pre-operative lymphoscintigraphy with technetium sulphur colloid and intraoperative isosulfan blue dye injection. The surgeon records the lymphatic basin containing the SLN at the time of surgery. SLNs are sent for routine pathologic analysis (as detailed below), although in the early years of this study, SLNs were sometimes evaluated with frozen section.

Lymph node evaluation

Sentinel lymph nodes are bivalved and paraffin embedded. Standard pathological analysis of SLNs involves three sections at different levels with hematoxylin and eosin (H&E) staining. In SLNs with no evidence of metastatic disease, immunohistochemical workup includes S-100P and Melan A. Lymph node specimens from CLND are separated from the surrounding fat and a single section per node is stained with H&E only.

Completion lymph node dissection

The decision to perform CLND and the extent of CLND following a positive SLNB were at the discretion of the individual surgeon in discussion with the patient. At the time of CLND it has been our standard practice to divide the lymphadenectomy specimen in the operating room into lymph node levels I–V. These specimens were then submitted separately for pathological analysis. Review of operative and pathology reports identified the lymph node basins dissected to identify sites of positive NSLN. An analysis of practice trends in completion lymphadenectomy over time was performed.

Statistical analysis

Categorical variables were compared using the Chi Squared test. Recurrence and survival outcomes were determined by the Kaplan Meier method and estimates of survival distribution differences were compared using the log rank test. The a priori level of alpha was 0.05.

Results

Patient details

Between January 1996 and June 2012, 387 patients with a primary cutaneous melanoma of the head and neck underwent SLNB at our institution. At least one positive SLN was identified in 54 patients (14%) and these patients constitute the study population. Immediate CLND was performed in 36 of these patients (67%); ten patients underwent CLND at the time of SLNB on the basis of positive frozen section diagnosis while five patients had a negative frozen section result with metastatic melanoma found on subsequent detailed examination (21 patients did not have frozen section and underwent CLND as a second operation. The remaining 18 patients with positive SLN were managed with a ‘watchful waiting’ approach (Table 1). The proportion of patients managed without CLND after a positive SLN has increased over the period of the study (Fig. 1). This is particularly the case for patients with low volume (<0.2 mm) metastatic disease in the SLN where

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<th>Details and demographics for patients undergoing completion lymph node dissection (CLND) or watchful waiting.</th>
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since 2007 less than half of patients have undergone CLND (Fig. 1).

Of the 36 patients who had CLND, a positive NSLN was identified in eight (22%). The only factor predictive of a positive NSLN was the size of the tumor deposit in the SLN \((p = 0.05)\) (Table 2). The extent of CLND was not associated with the presence of a positive NSLN \((p = 0.49)\). A full level I–V CLND was performed in 33% of cases, four levels were dissected in 53% \((89\%\) of these omitted level 1 and 11% omitted level 5) and 3 levels or less were dissected in 14% of cases. The extent of CLND was not associated with the incidence of positive NSLN. No difference was identified in primary tumor characteristics or in the number of SLNs harvested or the number of positive SLNs between patients with a positive or negative NSLN (Table 2). The ratio of positive to total SLNs was 0.6 and 0.7 for patients with positive and negative NSLNs respectively.

### Location of positive non-sentinel lymph nodes

The relationship of the location of positive NSLN to that of the positive SLN in 8 patients is illustrated in Fig. 2. Nine positive SLNs were identified in these eight patients. A further 18 positive NSLNs were found at CLND. Half of NSLNs \((50\%)\) were in the same lymph node level as the SLN and a further \(33\%\) were in an adjacent lymph node level. In one patient with a positive preauricular SLN, metastatic disease was identified in a level V NSLN and in another patient with a positive level I SLN, a level III NSLN was identified with metastatic melanoma.

