

A Positive Sentinel Lymph Node in Periocular Invasive Squamous Cell Carcinoma: A Case Series

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Purpose: The aim of this article was to describe positive sentinel lymph node biopsy (SLNB) findings in patients with periocular invasive squamous cell carcinoma (SCC).

Methods: This was a retrospective chart review of 5 patients with invasive SCC of the periocular region who underwent SLNB and were found to have regional metastasis.

Results: All patients had large (2.0–4.3 cm) primary tumors with poor differentiation on pathology. In all 5 patients, SLNB was positive in the absence of other signs or evidence of regional or systemic metastasis. While tumor cells may drain to the preauricular or the submandibular basin, the preauricular lymph node was identified as the sentinel lymph node on lymphoscintigraphy in all 5 patients. With a positive sentinel lymph node, the results of SLNB changed the clinical staging and influenced subsequent treatment recommendations for each patient. We identified no complications related to SLNB including facial nerve damage, lymphedema, or allergic reaction to radioactive tracing material.

Conclusions: In this series of patients with periocular invasive SCC, SLNB was well tolerated and uncovered regional metastasis in patients with no clinical signs of metastasis otherwise. The SLNB findings influenced subsequent oncologic management recommendations. The usefulness of SLNB for poorly differentiated SCC remains uncertain. Further research is necessary to establish the role of SLNB in periocular SCC.

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A sentinel lymph node is often the first site of malignant tumor spread before dissemination to more distant sites. Biopsy may be performed on a sentinel lymph node for histopathologic examination to determine the presence of microscopic metastasis. Unlike a lymph node dissection that traditionally involves removing a bulk of tissue with 10 to 15 lymph nodes, sentinel lymph node biopsy (SLNB) is less invasive and usually involves the biopsy of 1 or 2 lymph nodes.

The spread of tumor to sentinel nodes can carry prognostic implications. A positive SLNB may signify regional metastases otherwise undetected on imaging or clinical examination, thus upstaging a malignancy and altering the prognosis for the patient. Chemotherapy, radiation, or further surgery may be indicated based on the status of the sentinel lymph node.

The concept of imaging lymph nodes to identify the evidence of metastasis was first described by Cabanas and colleagues in 1967 for penile cancer.¹ Sentinel lymph node biopsy was first described by Morton et al.² in 1992 for cutaneous malignant melanoma, and has since been adopted for other solid tumors, such as breast, colon, penile, cervical, head and neck, and vulvar cancers.^{3,4} In the periocular region, Esmali et al.⁵ first reported the use of SLNB for conjunctival melanoma in 2001. Other periocular applications for SLNB include eyelid and orbital melanoma, sebaceous cell carcinoma, and Merkel cell carcinoma.^{6–15}

Squamous cell carcinoma (SCC) is the second most frequent malignancy in the periocular region, representing approximately 5% to 10% of all eyelid malignancies.^{16,17} SCC is a malignant epithelial neoplasm that may exhibit basement membrane invasion with direct extension or even distant metastasis, especially for the invasive subtypes. The overall rate of regional lymph node metastasis may be as high as 25%.^{18,19} Currently, there may be a lack of consensus in the management of invasive SCC.²⁰ The use of SLNB has been reported for SCC affecting other regions of the body.^{21–24} Recently, Maalouf et al.¹⁵ reported the use of SLNB in 8 patients with conjunctival and eyelid SCC with positive SLNB findings in 1 of the patients. We are aware of no other reports describing positive SLNB findings in patients diagnosed with stage N0 periocular SCC based on imaging.

METHODS

With institutional review board approval, we retrospectively reviewed the charts of 5 patients with periocular invasive SCC who also had SLNB. We compiled details of each case including the following: tumor location, type of resection, histologic features, history of previous treatments, patient's immune status, location of sentinel node, histology of sentinel lymph node, and side effects from SLNB such as lymphedema^{25–27} or facial nerve damage.^{21,22,28} The chief outcome measures were the histopathologic findings of the sentinel lymph node and subsequent management recommendations once that the malignancy was upstaged.

