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

Surgical Considerations in Advance Basal Cell Carcinoma, Cutaneous Squamous Cell Carcinoma, and Cutaneous Melanoma: a Head and Neck Perspective

Tom C. Zhou[1] · Antoine E. Eskander[2] · Matthew O. Old[1,3] · Stephen Y. Kang[1,3] · Theodoros N. Teknos[4,5]

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Abstract

Purpose of Review Skin cancers, including basal cell carcinoma, cutaneous squamous cell carcinoma, and cutaneous melanoma, are the most common cancer worldwide. The treatment of these cancers is primarily surgical, and when treated early and correctly, the prognosis is excellent. In this review, we aim to discuss the appropriate surgical management of skin cancers and associated controversies as it pertains to the head and neck.

Recent Findings Evidences guiding treatment have expanded enormously over the past decade. Studies have drastically improved our understanding of skin cancer including risk factors for tumor recurrence and metastasis, indicated margin size of surgical excision, the role of sentinel lymph node biopsy, and the management of occult and gross regional neck metastasis.

Summary Management of skin cancer poses a unique challenge in the head and neck region due to its proximity to anatomic sensitive areas and complex lymphatic drainage. Understanding how to efficiently manage the primary tumor site and the regional lymph nodes is paramount in minimizing locoregional recurrence and improving overall survival.

Keywords Basal cell carcinoma · Squamous cell carcinoma · Melanoma · Head and neck · Surgery · Review

Introduction

Skin cancer is the most common type of cancer worldwide, and its incidence rates continue to rise dramatically, raising public health concerns. It can be divided into cutaneous melanoma and nonmelanoma skin cancers (NMSCs); the latter includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). NMSCs account for the majority of skin cancers with a striking 5.4 million cases treated in the USA in 2012, a 35% increase from 2006 [1]. Historically, BCC contributed about 80% of all NMSCs while cSCC comprised the rest [2]. Recent trends however suggest that the ratio of BCC to cSCC has shifted to 2.5 to 1 over the past decade, and in certain population, the ratio is equal [1, 3, 4]. NMSCs are not reported to cancer registries, and therefore, statistics and trends of this entity are often overlooked.

While melanoma only accounts for 87,000 new cases each year and about 1% of skin cancers in the USA [5], it is responsible for the majority of skin cancer mortality. Its unique potential for metastasis is invariably associated with poor prognosis; 5-year survival rates reported for regional and distant stage melanomas are 63 and 20%, respectively [6]. Fortunately, while incidence is on the rise, melanoma has become one of the fastest evolving fields in cancer.

Melanoma and NMSCs are primarily treated surgically and, when treated early, have exceptional cure rates. However, advanced or aggressive skin cancer can present with

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✉ Theodoros N. Teknos
Theodoros.Teknos@UHHospitals.org

[1] Department of Otolaryngology – Head and Neck Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

[2] Department of Otolaryngology – Head and Neck Surgery, University of Toronto, Toronto, Ontario, Canada

[3] Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA

[4] Department of Otolaryngology – Head and Neck Surgery, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Lakeside 1071, Cleveland, OH 44106, USA

[5] Comprehensive Cancer Center, University Hospitals Seidman Cancer Center, Cleveland, OH, USA

operative dilemmas. Considerable attention is given on addressing primary tumor site and regional lymph nodes efficiently and effectively to improve locoregional recurrence and overall survival without causing undue morbidity from overtreatment. Evidence to support treatment decision of NMSCs and melanomas, especially those of advanced stages, are being elucidated.

A comprehensive review of cutaneous malignancies is beyond the scope of this article. Instead, we aim to discuss the most pressing and critical questions and controversies surrounding the management of BCC, cSCCm and cutaneous melanoma.

Basal Cell Carcinoma

Basal cell carcinoma is the most common cancer diagnosed in the USA, representing 30% of all new cancer diagnoses [7]. It is a locally aggressive tumor, known for its propensity to destroy surrounding tissue along with associated morbidity. Regional and distant metastasis have been reported via lymphatic and hematogenous routes but is exceedingly rare at rates of 0.0028–0.55% [8, 9]. Thus, research has focused on determining the most effective method for local control and on predicting risk for recurrence. In this section, we discuss the high-risk subclassification of BCC, recommendations on size of excision margins, and Mohs micrographic surgery as an alternative to standard surgical excision.

