Sentinel Node Biopsy for Nonmelanoma Skin Cancer of the Head and Neck

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KEYWORDS

• Cutaneous squamous cell carcinoma • Merkel cell carcinoma
• Sebaceous cell carcinoma • Sentinel lymph node biopsy

KEY POINTS

- Sentinel lymph node biopsy should be considered for all cutaneous malignancy with a 10% risk of occult regional lymph node metastasis.
- Patients with regional metastasis from cutaneous malignancy have a poor survival; therefore, sentinel lymph node biopsy offers the potential to improve outcomes.
- Exact criteria to guide sentinel lymph node biopsy for cutaneous squamous cell carcinoma remains to be determined, but patients with multiple high-risk features should be considered.
- All patients with Merkel cell carcinoma greater than 1 cm diameter should undergo sentinel lymph node biopsy.

INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most prevalent cancer in the world.[1] Basal cell carcinoma makes up the vast majority of these cases, but is a low-risk cancer in terms of potential for regional and distant metastasis. Other NMSC, especially cutaneous squamous cell carcinoma (cSCC) and Merkel cell carcinoma (MCC), have a significant risk for regional metastasis and, therefore, sentinel lymph node biopsy (SLNB) is an important consideration in management. Sebaceous carcinoma and other adnexal tumors are also known to have regional metastasis. Sentinel lymph node biopsy is standard in the treatment of melanoma and this experience can provide a framework for how to approach SLNB for NMSC (**Table 1**).

Well-established clinical and pathologic data have allowed a risk stratification profile for patients with melanoma. These pathologic features define the patient's risk of occult lymph node metastasis and need for SLNB or observation. In a prospective

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Table 1
Nonmelanoma sentinel lymph biopsy summary guide

Histology	Criteria for SLNB Consideration
Squamous cell carcinoma	1. BWH T2b (≥2 of the following: >2 cm, poorly differentiated, PNI, deep invasion beyond subcutaneous fat) 2. ≥3 of the following: >2 cm, poorly differentiated, deep invasion beyond fat, >5 mm depth of invasion, PNI, LVI, recurrent, occurring in scar, sarcomatoid/spindle feature, immunocompromised patient
MCC	1. All lesions >1 cm 2. Lesions <1 cm but LVI and high mitoses
Sebaceous carcinoma	>2 cm, LVI (discuss for all tumors given small existing data)
Others	Anticipated/estimated risk of occult metastasis >10%

randomized trial, MSLT-1, a survival benefit was demonstrated for patients who have microscopic regional metastasis identified by SLNB compared with those who present with macroscopic disease.[2] Additionally, SLNB has a practical benefit, helping to guide adjuvant treatment and surveillance. This framework can be applied to SLNB for NMSC. In this article, we consider cSCC as well as other rare tumors such as MCC and sebaceous carcinoma.

CONSIDERATIONS FOR CUTANEOUS SQUAMOUS CELL CARCINOMA

Rationale for Sentinel Lymph Node Biopsy

Cutaneous SCC is the second most common skin cancer.[1] It has a continually increasing incidence approaching almost 400 cancers per 100,000 people per year in Australia and more than 700,000 cases per year in the United States.[3–5] It disproportionately affects the head and neck region because of its chronic sun exposure. The vast majority of cSCC is cured with excision and 95% of all cSCC fall into this low-risk category.[6] However, owing to the high prevalence of cSCC patients, there are still an estimated 5604 to 12,572 patients per year who develop regional lymph node metastasis. These regional metastases lead to approximately 3932 to 8791 deaths per year from cSCC.[7] To put this in context, this is similar to the number of deaths per year from melanoma (6850).[8]

Although the overall survival from low-risk cSCC is in the very high 90s, once a patient has a regional metastasis, survival significantly decreases.[6] In a series from Australia in 2005 involving 181 patients, Clark and colleagues[9] reported a 39% disease-specific survival for patients with regional metastasis. Similarly, in 2017 Amoils and colleagues[10] reported a similar 5-year survival of less than 40% for patients with regional metastasis. Creighton and colleagues[11] published a series of 62 patients in 2018 showing a 56% overall survival. One of the best survival outcomes was reported in a prospective clinical trial also published in 2018. Porceddu and colleagues[12] reported a 5-year overall survival of 76% when comparing adjuvant radiation and chemoradiation. This study highlights the potentially improved survival in patients receiving the optimal and close care associated with a clinical trial. The regional lymph node basin is the first site of metastasis in approximately 85% of all cases. These survival statistics highlight the potential impact of SLNB.

