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Sentinel Lymph Node Biopsy for Eyelid and Conjunctival Tumors: What is the Evidence?

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Introduction

Sentinel lymph node (SLN) biopsy is a procedure for identifying subclinical, microscopic nodal metastasis from a malignant tumor. It is based on the principle that some tumors preferentially spread to a first draining or “sentinel” lymph node before they spread to distant sites. The SLNs may be assessed for involvement clinically by palpation and by high-resolution ultrasound, computed tomography, or magnetic resonance imaging; however, nodal micrometastasis may already be present before it becomes detectable by these methods. Previously, extensive lymph node dissection would be performed for tumors known to have a high risk of lymphatic spread. This procedure potentially causes significant morbidity[1] and has been shown to have no added value for patients with melanoma of the head and neck.[2] Thus, a less invasive and more selective method was needed for determining whether patients have micrometastases in the regional nodes at the time of initial diagnosis and are thus more likely to benefit from elective lymphadenectomy. The SLN biopsy technique was first proposed in a landmark study by Morton et al[3] for the intraoperative lymphatic mapping of cutaneous melanomas, and since then has become a standard part of management for various tumors in diverse locations[4,5] including the head and neck,[6,7] although its clinical benefits have been questioned.[8,9] With the exception of eyelid basal cell carcinoma, periocular malignancies have a propensity for metastasis to regional lymph nodes or distant organs. Esmaeli[10] used SLN biopsies for eyelid and conjunctival melanomas and carcinomas.

According to proponents of SLN biopsies, SLN histologic status provides important prognostic and therapeutic implications.[11,12] The benefits of SLN biopsy for cutaneous melanoma have been validated by the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1), a large clinical trial involving patients with intermediate thickness melanoma randomized to SLN biopsy versus observation. The MSLT-1 study results showed that biopsy-based management prolongs the disease-free survival and melanoma-specific survival.[13] The detection of a positive SLN influences the staging of the disease based on the American Joint Committee on Cancer TNM (primary Tumor, regional lymph Node, distant Metastasis) classification which, in turn, is a predictor of distant metastasis, and thus provides an opportunity for earlier intervention. If the SLN biopsy is positive, it is

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recommended to perform dissection of all nodes in the basin and parotidectomy if the parotid basin is involved. If additional positive nodes are found during dissection, adjuvant therapy such as postoperative radiation treatment, systemic administration of chemotherapy, or a combination, should be considered. If SLNs are evaluated as negative, the likelihood of involvement of other nodes or distant sites is low. This suggests that further treatment is not indicated, although close follow-up is still important due to the possibility of false negatives. In this article, we discuss the advances in SLN biopsies over the past decades and the latest evidence on the benefits and pitfalls of this procedure based on recent experiences with melanoma of the eyelid and conjunctiva, sebaceous, squamous cell, and Merkel cell carcinoma of the eyelid reported in the literature.

Lymphatic Drainage of the Eyelids and Conjunctiva

Regional lymph nodes are known to commonly be the first site of metastasis for the tumors of the periocular region and distant metastases are usually detected later. Studies have confirmed the role of the parotid, preauricular, and submandibular nodes in the drainage of the eyelid and conjunctiva. Non-human primate models have shown that the entire upper eyelid, medial canthus, and lateral lower eyelid lymphatics drain to the parotid and preauricular nodes, whereas the medial and central lower eyelid lymphatics drain primarily to the submandibular nodes.[14] Human cadaver studies suggest that lymphatics from the lateral upper and lower eyelids drain primarily into the parotid lymph nodes and that the lymphatics from the medial upper and lower eyelids drain into the submandibular nodes.[15] For the conjunctiva, the lateral half is known to drain into the parotid region, and the medial half into submandibular and deeper cervical nodes.[16,17] Lymphoscintigraphic mapping in non-diseased human subjects revealed that lymphatics in the upper and lower eyelids, both medial and lateral portions, drain most frequently to the preauricular nodes.[18] The tendency to drain into the preauricular lymph node basin was shown to be true also in patients with eyelid malignancies.[19] In the analysis of the pattern of nodal metastasis in conjunctival melanoma, it was noted that temporal lesions tended to metastasize to preauricular nodes and nasal lesions to the submandibular nodes.[20] However, several studies show that the lymphatic drainage patterns among individuals can be highly ambiguous and unpredictable and are not as systematic as has been anatomically described.[21–23]

