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HEAD & NECK: NON-MELANOMA SKIN CANCER OF THE HEAD AND NECK (J MOYER, SECTION EDITOR)

Management of the Neck for Non-melanoma Skin Cancer

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Abstract

Purpose of Review To summarize the current management of the neck lymph node basin for head and neck non-melanoma skin cancers.

Recent Findings Over the last 5 years, there have been updates to staging for cSCC and MCC. T classification of the AJCC staging system has been changed to match the UICC staging system. MCC staging has been updated based on data from the National Cancer Data Base. Sentinel lymph node biopsy, while established in MCC, is playing a growing role in the management of high-risk N0 cSCC.

Summary The optimal management of N0 neck varies by metastatic potential. In low-risk malignancy, no workup is necessary. In cSCC, risk stratification is necessary. High-risk tumors with N0 necks should undergo preoperative imaging with CT and targeted FNA of suspicious lymph nodes. If radiologically negative, a SLNB should be considered. Selective neck dissection should be performed for N+ disease and positive SLNB. Elective neck dissection is not routinely recommended and should be reserved for positive parotid nodal disease. Merkel cell carcinoma has high rates of nodal metastases and requires preoperative imaging with targeted FNA of suspected metastases. SLNB should be performed for N0 disease to guide prognostication and further treatment. Management of negative SLN is controversial, and most can be observed while radiation may be considered for high-risk patients. Positive SLN requires completion neck dissection and radiation.

Keywords Non-melanoma skin cancer · Cutaneous squamous cell carcinoma · Merkel cell carcinoma · Neck metastasis · Sentinel lymph node biopsy

Introduction

Skin cancer is the most common cancer affecting Caucasian men and women. The most common types of non-melanoma skin cancer include basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). The incidence of BCC and cSCC is difficult to determine as these cancers are not reported with the rigor of other tumor sites such as lung, breast, and prostate [1]. Nonetheless, the burden of this disease is high, with an estimated 5,434,193 in the USA in 2012 [2]. The rate of non-melanoma skin cancer varies worldwide. In Europe, the incidence of BCC is 33.6 to 114.2 per 100,000 and cSCC is 8.9 to 28.9 per 100,000 [3]. Australia has among the highest incidence of BCC and cSCC worldwide with a rate of 1271 per 100,000 [4]. The other, less common, types of non-melanoma skin cancer are Merkel cell carcinoma (MCC) and dermatofibrosarcoma protuberans (DFSP). These tumor types can occur at rates up to 1.6 per 100,000 in high incidence countries [5]. There are numerous rare tumors arising for the apocrine and eccrine glands that are beyond the scope of this chapter.

Global cancer registries indicate that the incidence of all non-melanoma skin cancers are rising [3]. This is particularly important to head and neck surgeons because the head and neck is the most prevalent site [5–7]. The primary site is treated with wide local excision and a minority of patients will require assessment and treatment of regional lymphatic basins. The rates of metastases from non-melanoma skin cancer vary greatly; MCC has the highest risk, cSCC has an intermediate risk, whereas metastasis from BCC and DFSP is not

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clinically relevant. It should be noted that the overall risk of metastasis is low, that there are known risk factors for metastasis, and that appropriate management of the regional lymph node basin is an important consideration in non-melanoma skin cancer. In this review, we discuss current practices for management of the neck in head and neck non-melanoma skin cancer.

Cutaneous Squamous Cell Carcinoma

Risk Factors

The prognosis of patients with cSCC is excellent with over 90% 5-year survival [8]. The risk of neck node metastasis from cSCC is low; however, for patients who do develop neck node metastases, their survival is adversely affected. Recent studies show the 3- and 5-year overall survival (OS) for patients with lymph node metastases is 59% [9] and 47% respectively [10]. For this reason, there has been a great effort to identify patients who are at high risk for nodal metastases, who may benefit from more specific assessment of the regional lymph node basin.

In cSCC, several risk factors have been associated with higher risk of recurrence and lymph node metastases. The following have been consistently reported in literature:

I. Location

Head and neck cSCC has been divided into different facial zones along embryologic fusion planes that correspond to different risks of recurrence and neck node metastases. Swanson was the first to identify the ear, preauricular area, nasolabial fold, nasal ala, and orbit as being areas of higher recurrence. Later studies identified the eyelid, periocular, cheek, lip, ear, and retroauricular area as sites with independent greater risk for metastases [11–13].

II. Size

There is an increased rate of lymph node metastases with tumors over 2 cm, with larger size associated with higher rates of metastases [10, 14]. Survival is also affected with increased tumor size. In a prospective study of 240 head and neck cSCC patients, tumors larger than 4 cm were associated with a 26% decreased disease-specific survival (DSS) at 3 years (93% versus 67%) [15].

