

Sentinel lymph node biopsy for ocular adnexal melanoma

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ABSTRACT.

Background: We sought to update our prior report of findings on sentinel lymph node biopsy (SLNB) and predictors of a positive SLN in patients with conjunctival or eyelid melanoma.

Methods: We reviewed the records of all patients with ocular adnexal melanoma who underwent SLNB at one institution during 2000–2015. We determined rates of positive and false-negative findings on SLNB, primary tumour features correlated with positive findings and rate of nodal recurrence (false-negative event) after negative findings.

Results: The study included 51 patients, 31 with conjunctival and 20 with eyelid melanoma. These patients include 30 patients who underwent SLNB during 2000–2008, described in our previous report, and 21 additional patients who underwent SLNB during 2008–2015. There were 30 women and 21 men with median age at SLNB of 62 years (range, 24–83). The nodal basins most commonly sampled were intraparotid (27 patients) and level II (14 patients). Ten patients had positive SLNB findings. Compared to tumours with negative findings, tumours with positive findings had greater median thickness (3.5 mm versus 2.2 mm, $p = 0.04$), greater median number of mitotic figures (6 versus 2, $p = 0.03$) and greater incidence of ulceration (80% versus 26%, $p = 0.003$). Perineural and vascular invasion were not significantly associated with positive findings. There were three false-negative events. Three patients (6%) had temporary marginal mandibular weakness which resolved spontaneously.

Conclusion: SLNB in patients with ocular adnexal melanoma is safe and identifies nodal micrometastasis in approximately 20% of cases. Histologic features associated with a positive SLN included greater tumour thickness, greater number of mitotic figures and ulceration.

Key words: biopsy – melanoma – ocular adnexa – sentinel lymph node

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Introduction

Lymph node status provides important prognostic and staging information in patients with conjunctival and cutaneous melanoma and is part of the American Joint Committee on Cancer (AJCC) Tumor, Nodes, Metastasis (TNM) staging system for these diseases. Sentinel lymph node biopsy (SLNB), a less invasive alternative to elective regional lymphadenectomy, is an effective method for detecting microscopic metastasis in regional lymph nodes. Adaptation of SLNB for ocular adnexal melanoma (eyelid and conjunctival melanoma) has been well established in the literature by our group and others (Esmali et al. 2001; Wilson et al. 2001; Ho et al. 2007; Esmali 2008; Savar et al. 2009). This report is an update of our experience to date with SLNB for ocular adnexal melanoma at the University of Texas MD Anderson Cancer Center. It provides long-term follow-up information on patients previously reported by our group and also covers patients who underwent SLNB after the period covered by our previous publication (Savar et al. 2009).

Methods

All eligible patients who agreed to undergo SLNB for conjunctival or eyelid melanoma as part of an ongoing

prospective clinical trial at MD Anderson Cancer Center between December 2000 and June 2015 were included in this report. All patients with ocular adnexal melanoma who underwent SLNB off protocol were also included ($n = 9$). Appropriate Institutional Review Board approval was obtained for this study.

During the period covered by this study, patients at our institution were eligible for SLNB if they met the following criteria:

- (1) Eighteen years of age or older.
- (2) Histologically documented malignant melanoma of the conjunctiva and/or eyelid at least 1 mm thick or < 1 mm thick but with evidence of ulceration, > 1 mitotic figure per mm² or Clark level IV (in the case of eyelid skin melanomas).
- (3) No evidence of metastasis on chest radiography, liver enzyme analysis, and computed tomography or magnetic resonance imaging of the head and neck.
- (4) No evidence of metastasis on sonography of regional lymph nodes within 6 weeks before study enrolment.

Females who were pregnant or nursing were not offered SLNB

Our technique for planning and performing intraoperative SLNB has been described in several previous reports by our group (Ho et al. 2007; Savar et al. 2009; Pfeiffer et al. 2013). Briefly, 0.3–0.4 mCi of technetium in 0.2 cc volume was injected around the site of the primary lesion. For conjunctival lesions, the injection was administered subconjunctivally. For eyelid skin or eyelid margin lesions, it was administered intradermally. In some patients with conjunctival melanoma, the conjunctival lesion had already been excised by the referring physician before the patient underwent SLNB at our centre. Sentinel lymph node biopsy has proven to be effective at identifying the correct draining node even in such patients. This observation was described in detail in one of our previous publications outlining exactly such a patient who had a histologically positive sentinel lymph node that was identified via SLNB 6 weeks after the excision of the primary bulbar conjunctival melanoma had taken place at an outside facility prior to referral to our centre (Esmali et al. 2003).

