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CLINICAL REVIEW

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Adjuvant therapy for high-risk cutaneous squamous cell carcinoma: 10-year review

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Abstract

Standard of care for high-risk cutaneous squamous cell carcinoma (cSCC) is surgical excision of the primary lesion with clear margins when possible, and additional resection of positive margins when feasible. Even with negative margins, certain high-risk factors warrant consideration of adjuvant therapy. However, which patients might benefit from adjuvant therapy is unclear, and supporting evidence is conflicting and limited to mostly small retrospective cohorts. Here, we review literature from the last decade regarding adjuvant radiation therapy and systemic therapy in high-risk cSCC, including recent and current trials and the role of immune checkpoint inhibitors. We demonstrate evidence gaps in adjuvant therapy for high-risk cSCC and the need for prognostic tools, such as gene expression profiling, to guide patient selection. More large-cohort clinical studies are needed for collecting high-quality, evidence-based data for determining which patients with high-risk cSCC may benefit from adjuvant therapy and which therapy is most appropriate for patient management.

KEYWORDS

adjuvant chemotherapy, adjuvant radiation therapy, cutaneous squamous cell carcinoma, immunotherapy, targeted therapy

1 | INTRODUCTION

While the majority of high-risk cutaneous squamous cell carcinoma (cSCC) tumors are resectable with clear margins by standard excision, wide local excision (WLE), or Mohs micrographic surgery (MMS), some are seen with high-risk factors that may warrant adjuvant treatment.[1–7] These high-risk factors are often associated with more aggressive cancer growth, which can lead to recurrence, metastasis, and disease-specific death (DSD).[1,8] Tumors located in the head and neck area account for more than 50% of new cSCC lesions,[9,10] are considered high risk by the National Comprehensive Cancer Network (NCCN) if located in the mask area of the face at any size or if located in other areas of the head and neck at ≥1 cm,[7] and pose unique challenges for surgical resection and treatment. The NCCN guidelines; as well as the American Joint Committee on Cancer (AJCC) Cancer Staging

Manual, Eighth Edition (AJCC8); Union for International Cancer Control (UICC), Eighth Edition; and Brigham and Women's Hospital (BWH) staging systems, use clinicopathologic features of the primary tumor to categorize risk of poor outcomes in cSCC.[7,11–15] The AJCC8, UICC, and BWH systems incorporate high-risk factors into tumor (T) classifications, while the NCCN guidelines define "high-risk" as having at least one high-risk factor.

Certain individuals are at higher risk for cSCC and aggressive recurrent or metastatic tumors due to additional risk factors, such as immunosuppression (e.g., organ transplant recipients [OTRs] and patients with autoimmune disorders), cumulative ultraviolet (UV) exposure, and history of previous skin cancer.[7,8] Given the high and growing incidence of cSCC,[7,8,16–18] the percentage of patients with cSCC who develop recurrence and/or metastasis corresponds to a substantial number of individuals who would benefit from more accurate prognosis for better-informed decision-making regarding follow-up and adjuvant treatment.[5,7,17,19–22] These high-risk patients may require more intensified management plans,[2,23–27] which often include adjuvant radiation therapy (ART) and/or systemic therapy (e.g., chemotherapy, immunotherapy, and/or targeted therapy). Thus, there is an unmet clinical need for improved prognostication to guide decision making by physicians and their patients with high-risk cSCC regarding adjuvant therapy and/or clinical trials involving these adjuvant treatment modalities.[7,23] Tumor-specific prognostic tools, such as molecular biomarker assays and gene expression profiling, have shown utility for guiding decisions on patient management in various types of cancer.[28–39] A recently validated, clinically available, 40-gene expression profile (40-GEP) test that identifies patients with cSCC at low, moderate, and high risk for developing metastasis[26] has clinical application for guiding management intensity decisions.[23] This test could potentially be used to determine which patients would most likely benefit from adjuvant therapy and warrants further investigation in this setting.

In this review, we discuss evidence-based research findings and key reports from the last 10 years which describe the possible roles for adjuvant radiation, chemotherapy, immunotherapy, and/or targeted therapy in the management of high-risk cSCC. Studies impacting current management guidelines are highlighted, including those involving adjuvant treatments in phases I, II, or III clinical trials. The requirements for and efficacy of adjuvant therapies in cSCC are unclear, and the gap in evidence for practice decisions regarding adjuvant therapy in patients with high-risk cSCC has been apparent for more than a decade.[40–42] Thus, further prospective clinical studies with large cohorts are needed for gathering high-quality data to (1) determine which patients with high-risk cSCC might benefit most from particular types of adjuvant therapy and (2) formulate more personalized, evidence-based patient management strategies for high-risk cSCC. Here, we describe different modalities of adjuvant therapy for cSCC, provide recent literature substantiating the clinical need for more high-level data, and discuss current guideline recommendations and ongoing clinical trials for these treatment modalities in cSCC.

1.1 | Adjuvant radiation therapy

Radiation therapy (RT) uses ionizing radiation to treat sites of high-risk cSCC tumors (Table 1). RT often uses photons in the form of external beam radiation therapy (EBRT)[43] delivered with either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated RT (IMRT) techniques, the latter of which can reduce doses to critical organs beyond the target in complex high-risk cases.[44–46] Orthovoltage or electron beam RT techniques are commonly utilized for superficial targets.[47,48] Protons can also be utilized in the form of proton beam RT (PBRT), which delivers even lower doses to tissue beyond the target and, thus, may have less toxic effects.[45,49,50] RT is usually administered following surgical excision (adjuvantly) and is not usually recommended as monotherapy or definitive treatment in resectable high-risk cSCC.[7,51] However, RT may be recommended as primary treatment (curative setting, or burden management and/or palliative setting) for nonsurgical candidates, in cases where adequate surgical resection may cause anatomically dysfunctional or cosmetically unfavorable outcomes, and/or when patients refuse surgical intervention.[7,40,51]

In the adjuvant setting, RT is used in high-risk cSCC to reduce the likelihood of recurrence and metastasis after surgical excision (Table 1).[51–53] Adjuvant RT (ART), also known as postoperative RT (PORT), may be used to treat the primary tumor site and/or high-risk or positive lymph nodes. More specifically, ART may be used to treat high-risk tumor sites having clear margins, as salvage therapy when tumor resections are incomplete, as elective treatment for sentinel and regional lymph nodes (LNs) having no clinical or radiographic evidence of metastasis, to treat positive lymph node (LN) basins in regional disease, and to treat patients with perineural invasion (PNI).[7] Historically, patients with PNI from cutaneous carcinomas (i.e., cSCC and basal cell carcinoma [BCC]) have been reported to benefit from RT and ART; however, outcomes were better for BCC versus cSCC and needs for improvement in local treatment were noted.[54–57] Other high-risk factors