III. Depth of invasion and bone invasion

The anatomic depth of invasion is a predictor of metastases with deeper invasion carrying higher risk of neck node metastases. In a prospective study, tumor thickness greater than 6 mm was associated with a 16% metastasis rate while tumors less than 2 mm thick had no evidence of metastasis [16]. Tumor extension to adipose tissue has a 4% risk of metastases compared to 12.5% when tumor extends to muscle or bone [17]. Bone invasion is of particular concern in the scalp due to the possibility of dural extension and need to obtain adequate bony margins.

IV. Perineural invasion

Perineural invasion has consistently been shown to be independently associated with an increased risk of primary site recurrence and poorer DSS [18•, 19]. The association with lymph node metastases is less clear. Some studies demonstrated an association with regional disease at presentation [18•] and others failing to find an increased association on multivariate analysis [19].

V. Histological grade

Poorly differentiated tumors are at higher risk for lymph node metastases [19], have higher rates of local recurrence [18•], and have decreased overall survival [20]. Desmoplasia, defined as the presence of an irregular invasive front and surrounding stromal reaction, is similarly associated with higher rates of recurrence and metastases [16, 21]. Adenosquamous and carcinosarcoma represent rare biphasic histologic subtypes of cSCC which have previously been included as high-risk features [22]. But these histologic subtypes have not demonstrated higher rates of metastases [8, 23, 24]. Acantholytic cSCC, also called adenoid or pseudoglandular, has historically been reported as a high-risk feature, but the most recent studies have not shown more aggressive tumor behavior [25].

VI. Immunosuppression

Organ transplant patients are at higher risk for multiple tumors and more aggressive tumors. Lott et al. showed that cSCCs in transplant patients were associated with higher rates of lymphovascular invasion and a trend towards nodal metastases [26].

Sites and Rates of Metastatic Spread

Identifying the appropriate lymph node basin is important because regional failure is the most common type of treatment failure, representing 73% of recurrences. Furthermore, it is difficult to salvage and cure patients after regional lymph node recurrence [27]. Veness et al. found that 70 to 80% of regional metastases occur within the first year post-treatment of the index lesion [28]. In head and neck cSCC, the parotid and neck are the lymph node basins of interest.

Parotid

The intraglandular lymph nodes of the parotid were identified as a common site of cSCC metastases as early as the 1960s [29]. In Australia, cSCCs represent the most commonly

encountered malignant mass in the parotid. The parotid is an important lymph node basin, particular for cSCC of the anterior scalp, ear, temple, and cheek. In a multicenter study that included 322 patients who presented with regional metastasis from cSCC, the parotid lymph nodes were involved in 81% and were the only site of metastasis in 68% of the study group [30].

Neck

The cervical neck lymph nodes are the next most common site of lymphatic metastases. In the same multicenter study referenced in the preceding paragraph, Andruchow et al. found these lymph nodes to be involved in 33% of cases, and in 19% were the only site of metastases [30]. Ebrahimi et al. examined the pattern of regional metastases from cSCC in a retrospective review spanning 22 years and 295 neck dissections. A coronal line drawn through the external auditory canal separates the anterior, scalp, face, and anterior external ear from the posterior ear scalp and neck. In cSCCs arising from the anterior scalp and face, they had higher rates of lymph node metastasis to level I, whereas cSSCs arising in the posterior ear, posterior scalp, and neck had higher rates of level V lymph node metastases (see Fig. 1). Out of 295 neck dissections, the highest rate of lymph node involvement (35.6%) was seen in level II, which importantly included the nodes lateral to the SCM along the external jugular vein, followed by level III (14.6%), then levels I, IV, and V (each 11.2%) [30]. Seventy-five percent of patients in this study underwent concurrent parotidectomy for evidence of nodal disease within the parotid prior to surgery. Patients who underwent elective parotidectomy were not included in this retrospective cohort. This study and others have shown that between 16 and 42% of patients with parotid metastases will harbor subclinical cervical neck metastases [10, 32, 33]. The decision to perform a parotidectomy should be made to resect suspicious positive regional disease or when a clinically and radiologically negative parotid is between a known primary site and a clinically or radiologically positive neck.