Disease was staged at the time of treatment according to the AJCC staging system for conjunctival melanoma or, for patients with eyelid margin or eyelid skin melanoma, cutaneous melanoma.

Patient records were reviewed for demographic, clinical and tumour characteristics. Demographic variables recorded included age and sex. Clinical characteristics recorded included date of presentation, date of excision of primary tumour, date of SLNB, AJCC stage and the development of recurrence or metastasis. The number of SLNs biopsied was recorded, as was the location of each SLN biopsied. Primary tumour characteristics recorded included anatomic site, histologic subtype, tumour thickness, mitotic figures, ulceration, perineural invasion and vascular invasion. Date of last contact and patient's disease status at last contact were also recorded.

Fisher's exact tests and Wilcoxon rank-sum tests were used to compare categorical and continuous variables between patients with positive and negative findings on SLNB, respectively. The Kaplan–Meier method was used to estimate the overall survival curve. All analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). p values ≤ 0.05 were considered statistically significant.

Results

During the study period, 52 patients with conjunctival or eyelid melanoma underwent intraoperative lymphatic mapping, and 51 (98%) had at least one SLN identified and biopsied. In one patient with a melanoma of the lower eyelid margin, the gamma probe did not reveal technetium in any of the regional lymph nodes at the time of primary tumour resection, and therefore, no biopsy was performed. In this patient, preoperative lymphoscintigraphy had demonstrated an unclear pattern of drainage in the bilateral submandibular areas and in the right posterior inferior cervical lymphatic chain. This patient was excluded from the analyses described below.

Demographic, clinical and histologic characteristics

The 51 patients included in the analyses included 30 patients previously reported by our group (Savar et al.

2009), along with 21 additional patients. Demographic, clinical and histologic characteristics are summarized in Table 1. The study included 30 women and 21 men. The median age at SLNB was 62 years (range, 24–83 years). There were 27 right-sided lesions and 24 left-sided lesions. Thirty-one patients (61%) had conjunctival melanoma, and 20 patients (39%) had eyelid skin or eyelid margin melanoma. The most common tumour sites were bulbar conjunctiva only (14 patients) and eyelid skin only (20 patients).

Histopathologic features were similar between conjunctiva melanoma and eyelid melanoma except for ulceration. Ulceration was present in 50% of cases of melanoma of the conjunctiva but only 20% of cases of melanoma of the eyelid margin or eyelid skin ($p = 0.04$).

The median follow-up time after diagnosis of melanoma was 63 months (range, 5–303 months), and the median follow-up time after SLNB was 61 months (range, 4–170 months). The 5-year survival rate after diagnosis of melanoma was 79% (Fig. 1).

Nodal basins sampled on SLNB and findings on SLNB

The median number of SLNs sampled was 2 (range, 1–5). The nodal basins most commonly sampled were the intraparotid basin, sampled in 27 patients and the level II (superior jugular and jugular/digastric nodes) basin, sampled in 14 patients (Table 2).

Ten patients (20%) had positive findings on SLNB: 6 of the 20 patients (30%) with a primary eyelid melanoma and four of the 31 patients (13%) with a primary conjunctival melanoma. In these 10 patients, tumour sites were as follows: eyelid skin, six patients; palpebral conjunctiva, two; bulbar conjunctiva, one; and both bulbar and palpebral conjunctiva and eyelid skin, one.

AJCC stage in patients with positive findings on SLNB

Of the four patients with conjunctival melanoma and positive findings on SLNB, one had T1cN1aM0 disease (melanoma of the bulbar conjunctiva), one had T2bN1aM0 disease (melanoma of the non-bulbar conjunctiva) and two had T3bN1aM0 disease (local invasion into the eyelids) (Table 3). All six patients with eyelid skin melanoma

Table 1. Demographic, clinical and histologic characteristics by findings on SLNB (*n* = 51).

