Ann Surg Oncol (2021) 28:9009–9030
https://doi.org/10.1245/s10434-021-10108-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

REVIEW ARTICLE – HEAD AND NECK ONCOLOGY

High-Risk Cutaneous Squamous Cell Carcinoma of the Head and Neck: A Clinical Review

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ABSTRACT

Background. Given the rapidly evolving nature of the field, the current state of "high-risk" head and neck cutaneous squamous cell carcinoma (HNcSCC) is poorly characterized.

Methods. Narrative review of the epidemiology, diagnosis, workup, risk stratification, staging and treatment of high-risk HNcSCC.

Results. Clinical and pathologic risk factors for adverse HNcSCC outcomes are nuanced (e.g., immunosuppression and perineural invasion). Frequent changes in adverse prognosticators have outpaced population-based registries and the variables they track, restricting our understanding of the epidemiology of HNcSCC and inhibiting control of the disease. Current heterogeneous staging and risk stratification systems are largely derived from institutional data, compromising their external validity. In the absence of staging system consensus, tumor designations such as "high risk" and "advanced" are variably used and insufficiently precise to guide management. Evidence guiding treatment of high-risk HNcSCC with curative intent is also suboptimal. For patients with incurable disease, an array of trials are evaluating the impact of immunotherapy, targeted biologic therapy, and other novel agents.

Conclusion. Population-based registries that broadly track updated, nuanced, adverse clinicopathologic risk factors, and outcomes are needed to guide development of improved staging systems. Design and development of randomized controlled trials (RCTs) in advanced-stage HNcSCC populations are needed to evaluate (1) observation, sentinel lymph node biopsy, or elective neck dissection for management of the cN0 neck, (2) indications for surgery plus adjuvant radiation versus adjuvant chemoradiation, and (3) the role of immunotherapy in treatment with curative intent. Considering these knowledge gaps, the authors explore a potential high-risk HNcSCC treatment framework.

Our understanding and management of head and neck cutaneous squamous cell carcinoma (HNcSCC) have evolved significantly during the last decade, yet significant barriers to delivery of high-quality cSCC patient care remain. Consensus is insufficient regarding shifting adverse risk factors, and dated population-based cSCC registries are ineffectual. Consequently, HNcSCC risk stratification is imprecise. Although recent therapeutic advances are promising, there is inadequate evidence to guide routine treatment decisions such as management of the clinically node-negative neck and adjuvant therapy for high-risk HNcSCC patients.

First Received: 4 December 2020
Accepted: 11 April 2021;
Published Online: 30 June 2021

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This clinical review recapitulates the recent advances and remaining barriers to progress in the field. Our primary objective is to facilitate up-to-date, evidence-based care of HNcSCCs patients. Our secondary objective is to highlight evidence gaps in HNcSCC epidemiology, risk stratification, and treatment that impede delivery of high-quality care.[1] Finally, we describe a potential framework to further guide treatment of high-risk HNcSCC.

PART 1: EPIDEMIOLOGY

Incidence

Cutaneous SCC (cSCC) is widely considered the second most common malignancy in the United States, although limited national cancer registry reporting requirements preclude precise estimates of its incidence.[2] The best available cSCC data in the United States was obtained by the National Cancer Institute (NCI) as part of a population-based study commissioned by the Clean Air Act Amendment of 1977. The study surveyed eight unique U.S. locations from 1977 to 1978 and identified 31,578 individuals with nonmelanoma skin cancer (NMSC).[3] Of the NMSCs, cSCC comprised 17.8%, and an estimated 80,000–100,000 individuals experienced cSCC annually.[3] Compared with earlier 1971–1972 survey data, the incidence of NMSC increased 15%–20% in the 6-year interval.[3]

While more recent models confirm the increasing incidence of cSCC, they also highlight the challenge of characterizing the true burden of the disease. Using population-based claims and governmental datasets, Rogers et al.[4] estimated the incidence of NMSC in the United States to be 3,507,693 in 2006 (assuming that 17.8% of the cases were cSCC,[3] the cSCC incidence in 2006 may have been 624,369). Using pooled hospital- and population-based cohort study data from 1971 to 1999, Karia et al.[5] projected that in 2012, cSCC was diagnosed for 186,157 to 419,543 white individuals in the United States. However, according to GLOBOCAN 2018, the International Agency for Research on Cancer (IARC) estimated that the global NMSC incidence was 1,042,056.[6] This appraisal is significantly lower than the NMSC incidence reported by Rogers et al.[4] in the United States alone. Divergent estimations by the IARC and Rogers et al.[4] again highlight the need for improved prospective population-based cSCC data collection.

Patient Characteristics and Risk Factors

Age, sex, race and ethnicity, and ultraviolet (UV) radiation exposure are primary common risk factors for cSCC (Table 6). According to the NCI survey, the male-to-female cSCC incidence rate (IR) ratio was 2.8–1, and the highest IRs occurred for individuals 75 years of age.[3] Black individuals rarely experienced NMSC. The age-adjusted IR among black participants was only 3.4 compared with 232.6 among white individuals.[3] A recent multicenter cohort study at 15 fellowship-trained academic and private Mohs micrographic surgery (MMS) practices across the United States corroborated these sociodemographic characteristics[1,7] Among the 647 patients with 745 cSCCs enrolled during 25 consecutive days, the average patient age was 75 years, and 72% of the patients were male (Fig. 1).[7]

Ultraviolet radiation exposure via sunlight, the most common cause of cSCC, is inversely associated with latitudinal gradient.[8] As such, the cSCC annual IRs among white males were lower in northern U.S. cities (30.0–50.8 per 100,000 population) than in southern U.S. cities (98.1–180.2 per 100,000 population). In addition to ultraviolet radiation, multiple other factors predispose toward the development of cSCC (Table 1).[8–16]

During the last several decades, cSCC risk factors have collectively evolved. Indoor tanning is emblematic. The first tanning salon in the United States opened in 1978,[17] and in 2015, 4% of adults reported that they had tanned indoors at least once in the last year.[18] Immunosuppression is another example. According to recent estimates, 3% of U.S. adults are immunosuppressed.[19] During the last 25 years, the armamentarium of immunosuppressive therapies for autoimmune disorders has expanded from conventional agents such as methotrexate and glucocorticoids to biologics, biosimilars, and tyrosine kinase inhibitors.[20–22] The degree to which emerging immunosuppressive drugs predispose autoimmune patients to cSCC has not been characterized to date. Similarly, solid organ and hematopoietic stem cell transplants were first executed in the 1950s and 1960s, and currently, more than 60,000 patients undergo transplantation annually in the United States.[23–25] The majority of these patients will require chronic immunosuppression, incurring a 65–250 times greater risk for the development of cSCC in the process.[12]

Tumor Characteristics

Clinical According to NCI survey data, 75% of cSCCs involved the head and neck in males and 60% of cSCCs involved the head and neck in females, respectively. The most common head and neck sites involved relative to the entire body were the scalp and forehead (18%) among males and the cheek, chin, and jaw (17%) among females. Involvement of the ear was common in males (14%) but rare in females (2%), presumably due to sunlight protection

TABLE 1 Clinical risk factors for the development of cutaneous squamous cell carcinoma (cSCC)

Risk factor category	Specific clinical disorders or exposures	Examples of quantifiably increased risk of cSCC
Light skin phototype (e.g., Fitzpatrick type 1 or 2)	Vitiligo, albinism	
Immunosuppression, immunocompromised state	Organ transplant recipients (OTRs), lymphoproliferative disorders (e.g.. chronic lymphocytic leukemia	OTRs: 65–250x[12]
Genodermatoses	Xeroderma pigmentosum (XP), oculocutaneous albinism	XP patients age <40 years: 700x [13]
Chronic skin disorders/dermatoses	Porokeratosis, discoid lupus, lupus vulgaris, lichen sclerosis, lichen planus, lymphogranuloma venereum, granuloma inguinale, acne conglobata, hidradenitis suppurativa, dystrophic epidermolysis bullosa	
Chronic scarring conditions	Sinus tracts, ulcers, osteomyelitis	
Viruses	α-Human papillomavirus (HPV), β-HPV, epidermodysplasia verruciformis (genetic susceptibility to β-HPV), human immunodeficiency virus (HIV)	β-HPV: 45% increased risk [14,15]
Chemical exposures	Arsenic, polycyclic aromatic hydrocarbons (tar, pitch, soot)	
Other exposures	Tanning bed use, radiation, tobacco and alcohol use, prior history of cSCC	