Features of High-Risk BCC

A formal staging system incorporating risk stratification specific to BCC is not available. Historically, BCC has been grouped with cSCC in the American Joint Committee on Cancer (AJCC) staging system, but this classification is rarely, if ever, used for patients with localized BCC. Instead, since the 1980s, studies have identified risk factors associated with recurrence which now form the cornerstone for prognosis and treatment decisions. As such, the National Comprehensive Cancer Network (NCCN) stratifies BCC into "low-risk" and "high-risk" categories. These risk factors include anatomic location, size, clinically ill-defined tumor borders, setting of immunosuppression, area previously exposed to radiation therapy for unrelated condition, pathologic subtypes, and perineural involvement [10••]; these are shown in Table 1. Lesions of any size were considered high risk if located in the "H-zone" or "mask areas" of the face which included central face, eyelids, eyebrows, periorbita, nose, lips, chin, mandible, preauricular and postauricular areas, temple, and ear. Lesions located elsewhere in the head and neck were considered high risk if size is ≥ 10 mm. Pathologic features of aggressive BCC include micronodular, infilitrative, sclerosing, and morpheaform (or desmoplastic) patterns. Basosquamous carcinomas are considered an aggressive type of BCC that also include histopathologic features of cSCC; these tumors tend to behave similar to cSCC, and therefore are managed similarly.

Size of Excision Margins and Mohs Micrographic Surgery

The primary goal of treatment for any cutaneous malignancy is for complete tumor removal while preserving function and cosmesis. Asymmetric subclinical extension of the visible tumor is commonplace, and thus, complete removal with histologically negative margins is the hallmark to ensure optimal oncological outcome. Lesions with incomplete excision had a 5-year recurrence rate of 17–38% [11–13], but when complete excision is achieved, the recurrence rates improve to 5–14% [13–15], although what constitutes as "negative margins" is not uniform. When a microscopic margin of ≥ 0.5 mm is obtained in primary BCCs, there is a 5-year recurrence rate of 1.2% in contrast to 12% for microscopic margin <5 mm [16]. This may account for the variable recurrence rates following "complete" excision in the literature.

There is controversy as to what is the ideal excision margin size for BCC. To date, there has not been a randomized controlled trial (RCT) comparing different margins size, and therefore, the basis of recommendations have been reliant on retrospective studies and prospective cohort studies. Furthermore, there is controversy surrounding the role of re-excision for positive margins. Although NCCN guidelines recommend re-excision or adjuvant therapy in setting of positive margins, some clinicians have adopted a watch-and-wait approach. This less than optimal approach is performed for various reasons including the variable rates in identifying residual BCC within re-excision specimens, the variable rate of recurrences becoming grossly apparent, the morbidity associated with additional resections, and patients' preferences [17]. However, the recurrence rate of histologically positive margins is not trivial [13].

Historically, scientific evidence for margin size was lacking and thus was based on individual surgeon's opinion. Then in 1983, Wolf and Zitelli found that a 4-mm margin was necessary to completely resect tumor of < 2 cm in 95% of cases [18]. This study has served as the basis for NCCN guidelines, which recommend 4-mm margin for low-risk BCC [10••] (Table 1). This recommendation is echoed in the American Academy of Dermatology (AAD) guidelines [19••]. The American Society of Clinical Oncology (ASCO) recommends 2–4-mm margin for low-risk BCC [20••].