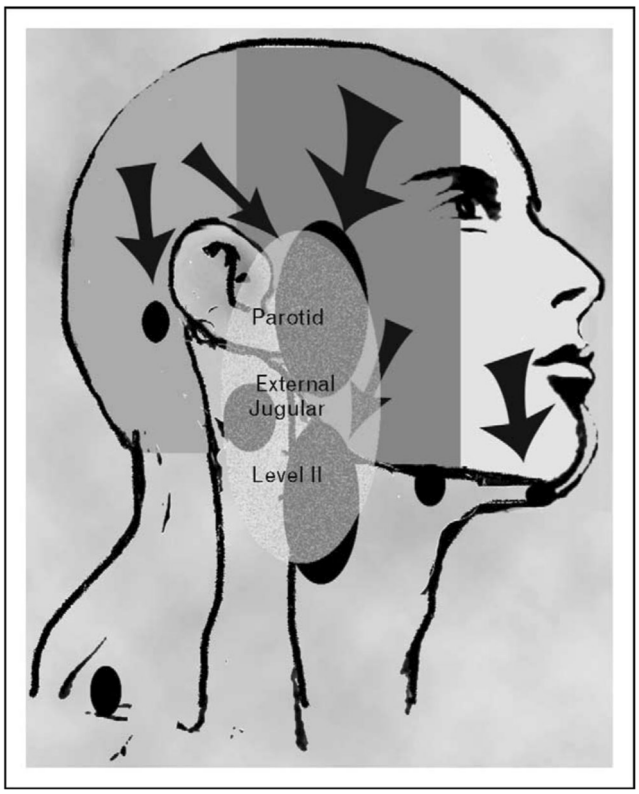

Fig. 1 Diagrammatic representation of patterns of nodal metastases based on primary tumor location. Borrowed with permission from D'Souza et al. [31]

Staging Systems

The staging of head and neck cSCC is evolving. The UICC and AJCC are actively updating and increasing the detail of the classification of tumors with each edition. Other staging systems that have been used in the past have had important elements incorporated into the UICC and AJCC classifications.

UICC and AJCC TNM Staging

There have been recent changes to the AJCC TNM staging system, such that it is now the same as the UICC staging. In the AJCC 8th edition, non-melanoma skin cancer high-risk features have been restructured. High-risk features have been removed. In the new T classification system, perineural invasion, deep invasion, and minor bone invasion have been reclassified to T3, while gross cortical bone or marrow invasion and skull base invasion upstage to T4a and T4b, respectively. In contrast to the O'Brien staging system, no distinction between parotid and neck metastases are made within N-staging.

According to the most recent staging systems, T1 tumors would not warrant neck management in clinically N0 necks, with the possible exception of immunocompromised patients or poorly differentiated tumors. T2, greater than 2 cm, head and neck cSCC may warrant management of the neck, based on tumor size alone as a high-risk feature [22].

O'Brien Staging

Studies showed high local control rates of parotid metastases with surgery and or radiation [34]. O'Brien et al. hypothesized different survival between parotid and neck LN metastases and proposed an alternative staging system that separated parotid (P) from neck (N) metastases. Parotid metastases were further stratified by size less than 3 cm (P1), 3–6 cm (P2), and

greater than 6 cm (P3). Multiple nodes were classified P2, while those with facial nerve or skull base involvement were classified P3. The staging for cervical LN metastases was simplified to N0, N1, and N2 based on size and number of lymph nodes [35].

O'Brien et al. demonstrated that patients with parotid metastases and no neck metastases (P + N0) had a better prognosis than patients with both parotid and neck metastases (P + N+). Furthermore, the parotid lymph node size and status of the facial nerve were predictive of local control [36]. These findings of decreased 5-year survival with advanced P stage (82% for P1 versus 69% for P2/3) and presence of neck nodal disease (79% for N0 versus 61% for N+) were validated in a multicenter international review [30].

Forest N1S3 Staging

The N1S3 staging system was developed in order to incorporate the parotid as a lymph node basin and stratify groups according to locoregional control rates, DSS, and OS [37].

This system stratifies into three groups according to size of largest lymph node (> 3 cm or < 3 cm) and the presence of single or multiple nodal metastases. Although an important conceptual contribution, this staging system has been supplanted by the UICC and AJCC systems.

Investigations

Ultrasound, Computed Tomography, and Magnetic Resonance Imaging

A review by Stamell-Ruiz et al. found that preoperative imaging with computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) was associated with lower risk of nodal metastases. Preoperative imaging also impacted treatment in 33% of patients, of which more than half had altered surgical approaches and 32% underwent additional parotidectomy or lymphadenectomy [38]. When there is clinical suspicion of high-risk disease, and therefore occult nodal metastases, the choice of modality may depend on the specific high-risk features. CT should be considered if bony invasion is suspected and can be helpful in evaluating tumor depth. MRI may be useful in evaluating perineural and bone marrow invasion. If any of these high-risk features are identified, the draining LN basin should be investigated.