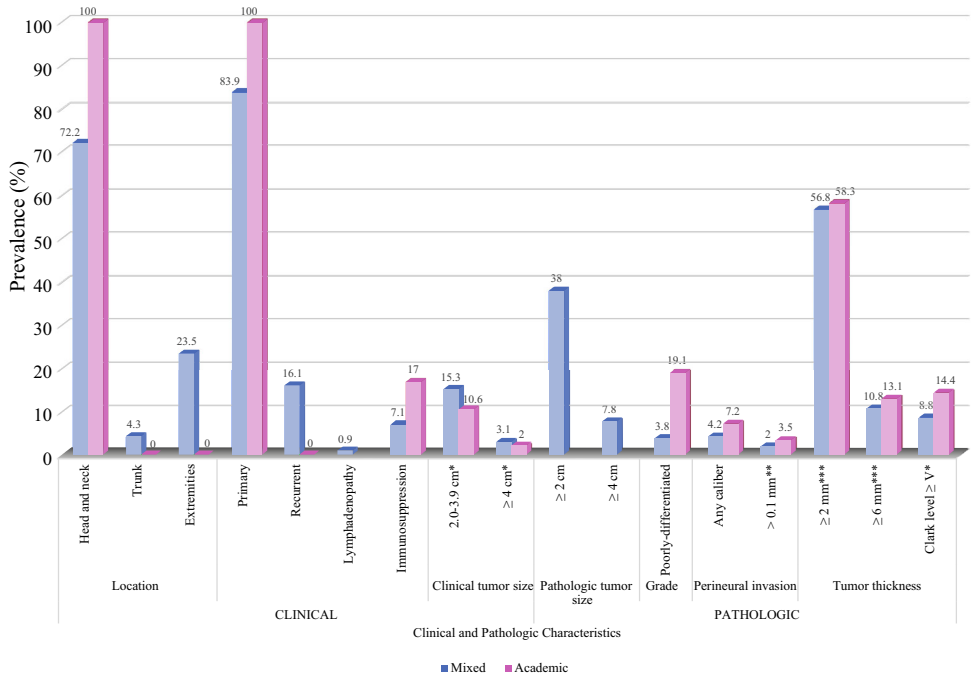

FIG. 1 Prevalence of clinical and pathologic characteristics in a mixed academic and community national and multi-institutional cohort compared with an institutional academic cohort. The "mixed" designation refers to a prospective multicenter study conducted at 15 different institutions (4 academic centers, 11 private practices) in 13 states (HI, CA, SC, FL, AL, AZ, MD, CO, MN, PA, NC, KS, OH). The "academic" designation refers to a retrospective cohort of exclusively head and neck cutaneous squamous cell carcinoma (HNcSCC) patients treated at the Dana Farber/Harvard Cancer Center. The diagram demonstrates the diversity in prevalence of clinical and pathologic characteristics in mixed versus academic settings. Notably, certain adverse clinical and pathologic characteristics predominated in the academic cohort relative to the mixed cohort: respectively, immunosuppression (17% vs 7%), poorly differentiated grade (19% vs 4%), any caliber perineural invasion (PNI) (7% vs 4%), ≥ Clark Level V tumor thickness (14% vs 9%). *Determined from Campoli et al 2014 data; **PNI is categorized as >0.1 mm by Tschetter et al.[7] and as ≥0.1 mm by Karia et al.[37] 2018/Ruiz et al.[26] 2019; ***Tumor thickness is categorized as >2 mm and >6 mm by Tschetter et al.[7] 2020 compared with ≥2 mm and ≥ 6 mm by Karia et al.[37]/Ruiz et al.[26]

afforded by hair covering their ears. The aforementioned multi-center cohort of cSCCs treated with MMS also corroborates these findings, with 72% of the cSCCs involving the head and neck (Fig. 1).[1,7]

The vast majority of cSCC patients present with early-stage disease. The Netherlands Cancer Registry reported the tumor characteristics of 57,277 incident cSCCs from 1989 to 2008 using a nonstandard pathologic staging system. In this cohort, 88.8% of the patients exhibited stage 1 disease (diameter <2 cm), and 9.5% had stage 2 disease (diameter >2 cm without other adverse features). Only a fraction of the patients exhibited stage 3 cSCC (1.6%; invasion of deep extradermal structures or regional metastasis) or stage 4 cSCC (0.1%; distant metastasis).

Application of new and recently updated cSCC staging systems and more contemporary patient data showed that approximately 20%–30% of cSCC patients in the United States exhibit American Joint Committee on Cancer, eighth edition (AJCC8) ≥T2 tumors or Brigham and Women's Hospital (BWH) T2a tumors.[7,26] Approximately 10%–20% exhibit BWH T2b–T3 or AJCC8 T3–T4 tumors.[7,26] Notably, Campoli et al.[1] and Tschetter et al.[7] reported a high frequency of pathologic upstaging according to tumor diameter (Fig. 1). This national multicenter cohort study also reported the following adverse pathologic feature prevalence rates: poorly-differentiated grade (4%), perineural invasion (PNI) greater than 0.1 mm (2%), and tumor invasion into the subcutaneous fat (Clark level V) (8%) (Fig. 1).[7]

Survival The lack of precise, population-based survival estimates using standard staging for cSCC is suboptimal. Karia et al.[5] estimated that 3932–8791 persons (~2.1%) died of cSCC in the United States in 2012. In a meta-analysis of four studies with 175,849 pooled cSCC patients, the individuals with cSCC exhibited a higher mortality hazard ratio (HR) than the general population (HR, 1.25, 95% confidence interval [CI], 1.17–1.32).[27] The relative 5-year survival rates in the Netherlands Cancer Registry according to nontraditional staging were as follows for females versus males: stage 1 (98% vs 95%), stage 2 (76% vs 76%), stages 3 and 4 (combined due to small subgroups; 46% vs 62%).[28] Although evidence supports a correlation between head and neck tumor location (particularly high-risk mask areas of the face) and compromised survival,[29] population-based survival estimates for the spectrum of HNcSCC have not been ascertained to date.

PART 2: DIAGNOSIS AND WORKUP

Risk Stratification and Staging

Prior cSCC Staging System Inferiority and Recent Advancements in Staging The need for improved cSCC risk stratification and staging to guide treatment has been robustly documented.[30–33] The AJCC seventh-edition system (AJCC7) was criticized for lacking all three features of a good staging system: distinctiveness (outcomes differ between stages), homogeneity (outcomes are similar within each stage), and monotonicity (outcomes worsen with increasing stage).[30,34–36] Karia et al.[37] substantiated the inferiority of the AJCC7 in their tertiary care, single-institution study of 680 HNcSCCs in 480 patients (Fig. 2a). During the last 10 years, the BWH staging system[34,35] was introduced, and both the AJCC[38] and National Comprehensive Cancer Center (NCCN)[39] systems were substantively updated. The AJCC8, BWH, and NCCN very-high-risk tumor classification system criteria are listed in Table 2. Other staging systems have been described (e.g., Brueninger et al.[36]) but are not discussed in detail in this review.

New and Updated cSCC Staging System Heterogeneity Despite these staging system improvements, the variety of included risk factors is disorienting (Table 2). Whereas BWH applies primary pathologic tumor characteristics only[34,35] NCCN incorporates patient and primary tumor characteristics,[39] and AJCC8 applies primary tumor and nodal characteristics. These staging systems also report differing outcomes of interest. The NCCN system features risk factors for local recurrence or nodal metastasis only,[39] whereas the AJCC8 and BWH systems also consider risk factors for mortality.[34,38] Finally, the distribution of patients according to stage or risk level has diverged according to staging system. According to single- and multi-institutional cohort analyses, whereas 80%–95% of primarily HNcSCCs are deemed "early stage" according to the AJCC8 and BWH systems[7,26] the vast majority of HNcSCCs (87%) were deemed "high risk" according to the prior NCCN classification system.[30]

Recently, however, the NCCN has introduced a "very high risk" classification category and in the context of identifying "patients at high risk for multiple primary cSCCs" defines an "aggressive" category of tumors.[39] These tumors exhibit "extension beyond cutaneous structures, perineural involvement, large [diameter], poorly differentiated [histology], or ≥3 risk factors for recurrence."[39] Given their distinctions, a brief evaluation analyzing the merits and deficiencies of the AJCC8, BWH, and NCCN cSCC staging systems is warranted.