Multiple randomized controlled trials comparing standard surgical excision (SE) of low-risk BCC with curettage and electrodessication, cryotherapy, topical therapy, or radiation therapy uniformly suggest lower recurrence rates following surgical excision [19••]. In addition, Mohs micrographic

Table 1 Risk factors for local recurrence or metastases and recommended surgical management of primary tumor site of basal cell carcinoma, squamous cell carcinoma, and melanoma

	BCC		cSCC		Melanoma	
	Low-risk	High-risk	Low-risk	High-risk	Low-risk[a]	High-risk[a]
Clinical features						
Size	< 10 mm	≥ 10 mm	< 10 mm	≥ 10 mm	< 0.8 mm thick	≥ 0.8 mm thick
Location	–	H-zone[b]	–	H-zone[b]	Lip, eyelid, ear	Scalp, neck, face
Age	–	–	–	–	Older age	Younger age
Borders	Well defined	Poorly defined	Well defined	Poorly defined	–	–
Primary vs recurrent	Primary	Recurrent	Primary	Recurrent	–	–
Immunosuppression	No	Yes	No	Yes	–	–
Site of prior RT	No	Yes	No	Yes	–	–
Site of prior burn/ulceration	–	–	No	Yes	–	–
Rapid growth	–	–	No	Yes	–	–
Neurologic symptoms	–	–	No	Yes	–	–
Pathologic features						
Pathology subtype	Nodular, superficial	Micronodular, infilitrative, sclerosing, morpheaform, and basosquamous[c]	Keratoacanthoma, verrucous, lymphoepithelioma-like, myxoid	Acantholytic, adenosquamo-us, demosplastic, metaplastic, basaloid	–	–
Degree of differentiation	–	–	Moderately to well differentiated	Poorly differentiated	–	–
Perineural involvement	No	Yes	No	Yes	No	Yes
Lymphovascular invasion	–	–	No	Yes	No	Yes
Mitotic rate, ≥ 1 per mm^2	–	–	–	–	No	Yes
Ulceration on pathology	–	–	–	–	No	Yes
Presence of in-transit, satellite, and/or microsatellite metastases	–	–	–	–	No	Yes
Presence of tumor-infiltrating lymphocytes	–	–	–	–	Yes	No
Surgical management						
Surgery of choice	SE	MMS favored; alternatively, SE with CCPDMA with IOFS analysis	SE	MMS favored; alternatively, SE with CCPDMA with IOFS or permanent section analysis	SE with wide margins	
Recommended minimum margins for surgical excision	NCCN 4 mm AAD 4 mm ASCO 2–4 mm	NCCN Variable AAD Variable ASCO 4–10 mm	NCCN 4–6 mm AAD 4–6 mm with a depth to mid-subcutaneous adipose tissue ASCO 4–6 mm	NCCN Variable AAD Variable ASCO 10 mm	NCCN AAD[d] ASCO[e]	Tis: 0.5 cm T1: 1.0 cm T2: 1.0–2.0 cm T3-T4: 2.0 cm

BCC basal cell carcinoma, *cSCC* cutaneous squamous cell carcinoma, *RT* radiation therapy, *SE* surgical excision, *MMS* Mohs micrographic surgery, *NCCN* National Comprehensive Cancer Network, *AAD* American Academy of Dermatology, *ASCO* American Society of Clinical Oncology, *CCPDMA* complete circumferential peripheral and deep margin assessment, *IOFS* intraoperative frozen section

[a] Low-risk and high-risk melanoma is defined as risk factors for sentinel lymph node positivity

[b] "H-zone" area includes central face, eyelids, eyebrows, periorbita, nose, lips, chin, mandible, preauricular and postauricular areas, temple, and ear

[c] Basosquamous are considered aggressive type of BCC but has histopathologic features of cSCC. These tumors behave similar to cSCC and should be managed similar to them

[d] Updated management guidelines on primary cutaneous melanoma anticipated from AAD in summer of 2018

[e] Guideline on management of the primary tumor site in cutaneous melanoma is not provided by ASCO

surgery (MMS) is believed to be superior to SE in certain circumstances. MMS is a surgical technique that histologically examines the entirety of the specimen using frozen sections. Ten-year recurrence rates were superior in MMS then SE for treatment of both primary (4.4% after MMS and 12.2% after SE) and recurrent BCC (3.9% after MMS and 13.5% after SE) [21]. Several other studies have corroborated that MMS may be the most effective method of eradicating BCC [22–24]. Another benefit of MMS is reduced surgical defects, sparing vital soft tissue associated with function and cosmesis [25]. MMS also affords the option of reconstruction at time of resection once margins are deemed adequate. Limitations of MMS include additional timing and expense as well as the lack of tissue blocks which may be useful for additional molecular testing to determine adjuvant therapy considerations.