With regard to detection of nodal metastases, both MRI and CT may be used. Older studies demonstrated better identification of metastatic nodes with CT compared to MRI [39]. A recent meta-analysis showed higher specificity with MRI (81% versus 72%), while CT maintained better sensitivity (77% versus 72%) [40]. Ultrasound (U/S) is also an effective and safe method for evaluating the draining nodal basins in cSCC. It can be used to better characterize small lymph nodes and should be considered in borderline high-risk tumors as an alternative to CT. As U/S becomes more readily available in clinic, it will play an increasingly important role in the physical exam.

Fine Needle Aspiration

For neck masses in high-risk patients, the AAO-HNS recommends CT scan and fine needle aspiration biopsy (FNAB) to evaluate for malignancy [41]. U/S-guided fine needle aspiration (FNA) can be particular useful in head and neck cSCC to accurately target the desired lymph nodes. Our review did not identify any studies comparing FNA to other imaging modalities or sentinel lymph node biopsy (SLNB) in cSCC. It is a useful practice to perform FNA on all patients who present with clinically and/or radiologically suspicious lymph nodes.

Positron Emission Tomography

18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) can help detect metabolically active lymph nodes that are more likely to harbor metastatic cancer. The reported sensitivity in this setting varies greatly depending on the inclusion criteria of individual studies [42]. In a meta-analysis, PET was not significantly better than CT, MRI, or U/S [43, 44]. Furthermore, the sensitivity of PET decreases with lymph nodes smaller than 8 mm [42, 45]. As such, PET is not reliable for the detection of small lymph nodes and is expensive compared to CT, FNA, and sentinel node and therefore not cost effective.

Sentinel Lymph Node Biopsy

In melanoma, the use of SLNB has become an important diagnostic procedure as demonstrated by the MSLT-I and MSLT-II trials [46, 47]. Recently, there has been increased interest in expanding SLNB in cSCC to better identify regional disease in high-risk patients who appear to be clinically and radiologically N0. The problem lies in reliably defining a high-risk group so that the prevalence of occult metastasis is sufficiently high to justify the additional intervention, time, and cost of SLNB.

There are several technical challenges to SNLB, including the following: shine through from the proximity of the primary lesion to the nodal basin, unexpected nodal drainage patterns, and multiple nodal basins. The issue of shine through can be addressed by initial excision of the primary prior to SLNB. To maximize SLN identification, appropriate biopsy should include triple localization with cutaneous lymphoscintigraphy with (99Tc)-labeled sulfur colloid followed by SPECT, intraoperative blue dye, and radiocolloid

detection with gamma probe. With respect to SLN cutoffs, the lowest false negative rate (presence of metastatic disease with negative SLNB) is achieved when all blue nodes and all nodes with > 10% gamma count of the hottest node are removed [48]. These cutoffs have been established in melanoma and have been extrapolated to other cutaneous malignancies. Durham et al. demonstrated a 94% identification rate in head and neck SCC with triple localization [49•]. In systematic reviews, the false omission rate (negative SLNB that failed in nodal basin) for head and neck cSCC was 4.76% with a positive SLNB rate of 13.5% [50]. Additionally, studies have reported lower false omission rates with the use of deeper LN sections and immunohistochemistry (IHC) [49•].

Management

Elective Neck Dissection

The overall rate of metastases in cSCC is low. Elective neck dissection (END) for high-risk N0 cSCC has not been established. While it has been recommended by some authors [51], this would fall outside of current guideline recommendations [22].

At present, the role of END in cSCC is limited to O'Brien stage P+ disease. In a multicenter international study, 32% of P+ patients had neck metastases [30]. Based on this, the NCCN guidelines recommend END for P + N0 disease [22]. These guidelines do not specify which levels should be resected. Our practice generally follows the recommendations of Ebrahimi et al. [32], level II–IV neck dissection with addition of level I for anterior lesions and level V for posterior lesions. Importantly, the neck dissection should always include the external jugular lymph nodes as this is a common drainage pathway for cSCC. This is contrast to mucosal SCC, which rarely metastasizes to the external jugular lymph nodes.

Completion Neck Dissection in SLN Positive

There is limited data on the appropriate management of SLN-positive cSCC. In melanoma, the MSLT-II trial showed no difference in melanoma-specific survival between completion neck dissection and observation in SLN-positive patients [47]. This data should not be extrapolated to cSCC, given the higher rate of distant metastases and more aggressive nature of melanoma that is metastatic to LN. Current standard of care is to perform parotidectomy and neck dissection for improved regional control in SLN-positive tumors. Comprehensive treatment of the at-risk lymphatic basins after positive SLNB should improve overall survival.