The main indication for SLNB in our case series was poor differentiation on microscopy in periocular SCC patients with no evidence of systemic metastasis clinically and on imaging (CT, ultrasound, or based on the distribution of glucose analog 2-deoxy-2-(18F)fluoro-D-glucose uptake on positron emission tomography-CT scan). In all cases, primary eyelid tumor biopsy results showed an aggressive tumor grade as signified by: poor cell differentiation, severe cytologic atypia, pleomorphic hyperchromatic nuclei, abnormal chromatin distribution, abundant eosinophilic cytoplasm, high mitotic rate, and abnormal mitotic figures. Histologic features indicative of invasive SCC include primary tumor grade and primary tumor infiltration (Breslow depth > 1 mm, Clark level > IV).

Sentinel lymph node biopsy was performed with the following technique in all cases. The sentinel lymph node was identified with

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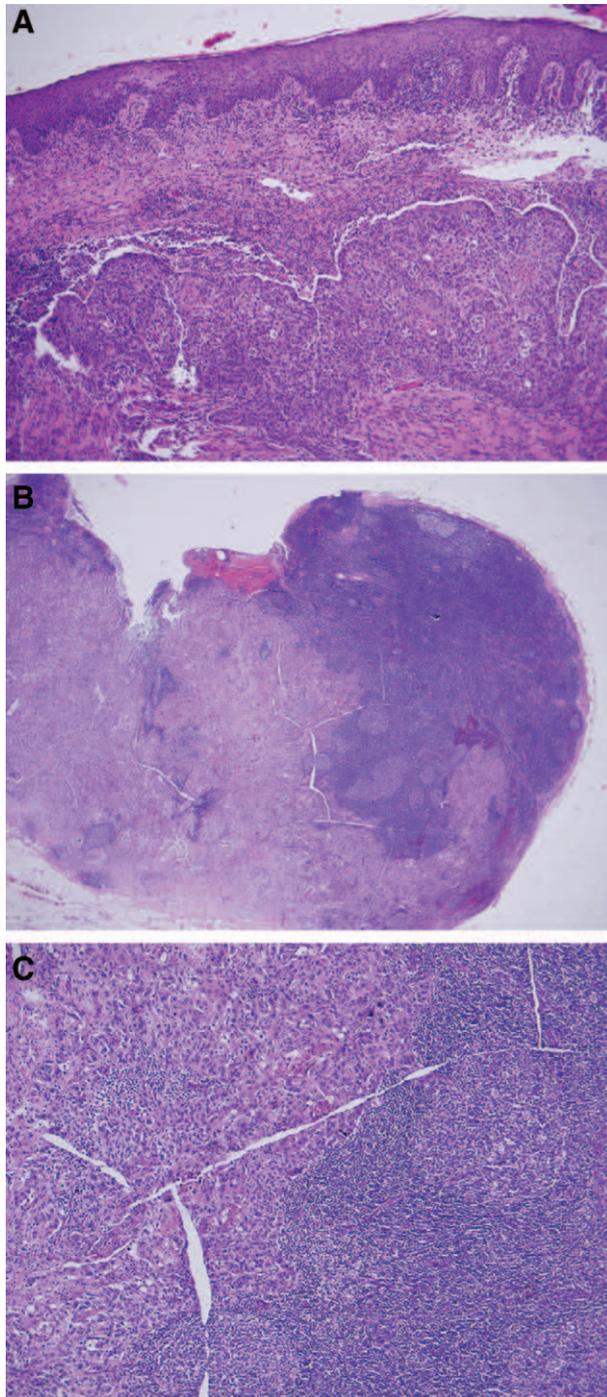


FIG. **A**, Hematoxylin-eosin stain of the primary eyelid lesion showing invasive SCC at $\times 40$. **B**, Hematoxylin-eosin stain of a positive sentinel lymph node biopsy at $\times 40$. **C**, Magnification of the lymph node at $\times 200$ showing poor cell differentiation, severe cytologic atypia, abnormal chromatin distribution, abundant eosinophilic cytoplasm, and abnormal mitotic figures in SCC. SCC, squamous cell carcinoma.

preoperative lymphoscintigraphy using a technetium Tc99m-labeled sulfur colloid injected around the primary lesion, and a γ scintillation camera to identify the site of focal radioactive uptake. Perioperative Tc-99m and intraoperative isosulfan blue injection with the aid of a transcutaneous probe were also used to mark the sentinel lymph node that was resected and sent for histopathologic analysis.