### Parotidectomy

Fourteen patients \((39\%)\) had a parotidectomy as part of their completion lymphadenectomy (Table 3). As expected, a higher proportion of patients with a positive intra-parotid or periparotid SLN had a superficial parotidectomy \((42\%)\) than patients with a positive SLN in another region \((21\%)\) \((p = 0.3)\). A positive intra-parotid NSLN was seen in only two patients, both of whom had a positive periparotid SLN. None of the nine patients who had superficial parotidectomy for a positive non-parotid SLN had a positive parotid NSLN \((p = 0.04)\). One patient with a positive level one sentinel lymph node had a positive periparotid NSLN (Fig. 2B) located high in the jugular chain, however the superficial parotidectomy specimen did not contain metastatic melanoma.

### Recurrence and survival outcome

After a median follow up of 27 months \((30\text{ months for CLND group and 25 months for no CLND})\), the nodal recurrence rate in patients undergoing CLND was \(11.1\% (4/36)\) compared with \(28\% (5/18)\) in those without CLND \((p = 0.15)\). Two of the four patients in the CLND group had positive NSLN at the time of their initial CLND. Two of the recurrences were in previously dissected nodal basins and two were parotid recurrences in patients who had not undergone parotidectomy at the time of primary CLND. Both patients with parotid recurrences had an SLN in level II, and high risk features (one patient had a positive NSLN and the other had an ulcerated primary with high mitotic rate). In all five patients with nodal...
recurrence in the observation group, the recurrent disease was in the same or in an adjacent lymph node level to the level containing the original positive SLN. Only one patient with a nodal recurrence presented with synchronous distant metastasis.

Of the seven patients with a positive parotid region SLN who did not undergo parotidectomy, two recurred in cervical lymph nodes (neither of whom had undergone initial CLND). Both patients subsequently underwent CLND without superficial parotidectomy and remain NED without recurrent disease in the parotid gland.

There was no difference in disease specific survival (DSS) between patients with positive and negative NSLN at the time of CLND (5-year DSS 67% vs. 35%, \( p = 0.7 \)). There was also no difference noted in RFS (\( p = 0.34 \)) or DSS (\( p = 0.41 \)) between patients undergoing CLND and those under observation (Table 1). The small number of patients in these groups does not allow meaningful interpretation of these survival data.

Discussion

SLNB has become routine in many centers since the publication of the multicenter selective lymphadenectomy trial-1 (MSLT-1) in 2006.\(^9\) Although this trial did not show a benefit in overall survival for SLNB and subsequent CLND over observation and delayed lymphadenectomy, it did demonstrate the strong prognostic significance of a positive SLNB. This trial also found a lower accuracy of SLNB in head and neck melanoma patients compared to other anatomic sites. This difference can be attributed to the complex lymphatic anatomy, small nodal size and frequent proximity of the SLN to the primary tumor in head and neck melanoma.\(^{10}\)

While the prognostic significance of a positive SLNB is clearly defined, the added prognostic or therapeutic benefit of CLND remains unclear.\(^{11}\) The latest guidelines from the American Society of Clinical Oncology and the Society of Surgical Oncology recommend CLND for all patients with
a positive SLNB. However, a report from the National Cancer Database found that only half of the melanoma patients with a positive SLN undergo CLND in the United States. In contrast a recent web-based international survey of melanoma surgeons found that 91.8% of respondents recommended CLND for patients with a positive SLNB. The current study describes a trend towards foregoing CLND for select patients with positive SLNB, notably those with microscopic nodal metastasis. This practice is supported by data from large retrospective studies which show that in patients with low volume micrometastatic disease in the SLN, the chance of identifying NSLN involvement at CLND is less than 10%. The move away from CLND has been described at our institution for melanoma of all primary sites. Significantly, as in this series, no difference was identified in recurrence free or overall survival between those with and without CLND. Caution must be used in interpreting these results given the selection bias in patient selection as evidenced by a higher proportion of patients with micrometastatic disease in the observation group. The results of the MSLT-2 trial are keenly awaited to formally identify the impact of CLND in these patients.