Radiation Therapy

Primary radiation therapy (RT) to the regional lymphatics is generally reserved for patients who are not operative candidates. Comparisons of RT to surgery have been limited to retrospective reviews with most showing better DSS with surgery compared to RT. Palme et al. [33] and Audet et al. [36] showed that surgery had statistically significant 5-year DSS benefit when compared to primary RT.

N+ disease was associated with a 75% 5-year DSS when treated with surgery and adjuvant RT compared to unimodality treatment, which was associated with a DSS of 52% for radiation alone and 18% for surgery alone [52]. The OS in this cohort was 50%, consistent with previous literature reports [10]. When compared to surgery, Veness et al. showed improved 5-year disease-free survival with multimodality treatment compared to surgery alone (73% versus 54%). Combined treatment confers a DSS benefit but the retrospective studies are underpowered to assess the impact on overall survival [33, 36, 52, 53].

NCCN guidelines acknowledge that there are subsets of patients who derive benefit from adjuvant RT, but it is difficult to determine the distinguishing features for identifying such patients. Current guidelines recommend adjuvant RT for any pathologically positive lymph node metastasis; however, for low-risk metastases, observation may also be considered [22]. Low risk refers to pathologically N1 (single lymph node, less than 3 cm, without extracapsular extension) who in a multi-institutional analysis were found to have a 100% 5-year DSS with surgery alone [54].

Summary of Recommendations

The manuscripts that defined high-risk features, patterns of nodal spread, prognosis of nodal metastases, and the role of SLNB are shown in Table 1. Head and neck cSCC should be evaluated for high-risk features including location, tumor size, depth and extent of invasion, perineural invasion, histological grade, desmoplasia, and immunosuppression. Tumors that are T3 and above and high-risk T1 and T2 that are clinically negative for nodal metastases should be investigated with CT scan followed by FNA of suspicious lymph nodes. If radiologically negative, a SLNB should be considered. For low-risk T1 and T2 tumors, ultrasound of the neck could be considered. SLN-positive tumors should undergo completion neck dissection (CND) that includes superficial parotidectomy when the parotid LN basin is at risk based on the location of the primary tumor. END is not first-line treatment, with the exception of P+ disease. In N+ disease, neck dissection of the draining nodal basin should be performed and adjuvant RT should be considered.

Table 1 cSCC landmark papers

Data source, year (ref. #)	Clinical question	Study population	Results	Significance and recommendations
Clayman et al. 2005 [15]	What features are associated with survival in cSCC?	250 HN cSCC tumors from MD Anderson 1996–2001*	3-year disease-specific survival: - Primary vs recurrent tumor: 88% vs 79% ($p = 0.05$) - Superficial invasion vs invasion beyond fat: 88% vs 73% ($p = 0.009$) - PNI− vs PNI+: 91% vs 64% ($p = 0.002$) Size < 4 cm vs ≥ 4 cm: 93% vs 67% ($p = 0.0003$)	Decreased survival with recurrent tumors, greater depth of invasion, PNI, and increased size.
Harris et al. 2016 [18•]	In patients with locally advanced cSCC, what factors are associated with regional disease at presentation and recurrence?	212 patients with HN cSCC from UC Davis 1998–2014	Associated with nodal disease (multivariate): - Ear primary: odds ratio (OR) 16.2 ($p = 0.016$) - Cheek/temple primary: OR 15.0 ($p = 0.017$) - Lip primary: OR 13.5 ($p = 0.037$) - PNI: OR 2.74 ($p = 0.05$) Associated with recurrence: - Recurrent tumor: OR 2.21 ($p = 0.041$) - PNI: 2.62 ($p = 0.028$) Poor differentiation: 2.34 ($p = 0.047$)	Location and PNI are associated with nodal disease. Poor differentiation, PNI, and recurrent tumor are associated with recurrence and therefore require aggressive local management.
Schmults et al. 2013 [19]	What are the major factors associated with lymph node metastases and survival in cSCC?	526 HN cSCC tumors from Brigham and Women's Hospital 2000–2009**	Association with nodal metastases (multivariate): - Ear or temple primary: subhazard ratio (SHR) 3.8 ($p = 0.04$) - Diameter ≥ 2 cm: SHR 7.0 ($p < 0.001$) - Poor differentiation: SHR 6.1 ($p < 0.001$) - Invasion beyond fat 9.3 ($p < 0.001$) Association with disease-specific death: - Ear or temple primary: SHR 5.9 ($p = 0.02$) - Diameter ≥ 2 cm: SHR 15.9 ($p < 0.001$) - Poor differentiation: SHR 6.7 ($p < 0.001$) - Invasion beyond fat 13.0 ($p < 0.001$) PNI: SHR 3.6 ($p = 0.03$)	Location, tumor diameter, poor differentiation, and depth of invasion are associated with nodal metastases and disease-specific death. PNI is associated with disease specific death, but not nodal metastases.
Ebrahimi et al. 2010 [32]	What is the pattern of regional lymph node metastases based on HN cSCC primary location?	282 patients with HN cSCC undergoing 295 neck dissections from Sydney Head and Neck Cancer Institute, Australia 1987–2009	Frequency level I nodal metastases: - Anterior primary: 17.9% - Other locations: 4.5–8.9% Frequency level V nodal metastases: - External ear: 15.6% - Posterior primary: 18.2% - Other locations: 5.4–11.1% Frequency level II nodal metastases: - Overall: 35.6% (30.4–40.3%) Frequency of occult neck metastasis in P+: - Overall: 21%	P+ should undergo neck dissection due to high incidence of subclinical neck metastases. Recommendations by primary site: Anterior/external ear: parotid and level I–III neck dissections Posterior: parotid and level II–V neck dissections
Andruchow et al. 2006 [30]	Does separation of parotid from neck metastases provide prognostic discrimination?	322 patients with metastatic HN cSCC from 6 centers in Australia and North America 1960–2003	5-year disease-specific survival: P1 vs P2/3: 82% vs 69% ($p = 0.02$) P + N0 vs P + N+: 26% vs 13% ($p = 0.27$)	There is improved survival with lower P stage compared to higher P stages and with P + N0 compared to P + N.