Risk Factors for Occult Metastasis

Histopathologic melanoma data identified the group of lesions with at least a 10% risk of occult lymph node metastasis and therefore the recommendation for SLNB. For

cSCC, defining such a criterion has been more difficult. One of the most frequently cited criteria is from the Brigham and Women's Hospital. In 2013 Jambusaria-Pahlajani and colleagues[13] reported a retrospective cohort study identifying 4 features predicting a higher risk of regional metastasis: size greater than 2 cm, deep invasion beyond the subcutaneous fat, perineural invasion (PNI), and poor tumor differentiation. Twenty percent of patients with more than 1 risk factor developed regional metastasis. Other retrospective cohort studies and case reviews reported additional histopathologic features, such as lymphovascular invasion (LVI), depth of invasion greater than 6 mm, bone invasion, and spindle or sarcomatoid features.[10,11,14,15] Less well-defined clinical features such as rapid growth, growth within the previous scar, and recurrence after previous treatment have also been shown to carry significance.[14–16] Practitioners are well aware that immunosuppressed patients have a large number of cSCC lesions and more high-risk lesions. Elghouche and colleagues[17] performed a meta-analysis assessing the impact of immunosuppression and found a hazard ratio of 2.2 for the risk of local and regional recurrence as well as a 3.61 ratio for disease-specific survival. It is likely that all of these features play a role in the risk profile for occult metastasis. Future research to better understand and quantify these risks will be key to defining the role of SLNB.

Review of Sentinel Lymph Node Biopsy Literature

Unlike melanoma, SLNB experience with cSCC is limited to single institution experiences. Wu and colleagues[16] published a prospective series of 83 SLNB patients based on the Brigham and Women's stage T2b criteria. Only 10% of biopsies in the T2b group were positive. Four patients developed a recurrence after a negative biopsy; however, all of these events occurred in the setting of a local recurrence following SLNB. Durham and associates[14] published a case review series from the University of Michigan, where they performed SLNB on 53 patients with a positivity rate of 15.1%. The criteria for their series was less well-defined in terms of specific inclusion criteria for SLNB. However, assessment of the data shows that LVI, PNI, and overall clinical size are associated with the presence of lymph node metastasis. This series identified 5 patients who underwent a more thorough processing of the tissue, including use of immunohistochemical staining, and 2 of the 5 cases reviewed were found to have microscopic disease initially considered negative. Unlike melanoma, the processing of SLNB tissue has not yet been standardized. This report suggests that immunohistochemical staining may be more accurate. Mooney and colleagues[15] recently published a prospective series from Sydney Australia. They reported on 105 patients with a 10% SLNB positive rate and a 14.3% total subclinical nodal metastasis. Similar to the series at the University of Michigan, a specific criterion for study enrollment was not defined. However, the data demonstrated several key factors to identify patients who may benefit from SLNB. No patient had a positive node with depth of invasion of less than 5 mm.

Additionally, the risk of metastasis further increased for tumors greater than 10 mm in thickness. When combining this depth of invasion with the presence of PNI the rate of lymph node metastasis increased to 28%. This group reported patients with 4 or more risk factors (size >2 cm, invasion into subcutaneous fat, depth of invasion >5 mm, poor tumor differentiation, PNI, PNI, local recurrence, ear or lip location, immunocompromised status, and carcinoma in a preexisting scar) having a greater than 20% risk of occult lymph node metastasis. The SLNB experience to date supports consideration of a broad inclusion criteria of risk factors and the importance of multiple high-risk factors increases risk for occult metastasis.

Impact of Sentinel Lymph Node Biopsy on Outcome and Management

The impact of SLNB on outcomes and clinical care remain to be determined. From a practical standpoint, SLNB can be used to help determine the need for follow-up and adjuvant radiation therapy. The SLNB series mentioned elsewhere in this article report a relatively high risk—approximately 10%—of local recurrence, in-transit metastasis, and even distant metastasis.[15,16] Therefore, patients who meet the criteria for considering SLNB should be closely monitored for 2 to 3 years, regardless of SLNB outcome.