Currently, NCCN, AAD, and ASCO recommend MMS for high-risk primary BCC and for recurrent BCC [10••, 19••, 20••] (Table 1). If MMS is not available, surgical excision with complete circumferential peripheral and deep-margin assessment (CCPDMA) using intraoperative frozen section (IOFS) analysis is a reasonable alternative. Margin recommendations are not clearly defined by NCCN or AAD due to wide variability in tumor characteristic accounting for subclinical extension [10••, 19••], but one may start with at least 4–10 mm per ASCO recommendations [20••]. There is further disagreement on recommended margins when comparing to guidelines from other countries.

Cutaneous Squamous Cell Carcinoma

cSCC is the second most common cancer diagnosed in the USA annually with more than 1.0 million cases diagnosed each year [1]. Only a small fraction of patients with cSCC will develop regional metastasis, and as such, the majority of patients with cSCC can be successfully treated with SE or MMS. The most commonly cited metastasis rate in patients with cSCC is approximately 5% [26–28]. Historically, development of regional metastasis results in 3-year disease-free survival rate of 56% and 5-year overall survival of 25–35%; 10-year overall survival is less than 20% [28]. However, newer studies show improved survival rates with modern, adjuvant therapy. Identifying patients with cSCC at risk for regional metastasis and delivering early therapeutic treatment to the regional lymph node basin in this patient population is critical. Importantly, the vast majority of patients with cSCC do not develop regional metastasis, and it is paramount to avoid overtreating this patient population. In this section, we review the latest data regarding features of cSCC at higher risk for recurrence and metastasis, choosing the appropriate margins size, the role of sentinel node biopsy, and management of regional disease.

Features of High-Risk cSCC

Progression of cSCC is ordered from local recurrence to regional spread and then distant metastasis. It is therefore not surprising that most disease-specific mortality events are preceded by regional metastasis and most regional metastases involve the head and neck region [29, 30]. Locoregional control is associated with lower recurrence rates and higher survival [29].

The Brigham and Women's Hospital (BWH) staging system is based on a single cohort of 1800 malignancies and is the largest and most robust database assessing outcomes [31]. The staging is based on a risk factor point system (T1, 0 points; T2a, 1 point; T2b, 2–3 points; T3, ≥4 points or bone invasion). Risk factors include diameter of ≥2 cm, poorly differentiated histological findings, perineural invasion of ≥ 0.1 mm, and invasion beyond subcutaneous fat. Bony invasion automatically upstages the patient to a T3. While BWH system has been validated as the superior prognostication prior to the AJCC 8th edition (AJCC-8) of the staging manual, it does not include nodal and distant metastasis classifications.

Many of these changes have been incorporated in the AJCC-8 [32•]. In particular, previous T3 and T4 classification were reserved for tumors with bony invasion, which is rare, thereby limiting the prognostic utility of the former staging system. In the AJCC-8, T3 tumors include tumors ≥4 cm in greatest dimension and/or perineural invasion and/or deeps invasion and/or minor bone invasion. Perineural invasion is specifically defined as invasion of a nerve lying beneath the dermis, or measuring ≥0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression. Deep invasion is defined as involvement beyond the subcutaneous fat or >6 mm.

Although, the AJCC-8 incorporates tumor size, thickness, depth of invasion, and perineural invasion, it fails to incorporate other important high-risk features. This is not due to lack of available knowledge about these factors but rather to keep the staging system parsimonious and brief. Other important high-risk features mentioned by the NCCN guidelines include poor histologic differentiation (as incorporated in the BWH system but not AJCC-8), histologic subtypes (acantholytic, adenosquamous, metaplastic, and desmoplastic), lymphovascular invasion, and anatomic location (specifically, hair-bearing lip and vermillion, ear, temple cheek, and other facial subunits in "H"-zone) [33••] (Table 1). Tumors arising in the background of a burn, ulceration or radiation are typically high-grade tumors [34–36]. Recurrent tumors and tumors that present with neurological symptoms are also considered high risk [33••]. Last but not least is immunosuppression, particularly for organ transplant recipients (heart and lung); this has not been incorporated into any staging system but is an independent risk factor for the development of cSCC and more aggressive disease behavior [37].