General Technique

Before an actual SLN biopsy, preoperative lymphoscintigraphy may also be performed to determine the expected site of the SLN.[24] This is a useful guide in the head and neck region where there are multiple nodal basins and in patients who have had multiple surgeries with significant scar tissue causing impedance of lymphatic drainage. Lymphoscintigraphy involves the injection of a radiolabeled tracer molecule, usually technetium (Tc)-labeled sulfur colloid, into the tissue immediately surrounding the tumor. A local anesthetic is applied to either the eyelid or conjunctival surface, then 0.3 to 0.4 mCi of filtered Tc-99m sulfur colloid in 0.2mL normal saline is injected in 3 or 4 spots around the lesion, intradermally for cutaneous eyelid lesions or subconjunctivally for conjunctival lesions. Given the proximity of these lesions to the globe, the Tc should be injected by an ophthalmic surgeon. Serial radiographic images are then obtained every 15 minutes then

every 30 minutes thereafter to follow the drainage of the tracer until the first SLN is detected. Lymphoscintigraphy is valuable in locating the first lymph node relay because of demonstrated variability in lymphatic drainage patterns among individuals. Recent studies have shown that the use of single photon emission computed tomography (SPECT/CT) allows for higher resolution imaging and more precise localization than conventional planar lymphoscintigraphy.[25]

SLN biopsy is usually performed at the time of surgical resection of the primary tumor, adding 30 to 90 minutes to the operating room time. It can also be performed as a secondary procedure if the resection of the ocular tumor has already been executed elsewhere. Identification of the SLN also involves the injection of Tc sulfur colloid as described earlier for lymphoscintigraphy. The injections are administered in the preoperative surgical holding area before the surgical removal of the primary tumor. The tracer travels through the lymphatics to the lymph nodes. After 1 to 1.5 hours, a handheld γ-probe[26] is then used intraoperatively to localize where the tracer has accumulated. Areas of focal radioactive uptake are identified and marked on the skin. SLNs or “hot” nodes are defined as lymph nodes that have radioactivity counts at least twice as high as the level of background radioactivity. These nodes are then carefully removed until little or no radioactivity is detectable in the nodal basin.[27] A significantly smaller volume of Tc-99m is used in the eyelid and conjunctiva compared with other anatomic locations, because larger volumes may drain to nodes not representative of the sentinel nodes draining the lesion of interest. It seems that this small volume is adequate in identifying SLNs during both lymphoscintigraphy and biopsy. Earlier protocols used large incisions that were suitable to permit exploration of the lymphatic basins at risk and elective removal of all the nodes in the draining basin. Nijhawan et al[21] now advocate the use of smaller incisions (1 to 3 cm) made directly over each SLN, demonstrating that this less invasive technique still yields a high rate of SLN identification. Completion lymph node dissection is then performed if any SLN is found to contain metastatic disease. Earlier studies have shown that vital blue dye (isosulfan or methylene blue dye) combined with the radiolabeled sulfur colloid enhances the detection of SLNs by staining them blue.[28] In contrast, other investigators suggest that the use of blue dye does not add much to the accuracy or efficiency of SLN identification compared with Tc alone,[21,23,29] especially for conjunctival tumors. In settings where nuclear medicine facilities are not available, SLN biopsy can still be performed without the radiotracer and using only blue dye, but with a lower SLN identification rate.[25] The use of indocyanine-green dye to guide SLN biopsies in periocular tumors has recently been introduced.[30]

SLNs are submitted for histopathologic evaluation. They are serially sectioned in a “breadloaf ” manner at 1 to 2mm increments and are routinely stained with hematoxylin and eosin. A skilled pathologist examines the slides for malignant cells. If no malignant cells are identified, additional sections should be submitted for immunohistochemical staining and/or molecular staging.[31,32]

