

# Sentinel lymph node biopsy in the management of conjunctival melanoma: current insights

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**Purpose:** To evaluate the role of sentinel lymph node biopsy (SLNB) in conjunctival melanoma (CM).

**Methods:** This article provides a review of the literature from PUBMED.

**Results:** Data on SLNB in the management of CM are scarce and only two relatively large cohorts have been reported. Although indication criteria for SLNB vary slightly, positive findings can be expected in 11%–13% of CM cases, including small tumors. False negative SLNB findings are rare (<10%). Failure to identify SLNB has been attributed to the surgical learning curve and recurrent tumors with scar tissue impeding spread of the tracer material. Reported 5-year survival rate following CM management including SLNB, is up to 79%, but there are no comparative cohort studies proving the assumed benefit. Adverse events reported were non-severe and transient.

**Conclusion:** Patients can potentially benefit from SLNB and the procedure can be offered to eligible patients. However, there is not enough evidence to support SLNB as a mandatory part of CM management.

**Keywords:** sentinel, biopsy, conjunctival melanoma, lymphatic spread, lymph node

## Introduction

With an annual incidence rate of 0.15–0.78/1,000,000, conjunctival melanoma (CM) (Figure 1) is the second most common malignancy of the ocular surface.<sup>1–3</sup> Therapy encompasses wide local excision using minimal-touch technique and subsequent adjuvant therapy to the former tumor site in the hope of minimizing the risk of local recurrence.<sup>4,5</sup> The many different approaches to adjuvant therapy comprise radiotherapy (proton beam radiotherapy, ruthenium-106 or strontium-90 brachytherapy), local chemotherapy (mitomycin C 0.04% eye drops) or topical immunotherapy (interferon  $\alpha$ 2b eye drops) for extermination of residual tumor cells.<sup>5–9</sup>

Despite all these efforts, CM is characterized by high recurrence rates of approximately 26%, 51%, and 65% within 5, 10, and 15 years after primary therapy, respectively.<sup>10</sup> Akin to the phenotypically related cutaneous melanoma, initial metastasis predominantly, though not exclusively, occurs to the regional lymph nodes (as opposed to uveal melanomas which typically initially metastasize to the liver) and can be observed in 16%, 26%, and 32% of patients within 5, 10, and 15 years, respectively. However, these rates tend to vary strongly between populations with one study reporting up to 41% lymph node metastasis within 6 years.<sup>10–13</sup>

Reported 10-year mortality rates range somewhere from 13%–32%.<sup>1,10,11,14</sup> These data, however, stem from an era before the availability of targeted therapies and checkpoint inhibition, which have become regular components in the

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**Figure 1** Melanoma of the temporal bulbar conjunctiva with a prominent feeder vessel in the left eye of a patient.

management of a multitude of tumors, including metastatic cutaneous melanoma, and hopes are high that patients with CM will be able to benefit from these as well.<sup>1,15,16</sup>

The goal of sentinel lymph node biopsy (SLNB), in general, is to detect putative subclinical micrometastases in the regional lymph nodes which otherwise escape detection by ultrasound imaging and clinical examination. These micrometastases are considered to be responsible for later tumor recurrence in the regional lymph nodes, ultimately resulting in morbidity and patient death.<sup>17–20</sup> In theory, the sentinel lymph node (SLN) is the first lymph node (or lymph nodes, as there can be several) to be encountered by tumor cells during lymphatic metastatic spread and a positive SLNB warrants radical lymphadenectomy of the affected basin.<sup>18</sup>

SLNB has been tried successfully in the management of CM, but due to the low incidence rate of the tumor, obtaining large case numbers has not been possible so far. Aside from a handful of case reports from different ophthalmic centers, the only two relatively large case series have been reported by Esmaeli et al and Cohen et al.<sup>18,21,22</sup> The former has been updated several times over the past decade and in the latest iteration reported on 31 CM patients undergoing SLNB.<sup>18</sup> Other than these, clinical data are scarce. Still, SLNB holds the promise of a potential benefit for CM patients, reducing the rate of regional metastases, and providing the clinician with additional prognostic information. Moreover, though similar in concept, there is some degree of variation in surgical technique between different ophthalmic centers that is worth elucidating.