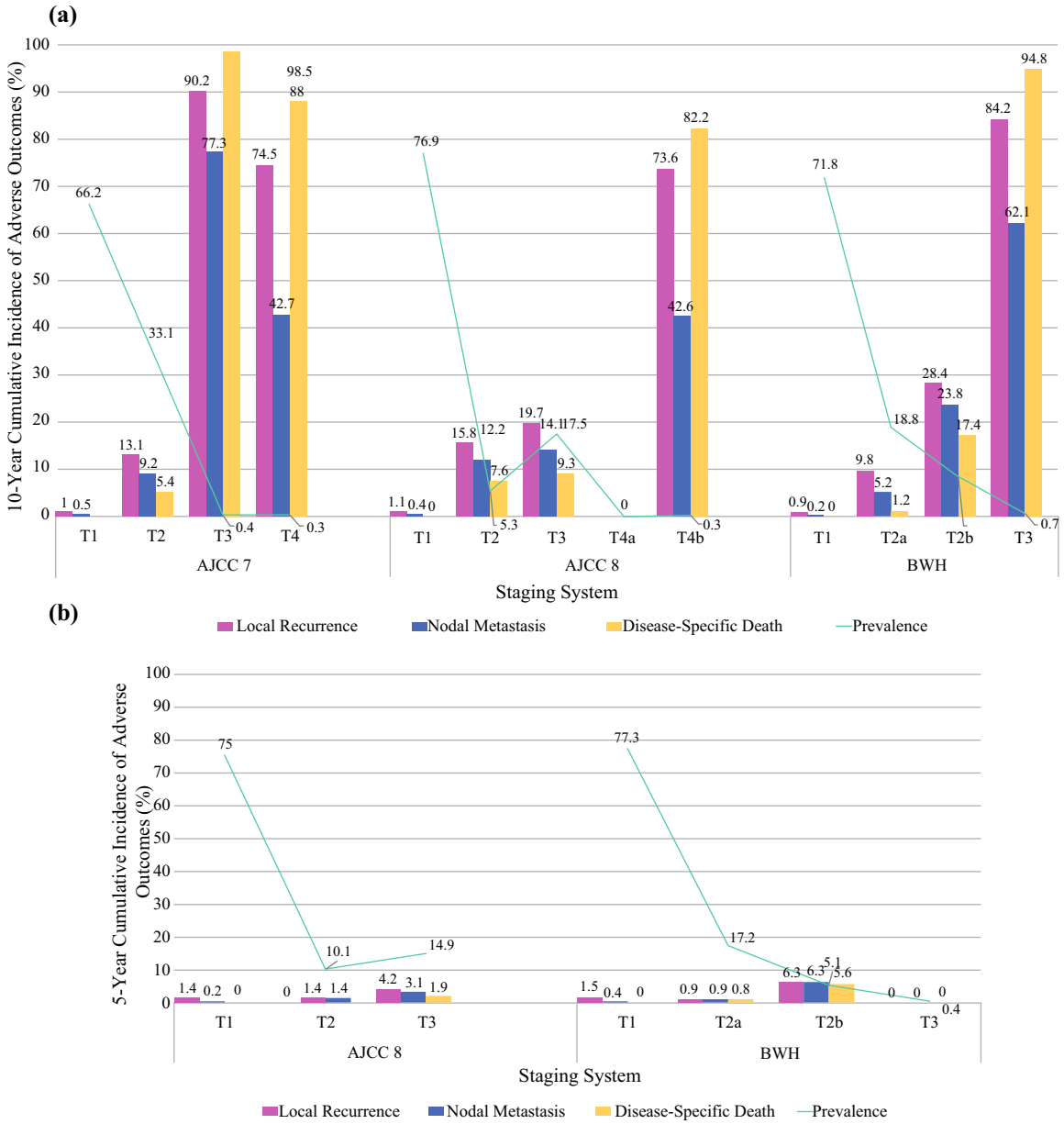

FIG 2 Distribution of academic and tertiary care patients as well as 10- and 5-year cumulative incidence rates of adverse outcomes according to staging system and tumor stage. **a** American Joint Committee on Cancer, seventh edition (AJCC7) exhibited inferior performance characteristics: 99.3% of cutaneous squamous cell carcinomas (cSCCs) in the cohort were classified as T1-T2 tumors, and relative to T3 disease, T4 tumors exhibited neither distinctive nor worsening outcomes.[36] Furthermore, the T2 group exhibited significant outcome heterogeneity: 43% were upgraded to AJCC8 T3 tumor stage, whereas 45% were downgraded to AJCC8 T1 tumor stage.[36] **b** The 10- and 5-year cumulative incidence (CIN) rates of local recurrence, nodal metastases, and disease-specific mortality outcomes ranged from 9% to 20% for AJCC8 T3 tumors in the Ruiz et al.[26] study and from 2% to 4% in the Tschetter et al.[7] study. Similarly, Brigham and Women's Hospital (BWH) T2b tumors exhibited (**a**) a 17%–28% 10-year CIN of adverse oncologic outcomes in the Ruiz et al.[26] study compared with (**b**) a 6% 5-year CIN in the Tschetter et al.[7] study. These findings highlight the suboptimal performance characteristics of existing staging systems because risk stratification varies according to the population studied. Furthermore, discrepancies in outcomes likely are only partially attributable to differences in length of the follow-up period.

Comparison of Staging Systems According to Patient Characteristics With the exception of neurologic symptoms, only the NCCN incorporates patient characteristics, including immunosuppression, prior radiation, and chronic inflammatory processes of the tumor site, into the high-risk category (Table 3).[39] The exclusion of these patient characteristics from other systems may be warranted. Although several patient characteristics predispose for cSCC development (Table 6), evidence that they have an adverse impact on

TABLE 2 AJCC, BWH, and NCCN staging system criteria

Primary tumor staging	AJCC 8th edition	BWH	NCCN very-high-risk[a]
Staging systems			
T1	Size <2 cm	0 High-risk features	
T2	Size ≥2 cm AND <4 cm		
T2a		1 High-risk feature	
T2b		2–3 High-risk features	
T3	Size ≥4 cm OR PNI[b] OR deep invasion[b] OR minor bone erosion	Bone invasion OR ≥4 high-risk features	
T4	Gross cortical bone/marrow, skull base, OR skull base foramen invasion		
T4a	Gross cortical bone/marrow invasion		
T4b	Skull base invasion OR skull base foramen involvement		

(Very) high-risk feature category	High-risk features	Very-high-risk features[c]
Location		
Histopathologic subtype		Desmoplastic
Size	≥2 cm	≥4 cm
Grade	Poorly differentiated	Poorly differentiated
Depth of invasion	Invasion beyond subcutaneous fat	>6 mm[c] or invasion beyond subcutaneous fat
Perineural invasion	Invasion of nerve ≥0.1 mm in caliber	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement		Lymphatic or vascular involvement

AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; NCCN, National Comprehensive Cancer Network; PNI, perineural invasion

[a]The presence of any very-high-risk feature denotes very-high-risk NCCN classification. The AJCC 8th edition, BWH, and NCCN staging systems substantially overlap but also incorporate unique adverse prognostic factors.

[b]Tumor cells within the nerve sheath of a nerve lying deeper than the dermis OR measuring 0.1 mm or larger in caliber OR presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

[c]Invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor).

oncologic outcomes is limited (Table 7). In the meta-analysis by Thompson et al.[29] even immunosuppression was associated with only one adverse oncologic outcome, a modestly increased risk of nodal metastases (relative risk, 1.59; 95% CI, 1.07–2.37).

Conversely, assessments about the importance of immunosuppression may be understated. Immunosuppressed populations exhibit heterogeneous diseases and degrees of immunosuppression. In their analysis of 796 HNcSCC patients, 147 of whom were immunosuppressed, Tam et al.[40] reported distinctions in the adjusted risk of disease-specific mortality according to type of immunosuppression as follows: hematopoietic malignant disease (adjusted hazard ratio [aHR], 3.50; 95% CI, 1.93–6.35), solid organ or stem cell transplants (aHR, 2.49; 95% CI, 1.05–5.86), insulin-dependent diabetes mellitus (aHR, 1.28; 95% CI, 0.72–2.28), and immunocompetent patients (ref). The Manyam et al.[41] multi-institutional study of 205 HNcSCC patients who had surgery and postoperative radiation also substantiates the importance of immunosuppression. In the adjusted analyses, immunosuppressed status (chronic hematologic malignancy, human immunodeficiency virus, or organ transplantation with immunosuppressive therapy ≥6 months) was more strongly correlated with locoregional recurrence (aHR, 3.79; 95% CI 2.24–6.41) than any other adverse risk factor, including recurrence status, histologic grade, and PNI.

TABLE 3 Cutaneous SCC high-risk features or upstaging criteria according to staging systems and risk stratification data

Category	High-Risk Feature or Upstaging Criteria (Beyond T1N0)	Staging/Risk Stratification Systems					Meta-Analytic Data					
		NCCN		AJCC 7th Ed	AJCC 8th Ed	BWH	Thompson et al					
							Recurrence		Metastases		Disease-Specific Death	
		HR	VHR				RR>1*	RR>5*	RR>1*	RR>5*	RR>1*	RR>5*
Clinical	Immunosuppression	■					--[c]	--[c]	■		--[c]	--[c]
	Prior radiation to site	■										
	Chronic inflammatory process at site	■										
	Neurologic symptoms	■			■							
Clinical Tumor	Location[a]	■		■			■		■		■	
	Poorly-defined borders	■										
	Recurrent	■										
	Radiographic perineural invasion				■							
Unspecified	Size/diameter[a]	■	■	■	■	■	■		■	■	■	■
Pathologic Tumor	Grade/differentiation[a]		■	■		■	■		■		■	■
	Histopathologic subtypes[b]	■	■									
	Depth of invasion[a]		■	■	■	■	■	■	■	■	■	
	Perineural invasion[a]	■	■	■	■	■	■		■			
	Lymphatic or vascular invasion		■									
	Invasion of bony structures[a]			■	■	■						
Nodal	Size			■	■							
	Number			■	■							
	Contralateral or bilateral			■	■							
	Clinical extranodal extension				■							
	Pathologic extranodal extension				■							

Legend:
AJCC: American Joint Committee on Cancer; BWH: Brigham and Women's Hospital; cTumor: clinical tumor; Ed: edition; HR: high-risk; NCCN: National Comprehensive Cancer Network; pTumor: pathologic tumor; RR: risk ratio; VHR: very-high-risk; *: significant ($p<0.05$); [a]: see Appendix Table 6 for additional detail; [b]: acantholytic/adenoid, adenosquamous, desmoplastic, metaplastic/carcinosarcomatous subtypes; --[c]: high-risk feature tested and was not significant; empty box: high-risk feature NOT included in the staging or risk-stratification system/study; grey box: high-risk feature included in the staging or risk-stratification system/study
Caption: The NCCN, AJCC7, ACCJ8 and BWH staging systems incorporate different clinical and pathologic risk factors for adverse oncologic outcomes. Here, we compare these to the findings of a comprehensive meta-analysis conducted by Thompson et al.