Table 1 (continued)

Data source, year (ref. #)	Clinical question	Study population	Results	Significance and recommendations
Durham et al. 2016 [49•]	What is the SLNB detection rate, positive rate, and false omission rate of SLNB for HN cSCC?	53 HN cSCC tumors from University of Michigan 2010–2015	Detection rate: 94% SLNB-positive rate: 15.1% False omission rate: 7.1%. Increased sections and IHC improved SLNB accuracy.	SLNB is feasible for HN cSCC. Serial sectioning and IHC is critical for accurate SLN diagnosis.
Ahmed et al. 2013 [50]	What is the SLNB positive rate and false omission rate of SLNB for HN cSCC?	73 patients with HN cSCC from 11 publications 2003–2011***	Detection rate: 100% SLNB-positive rate: 13.5% False omission rate: 4.8%	Demonstrated feasibility and reliability of SLNB.

Unless otherwise stated, papers are level 2B evidence as defined by the Centre for Evidence Based Medicine, Oxford (CEBM)

*Out of 210 patients with 276 cSCC tumors from all sites

**Out of 985 patients with 1832 cSCC tumors from all sites

***Systematic review with level 2A evidence

Merkel Cell Carcinoma

MCC is a readily metastasizing rare skin cancer with epithelial and neuroendocrine differentiation found typically in elderly and immunosuppressed patients. The head and neck is the most common presenting site [5, 55•]. The behavior of this disease warrants more aggressive management.

Risk Factors

Given the high rate of metastatic spread, risk stratification in N0 is less important. Even the smallest primary lesions require imaging and management of the draining lymph node basin. Single-institution studies have shown poorer survival in head and neck compared to non-head and neck MCC [56] while other studies have shown no difference in survival or even survival benefit with primary head and neck location [45, 57]. In one study, MCC arising from the lip was associated with worse survival relative to other head and neck sites [58]. Outside of tumor location, other factors including tumor thickness, size, invasion of underlying tissue, lymphovascular invasion, tumor growth pattern, tumor-infiltrating lymphocytes, and solar elastosis were identified as histologic features associated with poor survival [59]. Although the pathophysiology has been linked to polyomavirus [60], the role of polyomavirus in prognosis and regional spread is unclear [61].

Sites and Rates of Metastatic Spread

Early reports showed a 79% incidence of lymph node metastases [62]. The adjacent lymph node basin is a common site of spread [63], but predicting the exact drainage pattern is challenging. As with other cutaneous malignancies, the parotid basin is a well-established site of spread [64]. Within the head and neck, there are varying rates of lymph node metastasis depending on primary site location with tumors located on the ear having the highest rates of nodal metastases [58]. MCC can develop in-transit metastases and can metastasize to distant skin, lung, CNS, and bone [63]. The presence of either nodal or metastatic disease are important predictors of OS. The 5-year OS for local, nodal, and distant disease is 51%, 35%, and 14% respectively [55•].