Size of Excision Margins and Mohs Micrographic Surgery

While curettage and electrodessication is a reasonable option for select small, low-risk primary tumors, SE and MMS are the favored surgical options because they allow histologic margin assessment. For low-risk tumors, NCCN, AAD, and ASCO guidelines suggest a 4–6-mm margin [20••, 33••, 38••] (Table 1). Brodland and Zitelli found that complete resection was achieved 95% of time when 4-mm margins here used in low-risk tumors < 2 cm in diameter and when 6-mm margins here used in low-risk tumors ≥ 2 cm in diameter [39]. However, in high-risk cSCC ≥ 2 cm, 9-mm margin is required. Another study found 13.25-mm margin was required to attain 95% tumor clearance in certain high-risk cSCC [40]. Similar to the benefits afforded to BCC, MMS provides complete margin assessment which translates to improved local control compared to SE [41]. The largest prospective observational study with 1263 patients treated by MMS reported 5-year recurrence rate of 2.6 and 5.9% in patients with primary and recurrent cSCC, respectively [42]. However, to our knowledge, no randomized controlled trial (RCT) exist comparing outcomes between SE and MMS. Currently, NCCN, AAD, and ASCO recommend MMS for management of high-risk and recurrent SCC [20••, 33••, 38••]. If MMS is not available, surgical excision with complete circumferential peripheral and deep margin assessment (CCPDMA) using intraoperative frozen sections (IOFS) or permanent section analysis is an acceptable alternative; starting margins are not clearly defined by NCCN or AAD, but ≥ 10 mm is suggested by ASCO.

Role of Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) has recently gained traction in the management of cSCC. It carries the advantage of being able to identify early occult regional metastatic disease so that completion lymphadenectomy (CLND) can follow. This approach is both safe and feasible and, similar to SLNB in the management of melanoma, should include serial sectioning of the lymph node specimen with immunohistochemical staining [43, 44]. In one study, SLNB established a low false-negative rate with negative predictive value of 98% [43]. In BWH T2b and T3 tumors SLNB was positive in 29.4 and 50% of patients, respectively [45]. A pooled analysis demonstrated an overall SLNB positivity of 14.6% and that this was strongly associated with poorer prognosis [46]. Despite these early findings regarding the potential role for SLNB in management of cSCC, there are no randomized controlled trials comparing outcomes of SLNB to observation group [46]. Furthermore, the population of patients that may benefit most from this intervention needs to be better defined. Nonetheless, it is not known whether this approach offers any disease-free, disease-specific, or overall survival advantage.

Clinically Positive Neck Lymph Nodes

Intermediate and high-risk cSCC are staged using computed tomography (CT) or positron emission tomography-computed tomography (PET-CT) and if metastases are identified, a formal neck dissection is performed. In patients who are undergoing a major resection of the primary site in very high-risk patients, an elective neck dissection can be employed in combination with free flap reconstruction [47]. In many cases, the first nodal drainage basin is that of the parotid bed and a superficial parotidectomy is also required.

AJCC-8 staging system incorporates size, number, sidedness, and the presence of extranodal extension. Parotid and cervical lymph nodes are not treated separately. However, parotid metastases have unique presentation as well as survival implications. Parotid metastases present at a median of 27 months after treatment of the primary cancer and present with large (average 4.5 cm) nodal metastases [48]. Despite presenting with advanced disease, after extensive resection and reconstruction, these patients have moderate survival outcomes (5-year overall and disease-specific survival of 79 and 55%, respectively).