For those with a positive SLNB, potential next steps in management include observation, completion lymphadenectomy, and radiation. Ebrahimi and colleagues[18] reported a large series that showed patients with a single lymph node metastasis of less than 3 cm without ECS treated only surgically had 100% survival at 5 years. This finding suggests a limited benefit for adjuvant radiation after a single positive SLNB. In patients without local recurrence, lymph node recurrence after a negative SLNB is very low, limiting any benefit from adjuvant radiation.[15,16]

Consideration for completion lymph node dissection (CLND) is more complex. The SLNB series reported were not collected and managed in a manner to provide any clear guidance on this management. Melanoma data have shown approximately a 15% rate of nonsentinel lymph nodes identified at time of completion node dissection.[19] Durham and colleagues[14] reported 2 of 5 patients who underwent completion node dissection had positive nodes. Given the limited morbidity and potential to improve regional control, lymphadenectomy is a reasonable management option after a positive SLNB. Lymphadenectomy should be based on the primary lesion location and its expected at risk lymph node regions. The mapping from SLNB should also be used to help to guide this dissection.[20,21] Patients not undergoing completion lymphadenectomy need close observation with serial imaging.

The impact of SLNB on survival cannot be determined from the current literature. There has not been a study designed to answer this question. Series to date have reported survival rates of 20% to 100% at 3 years for positive SLNB.[14,15,22] This disparate experience makes any comparison with existing survival data on macroscopic lymph node metastasis impossible. However, given the poor survival reported for patients with macroscopic lymph node metastasis there is a potential opportunity to improve outcomes by detecting micrometastasis. A future clinical trial will be needed to answer this question.

The emerging role of immunotherapy is likely to have an impact on adjuvant treatment. Checkpoint inhibitors in the adjuvant setting are currently being explored in a clinical trial. Based on future data, the decision to give adjuvant immunotherapy could be determined by SLNB. This type of treatment could have a more significant impact on recurrence at the primary site, regionally, as well as distantly, thereby improving disease-specific and overall survival.

CONSIDERATIONS FOR MERKEL CELL CARCINOMA

MCC is a rare and aggressive cutaneous malignancy of neuroendocrine origin that predominantly occurs in the head and neck (43%) and upper limbs and shoulder (24%).[23] Regional lymph node metastasis is clearly associated with worse outcomes, and assessment of lymph node status is important from a prognostic and treatment planning perspective. SLNB is considered an important staging tool in patients with clinically node-negative MCC and is recommended by the National Comprehensive Cancer Network MCC practice guidelines.[24]

Risk Factors for Occult Metastasis

Although the majority of patients with MCC present without clinically evident nodal involvement, up to 40% of patients may ultimately develop regionally metastasis.[25] Several tumor factors are associated with increased risk of occult nodal metastasis, including tumor thickness, diameter, location, mitotic rate, LVI, and tumor-infiltrating lymphocyte burden.

Within the head and neck, anatomic subsite may independently predict risk of nodal metastasis and survival. A retrospective analysis of the Surveillance Epidemiology and End Results (SEER) database found that lip tumors are associated with the highest rates of local invasion (13.7%), whereas ear tumors had the highest rate of nodal metastasis (63.2%).[26]

Tumor depth and diameter have been identified as independent prognostic factors for SLNB status, as well as overall and disease-specific survival. In their study of 191 patients who underwent SLNB for MCC, Smith and colleagues[27] reported 31% SLNB positivity across all primary tumor sites. They found that the odds of SLNB positivity increased 1.4 times as tumor depth doubled and 1.7 times as tumor diameter doubled. In a study of 2104 patients with head and neck and non–head and neck MCC, tumor extension beyond the dermis was identified as a unique factor associated with worse disease-specific survival.[28] Stokes and colleagues[29] in their retrospective review of 213 patients who underwent SLNB or lymph node dissection found that only 4% of patients with tumors less than 1 cm had clinically evident regional lymph node metastasis at the time of presentation compared with 24% in patients who had tumors greater than 1 cm in size, suggesting that patients with MCC less than 1 cm may have a low risk of occult metastasis.