Staging Systems

AJCC TNM Staging

The MCC staging system was revised in the AJCC 8th edition. The new staging is derived from 9387 cases in the National Cancer Data Base. T staging is based on size ($\leq$ 2 cm, 2 to $\leq$ 5 cm, and > 5 cm) and invasion to underlying

structure upstages to T4. Clinical N stage is based on presence of nodal disease and in-transit metastases. Changes to the N staging were made to reflect improved prognosis of "unknown primaries," which had similar survival to patients with occult nodal metastases. A pN1a(sn) has been created to distinguish patients with regional metastases detected on SLN [55•].

Investigations

Ultrasound, Computed Tomography, Magnetic Resonance Imaging, and Fine Needle Aspirate Biopsy

The initial workup for MCC should include evaluation of the draining nodal basin and distant metastases. In evaluation of the LN basin, there is no agreed upon algorithm and a lack of evidence to select between U/S, CT, and MRI [65]. In clinically N-positive MCC, NCCN guidelines recommend performing a FNAB with immunopanel that includes cytokeratin-20 and thyroid transcription factor-1 as the initial investigation, followed by consideration of open biopsy if FNA is negative.

Positron Emission Tomography

PET has a growing role in MCC in the detection of distant metastases. In retrospective studies, PET changed the clinical stage in 22–44% of cases [66–68]. In a meta-analysis, FDG-PET or FDG-PET/CT demonstrated high sensitivity, 90%, and specificity, 98% [69]. PET should be considered instead of CT or MRI in evaluating regional and distant metastases when there is clinical suspicion of metastases. Some authors advocate for the use of PET in all MCC [68], but this is not currently the standard of care [70].

Sentinel Lymph Node Biopsy

The role of SLNB in MCC is well established. The rate of lymph node metastases from all sites is approximately 23–33% [45], and therefore, SLNB is recommended for all clinically N0M0 cancers [70]. SLN status has prognostic value with higher rates of recurrence noted in SLNB-positive patients. SLN cutoffs are the same as those used in melanoma [48]. When determining SLN status, IHC with cytokeratin-20 may help to identify micrometastases [71]. In a head and neck MCC cohort, Schlambach et al. showed that the addition of IHC can decrease the false negative rate from 30 to 12% [72]. As in cSCC, our practice is to obtain cross-sectional imaging prior to SLNB. Suspicious lymph nodes identified on imaging should be targeted for FNAB. SLNB technique is important in MCC to avoid altering lymphatic drainage.

Management

The regional failure rate of untreated clinically N0 in MCC is 33% [73]. SLNB is therefore important for prognostication.

Elective Neck Dissection

END has no established role for MCC. When END was compared to SLNB in a retrospective study of 240 cases of MCC of all body sites, the OS was 85.4% for SLNB and 89.2% for END and there was no significant difference in survival free of nodal recurrence [74]. This is of concern as these patients are exposed to increased surgical risk without a proven survival benefit over SLNB. Nonetheless, the need for evaluating the nodal basin is paramount in MCC and some authors advocate for END if SLNB is not available [75].

Sentinel Lymph Node Negative

There is disagreement regarding the role of adjuvant RT in SLNB-negative patients. The current NCCN guidelines state that RT can be considered for immunosuppressed patients and primary tumors in areas with higher false negative rates, such as the head and neck [70]. When SLNB is performed by experienced, high-volume surgeons, the false omission rate is low obviating the need for RT.

Sentinel Lymph Node Negative

SLN-positive patients require further treatment. Santamaria-Barria et al. showed that compared to SLN-negative patients, patients who were SLN positive had higher rates of recurrence, 39% vs 56% [76]. Options include radiation alone, or completion neck dissection with adjuvant radiation. Current practice is to offer completion neck dissection with adjuvant radiation to those patients who are surgical and RT candidates. We were unable to identify any direct comparison between these two options.

Radiation Therapy

RT to the nodal basin can be separated into elective and adjuvant treatment. Elective RT to the nodal basin is a treatment option for N0 MCC. In a randomized controlled trial comparing elective RT of the nodal basins to observation in 83 stage 1 MCC patients, elective RT decreased regional recurrence rates from 16.7% to none, but did not show a survival benefit [77]. As with END, elective RT predisposes patients to treatment risks, in this case acute and late radiation side effects, without proven benefit. In the adjuvant setting, RT may have a role following lymphadenectomy. A recent study showed that adjuvant RT after positive SLN or completion neck dissection improves locoregional control in N+ patients [78]. However,