Comparison of Staging Systems According to Tumor Characteristics Among the varied clinical and pathologic tumor characteristics included by at least one staging system, only tumor diameter, depth of invasion, and PNI are incorporated by all systems (Table 3). These tumor characteristics, together with tumor grade/differentiation, may be the most important determinants of outcomes according to Thompson et al.[29] Indeed, with the exception of PNI, all factors were associated with at least a five times greater pooled risk of at least one adverse oncologic outcome (Table 3).

Several other tumor characteristics are included by the NCCN but omitted by other staging systems. Desmoplastic histopathologic subtype and lymphovascular invasion are included in the NCCN "very-high-risk" category and have strongly predicted for adverse outcomes.[42–44] Additional NCCN high-risk characteristics include tumor location,[29,45] poorly defined borders, recurrent disease,[46] other histopathologic subtypes,[43] and presence of chronic inflammation.[47] (Table 3). Prospective population-based evaluation of these adverse tumor characteristics will be needed to determine their true prognostic significance.

Comparison of Staging Systems According to Nodal Characteristics Nodal characteristics such as size, number, and (bi)laterality are established poor prognosticators in HNcSCC. The AJCC8 introduced extranodal extension (ENE) as a high risk feature and upstages ENE-positive patients to cN3b stage and pN2a versus pN3b stages depending on the number and size of ENE-involved lymph nodes. Unfortunately, validation studies of this updated system have not been favorable. In a single-institution cohort study of 382 HNcSCC patients who had regionally metastatic disease treated with curative intent, Liu et al.[48] did not demonstrate any differences in disease-specific survival (DSS) or overall survival (OS) between AJCC8 pN1, pN2, and pN3 disease categories.

Current cSCC Staging System Performance Characteristics Because the updated NCCN risk stratification system has only now been issued, its performance characteristics are unknown. Although AJCC8 and BWH exhibit improved distinctiveness and monotonicity relative to AJCC7 (Fig. 2a), staging system

homogeneity is questionable (Fig. 2a, b). Indeed, outcomes appear to differ substantially among BWH T2a-T3 and AJCC8 T2–T4 tumors according to different validation studies. Poorer outcomes in the Ruiz et al.[26] study may be partially attributable to longer follow-up, exclusive head and neck tumor location, and treatment at an academic medical center with corollary increased prevalence rates of immunosuppression. Still, the Tschetter et al.[1,7] study was composed of predominantly HNcSCC patients (72%) treated at a mix of community and academic centers. Other validation studies have been less illuminating, with restriction of analyses to one oncologic outcome (e.g., nodal metastases).[49–51] Ultimately, this suboptimal homogeneity is unsurprising because the current staging systems were developed using primarily institutional data and therefore exhibit limited external validity.

cSCC Staging System Synthesis For the purpose of this review and on the basis of the aforementioned low-quality evidence, we define (1) N0 AJCC8 T3-T4, BWH T2b-T3, NCCN very high risk, or NCCN "aggressive" disease and/or (2) N+ disease as very-high-risk HNcSCC. We define N0 AJCC8 T1–T2 and BWH T1-T2a HNcSCC as high risk if the patient or tumor exhibit two NCCN high-risk factors and low risk if the head and neck location is the only NCCN high-risk factor described.

Other Tumor Markers

Evaluation of molecular tumor markers portending adverse outcomes is ongoing. Early data have demonstrated associations between deleterious oncologic outcomes and increased tumor programmed cell death ligand 1 (PD-L1) expression,[52–54] tumor epidermal growth factor receptor (EGFR) expression,[55–57] CD133,[58] CD147,[59] p300 transcriptional coactivator,[60] inositol polyphosphate 5-phosphatase (INPP5A) expression,[61,62] or the presence of telomerase reverse transcriptase (TERT) gene promoter (TERTp) mutations.[63]

Biopsy

The American Academy of Dermatology (AAD) recommends punch, shave, or excisional biopsy for diagnosis.[64] Pathologic biopsy reports should include, to the extent possible given sample size limitations, histologic subtype and presence of adverse pathologic features defined by AJCC8 and BWH.[64] The NCCN further recommends that clinicians supplement pathologic specimens with other NCCN-specific risk factors (Table 2).[39,64] The authors of this review emphasize that whenever possible, pathologists should report and clinicians should obtain information on all collective AJCC8, BWH, and NCCN adverse factors before treatment. Fine-needle aspiration generally is indicated for patients with palpable nodes or abnormal nodes detected by imaging.

Imaging

Introduction Imaging is not commonly indicated for patients with HNcSCC. As demonstrated in Fig. 2, more than 7 in 10 patients present with early-stage, AJCC8, or BWH T1 disease. According to Ruiz et al.,[26] these patients exhibit very low 10-year cumulative incidence rates of local recurrence ($\leq$1.1%) and nodal metastases ($\leq$0.4%). When very-high-risk disease is suspected, imaging should be performed to enhance staging accuracy, especially when improved staging augments disease prognostication and treatment planning. The advantages, disadvantages, and validity of various imaging methods are discussed in Table 4.

Evaluation of the Primary Tumor Imaging may be indicated to evaluate for risk factors such as depth of soft tissue invasion, presence of bony invasion, or PNI.[65] As described in Table 4, computed tomography (CT) generally is preferred for evaluation of bony invasion, whereas magnetic resonance imaging (MRI) better characterizes soft tissue invasion or PNI.[65,66] Discovery of these adverse features may alter the pre-imaging treatment plan including the need for more aggressive tumor ablation, additional nodal evaluation and management, postoperative radiation, or advanced defect reconstruction.

Evaluation of Regional and Distant Metastases Campoli et al.[1] highlighted the infrequency of cSCC patients presenting with clinical lymphadenopathy (Fig. 2, 1.1%). Importantly, however, the inadequacy of palpation alone for nodal staging is well described in mucosal head and neck squamous cell carcinoma (HNSCC).[67] Although not without controversy, evaluation and management of the mucosal HNSCC cN0 neck generally is indicated when the likelihood of occult nodal metastasis is at least 15%–20%.[68–70] Therefore, on the basis of mixed low-quality evidence (Fig. 2) and the potential to influence disease-related outcomes,[26] we contend that parotid/neck imaging generally is warranted for cN0 very-high-risk disease.

Evaluation of imaging method validity is poorly characterized in HNcSCC. In a meta-analysis of 23 studies comparing imaging validity for detection of nodal metastasis among patients with mucosal cN0 HNSCC, ultrasound, CT, MRI, and positron emission tomography (PET) all performed relatively similarly, with one exception: CT exhibited superior per neck specificity compared with ultrasound (Table 4).[71] At a theoretical 20% rate of occult metastasis, CT exhibited the highest positive

TABLE 4 Comparing advantages, disadvantages and, validity of different imaging methods in the evaluation of HNcSCC and other HNC patients

	Imaging method				
	Ultrasound	CT	MRI	PET	^{18}FDG-PET/CT
Advantages	Low cost	Widely available	Evaluation of bone marrow	Evaluation of metabolic activity	Evaluation of cortical bone
	Noninvasive, painless	Rapid	Evaluation of soft tissue invasion, perineural invasion		Evaluation of metabolic activity
	Can be augmented using color Doppler or elastography	Evaluation of cortical bone			
	Easily paired with FNA				
Disadvantages	Operator-dependent	Exposure to ionizing radiation	Long scan time	Does not evaluate structural features of disease	Pairing with contrast enhancement is uncommon
	Inferior spatial resolution		Sensitive to motion		
	Inferior evaluation of deeper, obstructed neck structures	Risks of intravenous contrast	Costly	Fasting required	Fasting required
			Magnet-related issues	Costly	Costly
Extrapolating from primarily non-cSCC mucosal HNSCC and other HNC data: meta-analyses evaluating diagnostic test validity of nodal metastasis detection					
Liao et al.[71a]: evaluation of the cN0 neck among patients with HNSCC on a per neck basis					
(n = 23 studies [8 US, 7 CT, 6 MRI, 11 PET])					
Test validity (TV)	PNB	PNB	PNB	PNB	
Sensitivity (95% CI)	66% (54–77%)	52% (39–65%)	65% (34–87%)	66% (47–80%)	
Specificity (95% CI)	78% (71–83%)	93% (87–97%)	81% (64–91%)	87% (77–93%)	
Sun et al.[72b]: evaluation of the cN0 and cN+ neck among patients with primary untreated mucosal HNSCC or salivary gland cancer					
(PNB: n = 8 studies; 734 neck sides; PNLB: n = 13 studies; 3460 neck levels)					
	Any conventional imaging studies: CT, MRI, and CT/MRI		^{18}FDG-PET/CT		
Test validity	PNLB		PNB	PNLB	
Sensitivity (95% CI)	63% (53–72%)		84% (75–90%)	84% (72–91%)	
Specificity (95% CI)	96% (95–97%)		83% (77–88%)	96% (95–97%)	

[a]The majority of the eligible studies included patients with mucosal SCC of the head and neck alone, whereas some studies also included patients with cutaneous SCC of the head and neck.