Possible Complications

SLN biopsy for eyelid and conjunctival malignancies is a relatively low risk and minimally invasive procedure with few reported complications such as mild temporary weakness of the facial nerve and/or its branches that resolved without intervention.[21,23,29] SLN dissection of the parotid area carries the risk of permanent paralysis of cranial nerve 7 and its branches, hence this is best performed at the hands of an experienced head and neck surgeon. Precautions such as the use of a nerve stimulator may be taken to ensure the integrity of the facial nerve.[33] Lymphedema after SLN biopsy for cutaneous melanomas has been reported but none of these cases were from the head and neck region.[34] Transient mild facial edema after SLN biopsy that subsided spontaneously within 72 hours has been reported.[25] The risk of radiation toxicity to the intraocular structures during SLN biopsy is negligible. The reduced dose of 0.3 mCi of Tc-99m sulfur colloid used emits an estimated dose of 0.2 cGy over a 6-hour period (the half-life of Tc-99), which is much less than the dose associated with radiation retinopathy or cataract formation.[27,35] Another issue is the inadvertent intraocular injection of Tc-99m, especially with administration in the subconjunctival space, although there have been no reports of this so far. This can be minimized by keeping the patient in a supine position, using an eyelid speculum, and having an experienced ophthalmic surgeon inject the Tc. There was also concern that the vital blue dye may lead to permanent discoloration but this has not been observed in the subconjunctival tissue nor periocular skin. Although the conjunctival surface may be blue for the first few hours after injection of the dye, the color dissipates over the first 24 hours and entirely disappears by 72 hours.[27]

The greatest pitfall of SLN biopsies is the risk of false-negative results. A false-negative event is defined as having no evidence of micrometastasis on SLN biopsy but with subsequent development of nodal disease during the follow-up period. Failure to identify occult metastatic disease by SLN biopsy may occur on account of variable and complex lymphatics of the head and neck, obstruction of lymphatic drainage by malignant cells or bulky tumor mass, injection in erroneous sites, surgical learning curve, or histologic analysis errors.[29] Injection failure pertains to failure of the radioisotope to localize to the SLN and may occur when there is scarring from surgery or radiotherapy which prevents the Tc from reaching the lymphatic channels.[4] Cohen and colleagues reported 4 cases of injection failure for SLN biopsy in patients with conjunctival melanoma who have had prior radiation and multiple prior surgeries, including exenteration. Patients should be informed of these potential complications before consenting. Given the possibility of false-negative findings, patients with high-risk features should be closely followed for the first 5 years following their diagnosis even if SLNs are negative.[29]

Melanoma of the Eyelid

The experience with SLN biopsy has been broadest in cutaneous melanomas. According to a relatively recent retrospective series, malignant melanoma of the eyelid metastasizes to the regional lymph nodes in 29% of patients. There is a significantly higher incidence of metastasis and decreased survival for eyelid skin melanomas with Breslow thickness >1.5mm or Clark level >III, as compared with thinner or more superficial tumors.[36] Current

indications for SLN biopsy for eyelid melanomas are: tumors ≥1mm thick, Clark level ≥IV, tumors with >1 mitotic figures per high-power field, and/or those with histologic ulceration. Immunohistochemical stains against melanoma antigens S100, HMB45, and Melan A/MART-1 are utilized to identify malignant cells in biopsy specimens. The use of reverse transcriptase polymerase chain reaction (RT-PCR) to detect messenger RNA for the tyrosinase gene has been reported to enhance the sensitivity of SLN biopsy for the detection of melanocytic cells.[37] Molecular staging of histopathology-negative SLNs by the quantitative real-time RT-PCR assay for established biomarkers (MART-1, MAGE, GalNac-T, and PAX3) has been shown to have prognostic significance.[38] Studies on patients with head and neck melanomas report SLN positivity rates of 15% to 21% for intermediate thickness melanomas (1.0 to 4.0 mm), or melanomas <1.0mm thick with high-risk features such as ulceration or Clark level of ≥IV.[39,40] According to a recent systematic review of SLN biopsies for melanomas of the head and neck, the median positivity rate is 15%, and false-negative rates for nodal recurrence range from 3.3% to 44%, with a median of 20.4%.[41] The reported rates for ocular adnexal melanoma are similar, with an SLN positivity rate of 17%and SLN false-negative rate of 8%.[42]