TABLE 1 Overview of adjuvant therapy options for treatment of high-risk cSCC

Adjuvant therapy	Description	References
Radiation therapy	Radiation (often EBRT with 3D-CRT or IMRT, orthovoltage or electron beam RT, or PBRT) to sites of high-risk tumors following surgical excision with clear margins to reduce risk of recurrence and metastasis, or following incomplete surgical resection as salvage therapy, and/or as elective therapy to sentinel LN and regional LNs. Adjuvant RT (ART) may be used to treat positive LNs and/or patients with PNI or other high-risk factors	7,43–53
Chemotherapy	Systemic therapy via oral or intravenous routes using one or more anticancer drugs (e.g., cisplatin, carboplatin, oxaliplatin, 5-FU, and vinca alkaloids) to kill or slow growth of any rapidly growing and dividing cancer cells that may remain after surgery and/or RT. Chemotherapy may be combined with ART (ACRT)	7,43,51,83
Immunotherapy and targeted therapy	Systemic therapy via small molecules (e.g., mAbs, cytokines, or other proteins or chemicals) that target certain cells, parts of cells, or immune system mechanisms (e.g., receptors or ligands) to help stimulate or suppress the immune system to fight cancer. Immunotherapy and targeted therapy are usually delivered intravenously; however, some therapeutics targeting specific cancer cells may be given orally. Immune checkpoint inhibitors and EGFR inhibitors are commonly used. Immunotherapy and/or targeted therapy may be used in the adjuvant setting, and have predominantly been used within the context of clinical trials. Local immunotherapies (e.g., oncolytic viruses) are also under investigation, as are first-line and neoadjuvant immunotherapies	7,43,45,92–98
Clinical trials	Recent clinical phases I, II, or III trials have tested or are testing concurrent ART and chemotherapy (ACRT) versus ART in high-risk cSCC, as well as systemic therapy using immune checkpoint inhibitors and/or EGFR inhibitors or other immune modulators in adjuvant and neoadjuvant settings	7,43,82,85,94–98,104,105,113–117

Note: Adjuvant treatment options following current standard-of-care surgical treatment for high-risk cSCC.
Abbreviations: ACRT, adjuvant chemotherapy plus adjuvant radiation therapy (adjuvant chemoradiotherapy); ART, adjuvant radiation therapy; cSCC, cutaneous squamous cell carcinoma; 3D-CRT, three-dimensional conformal radiotherapy; EBRT, external beam radiation therapy; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil (antimetabolite); IMRT, intensity-modulated radiation therapy; LN, lymph node; LNs, lymph nodes; mAbs, monoclonal antibodies; PBRT, proton beam radiation therapy; PNI, perineural invasion; RT, radiation therapy.

may exist for an individual patient that would be considered indication for the use of ART, including involvement of multiple LNs and/or extracapsular extension (ECE, also known as extranodal extension [ENE]); recurrent disease; lymphovascular invasion; and large, deeply infiltrative tumors. Below, we describe several recent studies of ART for cSCC, including the study type, cohort characteristics, and patient outcomes.

1.1.1 | Recent studies: Adjuvant radiation therapy

Most of the studies from the last 10 years have been retrospective in design and relatively small in sample size (Table 2). Results have been variable, providing low-level evidence, and controversies remain regarding ART. Even studies spanning the last 20–40 years on this topic have been mostly retrospective and included small sample sizes or case reports.[58–60] One exception is a prospective, multisite study by Leibovitch et al.[61] of 1177 patients with cSCC monitored by the Skin and Cancer Foundation of Australia. However, only patients with PNI ($n = 70$) were considered for ART, and the actual sample size receiving ART was small ($n = 37$). For patients followed for 5 years (PNI, $n = 25$; no PNI, $n = 311$), the authors reported a recurrence rate of 8% and 4% for patients with and without PNI, respectively ($p = 0.02$). However, they did not specify whether all patients with PNI and who were followed for 5 years received ART and, thus, did not report direct comparisons between patients receiving and not receiving ART.[61]

TABLE 2 Studies evaluating adjuvant therapy, immunotherapy, and/or targeted therapy for cSCC during the last 10 years

Study[a]	Study type	Multi- or single-site	No. of patients	Cohort characteristics	Findings
Improvement with ART					
Stevenson et al.[62]	Retrospective	Single	31	cSCC with negative surgical margins and PNI	Patients receiving MMS plus ART did not develop nodal metastasis, while all patients who developed nodal metastasis had MMS without ART ($p = 0.02$). Five-year DFS was significantly higher for patients having MMS plus ART vs. MMS alone ($p = 0.01$)
Miller et al.[63]	Retrospective	Single	32	cSCC with negative surgical margins	Surgical resection plus ART for BWH T2b-T3 tumors resulted in DFS for 91% of patients at last f/u or death
Harris et al.[64]	Retrospective	Multi	349	Advanced HNcSCC	OS and DFS were improved with surgery plus ART compared to surgery alone in patients with HNcSCC with PNI and/or regional disease
Coombs et al.[65]	Retrospective	Single	63	HNcSCC with metastasis to parotid gland	Patients receiving surgery plus ART had significantly higher 5-year DFS compared with patients treated with surgery alone (84% vs. 48%, respectively, $p = 0.008$)
Sapir et al.[66]	Retrospective	Single	30	HNcSCC with extensive PNI	Patients receiving surgery plus ART had significantly higher DFS compared with patients receiving surgery and observation only (73% vs. 40%, respectively, $p = 0.05$)
Kadakia et al.[67]	Retrospective	Single	53	HNcSCC of scalp, immune compromised	Patients receiving surgery plus ART had higher 3-year DFS and OS compared with patients receiving surgery alone (80% and 62% vs. 62.5% and 37.5%, respectively)
Wray et al.[68]	Retrospective	Single	71	cSCC of face, ears, and scalp	Elective ART to sentinel LNs in high-risk cSCC of the face, ears, and scalp provided regional control for 96% of patients at 5 years post-treatment, with 0% developing grade 3+ toxicity (patients had no previous regional LN surgery or evidence of LN metastasis)
Wang et al.[69]	Retrospective	Single	122	HNcSCC with cervical LN involvement	Surgery alone was compared with surgery plus ART; 55% compared with 23% of patients developed recurrence, respectively. DFS and OS were significantly improved with surgery plus ART ($p = 0.001$ and $p = 0.003$, respectively). Improved DFS was significantly associated with no ECE
Givi et al.[70]	Retrospective	Single	51	HNcSCC with metastasis to LNs of head and neck	Surgery alone was compared with surgery plus ART; OS was significantly improved with ART ($p = 0.002$)
Strassen et al.[73]	Retrospective	Single	67	Recurrent HNcSCC	Patients who received ART had significantly higher 5-year RFS and OS rates compared with patients who did not receive ART ($p = 0.02$ and $p < 0.05$)

(Continues)

TABLE 2 (Continued)

Study[a]	Study type	Multi- or single-site	No. of patients	Cohort characteristics	Findings
No improvement with ART or ACRT					
Ruiz et al.[75]	Retrospective	Single	62	cSCC with negative surgical margins, LN-negative	Surgery alone was compared to surgery plus ART; no significant differences were found in local recurrence, metastasis, or DSD rates
Trosman et al.[76]	Retrospective	Single	104	Advanced HNcSCC	Surgery alone was compared to surgery plus ART or plus ACRT; no significant differences were found in 2-year DFS
Amoils et al.[77]	Retrospective	Single	80	HNcSCC with metastasis to LNs	Surgery alone was compared to surgery plus ART or plus ACRT; no significant differences were found in 3-year OS. Decreased OS was significantly associated with primary tumor >2 cm and ECE ($p = 0.03$ and $p = 0.01$, respectively)
Improvement with ACRT versus *ART*					
Tanvetyanon et al.[86]	Retrospective	Single	61	High-risk HNcSCC with metastasis to LNs (≥2 LNs), ECE, or positive margins	ACRT was compared to ART alone (no comparisons to surgery alone were reported). Median RFS was higher for patients given ACRT versus patients given ART (40.3 versus 15.4 months, respectively); risk of recurrence was significantly reduced with ACRT (HR 0.31, $p = 0.01$)
No improvement with ACRT versus *ART*					
Porceddu et al.[82]	Prospective, phase III	Multi	321	Advanced HNcSCC	When ART was compared to ACRT (no comparisons to surgery alone were reported), no significant differences were found in DFS or OS. 2- and 5-year FFLRR rates were 88% and 83% for ART and 89% and 87% for ACRT, respectively. Carboplatin did not enhance ART toxicity
No improvement with adjuvant chemotherapy or targeted therapy plus ART versus *ART*					
Goyal et al.[91]	Retrospective	Single	32	Locally advanced HNcSCC	Systemic therapy (chemotherapy or targeted therapy) given concurrently with ART was compared to ART alone (no comparisons to surgery alone were reported). No significant differences were found in LRC, DC, or PFS. Median OS was significantly lower and risk of death was significantly higher for patients treated with systemic therapy plus ART ($p = 0.03$ and $p = 0.04$, respectively)
Improvement with immunotherapy or targeted therapy					
Migden et al.[98]	Prospective, phase II	Multi	78	Locally advanced cSCC without metastasis	Single-arm study of cemiplimab (3 mg/kg every 2 weeks) demonstrated an objective (complete or partial) response in 44% of the cohort; 13% complete and 31% partial response. Hypertension (8%) and pneumonia (5%) were the most common AEs