[b]Excluded cSCC patients entirely

CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; CT, computed tomography; ^{18}FDG, ^{18}F-fluorodeoxyglucose; FNA, fine-needle aspiration; HNC, head and neck cancer; HNcSCC, head and neck cutaneous squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; MRI, magnetic resonance imaging; PET, positron emission tomography; PNB, per neck basis; PNLB, per neck level basis

predictive value (66%), whereas the negative predictive values of all the tests were comparable (89–91%). In another meta-analysis of 13 studies evaluating 3460 neck levels in patients with mucosal HNSCC and salivary gland carcinoma, 18 fluoro-2-deoxyglucose (^{18}FDG)-PET/CT trended toward exhibiting improved per-neck-level sensitivity compared with CT, MRI, or CT/MRI.[72]

Extrapolation from this and other HNC data (Table 4) corroborates the NCCN recommendation: CT is a useful workhorse imaging method for cSCC staging. The role of ^{18}FDG-PET/CT in the evaluation of high-risk cN0 HNcSCC should be further evaluated given its high sensitivity (84%) for regional metastases in other HNCs.[72] Because the sensitivity of ultrasound was equivalent to MRI and PET-CT and non-significantly better than CT in the Liao et al.[71] meta-analysis, ultrasonographic surveillance of the observed cN0 neck in high-risk HNcSCC is strongly supported. Finally, evaluation for distant metastases can be accomplished with either chest/abdomen/pelvis CT or PET-CT of the full body. The NCCN recommends distant imaging only for patients with established regional metastasis.[39]

PART 3: MANAGEMENT OF THE HIGH- AND VERY-HIGH-RISK CUTANEOUS HNSCC PRIMARY TUMOR

Introduction

High-quality data comparing the efficacy of treatment methods for primary higher-risk HNcSCC are sparse. No RCTs comparing Mohs micrographic surgery (MMS), excision with complete circumferential peripheral and deep margin assessment (CCPDMA), and standard excision or radiation have been performed.[73] Moreover, pooled systematic reviews and meta-analyses of primarily institutional, retrospective cohort data have exhibited bias.[74] In the most robust meta-analysis of prospective or retrospective observational studies (n = 118) of the subject to date, Lansbury et al.[75] compared different treatment methods for non-metastatic low- and high-risk invasive cSCC[75] The pooled estimates of local recurrence rates were 0.8% (95% CI, 0.1–2.0%) for cryotherapy (8 studies, 273 cSCCs), 1.7% (95% CI, 0.5–3.4%) for electrodissection and curettage (ED&C) (7 studies, 1131 cSCCs), 3%, (95% CI, 2.2–3.9%) for Mohs micrographic surgery (10 studies, 1572 cSCCs), 5.4% (95% CI, 2.5–9.1%) for standard surgical excision (12 studies, 1144 cSCCs), and 6.4% (95% CI, 3.0–11.0%) for external radiotherapy (7 studies, 761 cSCCs).

Lansbury et al.[75] acknowledged that because cryotherapy and ED&C studies primarily included small low-risk cSCCs, the outcomes of these interventions are not comparable with those of other interventions. Comparative effectiveness analyses of other interventions are similarly constrained by heterogeneous lengths of follow-up time across studies and the lack of adjustment for confounding variables such as tumor location and stage. Nevertheless, local recurrence did not differ significantly between Mohs, standard surgical excision, and radiotherapy.[75] Risk of regional recurrence also was similar across treatment methods: Mohs (4.2%; 95% CI, 2.3–6.6%), standard excision (4.4%; 95% CI, 2.4–6.9%), and radiotherapy (2.6%; 95% CI, 0.04–8.9%).[75]

Curative HNcSCC Primary Tumor Interventions

Primary Surgery According to the NCCN, the primary goals of cSCC treatment are complete tumor removal and maximal preservation of function and cosmesis. Surgery is first-line therapy, and notwithstanding the lack of evidence, Mohs micrographic surgery (MMS) and excision with CCPDMA are the preferred treatment methods for high- and very-high-risk HNcSCCs. The MMS approach offers the following advantages:

- Real-time, 100% complete margin analysis with mapping of residual tumor
- Maximal tissue-sparing
- Procedure performed in office and under local anesthesia
- Treatment in a single day
- Cost-consciousness.

Excision with CCPDMA may be preferred when:

- Parotidectomy or composite resection (i.e., soft tissue and bone excision) is necessary to achieve negative margins.
- The anticipated defect will require regional or free tissue-transfer reconstructive surgery.
- Surgical evaluation or management of the neck is indicated (i.e., sentinel lymph node biopsy, elective vs therapeutic parotidectomy, and neck dissection).

Electrodissection and curettage, standard excision, cryosurgery, laser surgery, topical therapy (i.e., imiquimod, 5-fluorouracil), phototherapy, and intralesional interferon generally are reserved for precancers or NCCN low- or high-risk cSCCs and are not discussed further in this review.[39] We discuss indications for adjuvant radiation ± chemotherapy later in the discussion.

Primary Radiation ± Systemic Therapy Primary radiation therapy ± chemotherapy is favored for inoperable tumors, poor surgical candidates, anticipated unacceptable surgical cosmetic outcomes, and patient

preference.[9,36,76–78] Radiation alone generally is insufficient for locally advanced or regionally metastatic HNcSCC.[79,80] Still, given the limited data describing outcomes with multimodal regimens,[81] the NCCN advises that administration of concurrent chemotherapy and radiation be guided by a multidisciplinary tumor board or be performed in the context of a clinical trial. Because of high-quality evidence supporting concurrent radiation therapy with platinum-based chemotherapy regimens in locally advanced and/or regionally metastatic mucosal HNSCC,[82,83] oncologists often apply this treatment paradigm to cutaneous HNSCC patients with similarly advanced disease. Concurrent radiation and cetuximab, a second-line regimen for advanced mucosal HNSCC, might be considered in select circumstances[84,85] but is not currently supported by the NCCN.

Management of the High-Risk and Very-High-Risk HNcSCC Clinically Node-Negative Neck Evidence-based HNcSCC-specific indications for elective management of the neck have not been defined. Until disease-specific evidence is developed, clinicians may consider applying the aforementioned, broadly accepted mucosal HNSCC principle of treating the cN0 neck when the likelihood of occult nodal metastasis is at least 15%–20%.[68–70] We have adopted the lower threshold (15%) for the purpose of this review, as described in the following discussion.

<15% Likelihood of Occult Nodal Metastases In the absence of very-high-risk disease, the rate of occult nodal metastases in HNcSCC remains low. Imaging and management of the neck are not routinely indicated, although in shared decision-making, select patients may prefer a more aggressive approach.

≥15% Likelihood of Occult Nodal Metastases

Introduction Patients with very-high-risk HNcSCC are more likely to present with occult nodal metastases. Clinicians should use shared decision-making with patients in this category.

Observation With Serial Imaging According to Liao et al.,[71] among cN0 patients with a 20% likelihood of occult disease, ultrasound or neck CT exhibits a reassuring 89%–90% negative predictive value. Anecdotally, most oncologists initially recommend serial imaging every 3–6 months for patients who choose this "watchful waiting" approach.[86]

Elective Neck Dissection ± Parotidectomy Elective neck dissection END ± parotidectomy is a first-line treatment option for patients in this category.[87] Advocates cite institutional retrospective cohort data demonstrating improved risk stratification, regional control, disease-free survival, and overall survival.[87,88]

Sentinel Lymph Node Biopsy The use of SLNB has emerged as a viable option for select high-risk HNcSCC cN0 patients.[89] Detection of pathologic nodal metastasis via SLNB facilitates precision treatment with completion neck dissection ± parotidectomy ± adjuvant radiation.[90] A negative SLNB spares the patient the morbidity of an END ± parotidectomy. Recent meta-analyses of SLNB in cSCC have demonstrated positive SLNB rates of 13.5%–13.9%, with acceptable false-omission rates of 4.6%–4.8%.[91,92]

Management of the Clinically Node-Positive Neck ± Parotid According to a population-based New Zealand cSCC registry, among 132 metastases in 104 patients, the distribution of metastases according to location was as follows: regional (87%), distant (7%), and in-transit (6%).[93] According to institutional studies, 60%–82% of patients with cervical nodal disease also exhibit parotid involvement.[11,87]

First-line treatment consists of therapeutic neck dissection ± parotidectomy ± adjuvant radiation ± chemotherapy. Primary scalp or facial tumors anterior to the external auditory canal may warrant parotidectomy, external jugular node dissection, and levels 1 to 3 neck dissection.[94–96] Some investigators argue that level 1 dissection may be omitted for lateral facial primary tumors (e.g. external ear).[95,96] Primary disease posterior to the external auditory canal (EAC) may warrant postauricular suboccipital levels 2–5 neck dissection.[94–96] Primary tumors approaching, involving, or crossing the midline generally warrant bilateral neck ± parotid management. We describe the indications for adjuvant radiation ± chemotherapy in the following discussion.