Characteristic, no. (%)	All patients (<i>N</i> = 51)	Negative SLNB findings (<i>n</i> = 41)	Positive SLNB findings (<i>n</i> = 10)	<i>p</i> Value
Age at time of SLNB, yr*	62 (24–83)	61 (24–82)	65 (38–83)	0.51
No. of SLNs*	2 (1–5)	2 (1–5)	2 (1–4)	0.88
Tumour thickness, mm*	2.6 (0.6–14.0)	2.2 (0.6–14.0)	3.5 (1.4–7.2)	0.04
No. of mitotic figures*	3 (0.5–28)	2 (0.5–20)	6 (2–28)	0.03
Sex				0.72
Female	30 (59)	25 (61)	5 (50)	
Male	21 (41)	16 (39)	5 (50)	
Conjunctiva or skin location				0.16
Conjunctiva	31 (61)	27 (66)	4 (40)	
Skin	20 (39)	14 (34)	6 (60)	
Tumour site				0.29
Eyelid skin only	20 (39)	14 (34)	6 (60)	
Bulbar conjunctiva only	14 (27)	13 (32)	1 (10)	
Palpebral conjunctiva only	5 (10)	3 (7)	2 (20)	
Bulbar and palpebral conjunctiva	4 (8)	4 (10)	0 (0)	
Palpebral conjunctiva eyelid skin	4 (8)	4 (10)	0 (0)	
Bulbar/palpebral conjunctiva and eyelid skin	4 (8)	3 (7)	1 (10)	
Tumour side				0.73
Right	27 (53)	21 (51)	6 (60)	
Left	24 (47)	20 (49)	4 (40)	
Ulceration				0.003
Yes	18 (38)	10 (26)	8 (80)	
No	30 (62)	28 (74)	2 (20)	
Not available	3	3	0	
Perineural invasion				0.59
Yes	6 (12)	4 (10)	2 (20)	
No	43 (88)	35 (90)	8 (80)	
Not available	2	2	0	
Vascular invasion				0.15
Yes	7 (15)	4 (10)	3 (30)	
No	41 (85)	34 (90)	7 (70)	
Not available	3	3	0	
Ulceration with vascular invasion				0.11
Yes	3 (6)	1 (3)	2 (20)	
No	44 (94)	36 (97)	8 (80)	
Not available	4	4	0	
Ulceration, perineural invasion or vascular invasion				0.001
Yes	26 (55)	16 (43)	10 (100)	
No	21 (45)	21 (57)	0 (0)	
Not available	4	4	0	

* Presented in median (range).

and a positive SLN had a T3a or more advanced primary tumour (T3a: melanoma of 2–4 mm thick) (Table 4).

Histologic Features of Tumours with Positive Versus Negative Findings on SLNB

Median tumour thickness was significantly greater in patients with positive than in those with negative findings on

SLNB (3.5 mm versus 2.2 mm, *p* = 0.04). The median number of mitotic figures was also significantly greater in patients with positive than in those with negative findings on SLNB (6 versus 2, *p* = 0.03). Histologic ulceration was significantly more common in patients with positive than in those with negative findings on SLNB (80% versus 26%, *p* = 0.003).

Perineural invasion was present in two patients (20%) with a positive SLN and in four patients (10%) with a negative SLN. Vascular invasion was present in three patients (30%) with a positive SLN and in four patients (10%) with a negative SLN. Neither perineural invasion nor vascular invasion was significantly associated with positive findings on SLNB.

False-negative findings on SLNB

Three of the 41 patients with negative findings on SLNB subsequently developed clinically detectable nodal metastasis, for a false-negative rate of 7% (95% CI, 1.5–19.9). Two of these patients were reported and discussed in a previous report by our group.[3] One patient, patient 16 in the Ho et al. 2007 report, was a 70-year-old woman with melanoma involving the palpebral and bulbar conjunctiva with extension to the upper and lower eyelid skin. She was alive with parotid, liver and lung metastases at the time of that publication. One year after SLNB with negative findings, she developed recurrent disease in the parotid area.

The second patient with false-negative findings, patient 19 in the Ho et al. 2007 report, was a 57-year-old woman with melanoma involving the palpebral and bulbar conjunctiva with extension to the entire lower eyelid. She underwent wide local excision, cryotherapy and SLNB of one submandibular node. Pathology showed an epithelioid melanoma, superficial spreading type, with a tumour thickness of 12 mm, 14 mm of ulceration and six mitotic figures per square millimetre. She also underwent adjuvant external beam radiation therapy of 60 Gy. At 4 months after SLNB, she developed palpable nodes in the right submandibular and parotid area, which contained metastatic melanoma.