TABLE 2 (Continued)

Study[a]	Study type	Multi- or single-site	No. of patients	Cohort characteristics	Findings
Migden et al.[94]	Prospective, phase II	Multi	59	Metastatic cSCC	Metastatic disease cohort to determine tumor response, clinical benefit (OS and PFS), and duration of response to cemiplimab (3 mg/kg every 2 weeks). Tumor response was 47% and durable DC was 61% of the cohort. Diarrhea (27%) and fatigue (24%) were the most common AEs in the cohort
	Prospective, phase I	Multi	26	Locally advanced or metastatic cSCC	Expansion cohort to determine tumor response, safety, and side-effect profile of cemiplimab (3 mg/kg every 2 weeks). Tumor response was 50%, durable DC was 65%, and fatigue was the most common AE in 27% of the cohort
Rischin et al.[110]	Prospective, phase II	Multi	115	Metastatic cSCC	Cemiplimab produced substantial antitumor activity and durable response with acceptable safety profiles in weight-based (3 mg/kg every 2 weeks) and fixed (350 mg every 3 weeks) dosing cohorts with metastatic cSCC
Gross et al.[111]	Prospective, phase II	Multi	20	Locally advanced or metastatic cSCC	Neoadjuvant cemiplimab was well tolerated in stage III/IV (M0) (AJCC8) HNcSCC, with ORR of 30% and pathologic complete response and major pathology response rates of 55% and 15%, respectively
Grob et al.[112]	Prospective, phase II	Multi	105	Locally recurrent and/or metastatic cSCC	R/M cohort to determine efficacy and safety of pembrolizumab. ORR was 34%, DC was 52%, median PFS was 6.9 months, and median response duration (range, 2.7–13.1 +) and median OS were not reached. Common AEs were fatigue, asthenia, pruritus, pain, diarrhea, nausea
Maubec et al.[104]	Prospective, phase II	Multi	36	Locally advanced or metastatic cSCC	EGFR inhibitor (cetuximab) studied in unresectable cohort to evaluate efficacy and safety. DC was 69% at 6 weeks. AEs were acne-like rash (grade 1–2) in 78% of patients, and grade 3–4 reactions in three patients; no AE-related deaths. OS was 8.1 months, median PFS was 4.1 months
Lewis et al.[105]	Prospective, phase II	Single	22	Aggressive or recurrent cSCC	EGFR inhibitor (gefitinib) studied in the neoadjuvant and adjuvant setting to determine response rate (45.5% overall to neoadjuvant induction); 2-year OS (72.1%), DSS (72.1%), and PFS (63.6%; and toxicity (grade 1–3). Diarrhea, fatigue, rash, and nausea were the most common AEs. Study was terminated after first stage due to progressive disease rate (31.7%)

Abbreviations: ACRT, adjuvant chemotherapy plus adjuvant radiation therapy (adjuvant chemoradiotherapy); AE, adverse event; AEs, adverse events; AJCC8, American Joint Committee on Cancer Staging Manual, Eighth Edition; ART, adjuvant radiation therapy; BWH, Brigham and Women's Hospital; cSCC, cutaneous squamous cell carcinoma; DC, disease control; DFS, disease-free survival; DSD, disease-specific death; DSS, disease-specific survival; ECE, extracapsular extension (or spread, also known as extranodal extension [ENE]); EGFR, epidermal growth factor receptor; FFLRR, freedom from locoregional relapse; f/u, follow-up; HNcSCC, cSCC of the head and neck; LN, lymph node; LNs, lymph nodes; LRC, local regional control; MMS, Mohs micrographic surgery; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PNI, perineural invasion; RFS, recurrence-free survival; R/M, recurrent and/or metastatic.

[a]The studies are listed in order of mention in the text and by outcome findings per treatment modality.

Recently, Stevenson et al.[62] reported findings from a retrospective study of patients with cSCC with PNI ($n = 31$) (Table 2). The majority (71%) of the cohort had large-caliber PNI, while the remainder had small-caliber PNI plus other high-risk features. All patients were recommended for ART, although 16 refused the adjuvant treatment. The authors found a significant difference in the presence of nodal metastasis when comparing patients treated with MMS alone versus MMS plus ART to the local tumor site. All five patients who developed nodal metastasis did not receive ART, and none who received both MMS and ART developed nodal metastasis ($p = 0.02$). Four of the five cases with nodal metastasis had a BWH T2b and one had a BWH T3 primary tumor. The 5-year DFS rate was significantly greater for patients treated with MMS plus ART versus MMS alone ($p = 0.01$). There were no local recurrences in either group at 5 years of follow-up.

Miller et al. also reported results from a single-center retrospective analysis of clinical outcomes of patients with cSCC ($n = 32$) (Table 2).[63] Patients were treated with either MMS or WLE (with clear margins) plus ART. They found no evidence of local recurrence, LN metastasis, or DSD for 91% of the cohort at last follow-up or death (mean 4.96 years). Three patients had recurrence (all >2 cm in diameter, poorly differentiated, with PNI, and Brigham and Women's Hospital [BWH] T2b-T3 classification), and two of these resulted in DSD. Despite the study limitations, including small cohort size, lack of a control group, some undocumented deaths, and the fact that 28 of the 32 patients were BWH T2b-T3, the authors conclude that ART after surgical resection with clear margins is a reasonable treatment option for patients with BWH T2b-T3 tumors.

In another retrospective study with a larger, multisite cohort of patients ($n = 349$) with advanced cSCC of the head and neck (HNcSCC), Harris et al.[64] found via multivariate analysis that ART postsurgery was associated with improved overall survival (OS) for the whole cohort. They also found that patients with PNI and/or regional disease had improved OS and disease-free survival (DFS) when treated with surgery plus ART relative to surgery alone (Table 2).[64] Coombs et al. performed a retrospective analysis of patients ($n = 63$) who had HNcSCC with metastasis to the parotid gland.[65] They found that patients receiving surgery plus ART had a significantly higher 5-year DFS rate compared with patients who were treated with surgery alone (84% vs. 48%, respectively, $p = 0.008$). For a retrospective subcohort of patients ($n = 30$) with HNcSCC and microscopic extensive PNI (MEPNI; >2 nerves involved) which involved large-caliber (≥0.1 mm) nerves in several cases, Sapir et al.[66] reported that patients receiving surgery plus ART (delivered to the skin tumor bed, involved nerves, and ipsilateral LNs [$n = 19$]) had significantly higher 2-year DFS rates compared with patients receiving surgery plus observation only (73% vs. 40%, respectively, $p = 0.05$). In the same study, no significant benefit was observed from ART in another HNcSCC subcohort ($n = 37$) having microscopic focal PNI (MFPNI; 1–2 nerves involved) and involving only small-caliber nerves.[66]

In a retrospective cohort ($n = 53$) of immunocompromised patients with HNcSCC of the scalp, Kadakia et al. reported that patients receiving surgery plus ART had higher 3-year DFS and OS compared with those having only surgical intervention (80% and 62% vs. 62.5% and 37.5%, respectively; Table 2).[67] Patients were OTRs, had chronic lymphocytic leukemia (CLL), or were human immunodeficiency virus (HIV)-positive and may have had other comorbidities. The disparity in the numbers of patients receiving ART ($n = 45$) versus surgery alone ($n = 8$) limited statistical analysis. Wray et al. concluded that elective nodal irradiation (ENI) was a safe and effective alternative to elective neck dissection in a single-site, retrospective outcomes study of patients ($n = 71$) with high-risk cSCC of the face, ears, and scalp.[68] These patients had no clinical or radiographic evidence of LN metastasis and no history of regional LN surgery prior to treatment. They underwent elective ART to the primary site and sentinel LN, which was found to provide regional control for 96% of the patients at 5 years post-treatment (and none developed grade 3+ toxicity).