RESULTS

In all cases, clinical assessment and imaging were negative for tumor metastases. Thus, prior to SLNB, staging was N0 for SCC disease. In all patients, the preauricular node was identified as the sentinel node by preoperative lymphoscintigraphy with technetium, intraoperative detection of radioactivity with technetium, and intraoperative gross visualization with isosulfan blue. In all cases, the SLNB findings upstaged the disease and prompted additional treatment recommendations. Two patients (case 1 and case 4) refused additional therapy, while 3 patients (cases 2, 3, and 5) accepted facial radiation, with case 5 also receiving chemotherapy.

Case 1. An 82-year-old Caucasian man presented with a 4.3 cm ulcerating lesion on the central left lower eyelid extending into the anterior orbit. On clinical assessment and CT imaging, there was no evidence of regional lymph node involvement or distant metastases. He underwent local surgical excision and tumor debulking. Invasive SCC was diagnosed by pathology. The preauricular sentinel nodes identified by lymphoscintigraphy were sent for biopsy and exhibited SCC with similar histopathology as the eyelid and orbital tumor. An exenteration was performed due to orbital extension of the tumor. The anterior margins of the exenteration were free of tumor involvement by frozen section control. At 1 week and 8 weeks follow up, no lymphedema or facial nerve palsy was present. Systemic workup including positron emission tomography-CT, as well as radiation and chemotherapy were recommended; however, the patient refused. Given that distant metastasis could not be evaluated, TNM staging was incomplete and staged at T4N1 according to the American Joint Committee on Cancer guidelines.²⁹ At 5 months post initial biopsy, the tumor recurred in the lateral orbit. New masses, presumed to be tumor, were present along the left side of the neck. Left-sided mild lymphedema and left facial paralysis were present due to secondary tumor effects. One year later, the patient died. The cause of death was uncertain, as the patient was lost to follow up; records surrounding the death were also not available for review.

Case 2. A 75-year-old Asian man presented with a right upper eyelid mass and ptosis that was progressively worsening over several months. Examination revealed a firm upper eyelid mass measuring $3.5 \times 4 \text{ cm}^2$ with anterior orbital extension causing mechanical ptosis. On clinical assessment, there was no ulceration or evidence of regional lymph node involvement or distant metastases. MRI revealed an eyelid and superior orbital mass. Pathology from excision revealed invasive SCC. Systemic workup including positron emission tomography-CT scan was negative for metastatic SCC. The SLNB performed after localization by lymphoscintigraphy exhibited SCC with 1 positive preauricular sentinel lymph node. TNM staging was thus upstaged to T4N1M0. Further surgery including exenteration was considered, but the patient refused due to a desire to keep his eye. The patient underwent right-sided radiation treatment to the periocular region to the periparotid level 1B. No lymphedema or facial nerve paralysis related to SLNB was present postoperatively. At 1 year, no gross recurrence of SCC was detected, but the examination exhibited upper eyelid scarring and mechanical ptosis.

Case 3. An 81-year-old Caucasian man presented with a $2 \times 2.5 \text{ cm}^2$ ulcerating mass affecting the lateral right upper eyelid. On clinical assessment and ultrasound, there was no evidence of regional lymph node involvement or distant metastases. The lesion proved to be invasive SCC, and wide local excision with frozen section margin control was performed. The eyelid was reconstructed with a local myocutaneous flap and mucous membrane grafting. Positron emission tomography-CT was negative for metastatic disease. Two preauricular sentinel

nodes, identified by lymphoscintigraphy, exhibited SCC. Based on positive SLNB results, TNM staging was thus upstaged to T4N2bM0. Because he was a poor candidate for major facial and neck surgery, radiation involving the right orbit and right periparotid levels 1B and 2 was recommended and accepted by the patient. Further workup for metastatic SCC was negative. However, a large ulcerating lesion affecting the left shin was sent for biopsy and proved to be SCC. This was thought to be a primary lesion unrelated to the prior oculo-facial disease. The shin SCC was treated with radiation because it was diffuse and he was not systemically fit for aggressive surgery. At 1-year follow-up visit, the patient was doing well with no signs of recurrence and no lymphedema or facial nerve damage.