The third patient with false-negative findings on SLNB has not previously been reported. This patient was diagnosed with melanoma of the upper eyelid and brow at age 66 years. He underwent wide local excision and SLNB of two nodes, one parotid and one submandibular. Pathology showed an epithelial melanoma, superficial spreading type, with a tumour thickness of 0.62 mm, no ulceration, fewer than one mitotic figure per square millimetre and no perineural or

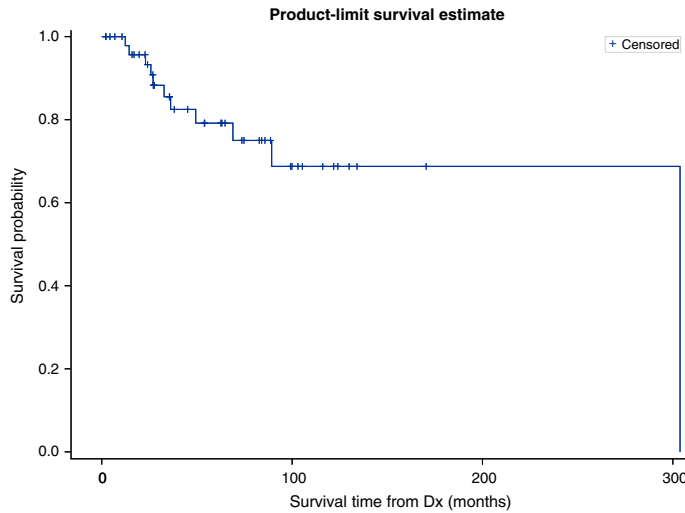


Fig. 1. Overall survival time after diagnosis. Five-year survival rate = 79.2% (95% CI, 62.2–89.1).

Table 2. Lymph node basins where SLNs were identified.

Basin	No. of SLNs identified*
External jugular	5
Facial	7
Level 1 (submandibular/submental)	11
Level 2	14
Level 3	4
Level 4	1
Level 5	1
Parotid	27
Preauricular	8

*Some patients had more than one nodal basin sampled.

Table 3. Findings on SLNB by AJCC T category in patients with conjunctival melanoma.

T Category	No. of patients with negative findings on SLNB	No. of patients with positive findings on SLNB
T1: Tumour of bulbar conjunctiva		
T1b	1	0
pT1b	2	0
T1c	1	1
pT1c	3	0
T2: Tumour of non-bulbar conjunctiva		
pT2b	3	1
T2c	1	0
pT2c	3	0
T2d	2	0
T3: Tumour with local invasion		
T3a	1	0
T3b	10	2

Table 4. Findings on SLNB by AJCC T category in patients with eyelid skin melanoma.

T Category	No. of patients with negative findings on SLNB	No. of patients with positive findings on SLNB
T1a	2	0
T1b	1	0
T2a	5	0
T3a	3	1
T3b	0	3
T4a	3	1
T4b	0	1

vascular invasion. Five years after SLNB, he developed metastatic disease in the parotid gland, which was treated with parotidectomy and neck dissection with radiation therapy. Nine years after SLNB, he developed metastatic disease in the liver, which was treated with radiofrequency ablation. At time of last contact, 10 years after SLNB, the patient's disease has been stable, and he has not required any other treatment.

These three false-negative events occurred in patients who underwent SLNB in 2003 and 2004. There were no false-negative events among patients who had SLNB during the last 11 years of this study.

Adverse events due to SLNB

Five adverse events due to SLNB were reported in the 51 patients in this

analysis. Three patients (6%) had temporary lower lip weakness in the distribution of the marginal mandibular branch of the facial nerve. The weakness of this nerve resolved spontaneously in all three patients without any specific interventions. One patient had a small haematoma of the neck, and one had a stitch abscess. Both adverse events resolved spontaneously without additional surgical interventions.

Discussion

Our findings in this series, which we believe is the largest series reported to date on SLNB for conjunctival and eyelid melanoma, expand on our earlier reports and suggest that SLNB identifies microscopic metastasis in the regional lymph nodes in close to 20% of patients with ocular adnexal melanoma. The SLN positivity rate was higher for eyelid margin or eyelid skin melanomas (30%) than for conjunctival melanomas (13%). The current report also confirms that histologic features of ocular adnexal melanoma that significantly correlate with positive findings on SLNB include greater tumour thickness, greater number of mitotic figures and presence of histologic ulceration.

We had previously reported on 30 of the patients in the present cohort; the current report provides a longer follow-up data for these 30 patients and also provides data on an additional 21 patients. Our report is based on a relatively large sample size, and several patients had a positive SLNB detected, which allowed us to analyse histologic features that may predict positive SLNB findings. The majority of reports from institutions other than ours to date on SLNB for ocular adnexal melanoma included one to four patients (Wilson et al. 2001; Vuthaluru et al. 2013; Wainstein et al. 2014). A prior study of SLNB for 18 patients with primary conjunctival melanoma showed that two patients had positive findings on SLNB, for a positivity rate of 11%. (Cohen et al. 2013) In that report, both of the conjunctival melanomas associated with positive SLNs were in non-bulbar locations. The SLNB positivity rate of approximately 20% in our current report is also greater than the 15% SLNB positivity rate previously reported for

intermediate-thickness cutaneous melanomas in non-ocular sites. (Morton et al. 2014; Bartlett et al. 2016).

