Guest Editorial

Dr. Mrittika Sen, Dr. Santosh G Honavar

Sentinel Lymph Node Biopsy: Guarding the Guardian

Sentinel, the dictionary defines the word as a soldier or guard whose job is to stand and keep watch. The sentinel lymph node, literally, then becomes the node keeping a lookout for the spread of disease and is the first to be attacked when metastasis starts. While it lights the beacons, it is up to us to pick up the signals and prepare for the battle.

A malignant tumour tends to metastasize preferentially to its regional lymph nodes before hematological dissemination and distant metastasis. Sentinel node is the first of the draining lymph nodes. Lymph node involvement from a malignancy can be identified clinically by palpation or by radiological investigations. The role of sentinel lymph node biopsy (SLNB) comes into play for identifying micrometastasis or subclinical metastasis in tumours with risk factors for lymphatic spread. If the sentinel node is negative, it is safe to conclude that the tumour is confined locally… or so it was thought.

SLN biopsy was introduced in 1960 by Gould for malignant lesions of parotid, but it was nearly 40 years before its role was established in the standard management of neoplasia especially breast cancer and cutaneous melanoma.[1] The technique was proposed by Morton et al for intraoperative lymphatic mapping of cutaneous melanoma.[2] Prior to this, radical and extensive nodal dissection was done for tumours with high risk of lymphatic spread with significant morbidity. SLN biopsy is a selective, minimally invasive method that allows identification of patients who would definitely benefit from extensive lymphadenectomy and adjuvant radiotherapy, while sparing the others from unnecessary additional trauma.

For periocular and conjunctival tumours, most of our knowledge about SLN biopsy comes from the extensive study done by Esmaeli et al at MD Anderson Cancer Centre.[3] Eyelid tumours, apart from locally invasive basal cell carcinoma, have a tendency for lymphatic spread to the regional lymph nodes i.e. the preauricular, parotid, the submandibular and deep cervical nodes. The lymphatic drainage of the ocular adnexa is anatomically well defined but recent studies have shown that the pattern of lymphatic drainage may, in fact, be quite unpredictable and ambiguous, with medially located tumours also draining into the preauricular and parotid nodes.[4-6] Thus, localization of the actual drainage basin is important before blind empirical dissection.

A preoperative lymphoscintigraphy is performed to outline the expected draining area and plan the site of biopsy using technetium labelled sulfur colloid (0.3-0.4 mCi of filtered Tc-99m sulfur colloid in 0.2ml normal saline), injected in 3-4 perilesional spots- intradermal or subconjunctival, depending on the site of tumour. Serial scanning is done every 15 minutes till the first SLN is detected or single photon emission computed tomography (SPECT/CT) is performed. SLN biopsy is performed intraoperatively during the time of excision of the lesion or it can be performed at a later stage once the histopathological risk factors for lymphatic spread are also determined. Secondary SLNB is preferred for conjunctival melanoma as it allows the histologic measurement of tumour thickness and also reduces the risk of tumour seeding.[6] The same radiolabeled tracer molecule described for lymphoscintigraphy is injected in the preoperative perilesional area. The tracer volume to be injected is much less for ocular adnexa as compared to other anatomical sites. A handheld gamma probe is then used after 1-1.5 hours, intraoperatively, to detect focal uptake. "Hot" nodes are the lymph nodes with radioactivity at least twice the level of background radioactivity. A small incision (1-3cm) made over each SLN, described by Nijhawan et al, is sufficient to excise the nodes.[4] The LN basin around the hot nodes are scanned for any more high radioactive uptake till little or no activity is detected.[7] Isosulphan or methylene blue dye and indocyanine green dye can also be used for SLN biopsy in places where nuclear medicine facilities are not available.[8,9] Combining vital blue dye with Tc-99m does not have additional benefit over using Tc-99m alone.[4,6,10]

The LN specimen undergo bread-loafing and histopathological evaluation with routine hematoxyline and eosin stains. If they are found to be negative for malignancy, additional sections are reviewed with immunohistochemical and molecular studies. Reverse transcriptase PCR is also utilized in some cases to identify molecular markers. If SLN biopsy is positive, dissection of all the nodes in the drainage basin,

including parotidectomy if the parotid basin is involved, is recommended. During dissection if additional nodes are found to be involved, adjuvant treatment like radiotherapy and systemic chemotherapy should be initiated.