Case 4. A 92-year-old Caucasian man with a history of skin malignancies elsewhere on the body presented with a 4 × 4 cm² bleeding and infected, ulcerating tumor affecting the left lower eyelid and cheek with anterior orbital extension. There was no clinical or CT imaging evidence of regional lymph node involvement or distant metastases. Biopsy of the primary tumor proved to be invasive SCC. Systemic workup for metastasis was negative. On lymphoscintigraphy, 2 preauricular lymph nodes were determined to be the sentinel nodes that were positive on histology. Surgical debulking, neck dissection, and facial radiation therapy were considered; however, the patient refused due to his age and overall condition. Given that distant metastasis could not be evaluated, TNM staging was incomplete and determined to be T4N2b. At 1 week and 6 weeks follow up, no lymphedema, facial nerve paralysis, or other complications of SLNB were evident. At 3 months postbiopsy, examination showed tumor progression into the inferior orbit that involved the entire upper cheek and lower eyelid region. Seven months later, the patient died; the exact cause of death is unknown, but complications of metastatic SCC are possible.

Case 5. A 51-year-old Caucasian woman presented with a 3 × 1 cm² fungating lesion of the left lateral lower eyelid that increased in size over 18 months. On clinical assessment, there was no evidence of regional lymph node involvement or distant metastases. Orbital imaging thereafter demonstrated tumor extension of the inferior orbit abutting the globe to the level of the equator. The initial eyelid excision showed invasive SCC with highly aggressive features. Systemic workup including positron emission tomography-CT scan was negative for metastatic disease. Lymphoscintigraphy demonstrated 3 signals at the preauricular area representing the sentinel lymph nodes. During SLNB, intraoperative γ probe revealed only 1 "hot" node that was found not to be blue despite isosulfan blue injection. From histology, a diagnosis of metastatic SCC with no extracapsular extension was made (Fig.). TNM staging was thus upstaged to T4N2bM0 based on positive SLNB. Due to the deep orbital extension, proximity to the globe, and the patient's young age, orbital exenteration was recommended and accepted by the patient. The left orbit resection demonstrated no evidence of invasion, and the surgical margins of resection were negative. At 1 week, 6 weeks, and 6 months follow up, no lymphedema, facial nerve paralysis, or other complications of SLNB were evident. With multidisciplinary input, including radiation oncology and surgical oncology, adjuvant therapy was recommended owing to an advanced local primary tumor and positive preauricular lymph node in a relatively young patient. The patient was subsequently treated with face and upper neck radiation delivered to the periparotid level 1B, 2, and upper 3 lymph nodal zones along with adjuvant cisplatin chemotherapy. At 1-year follow up, there was no evidence of tumor recurrence.

DISCUSSION

Our findings demonstrate that SLNB may be positive in poorly differentiated SCC of the periocular region. Sentinel lymph node biopsy may uncover regional metastasis not apparent on clinical evaluation or imaging. In our series, positive SLNB prompted the oncologic recommendation of radiation with 1 patient also being recommended chemotherapy, in addition to further surgery when appropriate. Importantly, young age was an additional factor for the recommendation of chemotherapy that otherwise may not be a typical treatment for SCC.