Our finding of a 20% SLNB positivity rate suggests that SLNB offers an opportunity for early identification of patients with ocular adnexal melanoma who harbour metastatic disease. This is particularly important given the availability of targeted and immune-modulatory drugs, immune checkpoint inhibitors, which offer a better prognosis for patients with metastatic melanoma compared with a decade ago when these drugs were not available. (Flaherty et al. 2010; Flaherty et al. 2012; Atkins 2015) The current report included a sufficient number of patients with ocular adnexal melanoma to permit assessment of the relationship between primary tumour histologic features and SLNB positivity. For the first time, we were able to demonstrate that tumour thickness, median number of mitotic figures and ulceration correlate with positive findings on SLNB in a statistically significant way. This is an important finding and can help guide recommendations regarding which patients with ocular adnexal melanoma should undergo SLNB. This finding can further support including these histologic features in reports of pathologic features of conjunctival melanoma and in the AJCC criteria for T category. Such features are already included as an integral part of AJCC criteria for skin melanoma. In a comprehensive review of histologic features of 44 patients with conjunctival melanoma, we previously reported that tumour thickness >2.0 mm, presence of histologic ulceration and more than one mitotic figure per square millimetre predicted regional nodal metastasis and death from disease. (Esmali et al. 2012) Finally, our findings in the current report support the prognostic importance of these histologic features, and thus, the importance of reporting these features specifically in all cases of conjunctival and eyelid melanoma and in all research reports on this topic.

In our cohort, age, sex, primary tumour site and laterality of the primary tumour, number of nodes biopsied, presence of perineural invasion and presence of vascular invasion were not significantly associated with SLNB positivity.

False-negative events occurred in only 7% (3 of 51) of the patients in

our series, and these false-negative events occurred only in the early years of our experience with SLNB for ocular adnexal melanoma (Ho et al. 2007). We have had no false-negative events among patients who had SLNB in the past 10 years. The only other published report of SLNB in a relatively large cohort of patients with conjunctival melanoma reported no false-negative events in 18 patients at a median follow-up of 20 months (range, 6–36 months), but the definition of false-negative-events was not specifically described in this report (Cohen et al. 2013). In general, long-term follow-up is needed to meaningfully report on false-negative events as highlighted in one patient in our current report with a false-negative event detected as late as 5 years after a negative SLN biopsy. There were no serious adverse events associated with SLNB in our cohort. The three cases of temporary weakness of the marginal mandibular branch of the facial nerve resolved spontaneously after a few weeks without any specific interventions. In previous reports of SLNB for ocular adnexal tumours, adverse events included temporary facial weakness in one patient (Savar et al. 2009; Cohen et al. 2013), dry mouth after parotid dissection (Vuthaluru et al. 2013) and mild-to-moderate facial oedema (Vuthaluru et al. 2013); all of these adverse events reportedly resolved without intervention within days to weeks.

Despite the fact that our cohort to our knowledge represents the largest reported series of SLNB in ocular adnexal melanoma patients, our patient number is still too small to be able to analyse statistically whether SLNB confers a survival benefit in patients with ocular adnexal melanoma. However, our overall 5-year survival rate after diagnosis in our cohort was 79% (95% CI, 62–89), which is on the high side of previously reported overall survival rates for patients with conjunctival and eyelid melanoma, which range from 50% to 79%. (Tuomaala et al. 2002; Heindl et al. 2011; Sheng et al. 2015). In the report by Cohen et al. 2013 on 18 patients with conjunctival melanoma who had SLNB, 17 of 18 patients were alive at a median follow-up time of 20 months after SLNB, although 5-year survival was not reported.

In conclusion, our analysis shows that SLNB is a safe and effective method for detecting micrometastasis in the regional lymph nodes in patients with ocular adnexal melanoma and has an overall positivity of about 20%. Sentinel lymph node biopsy provides important prognostic information with minimal added morbidity. Tumour thickness, histologic ulceration and mitotic figures are significantly associated with positive findings on SLNB. Particularly for bulbar conjunctival melanomas, it may be appropriate to use 2 mm as the cut-off point for selecting patients to have SLNB. These important findings and can help guide recommendations regarding which patients with ocular adnexal melanoma may be recommended for SLNB.

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