Complications are mild and temporary and include facial nerve palsy, lymphedema and inadvertent intraocular injection of the tracer. Radiation toxicity is negligible.[11] The main concern are the false negative results when patients with no evidence of micrometastases develop nodal involvement during follow up. Variable lymphatics of head and neck, obstruction to lymphatic drainage of tracer by tumour cells or bulky mass, incorrect injection site, surgical learning curve, error during histopathological evaluation and failure of tracer to identify SLN due to scarring from prior surgery or radiotherapy are some of the causes for this. It is important to counsel the patient preoperatively about the chances of false negative results and the need for close follow up, at least for the initial 5 years.[10,11]

Table 1 shows the rate of lymph node metastasis, indications for SLN biopsy, specific IHC and molecular markers, rates of SLNB positive and false negative results for common ocular adnexal malignancies.

Low yield of positive results, increase in surgerical time by 60-90 minutes and false negative results question the potential benefit of SLNB. The Multicentre Selective Lymphadenectomy Trial-1 (MSLT-1) results proved the benefit of SLN biopsy based management with longer disease free survival, rather than observation for LN involvement in patients with cutaneous melanoma.[12] MSLT-II concluded that in cases with SLN positive, immediate complete LN dissection improved regional disease control and reduced regional LN recurrence by nearly 70% but did not improve melanoma-specific survival.[13] As our experience with SLN biopsy continues to grow, the false negative rates have reduced. It is minimally invasive with very few complications. SLN biopsy is useful for staging eyelid and conjunctival malignancies by the AJCC TNM classification, and thereby, determine prognosis, predict distant metastasis and early adjuvant treatment for patients objectively rather than empirically and reduce unjustified surgical morbidity.[14,15] With the availability of immune checkpoint inhibitors and targeted molecular therapy for metastatic melanoma and squamous cell carcinoma, early detection of nodal disease becomes especially important for the initiation of treatment and improving the prognosis for survival.

Given the safety, feasibility, microscopic involvement of LN in the absence of clinical evidence and survival benefits of early detection and treatment of micrometastasis for cutaneous melanoma, it may be wise to carry out SLN biopsy in specific ocular adnexal malignancies. Further multi-institutional studies are required to determine the importance of SLN status and overall survival for eyelid and conjunctival malignancies.

Table 1: Common ocular adnexal malignancies and their rates of lymph node involvement, indications and outcomes of sentinel lymph node biopsy.

Ocular adnexal malignancy	*Rate of lymph node involvement*	*Indications for SLNB*	*IHC/molecular markers*	*Rate of SLNB positivity*	*False negative*
Eyelid melanoma	*29%*	*Tumours >/=1mm thick, Clark level >/=IV, increasing Breslow depth, >1 mitotic figure per HPF, histological ulceration*	*S100, HMB45, Melan A/MART-1, MAGE, GalNac-T, PAX-3*	*17%*	*8%*
Conjunctival melanoma	*15-41%*	*Tumours >/=2mm in histologic thickness, histologic ulceration, non- limbal location.* *(Melanoma in unfavourable locations, recurrent melanoma associated with florid phase of PAM)**	*S100, HMB45, Melan A*	*11-16%*	*8-16%*
Sebaceous gland carcinoma of eyelid and conjunctiva	*7-20%*	*Tumours >/=2b (AJCC 7), size >10mm in greatest diameter*	*Adipophilin, perilipin*	*17-20%*	*2 cases*
Squamous cell carcinoma of eyelid and conjunctiva	*1-24.3%*	*Tumours >2cm in diameter, locally recurrent, perineural invasion*	*Pancytokeratin cocktail-cytokeratin AE-1/3*	*12.5%-14%*	*No reports*
Merkel Cell carcinoma	*21-66%*	*Increasing diameter, thickness and mitotic rate, infiltrative growth pattern*	*Cytokeratin 20, chromogranin, Cam5.2*	*24-48%[$]*	*12%[#]*

**secondary selection criteria*
$-data for all anatomic location. Data on Merkel cell carcinoma of eyelid is insufficient
 # data for head and neck. Data on Merkel cell carcinoma of eyelid is insufficient.