In this article, we aim to give an overview of SLNB techniques, reported results, and postoperative complications.

## Treatment indications and techniques

Several criteria have been defined that render patients eligible for SLNB. While most centers reporting on SLNB generally have similar criteria, some variation can be found. In the largest study to date, requirements for SLNB were: no sign of metastasis, age >17 years, histological confirmation of CM, and tumor thickness of at least 1 mm or signs of ulceration.<sup>18</sup> Other centers offered SLNB only in cases with a tumor thickness of >2 mm.<sup>22–25</sup> Obviously, this requires correct handling of the tumor specimens. Cohen et al also included tumors in location associated with higher risk (forniceal, caruncular, tarsal melanomas) as well as recurrent melanomas after resection of primary acquired melanosis with atypia.<sup>22</sup> Additionally, the presence of >1 mitotic figures per microscopic field has been suggested as a criterion.<sup>25</sup> Recently, a CM management algorithm has been proposed based on four high risk features (non-limbal location, >2 mm thickness, ulceration, >1 mitotic figures per mm<sup>2</sup>), suggesting SLNB in cases where two or more of these features are present.<sup>23</sup>

Naturally, initial difficulties with the procedure have been attributed to surgical learning curve and most groups initially relied on a multimodal (preoperative lymphoscintigraphy, intraoperative radioactive mapping plus dye injection) approach to help with detection of SLNs.<sup>18,21,22</sup>

Reported by Nijhawan et al, preoperative lymphoscintigraphy was performed by local injection of technetium-99m (Tc-99m) nanocolloid and subsequent image acquisition using a gamma camera.<sup>18,21,26</sup> Alternatively, other groups have used single photon emission computed tomography for imaging of the SLNs.<sup>23,24</sup>

During surgery, Tc-99m nanocolloid is injected subconjunctivally at the former tumor site, and a gamma probe is used for lymph node mapping.<sup>21,24–26</sup> In comparison to cutaneous lymphatic mapping, smaller injection volumes have been suggested as spillage and scattering into the nasolacrimal system have led to difficulties in the past.<sup>27</sup> Other centers have performed preoperative imaging and intraoperative mapping both following one single injection of Tc-99m nanocolloid.<sup>22</sup> The additional concurrent injection of several different dyes has been described

by multiple groups. Commonly, isosulfan blue, methylene blue, lymphazurin blue, and indocyanine green have been used, all to varying success.<sup>21–25,28</sup> Several groups have since refrained from this practice however, since it often yielded inconsistent results (lack of visible lymph node staining) and did not apparently provide a significant additional benefit to Tc-99m injection.<sup>18,22</sup>

The classic teaching of ocular lymphatics is that the nasal adnexal regions drain via submandibular (and deep cervical) lymph nodes while the temporal adnexal regions drain via preauricular lymph nodes. However, clinical experience as well as SLNB results have shown that exceptions from this rule are not uncommon, and especially nasally located lesions may sometimes drain to the preauricular lymph nodes as well.<sup>22,29,30</sup>

Furthermore, attention has to be paid to the timepoint of SLNB relative to primary tumor resection. While the majority of groups report simultaneous primary tumor resection with SLNB in one combined procedure, Cohen et al in their study, performed SLNB within 6 weeks of tumor resection.<sup>18,22</sup> The advantage of this approach is that tumor thickness and patient eligibility can be evaluated prior to SLNB. However, it also holds the risk of disrupting or changing lymphatic pathways which may ultimately result in biopsying a lymph node other than the “original” SLN.<sup>22</sup>

The excised lymph node is then examined by a pathologist via serial sectioning, H&E staining, and immunohistochemistry of common melanoma markers, eg, S100, Melan-A and human melanoma black 45.<sup>24</sup>

Given that reports of positive SLNB results are exceedingly rare, there is no standardized management following such results. Where possible, complete dissection of the nodal basin can be considered carefully.<sup>22</sup> However, this is not standard practice in cutaneous melanoma management anymore, as it has not improved tumor-specific survival rates compared to lymph node observation.<sup>17</sup> In frail patients, radiotherapy to the lymph node basin has been tried as well.