Melanoma of the Conjunctiva

Conjunctival melanoma is an ocular surface malignancy that can arise de novo or from a preexisting primary acquired melanosis or nevus and apparently may have an increasing incidence.[43] It is potentially lethal with an average 10-year mortality rate of 30%.[44] The reported frequency of regional lymph node metastasis in conjunctival melanoma varies from 15% to 41%.[45–48] Risk factors for regional metastatic spread include nonlimbal location, tumor thickness >2mm, large basal diameter, positive resection margins, orbital extension, and nodular tumor shape.[46,49] Risk factors for distant metastasis are: unfavorable tumor location such as the fornices, plica, caruncle, and lid margins, tumor thickness >2mm, and a history of local recurrence.[50] For invasive malignant melanoma of the conjunctiva, determining the thickness of the tumor histologically may be difficult due to improper tissue handling and tangential sectioning. The use of a 20MHz ultrasound has been recommended to clinically measure tumor thickness. Current indications for SLN biopsy for conjunctival melanomas are: tumors ≥2mm in histologic thickness, histologic ulceration, and nonlimbal location.[51] Secondary selection criteria are: melanoma in unfavorable locations, and recurrent melanoma associated with the “florid” phase of primary acquired melanosis. It is preferable to excise the conjunctival lesion before lymphoscintigraphy and SLN biopsy, as this allows for measurement of tumor thickness as selection criteria to determine whether the patient is eligible for SLN biopsy, and minimizes the possible risk of tumor seeding.[23] Immunohistochemical staining against melanoma antigens S100, HMB45, and Melan A are used to aid in identification of tumor cells in SLN biopsies. For melanoma of the conjunctiva, the SLN positivity rate ranges from 11% to 16%[23,42] and false negativity rates have decreased from 16%[29] to 8% in the past years.[42]

Sebaceous Carcinoma of the Eyelid and Conjunctiva

Sebaceous/meibomian gland carcinoma is a rare malignancy that is most frequently found in the eyelid and is often clinically mistaken for benign conditions such as

blepharoconjunctivitis or chalazion. For sebaceous gland carcinoma of the ocular adnexa, retrospective analyses revealed regional node metastasis rates ranging from 7% to 20%.[52–55] Indications for undergoing SLN biopsy are not yet well established; however, it has been recommended for patients with tumors at stage ≥2b and tumor size >10mm in diameter due to the associated increased risk for metastasis.[56] The histologic diagnosis of sebaceous carcinoma is challenging. Immunohistochemical stains adipophilin and perilipin for the identification of lipid within specimens have proven to be useful.[57–61] Experience with the use of SLN biopsy in sebaceous carcinoma with ocular[29,33,62] and extraocular[63–65] involvement is limited. To date, SLN positivity rates range from 17% (2/12)[62] to 20% (1/5).[25] There are only 2 reported false negatives of SLN biopsies of sebaceous carcinoma from the periocular region.[29]

Squamous Cell Carcinoma (SCC) of the Eyelid and Conjunctiva

SCC is the second most common malignancy in the eyelid[66,67] and is one of the most frequent nonmelanocytic neoplastic lesions in the conjunctiva.[68] Reported rates of regional lymph node metastasis of SCC vary widely from 1.3% to 24.3% for the eyelids,[69–71] but the rate is very low at 1% for the conjunctiva.[72,73] Factors associated with high risk of development of nodal metastasis of cutaneous SCC are tumor size wider than 2 cm and histologic features of poor differentiation and aggressive tumor grade.[71,74,75] There is a lack of consensus as to the indications for SLN biopsy for periocular SCC, but it has been proposed for tumors that are >2cm in diameter, are locally recurrent, or have perineural invasion.[71] A pancytokeratin antibody cocktail including cytokeratin AE1/3 may aid in the histologic diagnosis of SCC. The pooled false-negative value calculated by a meta-analysis of SLN biopsy studies for head and neck SCC was 13.7%.[76] On the basis of the limited experience with SLN biopsies of SCC of the periocular region, the positivity rate is 12.5% (1/8)[22] to 14% (1/7)[25] with no reports of false-negative biopsies as of yet. One article describes positive SLN biopsy findings in all 5 patients with periocular invasive SCC in their series.[75]