Wang et al. reported lower recurrence rates and significantly higher survival rates (DFS and OS) for a retrospective cohort of patients ($n = 122$) with HNcSCC with cervical LN involvement when treated with surgery plus ART compared with surgery alone (Table 2).[69] The absence of ECE was associated with improved DFS. In another study of patients ($n = 51$) with HNcSCC and metastasis to the parotid and/or cervical LNs, Givi et al. found significantly higher OS after treatment with ART postsurgery compared with patients treated with surgery alone ($p = 0.002$).[70]

Outcomes for patients with high-risk cSCC have been shown to be significantly better when clear surgical margins were reported compared to positive or unreported margins.[8,71] Similarly, outcomes for patients with cSCC receiving ART postsurgery have been better with clear surgical margins.[51,71] Guo and Kiess suggest that, when possible, re-excision of positive margins should be performed.[72] They also indicate consideration should be given to whether a recurrence may be due to inadequate resection or biologically aggressive disease, and that ART should be reserved for treating aggressive cases. A retrospective study by Strassen et al. investigated management of recurrence in patients ($n = 67$) with HNcSCC

following resection of primary tumors, the majority (93%) of which were classified as T1-T2 and without locoregional metastases (Table 2).[73] The recurrent disease was treated with surgery, with or without ART, and they found that 5-year recurrence-free survival (RFS) and OS were significantly improved ($p = 0.02$ and $p < 0.05$, respectively) in patients treated with ART plus surgical resection compared with patients treated with surgery alone. Thus, ART may be important in the setting of recurrence following clear margins. However, the value of ART in salvage therapy following unclear margins and in the presence of other risk factors that are associated with poor outcomes (such as LN involvement, extensive PNI, or large-caliber nerve involvement) remains to be determined.[8,20,74]

The studies described above provide supporting evidence for effective use of ART in high-risk cSCC with respect to patient outcomes, while other recent studies suggest ART does not improve outcomes (Table 2). Ruiz et al. compared surgical monotherapy (SM) to surgery plus ART (S + ART) in a retrospective primary cSCC cohort ($n = 62$) having clear margins and negative LNs.[75] The authors matched for sex, age, immune status, surgery type, and tumor characteristics (i.e., diameter, depth, differentiation, and large-caliber [≥0.1 mm] nerve invasion [LCNI]). They also performed a subanalysis to compare SM versus S + ART within the LCNI subgroup ($n = 33$). No significant differences were found in local recurrence, metastasis, or DSD rates for the patients undergoing SM compared to those having S + ART; this includes the LCNI subgroup analysis. This study was nonrandomized and performed at a single academic center; both noted as limitations. The cohort's low (8%) overall risk for local recurrence was posited as one explanation for why ART did not improve outcomes. The disparity between mean follow-up times for the compared groups may have contributed to lower estimation of risk for poor outcomes in the SM group. However, the effects from different follow-up periods were likely minimal, as follow-up was >2 years and most recurrences have been reported to occur within 2 years of treatment.[7]

A retrospective study of advanced HNcSCC by Trosman et al. revealed that ART (either without or with adjuvant chemotherapy [ACRT]) plus surgery did not significantly improve 2-year DFS rates when compared to surgery alone for patients treated at a single, academic, tertiary care center ($n = 104$) (Table 2).[76] These patients underwent parotidectomy and neck dissection during definitive surgery. Both tumor size (>2 cm) and PNI were found to independently predict recurrence ($p = 0.006$ and $p = 0.04$, respectively), and PNI was found to have a strong association with lower DFS rates. The authors noted that none of the cases involved named nerves or extensive PNI and that ART may be more effective with respect to outcomes when extensive nerve invasion is seen. Amoils et al. reported that no significant differences were found in 3-year OS of patients ($n = 80$) with regionally metastatic (LN-positive) HNcSCC treated with either surgery alone (43% OS), surgery plus ART (52% OS), or surgery plus ACRT (49% OS).[77] They also found that 51% of the cohort studied had recurrence. While the most common high-risk features reported were PNI and ECE (41% and 31% of the cases, respectively), only primary tumor size >2 cm and ECE were significantly associated with OS ($p = 0.03$ and $p = 0.02$, respectively). The authors noted limitations, including the retrospective nature of the study and lack of randomization, relatively small patient number with multiple confounders, and insufficient data to adjust for certain clinical differences. Thus, the study was likely underpowered for detecting significant associations.

More prospective, multicenter, randomized controlled studies are needed in order to obtain high-quality data and, in turn, develop an evidence-based consensus with respect to which patients with high-risk cSCC might benefit from ART. Thus, evidence generated over the last 10 years to evaluate ART in the adjuvant setting lacks the consistency needed to make definitive decisions about patient management. However, many of the studies listed above provide evidence for patient management recommendations for national and international committees that oversee development of guidelines for the use of ART.

1.1.2 | Current guidelines: Adjuvant radiation therapy

Clinical practice guidelines for selecting patients with cSCC for ART lack standardization due to inconsistent and limited evidence-based findings. The National Comprehensive Cancer Network (NCCN) guidelines and the American College of Radiology (ACR) recommend ART for cSCC with extensive perineural invasion (PNI), large nerve involvement (nerve caliber ≥0.1 mm), or positive margins postsurgery (Table 3).[7,51,75,78] The American Academy of Dermatology (AAD) recommends consideration of ART to the primary cSCC site for concerning PNI, and when there is high risk for regional or distant metastasis (Table 3).[79] However, clear evidence is lacking regarding which high-risk patients may benefit from ART following cSCC resection with clear margins.[51,63] Additionally, the value of ART in cSCC, with or without clear margins, continues to be debated among clinicians due to lack of prospective, randomized clinical studies.[7,71,80] As described above, available literature is

TABLE 3 Recommendations and considerations for adjuvant therapy, immunotherapy, and targeted therapy for high-risk cSCC