Predictive models to determine patients at highest risk of NSLN involvement have identified clinicopathological factors predictive of positive NSLNs. These include primary tumor thickness, tumor regression, ulceration, number of sentinel nodes harvested, proportion of positive SLNs, sentinel node tumor burden, location of tumor deposit within the sentinel node, extranodal spread. The small number of patients in the current study does not provide the statistical power for a risk-prediction model. However, of the factors routinely analyzed by our pathologists, only SLN tumor burden was identified as predictive of NSLN status.

The largest study of CLND for patients with positive SLNB included 1080 patients of whom only 32 (3%) had melanoma of the head and neck. Previous series of CLND for patients with SLNB positive head and neck melanoma have revealed NSLN positive rates of 9–42%. The largest of these studies reports 69 patients with positive SLNB. Only one prior analysis correlates the location of NSLN with that of SLN in the head and neck describing five cases of positive NSLN, three of which were in the same level as the SLN, one in an adjacent level and one at a more distant (level III SLN, level I NSLN). The two cases with positive parotid NSLNs in that series correlated with an intraparotid SLN. These cases are consistent with the findings of the current study that the majority of positive NSLN are located in the same or an adjacent level to the SLN.

The anatomical distribution of NSLN is also demonstrated in the patterns of recurrence - nodal recurrences in the observation group were found in the same or an adjacent level to the SLN in all cases. As expected there was a trend toward increased nodal recurrence (p = 0.15) in the observation group compared to the immediate CLND group however this trend was not seen in RFS (p = 0.34) or DSS (p = 0.41). This finding reflects our rationale for not performing routine CLND for all patients with positive SLNB.

No guidelines exist regarding the extent of CLND for patients with positive cervical SLNB. In a recent international survey of melanoma surgeons, 34.9% reported that they would perform a comprehensive level I–V neck dissection for a positive SLNB regardless of site of the primary tumor and SLN location and 4.6% would routinely perform parotidectomy. In the remainder of respondents, the extent of operation was guided by the site of the positive SLN and lymphatic mapping pattern on lymphoscintigraphy. Data from our institution from the pre-sentinel lymph node era identified patients with a primary melanoma of the ear, face or anterior scalp at highest risk of metastatic spread to the parotid gland. However, most patients in that series underwent therapeutic lymphadenectomy for clinically involved nodes. The current study more accurately stratifies the need for superficial parotidectomy based on our finding that only patients with a positive intraparotid or periparotid sentinel lymph node were found to have a subsequent positive parotid NSLN.

Although the fraction of patients with a positive NSLN at CLND is small, the limited pathological analysis of lymph nodes at CLND may underestimate the true rates of nodal involvement. Less than half of positive SLNs are detected using routine pathological analysis and more thorough study of histologically negative lymph nodes at CLND has been associated with increased positivity. Furthermore, the recent move away from routine CLND means that the median follow up for the non-CLND group is only 25 months. A comprehensive analysis of relapse patterns in patients with stage III melanoma demonstrates that the majority of first relapses in these patients occur within the first 24 months and therefore longer follow up would not be expected to change our observations.

It is difficult to make recommendations regarding CLND or its extent for patients with a positive SLN in the head and neck on the basis of this small, selected group of patients. The decision for CLND after a positive SLNB should therefore be based on a clinical estimation of risk vs. benefit. When CLND is considered for management, knowledge of the likely location of NSLN may be helpful to the surgeon when planning their nodal dissection.

Conclusion

The optimal management of patients with positive SLNs in head and neck cutaneous melanoma remains controversial. This study describes a single center experience of CLND for head and neck melanoma and demonstrates that after a positive SLNB in the neck, the NSLN positive rate is 22%. Furthermore, the majority of positive NSLNs are found within or immediately adjacent to the nodal level containing the SLN. Positive intraparotid NSLNs are only found in cases...
of positive periparotid SLNs and if CLND is performed, superficial parotidectomy should be reserved for these patients.

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Conflict of interest statement

No authors have any conflicts of interest to disclose.

References