Squamous cell carcinoma is the second most frequent malignancy in the periocular region, representing about 5% to 10% of all eyelid malignancies.^{16,17} Squamous cell carcinoma may behave aggressively and spread by perineural invasion or through lymphatics.^{16,30} The overall rate of regional lymph node metastasis has been reported to be as high as 25% in periocular SCC, with an average duration of 1 year from the onset of cutaneous lesion to the diagnosis of orbital invasion.^{18–20,31,32} Currently, there is no established consensus for the management of invasive SCC.²⁰

Broadly speaking, the indications for SLNB in primary periocular malignancies depend on the aggressiveness of the disease process as well as the histologic staging of the primary tumor. For instance, SLNB is not commonly performed for basal cell carcinoma secondary to the extremely rare rates of metastasis.^{33,34} Similarly, small and well-differentiated SCC also may not require extensive workup or adjuvant treatment.

The primary rationale for SLNB in our patients with periocular SCC was poor differentiation on histology that may portend more aggressive disease. Nevertheless, many factors should be considered in SCC because even small carcinomas can metastasize.^{35,36} These include the patient's immune status, desmoplasia, angioinvasion, ulceration, maximum diameter, poorly differentiated histology, mitotic index, grading, perineural invasion, plasma cells and eosinophilic inflammatory response, and depth of tumor invasion (Clark level, Breslow depth).^{35,37} The indications for SLNB in SCC remain uncertain, and further research is warranted.

Sentinel lymph node biopsy has been described in other malignancies of the periocular region including sebaceous cell carcinomas,¹³ and Merkel cell carcinomas.⁸ Owing to the aggressive nature of these neoplasms, histologic sentinel lymph node analysis may allow more accurate staging that may influence treatment and outcomes.^{13,38–45} For instance, SLNB has been shown to be the most significant prognostic factor with respect to recurrence and survival in patients with oculo-facial cutaneous melanoma.^{6–15}

While SLNB has been reported to be efficacious in determining regional nodal status of SCC affecting the head and neck²³ and inguinal²⁴ regions, the usefulness of SLNB for poorly differentiated periocular SCC remains unknown. Our review of the literature elicited 1 case of a positive SLNB in Stage N0 periocular SCC.¹⁵ This patient had a periocular SCC that recurred twice after resection, but additional clinical and histopathological features was not provided; it was also unclear whether the primary SCC involved conjunctiva or skin.¹⁵ Nevertheless, the positive SLNB findings prompted radiotherapy.¹⁵

Although none of the patients in this series suffered negative sequelae, facial SLNB is associated with risks. These include: lymphedema,^{25–27} facial nerve damage,^{21,22,28} allergic reaction to the tracer,⁴⁶ and inherent risks with a second surgical site and longer operating times.

Transient or permanent facial nerve damage is an important SLNB risk, especially with preauricular node biopsy.^{21,22,28} Typically and based on cadaveric studies, the preauricular or parotid lymph nodes receive lymphatic drainage from the

central and lateral upper eyelid, as well as the lateral lower eyelid. The submandibular lymph nodes receive lymphatic drainage from the medial upper eyelid and the medial lower eyelid via the angular and facial vessels.^{28,47} All of our cases involved the preauricular lymph node, even if the primary tumor included medial lower eyelid and medial canthus. These findings are consistent with more recent studies that demonstrate usual drainage to the preauricular node regardless of location on the eyelid.²⁸

A false-negative result is another important risk because it may complicate the clinical picture. While a negative SLNB implies no need for further dissection, false negatives may occur rarely due to obstruction of lymphatic drainage of malignant cells due to fibrous bands from previous surgery or compression by a neighboring mass.

The authors acknowledge several limitations of this study. The design is a retrospective, small case series of patients with variable underlying characteristics, short follow up, and no control cohort. The series provides insufficient data to draw significant conclusions of SLNB impact on tumor recurrence or survival.

In summary, SLNB was well tolerated and helped detect regional metastasis in 5 patients with periocular poorly differentiated SCC. Positive findings in SLNB may guide staging and further management of the disease. These include further metastatic workup and adjuncts to surgery such as radiation, chemotherapy, or both. Importantly, the usefulness of SLNB for poorly differentiated periocular SCC remains unknown. Further work is warranted to assess the impact upon survival, recurrence, and cost to delineate the role of indications for SLNB in ocular adnexal SCC.

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