Treatment	NCCN[7,78]	AAD[79]	ASTRO Task Force[40]
Radiation therapy	Recommends ART to primary site[a]: • for extensive PNI • with large (nerve caliber ≥0.1 mm) nerve involvement • when there are positive margins postsurgery	Recommends consideration of ART to primary site: • for concerning PNI • for high risk for regional or distant metastasis	Strongly recommends ART to primary site: • for clinically or radiologically apparent gross PNI • when further surgery cannot correct or close positive margins • when there is recurrence following a margin-negative resection • for T3 and T4 tumors (AJCC8) • for chronically immunosuppressed patients with desmoplastic or infiltrative tumors
Chemotherapy	Recommends: • against use of systemic therapy for local disease amenable to surgery • potential use with ART when further surgery is not an option (ACRT) • consideration for regional recurrence if patient is ineligible for immunotherapy and clinical trials (palliative rather than adjuvant therapy)	N/A	N/A
Immunotherapy and targeted therapy	Recommends: • against use of systemic therapy for local disease amenable to surgery • potential use of immunotherapy (checkpoint inhibitor) with RT in a clinical trial for residual disease in locally advanced cSCC when further surgery is not an option, and in complicated cases when curative surgery and RT are not feasible (palliative therapy) • immunotherapy with checkpoint inhibitor (cemiplimab or pembrolizumab) is preferred in regional recurrence when curative surgery and curative RT are not feasible • if patient is ineligible for immunotherapy and clinical trials, consideration of targeted therapy (e.g., EGFR inhibitor) in regional recurrence	N/A	N/A
Clinical trials	Recommends: • consideration of clinical trial enrollment (e.g., checkpoint inhibitor) for potential use with RT for locally advanced disease when further surgery is not an option • clinical trial enrollment (e.g., cemiplimab, pembrolizumab, or other checkpoint inhibitor) for regional recurrence	Recommends careful consideration of: • immunosuppressed individuals with high-risk localized (or metastatic disease) and multidisciplinary consultation	Recommends: • prospective clinical trial enrollment and multidisciplinary approaches • patient outcomes should be documented in clinical trials and registries when possible to increase quality of data for RT in cSCC

Note: Adjuvant treatment recommendations and considerations following current standard-of-care surgical treatment for high-risk cSCC.

Abbreviations: AAD, American Academy of Dermatology; ACR, American College of Radiology; ACRT, adjuvant chemotherapy plus ART (adjuvant chemoradiotherapy); AJCC8, American Joint Committee on Cancer Staging Manual, Eighth Edition; ART, adjuvant radiation therapy; ASTRO, American Society for Radiation Oncology; cSCC, cutaneous squamous cell carcinoma; EGFR, epidermal growth factor receptor; N/A, not applicable; NCCN, National Comprehensive Cancer Network; PNI, perineural invasion; RT, radiation therapy.

[a]NCCN and ACR recommendations are the same for ART in high-risk cSCC.

mostly from retrospective, small cohort, single-site studies, and reported findings are conflicting regarding the effectiveness of ART in cSCC.[63–66,68–70,73,75–77]

The American Society for Radiation Oncology (ASTRO) recently published an executive summary of its clinical practice guideline for RT in cSCC.[40] This published summary of recommendations is the result of a systematic review and expert opinions by an ASTRO-appointed task force. The task force was made up of dermatologists, dermatopathologists, cutaneous surgeons, medical oncologists, radiation oncologists, and a medical physicist who addressed five key questions about indications for RT in cSCC (as well as BCC, not reported here) and made recommendations for defining clinical practice guidelines for RT in cSCC. Due to the limited number of high-quality, randomized studies of patients with cSCC having RT, the recommendations are based on meta-analyses of mostly retrospective studies and expert opinions. As shown in Table 3, the ASTRO task force reported that ART is strongly recommended for clinically or radiologically apparent gross PNI, when further surgery cannot correct positive margins, when there is recurrence following a margin-negative resection, for American Joint Committee on Cancer, Eighth Edition Cancer Staging Manual (AJCC8) T3 and T4 tumors,[13] and for chronically immunosuppressed patients with desmoplastic or infiltrative tumors.[40]

With respect to LN involvement, the NCCN recommends either ART or observation alone for one positive LN ≤3 cm and no ECE (Table 4). For two or more positive LNs or one positive LN >3 cm (no ECE), the NCCN recommends ART. For any node with ECE or incompletely excised LN disease, the NCCN recommends ART and consideration of concurrent adjuvant systemic therapy (described below).[7] The ASTRO task force strongly recommends ART for treating regional LNs and regional disease in clinically apparent regional LN metastasis following LN dissection (with the exception of patients with one small [<3 cm] carcinoma-positive cervical LN without ECE) (Table 4). When patients are undergoing primary site RT for tumors >6 mm and there is LN basin overlap, the task force conditionally recommends elective ART for the LN basin. For patients at high risk for regional LN metastasis, the task force conditionally recommends sentinel lymph node biopsy (SLNB) and imaging to help determine if ART for the LN basin would have clinical value. Close clinical follow-up of the LN basin is recommended, even when SLNB is negative (i.e., SLNB may be inaccurate after extensive primary resection or reconstruction due to head and neck tumor location).[40] As shown in Table 4, the AAD guidelines for management of cSCC also recommend consideration of ART to the local tumor site postsurgery when there is high risk for LN metastasis,[79] while reminding clinicians and patients that high-level evidence is lacking regarding effectiveness of this approach.[79,81] The AAD guidelines also recommend considering LN dissection and ART, with or without concurrent systemic therapy for regional LN disease; in cases with inoperable LN metastasis, they recommend considering combination ART plus chemotherapy.[79]

In cases with locally advanced disease, the NCCN guidelines recommend considering, with or without ART, systemic therapy in the context of a clinical trial when further surgery is not an option (Table 4).[7] The ASTRO task force strongly recommends against the use of the chemotherapeutic agent carboplatin with ART in locally advanced disease, due to finding no benefits from addition of the radiosensitizing agent to ART in a prospective randomized trial for patients with high-risk cSCC.[40,82] The AAD does not specifically recommend ART for advanced locoregional disease, but does recommend consideration of multidisciplinary consultation and clinical trials.[79] The use of ART is not recommended for distant metastasis.[7,79] Doses of 50–70 Gy over 5–7 weeks, depending on extent of disease, have been recommended by the NCCN for ART in cSCC.[7] In an effort to reduce variations in treatment by clinicians and promote harmonization of PORT, and perhaps entice collaboration between committees to promote standardization, Porceddu et al. recently reported consensus guidelines from the Head and Neck Cancer International Group (HNCIG) for defining specific PORT volumes and minimum doses for complex cSCC of the head and neck following primary tumor resection.[44]

1.2 | Adjuvant chemotherapy

Chemotherapy is a systemic approach that may be used in certain situations to treat cSCC via oral or intravenous delivery of anticancer drugs (e.g., platinum-based drugs, such as cisplatin and carboplatin; antimetabolites, such as 5-FU; and inhibitors of mitosis) (Table 1).[43,83] It may be combined with ART as adjuvant chemoradiation therapy (ACRT) following resection without clear margins; however, this would most likely be considered in the context of a clinical trial.[7] For incurable situations, such as advanced cSCC that is inoperable or has been managed inadequately by surgery or RT, chemotherapy may be used as palliative treatment.[7,51]

The use of chemotherapy in cSCC has limitations due to lack of efficacy and the toxic effects it often has on otherwise healthy and rapidly dividing cells, including hair loss, oral sores, nausea and vomiting, diarrhea, and fatigue. Other potential dose-limiting side effects

TABLE 4 Adjuvant treatment recommendations in high-risk cSCC with nodal metastasis and advanced disease