Management of In-Transit Dermal Metastasis In-transit metastases occur along the lymphatic drainage pathway from the primary cSCC to the most proximal regional nodal basin and present as discrete dermal or subcutaneous papules located more than 2 cm from the primary tumor. Evidence regarding in-transit metastasis is limited, although a strong association with immunosuppression has been noted.[97] The prognosis for these patients is poor, with multidisciplinary discussion and shared decision-making regarding treatment with curative[98] or palliative intent indicated.[97,99]

Adjuvant Radiation ± Chemotherapy in High-Risk and Very-High-Risk Cutaneous HNSCC In the absence of high-quality evidence to guide treatment intensification for patients with very-high-risk HNcSCC[100,101] oncologists have largely extrapolated treatment paradigms from phase 3 RCTs for high-risk locoregionally advanced mucosal HNSCC.[102–104] Recent publication of the Trans-Tasman Radiation Oncology Group (TROG) 05.01 study results,[105] American Society of Radiation Oncology (ASTRO) guidelines,[106] and updated NCCN guidelines[39] collectively provide the best available indications for adjuvant radiotherapy. The TROG 05.01 is the only phase 3 RCT that has evaluated adjuvant therapy for HNcSCC patients.[105] Eligible high-risk patients exhibited AJCC6 T3–T4 tumors, in-transit disease, two or more lymph nodes, a pathologic lymph node 3 cm or larger in greatest dimension, or extracapsular extension.[105] The ASTRO guidelines recommend that adjuvant radiation also be administered for "gross perineural spread" that is "clinically or radiologically apparent," close or positive margins that cannot be corrected with further surgery, recurrent disease after a previous margin-negative surgery, and desmoplastic or infiltrative tumors in the setting of chronic immunosuppression.[106] Although it agrees with the TROG 05.01 eligibility criteria, the NCCN differs slightly from ASTRO in that it favors adjuvant radiation therapy for extensive PNI or PNI involving large (≥0.1 mm) or named nerves, positive margins, or "other high-risk" features.[39]

Notably, the TROG 05.01 results established the controversial precedent that the role of adjuvant systemic therapy in HNcSCC is unclear and at best limited. The trial compared adjuvant RT ± carboplatin in high-risk HNcSCC and found no significant differences between radiation alone and concurrent chemoradiation in 5-year locoregional control (83% vs 87%), 5-year disease-free survival (67% vs 73%), or 5-year overall survival (76% vs 79%).[105] However, critics of the trial argue that the matter is not settled, maintaining that the efficacy of carboplatin is inferior to that of cisplatin[107,108] the first-line adjuvant systemic agent for mucosal HNSCC. Pointing to the comparative analysis between the mucosal HNSCC RTOG 9501 trial and European Organisation for Research and Treatment of Cancer (EORTC) 22931 trial,[102] some oncologists favor designating positive margins and ECE as indications for adjuvant chemoradiotherapy for cutaneous HNSCC patients. Ultimately, a multidisciplinary approach and shared decision-making with the patient should guide adjuvant therapy recommendations.

A Potential HNcSCC Treatment Framework We have heretofore established the lack of both population-based evidence to guide risk stratification and staging and high-quality trials to guide treatment in very-high-risk HNcSCC. Because the clinical care of these patients continues despite this lagging evidence, we offer a potential framework for the management of HNcSCC (Fig. 3) until higher-quality data to guide decision-making is available.

Management of Unresectable Locally Advanced or Recurrent/Metastatic HNcSCC The treatment options for HNcSCC patients with locally advanced (LA) or recurrent/metastatic (R/M) disease who are not eligible for curative surgery or radiation have expanded considerably. The NCCN appropriately advocates for immunotherapy or clinical trial enrollment.[39] For patients who are ineligible for both, systemic chemotherapy or EGFR inhibitors are options.[39]

Systemic Chemotherapy Cisplatin-based systemic chemotherapy, administered alone or with other cytotoxic agents, was the longstanding traditional first-line therapy for these patients.[109–112] Currently, the NCCN favors the use of cisplatin, concurrent cisplatin, and 5-fluorouracil (5-FU) or carboplatin when indicated.[39,113]

Immune Checkpoint Inhibitors Immune checkpoint inhibitors generate an antitumor response by targeting receptors including programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Phases 1 and 2 studies evaluating cemiplimab or pembrolizumab for LA or R/M cSCC patients have demonstrated response rates ranging from 34% to 50%, a response duration of 6 months or longer for 54%–68% of patients, and a 13% complete response rate.[114–116] The role of immunotherapy is limited for immunosuppressed transplant patients due to the risk of allograft rejection.[117,118]

Targeted Biologic Therapy Investigators have made substantial progress characterizing molecular alterations in patients with very-high-risk cSCC. Notably, they have highlighted the adverse prognostic significance of TP53 and KMT2D mutations,[119] mutations in novel tumor suppressors (PARD3, RASA1),[120] and four targetable gain-of-function mutations (PIK3CA, FGFR3, BRAF, and EGFR)[121], Morris et al.[122] sequenced 135 R/M head and neck tumors, of which 21 were HNcSCC and 21% exhibited potentially actionable molecular alterations. Sequencing ultimately guided therapy for 14% of these patients,[122] highlighting the potential importance of tumor genomics for patients with refractory R/M HNcSCC.

Despite a wide array of actionable molecular aberrancies in cSCC tumors,[123] most current clinical trials are trained on agents targeting the EGFR (Table 5). Earlier phase 2