It is therefore our practice in patients with head and neck cSCC to perform a compartmental neck dissection in patients with occult and gross regional metastases. In patients whom the parotid bed is the first drainage basin, a superficial parotidectomy with facial nerve preservation is safe and feasible in experienced hands. Early detection of metastases to this basin can prevent major morbidity in the form of facial nerve branches or main trunk sacrifice. In patients with parotid metastases, dissection of the ipsilateral neck is necessary due to the high rate of both clinical (26%) and occult (35%) neck disease [49, 50]. Lesions anterior to a vertical line from the external auditory canal have a propensity for metastases to the parotid basin as the first echelon of nodes, and therefore, a parotidectomy with level I-IV neck dissection is warranted in cases with nodal metastases. Lesions posterior to this line have a propensity for metastases to the posterior neck (level V) as the first echelon of nodes. In these cases, the parotid basin can be avoided but a posterolateral (level II–V) neck dissection is warranted with a formal accessory dissection to the trapezius.

Melanoma

Cutaneous melanoma has the worst prognosis among skin cancers. The most important prognostic feature is depth of invasion as measured by Breslow thickness. In general, the prognosis is excellent in tumors < 1.0 mm in thickness, with 5-year survival > 90%. However, if tumor thickness is ≥ 1 cm and contains high-risk features, the 5-year survival rate decreases to 50–90%. This further drops to 20–70% when

regional disease is present [51]. Approximately 18% of newly diagnosed melanoma arise in the head and neck, and melanoma from this region has been shown to have worse survival than those arising from the truck and extremities [52]. The field of melanoma is one of the fastest evolving and with that, one of the most controversial. In fact, much of the literature involves anatomic sites throughout the body, and controversy exists on whether these findings can be generalized to the head and neck region. While clinical guidelines are helpful in formulating evidence-based approaches to treatment, they does not replace clinical experience and intuition as these guidelines are not intended to capture all clinical variations. The purpose of this section is to discuss the most common controversies in melanoma including the margins of resection, the role of SLNB in clinically negative neck disease, and the role of lymph node dissection in both occult and gross regional disease as it pertains to the head and neck region.

Indicated Margins of Resection

The cornerstone for treatment of melanoma remains surgical via wide local excision. For decades, wide excision with margins of 3 to 5 cm was universally accepted as the managing standard for melanoma until 1977, when Breslow and Macht reported that narrow resection margins may an option for very thin melanomas [53]. Since then, several large-scale RCTs have specifically looked at the promising opportunity of obtaining smaller margins around the primary lesion [54–59]. Two studies looked at patients with melanoma < 2 mm thick; there was no difference between overall survival (OS) and disease-free survival (DFS) between 1–2-cm margin group and 3–5-cm margin group [54, 57]. For patients with ≥ 2-mm melanoma thickness, 2- and 5-cm margins had similar 5-year OS [59], but 1-cm carried a greater risk of locoregional recurrence compared to 3 cm [58]. Further studies on intermediate-thickness melanoma (0.8 to 4 mm) found no difference between 2- and 4–5-cm margin in OS and recurrence-free survival [55, 56]. To our knowledge, there are no RCTs comparing 1- to 2-cm margins. However, currently ongoing is the MelmarT Melanoma Margins Trial. This trial is a phase III, multi-institutional RCT investigating difference in the local recurrence rate and melanoma-specific survival in patients with primary melanoma > 1 mm undergoing wide excision with 1- vs 2-cm margins. We anticipate results from this trial in the upcoming years. Current NCCN guidelines recommend an excision margin of at least 0.5 cm for primary tumor T stage of Tis, 1.0 cm for T1, 1.0–2.0 cm for T2, 2.0 cm for T3, and 2.0 cm for T4 [60••] (Table 1). Latest guidelines from AAD are from 2011 but provide similar recommendations [61•]; updated AAD guidelines are anticipated in summer of 2018.

Role of Sentinel Lymph Node Biopsy

Management of regional lymph nodes has been a topic of debate for the past two decades, especially in patients with clinically negative regional metastasis. RCTs found no overall survival advantage of performing elective lymphadenectomy [62–65]. Since the 1990s, advances in lymphatic mapping and SLNB afford important prognostic information without the morbidity associated with compartment lymphadenectomy such as lymphedema. It is an effective and safe procedure with good success rate when performed by experienced team [66, 67]. In addition, it can be safely performed in the head and neck region with low risk of facial nerve injuries, damage to other cranial nerves, or clinically significant vascular injuries [67]. Also, by identifying high-yield regional lymph nodes from SLNB, it allows more efficient and accurate histopathologic evaluation. Occult lymphatic metastasis can be difficult to detect and require rigorous assessment by pathologists via serial sectioning and immunohistochemistry; micrometastasis are less likely to be overlooked when evaluating selected high-yield sentinel nodes than larger nodal numbers.