Additional prognostic factors have been associated with SLN positivity in retrospective reviews. In 1 study of 153 patients who underwent SLNB, Fields and colleagues[30] identified tumor size greater than 2 cm and the presence of LVI as independent factors associated with SLNB positivity. In their review of 95 patients with clinically node-negative MCC at the University of Michigan, Schwartz and colleagues[31] identified increased tumor thickness, infiltrative (vs circumscribed) growth pattern, and increased mitotic rate as independent predictors of SLN positivity in multivariable models. Notably, no subgroup in their study was identified as having less than a 15% risk of SLN positivity.[31] Tumor-associated immune infiltrates at the tumor margin have also been identified as a prognostic indicator.[32]

Review of the Sentinel Lymph Node Biopsy Literature

Sentinel lymph node biopsy has been used widely among institutions who care for patients with MCC. A large systematic review of 721 patients with tumors in any location from 36 published studies found that SLNB positivity was 29.6% with a false-negative rate of 17.1%.[33] In a systematic review of 136 patients with head and neck MCC from 29 publications, SLNB positivity was 30.9% with a false-negative rate of 19.2%.[34]

Unique to head and neck MCC, complex lymph node drainage patterns may limit its reliability and prognostic value owing to the higher risk of false-negative results.[35] However, other studies have shown SLNB in the head and neck to be very reliable, with false-negative rates of less than 5%.[14,15] Discordant drainage pathways have historically limited widespread use of SLNB across many cancer subtypes; however, several single-institution studies have supported the use of SLNB in the workup of patients with clinically node-negative MCC of the head and neck.[25,36–39] This discrepancy may be the result of a different biologic behavior of MCC or potentially a different set of head and neck experiences among surgeons performing SLNB for MCC.

Large series are uncommon owing to the inherent rarity of MCC. In a review of 122 clinically node-negative patients at the Dana-Farber Cancer Institute, a 32% SLNB positivity rate was reported.[40] In a series of 76 patients with clinically node-negative MCC who underwent SLNB, Harounian and colleagues[41] identified SLN positivity in 29% of patients. Of note, this series did not identify an association between primary tumor site, diameter, patient age, sex, or immune status with SLNB positivity.[41,42]

Impact of Sentinel Lymph Node Biopsy on Outcome and Management

The impact of SLNB on MCC disease-specific and overall survival has been assessed across multiple studies, although findings are variable, in large part owing to differences in SLNB techniques, histologic analysis, false-negative SLNB rates, center-specific treatment paradigms based on SLNB results, and multiple lymph node positivity. Several studies demonstrated an association between SLNB status and disease-free and overall survival. A National Cancer Database analysis of 1174 patients who underwent SLNB found a significant association between SLN positivity and decreased overall survival.[41] A multicenter observational trial from Europe of 87 patients with clinically node-negative MCC who underwent SLNB found significantly increased overall and disease-free survival among patients with a negative SLNB. Notably, all patients in this series underwent wide local excision with adjuvant radiation to the primary site, and node-positive patients additionally underwent lymph node dissection and regional adjuvant radiation therapy.[43] A 2003 to 2009 SEER registry review of 1193 patients, of which 474 underwent SLNB, found that a negative SLNB was associated with a significantly improved 5-year disease-specific survival.[44]

However, several other studies failed to demonstrated any association between SLNB status and survival outcomes. In their review of 150 patients treated at the Mayo Clinic, Sims and colleagues[45] found no significant difference in disease-specific survival at 1, 3, or 5 years among patients with a positive versus a negative SLNB status. Among patients with a positive SLNB who received treatment to the nodal basin, disease-specific survival and overall survival were also similar to patients with negative SLNB. Fields and colleagues[30] found no significant difference in recurrence or disease-free survival between SLNB-positive and -negative patients in their cohort of 153 patients who underwent SLNB; however, the majority of SLNB-positive patients received radiation or chemotherapy. In their SEER registry database analysis of 721 patients with cutaneous head and neck MCC who underwent SLNB, Fritsch and colleagues[46] found an SLN positivity rate of 23.1% and no association between survival outcomes and SLN positivity.

There are additional conflicting reports in the literature as to whether SLNB itself may be associated with a decreased risk of recurrence or disease progression. In a SEER study of 1193 patients with stage I and II MCC, 474 underwent SLNB and 719 were observed in the regional lymph node basin. Patients who underwent SLNB had a 5-year disease-specific survival benefit when compared with those who were observed.[44] Single-institution studies, however, have not demonstrated any survival benefit associated with SLNB itself.[47] At present, SLNB remains a diagnostic rather than therapeutic tool in the workup and management of MCC.