References

1. Dogan NU, Dogan S, Favero G, Köhler C, Dursun P. The Basics of Sentinel Lymph Node Biopsy: Anatomical and Pathophysiological Considerations and Clinical Aspects. Journal of oncology, 2019; 2019.
2. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, Foshag LJ, Cochran AJ. Technical details of intraoperative lymphatic mapping for early stage melanoma. Archives of surgery, 1992; 127(4):392-9.
3. Pfeiffer ML, Savar A, Esmaeli B. Sentinel lymph node biopsy for eyelid and conjunctival tumors: what have we learned in the past decade?. Ophthalmic Plastic & Reconstructive Surgery, 2013; 29(1):57-62.
4. Nijhawan N, Ross MI, Diba R, Gutstein BF, Ahmadi MA, Esmaeli B. Experience with sentinel lymph node biopsy for eyelid and conjunctival malignancies at a cancer center. Ophthalmic Plastic & Reconstructive Surgery, 2004; 20(4):291-5.
5. Maalouf TJ, Dolivet G, Angioi KS, Leroux A, Genin P, George JL. Sentinel lymph node biopsy in patients with conjunctival and eyelid cancers: experience in 17 patients. Ophthalmic Plastic & Reconstructive Surgery, 2012; 28(1):30-4.
6. Cohen VM, Tsimpida M, Hungerford JL, Jan H, Cerio R, Moir G. Prospective study of sentinel lymph node biopsy for conjunctival melanoma. British Journal of Ophthalmology, 2013; 97(12):1525-9.
7. Chaugule SS, Esmaeli B. Sentinel Lymph Node Biopsy for Conjunctival and Ocular Adnexal Tumors. InSurgical Ophthalmic Oncology (Springer, Cham), 2019; 59-65.
8. Gershenwald JE, Tseng CH, Thompson W, Mansfield PF, Lee JE, Bouvet M, Lee JJ, Ross MI. Improved sentinel lymph node localization in patients with primary melanoma with the use of radiolabeled colloid. Surgery, 1998; 124(2):203-10.
9. Rubinstein TJ, Perry JD, Korn JM, Costin BR, Gastman BR, Singh AD. Indocyanine Green–Guided Sentinel Lymph Node Biopsy for Periocular Tumors. Ophthalmic Plastic & Reconstructive Surgery, 2014; 30(4):301-4.
10. Ho VH, Ross MI, Prieto VG, Khaleeq A, Kim S, Esmaeli B. Sentinel lymph node biopsy for sebaceous cell carcinoma and melanoma of the ocular adnexa. Archives of Otolaryngology–Head & Neck Surgery, 2007; 133(8):820-6.
11. Mendoza PR, Grossniklaus HE. Sentinel lymph node biopsy for eyelid and conjunctival tumors: what is the evidence? International ophthalmology clinics, 2015; 55(1):123.
12. Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, Hoekstra HJ, Karakousis CP, Puleo CA, Coventry BJ, Kashani-Sabet M. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. New England Journal of Medicine, 2014; 370(7):599-609.
13. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, Jahkola T, Bowles TL, Testori A, Beitsch PD, Hoekstra HJ. Completion dissection or observation for sentinel-node metastasis in melanoma. New England Journal of Medicine, 2017; 376(23):2211-22.
14. Campbell AA, Grob SR, Freitag SK. Controversies in sentinel lymph node biopsy for ocular neoplasms. International ophthalmology clinics, 2015; 55(4):73-9.
15. Ford J, Thakar S, Thuro B, Esmaeli B. Prognostic value of the staging system for eyelid tumors in the 7th edition of the American Joint Committee on Cancer Staging Manual. Ophthalmic plastic and reconstructive surgery, 2017; 33(5):317-24.

Dr. Mrittika Sen *(MD)*

Dr. Santosh G Honavar *(MD, FACS)*

Dept of Ophthalmic Plastic Surgery and Ocular Oncology
Centre for Sight, Road No 2, Banjara Hills, Hyderabad 500034
e-mail: santosh.honavar@gmail.com

DOI: http://dx.doi.org/10.7869/djo.536