National organization	Metastasis or advanced disease	Recommendations	References
NCCN Guidelines[a]	One positive LN ≤3 cm, no ECE	Either ART or observation	7
	Two or more positive LNs, no ECE	ART	
	One positive LN >3 cm, no ECE	ART	
	Incompletely excised LN disease	ART and consideration of concurrent adjuvant systemic therapy	
	One or more nodes with ECE	ART and consideration of concurrent adjuvant systemic therapy within a clinical trial	
	Locally advanced disease	Consider with ART, chemotherapy and/or immunotherapy (clinical trial) when further surgery is not an option for patients with residual disease; consider systemic therapy (clinical trial, palliative setting) when curative surgery and RT are not feasible	
	Distant metastasis	Immunotherapy (cemiplimab, pembrolizumab) preferred in a clinical trial when curative surgery and RT are not feasible; consider targeted therapy and/or chemotherapy when ineligible for immune checkpoint inhibitors and clinical trials	
ASTRO Task Force[b]	Clinically apparent regional LN metastasis following LN dissection (except when there is only one small [<3 cm] carcinoma-positive cervical LN, without ECE)	Strongly recommends ART for treating regional LNs	40
	LN basin overlap with primary site when patients are undergoing primary site RT (primary tumor >6 mm)	Elective ART is conditionally recommended for the LN basin	
	High risk for regional LN involvement	SLNB and imaging are conditionally recommended to determine the need for ART	
	Locally advanced disease	Strongly recommends against concurrent use of carboplatin with ART	
AAD Guidelines	High risk for LN metastasis	Consider ART to local tumor site following surgical treatment	79
	Regional LN metastasis	Consider LN dissection and ART, with or without concurrent systemic therapy	
	Inoperable LN metastasis	Consider combination ART and chemotherapy (ACRT)	
	Locally advanced disease or metastasis	Consider ACRT or combination systemic therapy (chemotherapeutic agents and/or immunotherapy or targeted therapy) and multidisciplinary consultation, particularly for immunosuppressed patients	

Note: Adjuvant treatment recommendations following current standard-of-care surgical treatment for high-risk cSCC.

Abbreviations: AAD, American Academy of Dermatology; ACRT, adjuvant chemoradiotherapy; ART, adjuvant radiation therapy; ASTRO, American Society for Radiation Oncology; cSCC, cutaneous squamous cell carcinoma; ECE, extracapsular extension (also known as extranodal extension [ENE]); LN, lymph node; LNs, lymph nodes; NCCN, National Comprehensive Cancer Network; SLNB, sentinel lymph node biopsy.

[a]When multimodality treatment is recommended, the NCCN guidelines recommend consultation with multidisciplinary teams.

[b]The ASTRO task force encourages prospective clinical trial enrollment and multidisciplinary approaches when possible, and documentation of patient outcomes in clinical trials and registries to increase the quality of data for cSCC.

(or adverse events [AEs]) include, but are not limited to, nephrotoxicity, hepatotoxicity, cardiotoxicity, and/or cachexia.[83,84] Administration of some chemotherapeutic agents (e.g., cisplatin) in elderly patients with comorbidities and in immunosuppressed individuals may be contraindicated due increased risk of toxic effects.[82,83,85]

Some chemotherapeutic agents may be used as radiosensitizers to make cancer cells more susceptible to ART.[86,87] Several studies have demonstrated efficacy (e.g., reduced recurrence and increased survival) of administering concurrent adjuvant chemotherapy with ART (adjuvant chemoradiotherapy [ACRT]) for treating high-risk mucosal/oral squamous cell carcinoma of the head and neck.[88–90] However, the effectiveness of adjuvant chemotherapy for treating high-risk cSCC, either alone or as part of ACRT, has historically not been studied extensively. Thus, there is not clear evidence that supports the use of adjuvant chemotherapy in cSCC. Nevertheless, in the adjuvant setting, ACRT may be considered in certain cases and utilized in efforts to optimize control of disease postsurgery, including when further surgery is not an option.[7,51,76] A recent phase III randomized study (described next) sheds some light on this, but controversy still exists in this setting.

1.2.1 | Recent studies: Adjuvant chemotherapy

The limited studies of adjuvant chemotherapy in high-risk cSCC are mostly retrospective, with the exception of a recent randomized, phase III clinical trial (NCT00193895) by Porceddu et al.[82] In this benchmark, prospective trial, the Trans-Tasman Radiation Oncology Group (TROG) found that when concurrent chemotherapy with carboplatin was added to ART (ACRT) for treatment of high-risk HNcSCC following primary resection, no significant differences were found in DFS or OS compared to treatment with ART alone (Table 2). The rates for 2- and 5-year DFS were 78% and 67% for ART, respectively, and 83% and 73% for ACRT ($p = 0.44$). For OS, the 2- and 5-year rates were 88% and 76% for ART, respectively, and 88% and 79% for ACRT ($p = 0.86$). The authors also reported no significant differences in the rates of FFLRR for the patients given ACRT and ART at 2 and 5 years postrandom assignment to the study groups. The cohort included only patients who had complete macroscopic resection, with or without microscopic positive margins, and either high-risk LN disease or advanced primary disease (which included in-transit disease). The majority of patients (77%) had high-risk LN disease, 19% had high-risk primary tumors or in-transit disease, and 4% of the cohort had both. Study criteria defined high-risk LN disease as either intraparotid nodal disease (one or more LNs, with or without ECE) and/or cervical nodal disease (two or more LNs, or LN ≥3 cm, or ECE), which could have been from a previously resected tumor (<5 years), while advanced primary disease was defined as AJCC6 T3 or T4. Median follow-up time was 5 years. The authors reported that carboplatin did not enhance RT toxicity. As survival rates were relatively high in both arms of this study, some may contend that patient risk for poor outcomes may have been too low to demonstrate benefits from chemotherapy. Also, the choice of chemotherapy in this study may be controversial, as cisplatin is the evidenced-based agent of choice in head and neck mucosal SCC.[88]

As mentioned earlier under ART, and pertinent to discussion of adjuvant chemotherapy, Trosman et al. reported that addition of adjuvant chemotherapy (cisplatin, carboplatin with or without paclitaxel, or docetaxel with cetuximab) to ART postsurgery did not improve survival in a retrospective study of advanced HNcSCC (Table 2).[76] Interestingly, the percentages of patients with PNI and ECE were higher in the subgroup of patients who received surgery plus ACRT (i.e., more aggressive disease or higher risk factors warranted more intensified treatment), and this may have contributed to the outcomes regardless of treatment. Similarly, Amoils et al. found that addition of chemotherapy to ART did not increase 3-year OS in patients with HNcSCC and LN metastasis (Table 2).[77]

Goyal et al. reported for a cohort of patients ($n = 32$) with locally advanced HNcSCC treated with ART, with ($n = 14$) or without ($n = 18$) concurrent systemic therapy (chemotherapy or targeted), that no significant differences were found between the two groups for local regional control, distant control, or progression-free survival (PFS) (Table 2).[91] However, the median OS rate was significantly lower for patients treated with ART plus systemic therapy compared with ART alone ($p = 0.03$), and patients treated with concurrent systemic therapy had an increased risk of death, with most receiving cytotoxic chemotherapy (HR 3.5, $p = 0.04$). Of note, outcomes for surgery alone versus ART with or without chemotherapy or targeted therapy were not reported in this study. Limitations noted by the authors include retrospective study, small cohort, heterogeneity of ART and systemic therapy doses and agents, and variability in follow-up time.

In contrast, another single-institution retrospective study reported that concurrent chemotherapy with ART improved outcomes. Tanvetyanon et al. compared outcomes of patients with high-risk HNcSCC ($n = 61$) treated with either ART ($n = 27$) or ACRT ($n = 34$) (Table 2).[86] The high-risk patients had metastasis to two or more LNs, ECE, and/or positive surgical margins.

Concurrent chemotherapy included treatment with either cisplatin ($n = 24$) or carboplatin ($n = 10$). Median RFS was higher for patients receiving ACRT compared with patients who received only ART (40.3 vs. 15.4 months, respectively), and ACRT decreased the risk of recurrence significantly (HR 0.31, $p = 0.01$). However, the rates for OS were not significantly different between the groups. No comparisons to treatment with surgery alone or between treatment with cisplatin versus carboplatin were reported.