The decision to offer SLNB to patients without gross neck disease depends on the risk of occult disease. Information gained by SLNB provides prognostic stratification, treatment decision of occult regional disease if positive, and aiding selection for adjuvant therapy. Some argue that SLNB should be offered when there is a greater than 5% risk of occult regional disease, which is the case in melanomas ≥ 0.76 mm in thickness [68]. Melanoma thickness is the most predictive factor for regional metastasis [69], and therefore, decision to perform SLNB is guided mainly by Breslow thickness of the primary tumor.

A number of studies have compared outcomes in patients who underwent wide local excision plus SLNB to wide local excision plus nodal observation. Overall, patients who underwent SLNB have improved DFS but no difference in melanoma-specific survival (MSS). The Multicenter Selective Lymphadenectomy I (MSLT-I) trial demonstrated improved 10-year DFS with SLNB followed by CLND compared to nodal observation group [70]. However, there is no difference in 10-year MSS between the two groups. Several retrospective cohort studies have shared similar finding [71–75]. Although SLNB did not show an overall survival advantage, the SLN status afforded by the biopsy was a robust predictor of survival (5-year DSS of 75.3% in negative SLN vs 44.1% in positive SLN; $p < .0001$) [71]. Therefore, authors argue in favor for SLNB for its utility in prognostic stratification [72, 76–78].

The indication for SLNB in melanoma < 1.0 mm thick is less clear. The prognostic utility is thus weighed against the risk of the procedure and risk of occult regional disease. Overall, in clinically node-negative head and neck patients, SLNB identified occult disease in about 10–20% of these

patients [52, 67, 79, 80]. However, in patients with primary melanomas < 1.0 mm, this rate decreased to 2–12% [80–84]. Risks factors for SLN positivity in thin melanoma < 1.0 mm has been of interest to define a subpopulation of patient that would benefit more from SLNB. This includes thickness (especially Breslow thickness ≥ 0.75 mm) [80, 82, 83], Clark level ≥ IV [82, 83], microsatellites [82], ≥ 1 mitosis/mm^2 [82, 85], ulceration [80, 83], younger age [80], and location within head and neck (scalp, neck, or face lesions more likely for SLN positivity than lip, eyelid, and ear lesions) [80]. Absence of tumor-infiltrated lymphocytes was identified as another risk factor for SLN positivity in intermediate-thickness melanomas [86]. These risk factors are showed in Table 1 and used to classify "high-risk" melanoma. Several studies however had mixed result for mitotic rate [83, 85]. In AJCC-8, T1 subcategory definitions have been revised to exclude mitotic rate as part of staging.

The NCCN and ASCO/Society of Surgical Oncology (SSO) offer guidelines on when SLNB should be considered [60••, 87••]. Both do not recommend routine SLNB for patients with T1a melanoma (nonulcerated lesions < 0.8 mm in thickness). In patients with T1b melanoma (ulcerated lesions < 0.8 mm thick or lesions 0.8–1.0 mm in thickness), SLNB should be considered after discussion with patient regard the potential benefits and risks associated with the procedure. Patients with T2–T4 melanoma (lesions > 1.0 mm) should be offered SLNB. Recommendations from 2011 AAD guidelines used previous AJCC staging and therefore are not reported here [61•]; new guidelines are expected summer 2018.

Occult and Clinically Positive Neck Lymph Nodes

In patients with occult or clinically positive regional metastasis, imaging is recommended for baseline clinical staging. Those with clinically positive regional metastasis but without distant metastasis should undergo therapeutic neck dissection. Similar to cSCC, choice in compartmental neck dissection will vary pending location of primary lesion in relationship to vertical line from external auditory canal. If the parotid bed is involved with either occult or gross disease, a superficial parotidectomy is recommended in addition to neck dissection in occult and gross disease within parotid bed [88], although there is a study suggesting a total parotidectomy may be associated with lower nodal recurrence rate [89]. Following neck dissection and pathologic staging, additional adjuvant therapy may be considered on select high-risk patient based on nodal location, size, numbers involved, and presence of extracapsular extension.