Table 2 MCC landmark papers

Data source, year (ref. #)	Clinical question	Study population	Results	Significance and recommendations
Allen et al. 2005 [45]	What factors are associated with survival in MCC?	73 HN MCC from Memorial Sloan-Kettering, 1970–2002*	Associated with survival: HN vs non-HN: 87% vs 62% ($p = 0.02$) - Size < 2 cm vs ≥ 2 cm: 77% vs 59% ($p = 0.02$) - cN0 vs cN+: 75% vs 49% ($p = 0.002$) - pN0 vs pN+: 97% vs 52% ($p < 0.001$)	Location, size, and nodal status are associated with survival.
Harms et al. 2016 [55•]	What is the survival for MCC?	6144 HN MCC from a national database, 1998–2012**	5-year survival: - Local vs nodal metastases vs distant metastases: 50.6% vs 35.4% vs 13.5%	Largest series of MCC patients demonstrating decreased survival with presence of metastases; formed the basis for AJCC 8th edition staging.
Andea et al. 2008 [59]	Which parameters are prognostic markers in stage I and II MCC?	58 HN MCC from Memorial Sloan-Kettering, 1980–2005***	5-year survival (univariate): - Extension to dermis vs subcutaneous tissue vs deeper fascia: 93.1% vs 85 vs 0% ($p < 0.00001$) - Nodular vs infiltrative growth pattern: 100% vs 65.6% ($p = 0.002$) - Lymphovascular invasion absent vs present: 92.8% vs 73.7% ($p = 0.006$) - Tumor-infiltrating lymphocytes present vs absent: 91.2% vs 74.2% ($p = 0.05$)	Tumor extension, growth pattern, and presence of infiltrating lymphocytes are associated with survival.
Santamaria-Barria et al. 2013 [76]	What factors are associated with recurrence and survival in MCC?	65 HN MCC from Massachusetts General Hospital, 1980–2010****	SLNB-positive rate: 33% Recurrence: - SLN positive vs negative: 56% vs 39%	Long-term study demonstrating high rates of SLN positivity and variable survival with stage. There is increased recurrence in SLN positive patients.

All papers are level 2B evidence as defined by the Centre for Evidence Based Medicine, Oxford (CEBM)

*Out of 251 total patients with MCC

**Out of 14,414 patients with MCC (42.6% arising from the HN), 9387 patients had sufficient data for inclusion in final analysis

***Out of 156 patients with MCC

****Out of 161 patients with MCC

this study along with larger retrospective reviews has failed to show improved OS with the use of RT in N+ patients [78, 79].

Summary of Recommendations

The landmark papers that described prognostic factors, survival, and the role of SLNB are shown in Table 2. Imaging of the neck and parotid should be performed for all head and neck MCC. FNAB should be performed in patients with possible metastatic lymph nodes. PET should be performed if there is suspicion of regional or distal metastases. In N0 patients, SLNB should be performed after initial imaging for prognostication and to guide further treatment in the radiologically N0 patient. Management of the neck in SLN-negative disease is controversial. Most patients can be observed, while RT should be reserved for the highest risk groups. Current guideline for SLN positive is neck dissection with adjuvant RT. Further studies are needed to evaluate the benefit of completion neck dissection because current guidelines recommend RT with or without completion neck dissection.

Other

Basal Cell Carcinoma

The most common skin cancer is BCC. Nodal and distal metastases almost never occur and, as such, investigation of the draining lymph node basin is not necessary. In head and neck BCC, neck dissection should be reserved for the extremely rare occurrence of N+ disease.

Tang et al. reported on five cases of head and neck BCC with nodal metastases. All received a neck dissection and adjuvant RT. In two, parotidectomies were performed metastases to this area. Survival ranged from 9 months to 17 years [80]. Lo et al. reported a case series of 12 patients with metastatic BCC, 10 of these primary lesions arose in the head and neck. These patients were treated with a combination of surgery, radiation, and chemotherapy and had a mean survival of 23.4 months [81].

Dermatofibrosarcoma Protuberans

DFSP is a rare tumor arising from the fibroblasts in the dermis. It has a predilection for deep tissue invasion and high rates of local recurrence. The rate of regional metastasis is approximately 1% [82]. Generally, imaging has been indicated to assess soft tissue spread (MRI), bony invasion (CT), but not nodal metastases.

Conclusion

The management of the neck in non-melanoma skin cancer is variable based on tumor pathology. In cSCC, appropriate staging and risk stratification is necessary to determine patients who require further imaging of the neck and SLNB. Patients with positive SLN, parotid metastases, or clinically positive neck lymph nodes should undergo neck dissection. In MCC, all patients should undergo appropriate staging investigations, including SLNB for clinically N0 disease. Completion neck dissection and adjuvant RT is recommended for SLN-positive patients. BCC and DFSP do not require investigation or surgery for nodal metastases, with the rare exception of patients with BCC who have confirmed nodal metastases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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