Based on recent data, some experts do not recommend adjuvant chemotherapy for high-risk cSCC,[72] while others advise it should be considered in specific cases (e.g., in combination with ART [ACRT] for high-stage regional LN or distant metastasis, or cases of inoperable LN metastasis).[27,79] The addition of systemic therapy to ART for the treatment of high-risk cSCC has not been studied broadly; thus, data have been scarce in the literature. Above, we described four recent studies (one prospective, randomized clinical trial and three retrospective studies) that reported ACRT does not improve patient outcomes in cSCC compared to ART, and one retrospective study that reported improved outcomes with ACRT versus ART. Some of these findings have contributed to development of recommendations for patient management. However, more prospective, randomized clinical trials are needed to determine the efficacy of this treatment modality in high-risk cSCC and to refine current guidelines for optimum cSCC patient management.

1.2.2 | Current guidelines: Adjuvant chemotherapy

The NCCN does not recommend systemic therapy for local disease that is amenable to surgery.[7] It does recommend use of chemotherapy concurrently with ART (ACRT) for residual disease in locally advanced cSCC when further surgery is not an option, and consideration of chemotherapy for regional recurrence if the patient is ineligible for immunotherapy and clinical trials (Table 3).[7] For cSCC with incompletely excised LN disease, the NCCN guidelines recommend consideration of systemic therapy concurrently with ART and multidisciplinary consultation, and in the context of a clinical trial when ECE is seen (Table 4).[7] In cases with distant metastasis, systemic therapy is standard-of-care therapy using chemotherapy, immunotherapy, and/or targeted therapy with or without a clinical trial. The NCCN guidelines do not recommend chemotherapy for cSCC in cases of fully resected regional disease or in high-risk cSCC with completely resected ECE, unless via a clinical trial (e.g., as ACRT). In cases where other therapy is not feasible or patients are ineligible, chemotherapy may be considered as palliative treatment.

In patients with locally advanced cSCC, the ASTRO task force strongly recommends against the concurrent use of carboplatin with ART following primary resection due to failure to demonstrate a benefit in the prospective randomized TROG trial by Porceddu et al. (Table 4).[40,82] The AAD guidelines recommend consideration of ACRT or other systemic therapy concurrently with ART, as well as LN dissection, when there is regional LN metastasis (Table 4).[79] When LN metastasis is inoperable, the AAD recommends considering ACRT, as described above by Tanvetyanon et al.[86] For advanced locoregional disease or distant metastasis, the AAD guidelines recommend multidisciplinary consultation with consideration of clinical trials and various systemic therapies, particularly for immunosuppressed patients.[79]

1.3 | Immunotherapy and targeted therapy

Immunotherapy exploits the patient's immune system to fight cancer cells and targeted therapy targets molecules within or on the surface of cancer cells (e.g., gene sequences or proteins, such as epidermal growth factor receptor [EGFR]). Immunotherapeutic and targeted therapeutic agents are usually administered intravenously, although some may be delivered orally.[43] Immunotherapy and targeted therapy have replaced chemotherapy as front-line systemic treatments for many cancer types, including advanced and metastatic cSCC (Table 1).[45,92,93] These treatment modalities are being studied in the adjuvant and neoadjuvant settings in cSCC within clinical trials. Thus, it is helpful to understand the current utility of these therapeutics and further potential application in adjuvant settings in high-risk cSCC.

Individuals with hypermutated tumors (e.g., most patients with cSCC, due to chronic UV light exposure) are likely to respond to immune checkpoint inhibitors.[94] The immunotherapeutic agent cemiplimab, a monoclonal antibody (mAb) specific to programmed death receptor-1 (PD-1), is a checkpoint inhibitor that blocks interaction with programmed death ligands 1 and 2 (PD-L1 and PD-L2, respectively), which, in turn, reactivates cytotoxicity of immune cells.[92,95–97] The U.S. Food and Drug Administration (FDA) approved cemiplimab in September of 2018 and the European Union (EU) approved it in June of 2019 for treatment of patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or curative RT, following results from two, open-label, phase II trials (see below).[94–96,98–100] Another PD-1 inhibitor, pembrolizumab, was also recently approved

by the FDA for treating recurrent or metastatic cSCC that is not curable by surgery or RT, based on results from the KEYNOTE-629 trial (see below).[101]

Cetuximab, an EGFR-targeting mAb, has been approved by the FDA for treatment of advanced colorectal cancer[102] and late-stage head and neck cancer[103] and has been used off-label for the treatment of cSCC.[92,95,97] This chimeric mAb targets EGFR on the surface of epithelial cells, blocking its interaction with various growth factors that may lend to cancer cell growth. Findings that support the efficacy of EGFR inhibitors (e.g., cetuximab and gefitinib) for targeted therapy in cSCC are limited, especially in the adjuvant setting, as these agents are predominantly used when disease is unresectable.[7,104,105] However, several current clinical trials are investigating checkpoint and/or EGFR inhibitors in the adjuvant and/or neoadjuvant settings (Table 5), as well as for disease burden management.

Interestingly, gene expression profiling and tissue of origin have been reported to be important factors for determining in vitro tumor sensitivity to targeted therapy.[106,107] Also, investigations of cell signaling pathways associated with development of cSCC have led to identification of molecules (e.g., PD-1 and EGFR) being targeted in current systemic therapy for patients with high-risk cSCC.[108,109] Although immunotherapy and targeted therapy are relatively new treatment modalities for high-risk cSCC, the available evidence, albeit limited, and ongoing investigations in the cSCC arena corroborate the importance of a multidisciplinary approach for more personalized therapy in high-risk cSCC.

1.3.1 | Recent studies: Immunotherapy and targeted therapy

Findings from open-label, phases I and II clinical trials by Migden et al. were recently reported for the phase I expansion cohort ($n = 26$, locally advanced or metastatic cSCC, NCT02383212) and a metastatic cohort ($n = 59$, nodal or distant disease) from the phase II study (NCT02760498) (Table 2).[94] In the expansion cohort, 50% of the patients responded to cemiplimab. Durable disease control (DC, absence of progressive disease for ≥105 days) was obtained in 65% of the cohort.

In the metastatic cohort of the phase II study, Migden et al. investigated not only tumor response, but also clinical benefits of cemiplimab with respect to outcomes (OS and PFS).[94] Almost half (47%) of the cohort responded to the immune checkpoint inhibitor and durable DC was obtained in 61% of the cohort. Complete response was observed in four patients (6.8%) and a partial response was seen in 24 patients (40.7%). The toxicity profile and events were similar to the experience with other PD-1 inhibitors in other cancers. The majority of patients in both phases of the study had received previous systemic therapy for cSCC (58% and 56% for phases I and II, respectively), and previous RT for cSCC (77% and 85% for phases I and II, respectively). Immunocompromised patients were not enrolled in either phase of the study.

More recently, Migden et al. reported findings from a cohort with locally advanced cSCC without metastasis ($n = 78$) in the phase II study (NCT02760498) and demonstrated that cemiplimab had antitumor activity and an acceptable safety profile.[98] In this single-arm study, an objective response (i.e., complete or partial) was obtained in 44% of the patients. A complete response was observed in 10 (13%) and a partial response was observed in 24 (31%) patients. Durable DC was observed in 63% of the cohort. Based on this study and findings reported in 2018, Migden et al. suggest that cemiplimab is an effective and safe therapy for both locally advanced and metastatic cSCC. Importantly, patients enrolled in these studies were not candidates for surgery and/or ART, as this would have resulted with considerable morbidity or disfigurement.