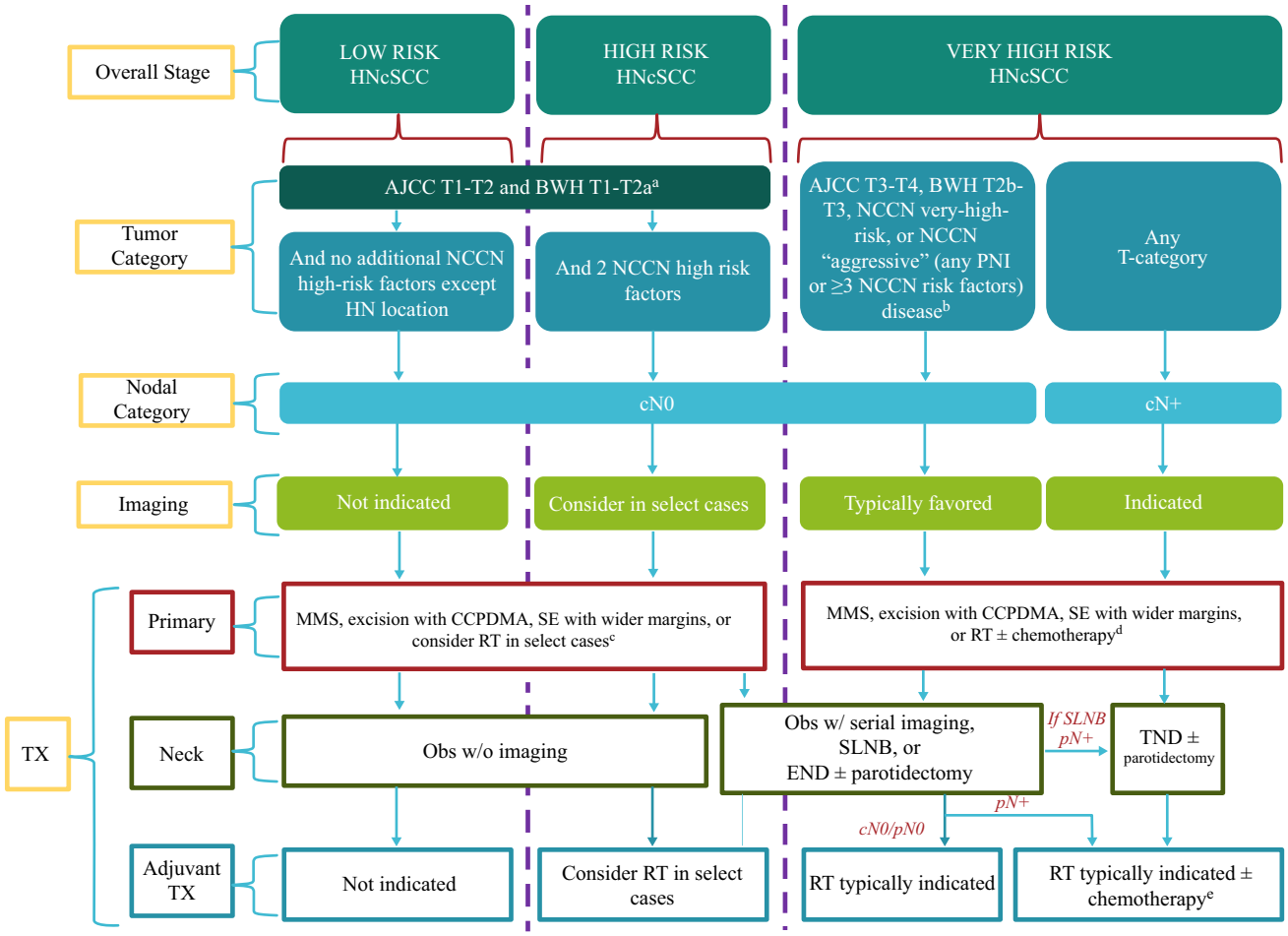

FIG. 3 Potential curative-intent treatment framework for head and neck cutaneous squamous cell carcinoma (HNcSCC) according to risk status. This proposed treatment algorithm incorporates American Joint Committee on Cancer, seventh edition (AJCC8), BWH, and NCCN risk factors to distinguish "low-risk," "high-risk," and "very-high-risk" cSCCs of the head and neck. Tumors should be assigned the highest risk designation for which they qualify. N0 AJCC8 T1–T2 and BWH T1–T2a HNcSCC is defined as "high risk" if the patient or tumor exhibits two NCCN high-risk factors and "low risk" if the head and neck location is the only NCCN high-risk factor described.[26,137] Specifically, AJCC8 T3-T4, BWH T2b-T3, NCCN very-high-risk and NCCN "aggressive" tumors or cN+ disease are designated a "very-high-risk" disease. Notably, NCCN "aggressive" tumor characteristics largely overlap with other categories with two exceptions: unqualified perineural invasion or ≥3 NCCN high-risk factors. Under this scenario, a patient with extensive perineural invasion <0.1 mm would be considered very high risk. Furthermore, an immunosuppressed patient with a recurrent <4-cm cSCC of the head or neck without other risk factors would be considered very high risk. Additionally, clinicians may consider designating cSCCs in the head and neck with one other NCCN risk factor (i.e., total of two NCCN risk factors) as high-risk HNcSCC. Within this category, select tumors may warrant consideration for treatment intensification on a case-by-case basis. Examples may include a recurrent <4-cm HNcSCC or a <4-cm HNcSCC in an immunosuppressed patient. Finally, as demonstrated by the Ruiz et al.[26] data highlighted in Fig. 2, a majority of HNcSCCs exhibit very low rates of recurrence and nodal metastases, do not warrant treatment intensification beyond surgery at the primary site, and therefore may safely be designated as "low risk". This figure graphically recapitulates the findings and recommendations described in this review. [a]NCCN high-risk features include head and neck site, poorly defined borders, any PNI (including <0.1 mm), immunosuppression, prior radiation to the site, chronic inflammatory process at the site, recurrence, and aggressive histopathologic subtype (other than desmoplastic). [b]NCCN "aggressive" tumors exhibit extension beyond cutaneous structures, perineural involvement, large [diameter], poorly differentiated [histology], or ≥3 risk factors for recurrence. [c]Definitive radiation may be considered for poor surgical candidates or when surgical resection would lead to an unacceptable cosmetic result. [d]Definitive radiotherapy + chemotherapy may be considered for poor surgical candidates when surgical resection would lead to an unacceptable cosmetic result or for unresectable disease. Irradiation of nodal basins may be considered. AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; cN0, clinically node-negative; cN+, clinically node-positive; CCPDMA, complete circumferential peripheral and deep margin assessment; cSCC, cutaneous squamous cell carcinoma; END, elective nodal dissection; LVI, lymphovascular invasion; MMS, Mohs micrographic surgery; NCCN, National Comprehensive Center Network; Obs, observation; pN0, pathologically node-negative; pN+, pathologically node-positive; RT, radiation therapy; SLNB, sentinel lymph node biopsy; TND, therapeutic neck dissection; Tx, treatment; WLE, wide local excision; W/, with; W/O, without

TABLE 5 Selected active phases 2 and 3 cutaneous squamous cell carcinoma clinical trials[a]

Study category and identifier	Sponsor	Phase	Estimated enrollment (*n*)	Eligibility	Intervention	Control	Primary outcome
Neoadjuvant therapy							
NCT03565783	M.D. Anderson Cancer Center	2	44	Recurrent stages 3 & 4 HNcSCC	Cemiplimab IV q3weeks	N/A	ORR
NCT04154943	Regeneron Pharmaceuticals	2	76	Stages 2 to 4 (M0) cSCC	Cemiplimab IV q3weeks	N/A	Pathologic CR
NCT04315701	University of Southern California	2	34	Stages 1 to 3 Recurrent or Regionally advanced, resectable cSCC	Cemiplimab IV q3weeks	N/A	Pathologic PR
Adjuvant therapy							
NCT01979211	University of Cincinnati	2	40	Clinical stage ≥T3 or ≥N1, M0 cSCC	Surgery + PORT + cetuximab IV	N/A	LRR
NCT03833167	Merck Sharp & Dohme Corp.	3	570	High-risk cSCC	Surgery + PORT + pembrolizumab IV q6weeks	Surgery + PORT + placebo	RFS
NCT03969004	Regeneron Pharmaceuticals	3	412	High-risk cSCC	Surgery + PORT + cemiplimab IV q3weeks	Surgery + PORT + placebo	DFS
Systemic/palliative							
NCT01198028	M.D. Anderson Cancer Center	2	333	R/M cSCC	Erlotinib PO daily	N/A	ORR
NCT02721732	M.D. Anderson Cancer Center	2	11	Unresectable cSCC	Pembrolizumab IV q3weeks	N/A	Non-progression rate and incidence of AE
NCT02760498	Regeneron Pharmaceuticals	2	266	Unresectable LA/M cSCC	Cemiplimab IV q2weeks	N/A	ORR
NCT03082534	Assuntina G. Sacco	2	83	R/M cSCC	Pembrolizumab IV q3week with cetuximab IV q1week	N/A	ORR
NCT03108131	M.D. Anderson Cancer Center	2	60	Advanced tumors including cSCC	Cobimetinib PO daily for 3 weeks + atezolizumab IV q2weeks	N/A	ORR
NCT03284424	Merck Sharp & Dohme Corp.	2	150	Unresectable LA or R/M cSCC	Pembrolizumab IV q3weeks	N/A	ORR
NCT03737721	AHS Cancer Control Alberta	2	20	Unresectable stages 1 to 4 (M0) cSCC	Avelumab IV q2weeks + RT 63-66Gy/30fx	N/A	ORR
NCT03944941	Alliance for Clinical Trials in Oncology	2	59	Unresectable LA/M cSCC	Avelumab IV q2weeks + cetuximab IV q1week	Avelumab Monotherapy IV q2weeks	PFS
NCT04204837	Salzburger Landeskliniken	2	31	Unresectable LA/M cSCC	Nivolumab IV q2weeks	N/A	ORR
Intratumoral							
NCT03714828	University of Arizona/ Amgen	2	28	Low-risk cSCC	Talimogene laherparepvec (TVEC) IT injection at baseline, 3, 5, 7 weeks	N/A	ORR
NCT04362722	Philogen S.p.A.	2	40	Localized cSCC	L19IL2/L19TNF IT Injection q1week	N/A	ORR

TABLE 5 continued[a]

Study category and identifier	Sponsor	Phase	Estimated enrollment (*n*)	Eligibility	Intervention	Control	Primary outcome
Systemic + intratumoral							
NCT02955290	Roswell Park Cancer Institute	1/2	181	Advanced HNcSCC	CIMAvax IM and Nivolumab IV q2weeks	N/A	Dose limiting toxicity and OS
NCT03684785	Exicure, Inc.	1b/2	130	Advanced HNcSCC	Cavrotolimod IT and Cemiplimab IV	N/A	Incidence of AE and ORR
NCT04050436	Replimune Inc.	2	240	Unresectable LA/M cSCC	Cemiplimab IV q3weeks + RP1 IT injection	Cemiplimab Monotherapy IV q3weeks	ORR
NCT02978625	National Cancer Institute (NCI)	2	68	Treatment-refractory or advanced/ unresectable cSCC	Talimogene laherparepvec (TVEC) IT injection	N/A	ORR
Immunocompromised populations							
NCT04242173	H. Lee Moffitt Cancer Center and Research Institute	2	27	Immunocompromised (HIV or hematologic malignancies) patients with Unresectable LA/M cSCC	Cemiplimab IV q3weeks	N/A	ORR
NCT04329221	Massachusetts General Hospital	2	62	OTR with actinic keratosis and a history of non-melanoma skin cancer	Topical Calcipotriol + 5-FU cream to face, scalp, upper extremities BID for 6 days	Topical Vaseline & 5-FU to face, scalp, upper extremities BID for 6 days	Proportion of OTR patients with new cSCC on treated anatomic sites
Phototherapy + immunotherapy							
NCT04305795	Rakuten Medical, Inc.	1b/2	54	Unresectable LA or R/M cSCC	ASP-1929 Photoimmunotherapy + pembrolizumab IV q 3weeks	N/A	ORR

[a]Immune checkpoint therapy inludes inhibitors targeting PD-1 receptors (cemiplimab, nivolumab, pembrolizumab), PD-L1 (durvalumab, avelumab, atezolizumab), and CTLA-4 receptors (ipilimumab); Other biologic therapies targeting cell signaling pathways include: EGFR (cetuximab, erlotinib, gefitinib), MEK (cobimetinib), recombinant EGF-rP53K/montanide ISA51 vaccine (recombinant EGF-rP53K/montanide ISA51 vaccine), and TLR9 agonist (cavrotolimod); green font signifies oncolytic viruses: genetically-modified HSV-1 (talimogene laherparepvec, RP1).