The management of occult regional lymph nodes is much more complex and controversial. Recent RCT trials by German Dermatologic Oncology Cooperative Group (DeCOG-SLT) and MLST-II provided stunning findings on CLND in patients with occult regional disease [90, 91•]. In both trials, patients with positive sentinel nodes were randomized to CLND or to observation with frequent follow-up evaluations (MLST-II used serial nodal ultrasonography). Both trials found no difference between two groups in OS, MSS, and distant metastasis-free survival. However, MSLT-II reported improved DFS in patients who underwent CLND (68 vs 63%). In addition, patients with underwent CLND were more likely to develop lymphedema (24.1 vs 6.3%). Of note, DeCOG-SLT trial did not include patients with head and neck melanoma. In addition, findings for these studies may have limited applicability toward patients who are unable to present for regular follow-up evaluations or unable to obtain high-quality nodal ultrasonography during follow-up evaluations.

The findings from these two studies suggest that CLND may not provide a survival advantage in patients with positive sentinel node. It is conceivable that SLNB has a therapeutic effect especially in patients with low tumor burden in regional nodal basin. However, in MSLT-II, regional recurrence was higher in the observation group at 3-year (22.9 vs 17.9%) and 5-year (26.1 vs 19.9%), and regional recurrence is highly associated with poorer prognosis. Furthermore, it is unclear whether these findings could be generalized to patients with higher sentinel node burden such as those with ≥ 3 nodal involvement or > 1 mm micrometastatic disease. Due to predominance of lower tumor burden in regional nodal basin in the study, there is not sufficient statistical power in those studies to help answer whether sentinel-node tumor burden could identify a subset patient population who may benefit from CLND given risk of disease progression to downstream regional nodal basins.

Prior to these studies, patients with a positive sentinel node have been advised to proceed with CLND, due to historical finding that it improves survival [64]. From studies on CLND following positive SLNB, there is 20% risk of additional positive nonsentinel node (NSLN) [92]. A positive NSLN was associated with higher rates of recurrence and lower rates of DFS, MMS, and OS [93–95, 96].

The decision to perform neck dissection in clinically node-negative neck is a controversy reflected in many other head and cancers. The new guidelines by NCCN and ASCO/SSO recommend either CLND or close observation are reasonable options following positive SLNB in clinically negative neck [60••, 87••]; however, a thorough discussion of these options with patient is recommended, particularly on the risk of positive NSLN and its significance, morbidity associated with procedure, and findings from the two RCTs. In our practice, we strongly favor performing CLND due to well-known benefit of providing elective neck dissections to patients with mucosal head and neck cancers when there is a ≥ 15–20% risk of occult metastatic disease. If there is a 20% risk of additional positive nodes following a positive SLNB, we believe a CLND provide added prognostic and therapeutic benefits. In addition, it remains unclear whether the outcome reported

from DeCOG-SLT and MSLT-II can be reproduced in the head and neck patient population. Additional studies are needed to assess the role of CLND specifically in head and neck patients.

Conclusion

Skin cancers have a strong predilection for the head and neck region, and the incidence continues to steadily rise. It is estimated that one in five Americans will develop skin cancer in course of their lifetime [97]. BCC, cSCC, and cutaneous melanoma, when treated early with good margin control, have excellent prognosis. When addressing the primary tumor, it is important to identify those considered as high-risk which may affect selection on margin size, choice in surgical procedure, and in cases of cSCC and melanoma, decision to address regional lymph nodes. Sentinel lymph node biopsy is a safe and effective way to identify occult regional metastasis, but in patients with gross regional disease, a completion lymphadenectomy may be indicated. Although not address in this review, other treatment options should also be considered for special circumstances. Ultimately, in patients with one of these cutaneous malignancies, understanding the most efficient and effective surgical treatment options of primary and regional disease is essential for improved locoregional control and overall survival while minimizing morbidity.

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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- • Of importance
- •• Of major importance

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