## Published results

Published data seem to be not only scarce, but also hardly comparable, since study design varies substantially among reports. In particular, most cohorts comprise not only CM cases but oftentimes also other entities including eyelid skin melanoma, sebaceous cell carcinoma, conjunctival squamous carcinoma, and eyelid Merkel cell carcinoma.<sup>21,31</sup> In fact, there are currently only two larger series of CM cases available (Table 1).<sup>18,22</sup>

In their 2017 update, Pfeiffer et al reported on 31 CM (and 20 eyelid melanoma) patients who underwent SLNB.<sup>18</sup> Of those, four (13%) had positive biopsy results leading to dissection of the respective lymphatic basin. This rate of positive findings was lower than that in the subgroup of eyelid melanomas (20 patients), where 30% of sampled SLNs were positive. Similar rates have been found in cutaneous melanoma SLNBs.<sup>32</sup> However, there were also two (7%) cases of

**Table 1** Comparison of the two largest cohort studies investigating sentinel lymph node biopsy (SLNB) in conjunctival melanomas (CMs)

	Pfeiffer et al, 2017 <sup>18</sup>	Cohen et al, 2013 <sup>22</sup>
Number of patients	31	22
Median age	62 years (includes eyelid melanoma)	59 years
Requirements	No signs of metastasis, >17 years old, histologically confirmed CM, ≥1 mm or ulceration	>2 mm, unfavorable location, recurrent melanoma
SLNB not found	0/31 (0%)	4/22 (18%)
SLNB positive	4/31 (13%)	2/18 (11%)
SLNB false negative	2/27(7%), early cases	0/18 (0%)
Technique	Technecium-99m (Tc-99m) ± isosulfan blue	Tc-99m ± methylene blue
Median number of lymph nodes sampled	2	2
Follow-up	Median 61 months (includes eyelid melanoma)	Median 20 months
Recurrence-free survival	N/A	N/A
Metastasis-free survival	N/A	N/A
Overall survival	79% at 5 years (including cutaneous melanoma)	N/A
Complications	Facial nerve palsy (6%), neck hematoma (2%), stitch abscess (2%)	Blue staining of the conjunctiva (31%), facial nerve palsy (6%)

false negative SLNB results in the CM cohort with patients developing late tumor recurrence in the regional lymph nodes. Since these were early cases, the authors attributed the false negative results to surgical learning curve and lack of experience at the time.<sup>18</sup> The group reported a median follow-up of 61 months and combined 5-year overall survival of 79% of conjunctival and eyelid melanoma patients. Correlating American Joint Committee on Cancer staging with SLNB positivity was not possible due to low case numbers.<sup>18</sup> Similarly, Cohen et al reported on their experience in a cohort of 22 CM patients.<sup>22</sup> Intraoperative lymphatic mapping failed to identify an SLN in four (18%) cases and succeeded in 18 (82%). Failure to identify SLNs was attributed to prior surgery or radiotherapy in cases of recurrent CM, highlighting the role of scar tissue in the distribution of radiotracers. Of the successful biopsies, two (11%) were reported positive and 16 (89%) negative, with no false negative results recorded over the relatively short median 20 months follow-up period. Of note, six of those patients had recurrent CM (one of those had positive SLNB) and three had advanced CM. Survival rates were not reported in this study.<sup>22</sup>

Overall, neither study reported recurrence-free survival or metastasis-free survival.<sup>18,22</sup>

Apart from these two studies, a review of literature reveals a modest number of case reports and short case series of patients undergoing SLNB for CM, for a combined total of 18 CM cases.<sup>11,23–25,27,28,31,33–36</sup> With the exception of one study reporting two positive SLNB findings in two patients with forniceal CM, all of the listed articles reported negative SLNB findings.<sup>28</sup> Although all

centers used Tc-99m based lymphoscintigraphy for lymphatic mapping, there was some variation in what dye was injected concurrently.<sup>18</sup> Table 2 gives an overview of reported case numbers and lymphatic mapping techniques.