AE, adverse events; BID, twice daily; CR, complete response; cSCC, cutaneous squamous cell carcinoma; DFS, disease-free survival; 5-FU, 5-fluorouracil; Fx, fraction; Gy, gray; HNcSCC, head and neck cutaneous squamous cell carcinoma; IM, intramuscular; IT, intratumoral; IV, intravenous; LA, locally-advanced disease; LRR, local recurrence rate; M, metastatic disease; N/A, not available; ORR, overall response rate; OTR, organ transplant recipients; PFS, progression-free survival; PO, per os/by mouth; PORT, postoperative radiation therapy; PR, partial response; q, every; R, recurrent disease; RFS, recurrence-free survival; RT, radiation therapy; RFS, recurrence-free survival

trials highlighted their promise that anti-EGFR monoclonal antibodies including cetuximab, panitumumab, erlotinib, and gefitinib have demonstrated overall response rates of 28%,[124] 31%,[125] 10%,[126] and 16%,[127] respectively. Current studies are testing EGFR inhibitors alone, in combination with traditional oncologic therapies, and in combination with immune checkpoint inhibitors (Table 5). Trials investigating other targeted biologic therapies, such as cobimetinib, a MEK inhibitor, also are underway (Table 5).

Other Selected Investigational Therapies Investigators also are evaluating an array of novel therapies including intra-tumoral agents and photodynamic therapy (PDT). Oncolytic viruses are genetically modified to "launch a multipronged attack" on cancer cells by entering, replicating, and lysing tumor cells, and also by releasing local inflammatory signals and tumor antigens.[128] Notwithstanding a recent negative mucosal SCC study,[129] cSCC trials evaluating talimogene laherparepvec (T-VEC) and RP1 (genetically-modified herpes viruses) are ongoing (Table 5).[130,131] Another study is investigating intratumoral cavrotolimod (an immunogenic toll-like receptor 9 [TLR9] agonist that activates CD4+ T cells) in combination with systemic cemiplimab.[132] Still another trial is evaluating systemic nivolumab in combination with the intratumoral CIMAvax-EGF therapeutic vaccine, which consists of recombinant EGF-conjugated adjuvant immunogenic proteins (rP64K, montanide ISA 51).

Photodynamic therapy (PDT), applied in oncology for more than a century[133] is an established second-line treatment option for actinic keratoses and early-stage NMSCs.[134–136] The PDT procedure involves administration of a photosensitizing agent, which localizes to a target cell or tissue, followed by a specific wavelength of light to generate reactive oxygen species and indiscriminately kill nearby cells.[133] One ongoing cSCC trial is evaluating ASP-1929, an intravenously administered antibody drug conjugate of cetuximab and IRDye 700 (a light-activatable dye).

CONCLUSION

Our inadequate understanding of the distribution and determinants of HNcSCC and failure to rigorously evaluate curative interventions constrain control of the disease. Population-based registries tracking current adverse risk factors and outcomes are needed to guide risk stratification and development of improved staging systems. Comprehensive biopsy reporting and establishment of clear indications for imaging will facilitate accurate staging, and consequently, precision treatment. Design and development of RCTs are needed to assess treatment of the very-high-risk HNcSCC cN0 neck, indications for adjuvant (chemo)radiation, and the role of immune checkpoint inhibitors for very-high-risk HNcSCC managed with curative intent.

APPENDIX

See Tables 6 and 7

TABLE 6 Detailed cutaneous squamous cell carcinoma (cSCC) primary tumor high-risk features or upstaging criteria according to staging systems and risk stratification data[a]

Category	High-Risk Feature or Upstaging Criteria (Beyond T1N0)	Staging/Risk Stratification Systems					Meta-Analytic Data					
		NCCN		AJCC 7th Ed	AJCC 8th Ed	BWH	Thompson et al					
							Recurrence		Metastases		Disease-Specific Death	
		HR	VHR				RR>1*	RR>5 *	RR>1 *	RR>5 *	RR>1 *	RR>5 *
Clinical Tumor	*Location*	■		■			■		■		■	
	Head, neck, hands, feet, anogenital, pretibia	■										
	- Temple	■					■		■		--[c]	
	- Ear	■		■			--[c]		■		■	
	- Lip	■		■			--[c]		■		■	
	- Cheek	■							--[c]			
	Other trunk or extremity											
Unspecified	*Size/diameter/location*			■	■	■	■		■	■	■	■
	Any size: head, neck, hands, feet, anogenital, pretibia	■										
	≥ 2- <4 cm, trunk or extremity	■										
	≥ 2 cm				■	■						
	> 2 cm			■			■		■	■	■	■
	≥ 4 cm		■		■							
Pathologic Tumor	*Grade/differentiation*			■		■	■		■		■	■
	Poorly-differentiated grade		■	■		■	■		■		■	■
	Undifferentiated grade			■								
	Depth of invasion			■	■	■	■	■	■	■	■	
	Clark level[a] ≥ IV			■								
	> 2 mm Breslow depth/thickness[b]			■			■	■	■	■		
	> 6 mm Breslow depth/thickness[b]						■	■	■	■		
	> 6 mm: granular layer adjacent dermis to base of tumor		■		■							
	Invasion beyond subcutaneous fat		■		■	■	■	■	■	■	■	
	Perineural invasion			■	■	■	■		■			
	Perineural involvement/invasion, unspecified			■			■		■		■	
	Tumor cells within nerve sheath of nerve deeper than dermis		■		■							
	Invasion of nerve ≥ 0.1 mm in caliber		■		■	■						
	Lymphatic or vascular invasion		■									
	Invasion of bony structures			■	■	■						
	Unspecified					■						
	Minor, unspecified				■							
	Gross cortical bone/marrow invasion, unspecified				■							
	Maxilla, mandible, orbit, temporal bone			■								
	Axial or appendicular skeleton			■								
	Skull base				■							
	Skull base foramen				■							
	Skull base, perineural invasion			■								

Legend: AJCC: American Joint Committee on Cancer; BWH: Brigham and Women's Hospital; cTumor: clinical tumor; Ed: edition; NCCN: National Comprehensive Cancer Network; pTumor: pathologic tumor; RR: risk ratio;*: significant ($p<0.05$);

[a]: Clark levels - cancer involves the: I: epidermis only; II: papillary dermis; III: papillary dermis and papillary-reticular dermal interface; IV: reticular dermis; V: subcutaneous tissue (NCI Dictionary)

[b]: Breslow depth/thickness: top of the tumor to the deepest tumor cells and if ulcerated, base of the ulcer to the deepest tumor cells

--[c]: high-risk feature tested and was not significant; empty box: high-risk feature NOT included in the staging or risk-stratification system/study; grey box: high-risk feature included in the staging or risk-stratification system/study

Caption: This table comprehensively describes the different clinical and pathologic risk factors for adverse oncologic outcomes incorporated by the NCCN, AJCC7, ACCJ8 and BWH staging systems. We also compare these to the results of the meta-analysis conducted by Thompson et al.

TABLE 7 High-risk features unique to the NCCN risk-stratification system and evidence from selected studies[a]

Category	Unique NCCN High-Risk Feature	Outcomes from Selected Studies (RR/OR/HR)								
		Recurrence			Metastases			Disease-Specific Death		
		>1-1.9	2-5	>5	>1-1.9	2-5	>5	>1-1.9	2-5	>5
Clinical	Immunosuppression	--[f]	--[f]	--[f]	MA[29]			--[f]	--[f]	--[f]
	Prior radiation to site									
	Chronic inflammatory process at site	PSI[47]								
	Neurologic symptoms									
Clinical	*Location*									
Tumor	Area H: Mask areas of the face [b]									
	Temple alone		MA[29]			MA[29]		--[f]	--[f]	--[f]
	Ear alone	--[f]	--[f]	--[f]		MA[29]			MA[29]	
	Lip alone	--[f]	--[f]	--[f]		MA[29]			MA[29]	
	Nose alone	--[f]	--[f]	--[f]						
	Any mask area of the face[c]		RSI[45]							
	Area M: Cheeks, forehead, scalp, neck									
	Cheek alone				--[f]	--[f]	--[f]			
	Any medium-risk location[d]	--[f]	--[f]	--[f]						
	Poorly-defined borders									
	Recurrent		PSI[46]							
Pathologic	*Adverse histopathologic subtypes* [e]									
	Acantholytic (adenoid) alone									
	Adenosquamous alone									
	Desmoplastic alone						RMI[43]			
	Metaplastic (carcinosarcomatous) alone									
	Lymphovascular invasion									
	Lymphatic invasion alone									
	Vascular invasion alone							RMI[43]		
	Lymphatic or vascular invasion	-					RMI[42]			RMI[42]
	Lymphatic and vascular invasion			RSI[44]						

Abbreviations: Hazard Ratio (HR); Meta-analysis (MA); Retrospective Multi-institution (RMI); Retrospective Single-Institution (RSI);Risk Ratio (RR); Odds Ratio (OR); Prospective Single-Institution (PSI)
[a]Displays the design of the selected study reporting significant association between the corresponding high-risk feature and outcome
[b]: central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear;
[c]Describes periorbital area as a mask area
[d]Describes neck as a medium-risk area
[e]: acantholytic/adenoid, adenosquamous, desmoplastic, metaplastic/carcinosarcomatous subtypes
--[f]: high-risk feature tested and was not significant
empty box: high-risk feature NOT included in the staging or risk-stratification system/study
grey box: high-risk feature included in the staging or risk-stratification system/study
Caption: This table demonstrates all available evidence providing regression or meta-analytical data that demonstrates significance of these unique NCCN high-risk features and a corresponding RR, OR, or HR. Many of the available evidence stems from prospective and retrospective single and multi-institutional studies; while this available evidence holds great merit, further investigation to verify these data is warranted.

DISCLOSURE There is no conflicts of interest.

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