Although it is not clear that SLNB positivity is strongly associated with overall survival outcomes, current guidelines strongly advocate for the use of SLNB in clinically node-negative MCC as an important prognostic and staging tool. Unlike melanoma, and similar to cSCC, prior studies have not identified primary tumor subgroups with a lower than 15% risk of SLNB positivity; therefore, SLNB is advocated for all patients.[31] Patients with lesions less than 1 cm and no LVI may be the exception to this recommendation.

Among patients with SLNB positivity, current guidelines support CLND, regional radiation therapy, or both. An National Cancer Database analysis of 447 MCC SLNB-positive patients compared survival outcomes for CLND alone versus CLND with adjuvant radiation or adjuvant radiation alone. CLND alone was associated with worse survival outcomes compared with the other treatment regimens.[48] Lee and colleagues[49] compared CLND alone with radiation therapy alone in their cohort of 163 patients and reported no difference in disease-specific 5-year survival (71% vs 64%) or disease-free survival (52% vs 61%). Perez and colleagues[50] similarly found no difference in overall survival between patients who underwent CLND alone, radiation alone, or CLND with radiation at Moffitt Cancer Center. Morbidity was low across all treatment groups (lymphedema and surgical site infections).

Among patients with SLNB negativity, providers may consider observation, elective radiation, or elective CLND to the nodal basin.[51] Elective radiation may be used in higher risk patients, for example, those in whom appropriate immunohistochemistry was not performed or patients in whom the primary lesion was excised without an adequate assessment of high-risk features. Of note, there is potentially an increased risk of false-negative SLNB result in the head and neck owing to the complex lymph node drainage.[21] Nontraditional SLNB locations must be carefully assessed to appropriately guide further treatment. Further analysis of elective treatment of SLN-negative patients is necessary, including an assessment of disease and overall survival parameters.

CONSIDERATIONS FOR OTHER NONMELANOMA SKIN CANCERS

Sebaceous cell carcinoma is a rare malignant tumor that arises from the sebaceous glands, most commonly occurring in the head and neck, particularly in the eyelids, where it may arise from the meibomian glands. SLNB has been reported in a small retrospective series, although it remains relatively uncommon.[52–54] In a study of 10 patients with eyelid sebaceous cell carcinoma who underwent SLNB, no positive SLN were identified; however, 2 of 10 patients went on to develop recurrence in regional lymph nodes, raising concern for a high false-negative rate and reinforcing the risk for regional metastasis. Imaging or SLNB should be considered.[52] Sentinel lymph node biopsy for sebaceous carcinoma has been successfully used in a larger series with other periocular lesions. These series highlight the feasibility of SLNB for periocular tumors and the occurrence of occult metastasis. However, studies did not identify a clear criterion for performing SLNB or demonstrated a survival benefit given the relatively small sample size.[54,55]

SUMMARY

When considering SLNB for any cutaneous tumor, it is important to assess the prognostic value, false-negativity rate, and implications for treatment planning. The technique itself has been well-described and with imaging adjuncts is a safe and efficient procedure in the head and neck. Therefore, applying a broad consideration of any tumor with a greater than 10% risk of occult metastasis, SLNB should be considered. SLNB for MCC is an established important diagnostic and prognostic procedure. It should be discussed for all patients with MCC. Although the role for SLNB in cSCC remains to be defined, SLNB does offer the potential for important diagnostic information that can be used to personalize care. Additional data are needed to define who needs this procedure and how its outcome directs additional care. Clinical experience and multidisciplinary discussions remain key to identifying patients who may benefit from SLNB.

CLINICS CARE POINTS

- Disease survival from regionally metastatic cSCC is approximately 50% based on multiple studies.
- BWH stage T2b has approximately a 10-20% risk of occult regional lymph node metastasis.
- MCC has a high rate (>40%) of regional metastasis and survival is dramatically decreased in those with regional metastasis.
- MCC has a higher rate of false negative SLNB and those with negative SLNB need continued close surveillance.

DISCLOSURE

R. Sethi – No disclosures. K. Emerick – Consultant; Regeneron and Sanofi; This work does not directly relate to sentinel lymph node biopsy and this content. Work does relate to systemic therapy for cSCC.

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