## Adverse events

In general, the rate of adverse events following SLNB is relatively low and severe complications requiring an intervention have not been described to date. Most commonly, transient facial nerve palsy lasting up to several weeks (6%, usually of the marginal mandibular branch) can occur, especially following biopsy of an SLN in the parotid region.<sup>18,22</sup> Furthermore, dry mouth and facial edema have been reported.<sup>37</sup>

The injection of a dye can lead to prolonged staining of the conjunctiva and has been reported especially with isosulfan blue.<sup>18</sup> Lymphazurin blue, which has been used more commonly in cutaneous melanoma SLNB, can permanently tattoo skin when injected, but is uncommon in SLNB for tumors of the ocular adnexa.<sup>28</sup> In conclusion, SLNB, as reported so far, seems to be a relatively complication-free procedure.

## Caveats and conclusions

Reports of CM biopsy cases are unfortunately even scarcer than would appear at first glance. This is because initially published case reports are often re-reported as part of case series. On top of that, these case series are updated every so often with the addition of a handful of new patients to the existing cohort.<sup>18,21,38</sup> Obviously, these updates are important, especially given the extremely low incidence of the tumor, but one has to pay close attention to this when reviewing the literature. In

**Table 2** List of sentinel lymph node biopsy (SLNB) reports in conjunctival melanoma and applied lymphatic mapping technique

	Number of patients	SLNB positive	Technique
Pfeiffer et al, 2017 <sup>18</sup>	31	4	Technecium-99m (Tc-99m) + isosulfan blue
Cohen et al, 2013 <sup>22</sup>	22	2	Tc-99m + methylene blue
Waintstein et al, 2014 <sup>24</sup>	3	0	Tc-99m + isosulfan blue
Aziz et al, 2015 <sup>23</sup>	1	0	Tc-99m + ICG
Rubinstein et al, 2014 <sup>25</sup>	4	0	Tc-99m + ICG
Rubinstein et al, 2015B <sup>34</sup>	1	0	
Rubinstein et al, 2015A <sup>33</sup>	1	0	
Motomura et al, 2010 <sup>35</sup>	1	0	Tc-99m + vital blue
Maalouf et al, 2012 <sup>31</sup>	2	0	Tc-99m
Schwarz et al, 2008 <sup>27</sup>	1	0	Tc-99m
Baroody et al, 2004 <sup>28</sup>	2	2	Tc-99m + lymphazurin blue
Esmaeli et al, 2001 <sup>11</sup>	1	0	Tc-99m + isosulfan blue
Wilson et al, 2001 <sup>36</sup>	1	0	Tc-99m



total, there have been only eight positive SLNBs throughout the complete literature, spread over three reporting groups (Pfeiffer et al, 2017: four; Cohen et al, 2013: two; Baroody et al, 2004: two). It is interesting however, that SLN positivity was shown to be detectable even in cases of small T1 tumors, as well as recurrent melanomas staged for exenteration.<sup>18,22</sup> These findings highlight the potential benefit of SLNB even in seemingly low grade cases where there is little suspicion of lymphatic spread. Considering that melanoma cells can be found in approximately 13% of biopsied lymph nodes, it is justifiable to offer this procedure to patients with CM. Exact criteria for SLNB will have to be reviewed in the future, but for now, most centers seem to agree on those cited in this article, tumor thickness being the primary factor. The procedure should be performed only in a specialized center in order to minimize false negative results and failure to find an SLN, especially in cases of recurrent melanoma, where scar tissue may complicate the procedure even further.<sup>22</sup> Finally, it is unknown if lymph node dissection following positive SLNB for CM will actually benefit patients. Although evidence points in that direction, there is no study proving a survival benefit in CM.<sup>18,3,229</sup>

In conclusion, SLNB is a relatively safe procedure that can be offered to eligible patients with CM, but data are still too scarce to definitively accept SLNB as an obligatory procedure in the management of CM.

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## Disclosure

The authors report no conflicts of interest in this work.

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