Merkel Cell Carcinoma (MCC) of the Eyelid

MCC is a rare but aggressive malignancy, with eyelid tumors accounting for 10% of all cases. The rate of regional node metastasis in the eyelid is 21%according to the largest and most recent series,[77] but has previously been suggested to be as high as 66%.[78] In other anatomic locations, the frequency of nodal involvement ranges from 25% to 50%.[79–81] Because of the relatively high risk of nodal metastasis, some practitioners advocate empiric radiation therapy for all patients with MCC of any size, whereas others promote SLN biopsy and further therapy only for those with a positive SLN. Cytokeratin 20 is the most sensitive and specific immunohistochemical marker for MCC.[82] Neuroendocrine markers chromogranin and Cam5.2 may also be utilized to aid in identification of MCC in lymph node biopsies.[83] The rate of SLN positivity correlates with increasing diameter, thickness, and mitotic rate of the lesion, as well as infiltrative growth pattern.[84,85] A study on SLN biopsies for MCC of the head and neck region found positive sentinel nodes in 20% and false-negative nodes in 12% of patients.[82] The SLN positivity rate for MCC in all anatomic locations falls between 24% and 48%.[86,87] Some authors assert that SLN mapping can

improve disease-free survival by significantly lowering recurrence rates compared with nodal observation.[88,89] The number of involved nodes has been shown to be strongly predictive of survival.[85] In contrast, other studies show that SLN status does not significantly affect recurrence rates or survival.[86,90] Data on MCC of the eyelid are insufficient to determine the effect of SLN status on recurrence rates and prognosis; therefore, practitioners usually rely on data from other anatomic sites. SLN positivity was found in 1 of 4 patients in 1 series of MCC of the eyelid, with 1 false-negative event.[22] There has been 1 other report of a single case of positive SLN detected in MCC of the eyelid.[91]

Conclusions

Most of the data regarding SLN biopsies for conjunctival and eyelid cancers are for melanoma, with some studies on relatively small cohorts of patients for MCC, sebaceous carcinoma, and SCC due to their rarity (Table 1). The majority of these reports were generated from a single center in the United States (MD Anderson Cancer Center, Houston, TX).[10,21,24,29,42] These published articles suggest that SLN biopsy is a feasible and safe procedure with positive and false-negative rates similar to other anatomic sites. SLN biopsy for periocular tumors has evolved from being considered experimental to being part of the standard of care in some institutions; it is still not universally applied in the management of periocular malignancies. Through the years, false-negative rates have decreased significantly as more experience has been gained with the technical nuances of SLN biopsies, and more specific clinical and histologic criteria for patient selection have been defined. SLN biopsies have improved our ability to accurately stage eyelid and conjunctival malignancies, and have reduced surgical morbidity from unnecessary radical lymph node dissections. Continued application of this procedure is appropriate for patients with ocular adnexal tumors that have the potential risk for lymph node metastasis, but have no clinical evidence of nodal disease based on examination and radiographic imaging. There is a need to elucidate the relationship between SLN status and clinical outcomes such as tumor recurrence and patient survival. Successful SLN biopsies require a multidisciplinary approach involving an ophthalmic surgeon, a head and neck surgeon, or possibly a surgical oncologist with experience in the head and neck area. Multi-institutional controlled trials using uniform techniques are needed to validate published observations and consolidate emerging data.

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Table 1

Sentinel lymph node biopsy studies on eyelid and conjunctival tumors

	Eyelid Melanoma				Conjunctival Melanoma				Sebaceous Carcinoma				SCC			MCC
References	**Ho et al[29]***	**Savar et al[42]***	**Maalouf et al[22]**	**Vuthaluru et al[25]**	**Baroody et al[92]**	**Ho et al[29]***	**Savar et al[42]***	**Cohen et al[23]**	**Wilson et al[33]**	**Ho et al[29]***	**Savar et al[62]***	**Vuthaluru et al[25]**	**Maalouf et al[22]**	**Chak et al[75]**	**Vuthaluru et al[25]**	**Maalouf et al[22]**
No. patients	8	4	2	4	2	7	26	18	2	10	12	5	8	5	7	4
Median length of follow-up (months)	24.5	24	27.2	NS	12.5	30	24	20	8.5	24.5	36	NS	22	24	NS	18.7
SLN positive	1	1	0	1	2	1	4	2	0	1	1	1	1	5	1	1
SLN false negative	1	1	0	1	0	1	2	0	0	2	0	0	0	0	0	1
Recurrence/death	1	0	0	0	1	2	3	1	0	1	0	0	0	2	0	0

*Authors are from the same institution; some patients in earlier publications were featured again in later reports.

MCC indicates Merkel cell carcinoma; NS, not specified (length of follow-up was not specified for each type of tumor but median follow-up for all patients in the study was 12.25 mo); SCC, squamous cell carcinoma; SLN, sentinel lymph node.