Further findings recently reported by Rischin et al. from this same phase II trial (NCT02760498) demonstrate that cemiplimab produced substantial antitumor activity with durable responses and acceptable safety profiles in both weight-based ($n = 59$, 3 mg/kg every 2 weeks) and fixed-dosing ($n = 56$, 350 mg every 3 weeks [Q3W]) cohorts with metastatic cSCC (Table 2).[110] In the neoadjuvant setting and as part of an on-going phase II trial (NCT03565783), Gross et al. reported promising results from a small cohort of patients ($n = 20$) with stage III/IV (M0) (AJCC8) HNcSCC treated with two doses of cemiplimab (Q3W) prior to surgery. The overall response rate via imaging was 30%, while pathologic complete responses and major pathology responses were observed in 55% and 15% of the patients, respectively. The agent was well tolerated (Table 2).[111] Cemiplimab is FDA- and EU-approved for treating patients with locally advanced or metastatic cSCC who are not eligible for curative surgery or curative RT, and the approved regimen is 350 mg intravenously Q3W.[99,100,110]

Results reported by Grob et al. from an ongoing, multicenter, phase II study (NCT03284424) of pembrolizumab (KEYNOTE-629) for treatment of locally recurrent and/or metastatic cSCC ($n = 105$) demonstrated encouraging response rates and efficacy, which led to the recent FDA approval of use of pembrolizumab in this setting (Table 2).[101,112] With an objective response rate (ORR) of 34%, 32 patients (30.5%) achieved partial response and 4 patients (3.8%) achieved complete response. The disease

TABLE 5 Recent and ongoing clinical trials for adjuvant therapy in cSCC

Identifier	Drug/agent/ intervention	Setting	Description	Phase	Status	Start date	Estimated completion
NCT01979211	Cetuximab and ART	Adjuvant	Open-label, postoperative RT with cetuximab for locally advanced HNcSCC	II	Active, not recruiting	October 2013	October 2022
NCT02324608	Cetuximab	Neoadjuvant	Open-label, pilot study of neoadjuvant cetuximab in advanced cSCC	NA	Recruiting	January 2015	November 2020
NCT02923570	Proton versus Photon ART	Adjuvant	Open-label, randomized study of PBRT versus photon IMRT in head and neck cancer, including HNcSCC	II	Recruiting	October 2016	October 2021
NCT03057613	Pembrolizumab and ART	Adjuvant	Open-label, addition of pembrolizumab to postoperative RT (IMRT) in HNcSCC	II	Recruiting	May 2017	August 2022
NCT03565783	Cemiplimab	Neoadjuvant	Open-label, cemiplimab (REGN2810) prior to surgery (neoadjuvant) for advanced, recurrent, and resectable head and neck SCC; and for AJCCv8 stage III-IV HNcSCC	II	Recruiting	July 2018	July 2021
NCT03833167	Pembrolizumab	Adjuvant	Randomized, placebo-controlled, double-blind, study of adjuvant therapy with pembrolizumab versus placebo following surgery and ART in locally advanced cSCC (MK-3475-630/KEYNOTE-630)	III	Recruiting	April 2019	September 2027
NCT03836105	Cemiplimab-rwlc	Neoadjuvant or adjuvant	Prospective, observational study of patients receiving Cemiplimab as first-line therapy (neoadjuvant) or as adjuvant therapy in immunosuppressed and immunocompetent patients; Cemiplimab Survivorship Epidemiology (CASE) study	NA	Recruiting	June 2019	December 2023
NCT03889912	Cemiplimab	Neoadjuvant	Open-label study of pre-operative (neoadjuvant) cemiplimab administered intralesionally in recurrent cSCC	I	Recruiting	April 2019	August 2020
NCT03969004	Cemiplimab	Adjuvant	Randomized, placebo-controlled, double-blind study of adjuvant cemiplimab versus placebo after surgery and ART in high-risk cSCC	III	Recruiting	June 2019	February 2026
NCT04154943	Cemiplimab	Neoadjuvant	Open-label study of neoadjuvant cemiplimab in stage II-IV cSCC	II	Recruiting	March 2020	December 2024

TABLE 5 (Continued)

Identifier	Drug/agent/ intervention	Setting	Description	Phase	Status	Start date	Estimated completion
NCT04315701	Cemiplimab	Neoadjuvant	Open-label, study of PD-1 checkpoint inhibitor (cemiplimab) prior to surgery (neoadjuvant) for high-risk localized, locally recurrent, or regionally advanced cSCC	II	Not yet recruiting	April 2020	October 2022
NCT04428671	Cemiplimab	Neoadjuvant and adjuvant	Open-label, cemiplimab before and after surgery (or after RT) for treatment of high-risk cSCC	I	Active, not recruiting	May 2020	October 2030

Note: From ClinicalTrials.gov (accessed June 13, 2020). The trials are listed in order of the national clinical trials (NCT) number.
Abbreviations: ART, adjuvant radiation therapy; AJCCv8, American Joint Committee on Cancer Staging Manual, Eighth Edition; cSCC, cutaneous squamous cell carcinoma; HNcSCC, head and neck cutaneous squamous cell carcinoma; IMRT, intensity-modulated radiation therapy; NA, not applicable; PBRT, proton beam radiation therapy; RT, radiation therapy.

control rate was 52%. Patients were given pembrolizumab (200 mg) intravenously every 3 weeks until disease progressed, there was unacceptable toxicity, or for a maximum of 2 years. Tumors were assessed every 6 and 9 weeks during the first and second years, respectively, via blinded independent central review using response evaluation criteria in solid tumors (RECIST v1.1). Patients had similar AEs as those in patients receiving pembrolizumab monotherapy in other clinical trials.[112]

Several studies of EGFR inhibitors (e.g., cetuximab, gefitinib, panitumumab, and erlotinib) have demonstrated positive responses in patients with high-risk cSCC, although most of these have focused on the neoadjuvant setting or first-line monotherapy in the palliative setting for unresectable disease.[104,105,113–116] For example, Maubec et al. studied the efficacy and safety of cetuximab as a first-line monotherapy in patients ($n = 36$) with unresectable cSCC and reported a 69% disease control rate at 6 weeks with limited toxicity (Table 2).[104] Overall response was 28%, with eight patients (22%) having partial and two patients (6%) having complete responses. The OS was 8.1 months and median PFS was 4.1 months. This open-label, multicenter, phase II study was one of the first reported studies of cetuximab off-label use in cSCC and coincided with the FDA approval of the agent for treatment of late-stage mucosal head and neck cancer.

In the adjuvant setting, the prospective, phase II clinical trial conducted by Lewis et al. evaluated the EGFR inhibitor gefitinib given neoadjuvantly and also postoperatively in patients with aggressive or recurrent cSCC ($n = 22$) (Table 2).[105] Interestingly, ≥90% of the patients had lesions in the head and neck region, >70% had regional LN metastasis, and >50% had been treated previously with surgery or surgery plus RT. The overall response rate to neoadjuvant induction was 45.5%, and 2-year OS, disease-specific survival (DSS), and PFS for the cohort were 72.1%, 72.1%, and 63.6%, respectively. This study was designed for two stages. However, due to the relatively high progressive disease rate, the trial was terminated after the first stage.

While some of the above findings have helped to shape current guidelines, more prospective clinical studies on the efficacy of immunotherapy and targeted therapy in high-risk cSCC are needed. Several clinical trials evaluating these treatment modalities with several different therapeutic agents are currently underway (Table 5) with promising results.

1.3.2 | Current guidelines: Immunotherapy and targeted therapy

As mentioned earlier, for local cSCC that is amenable to surgery, the NCCN guidelines do not recommend systemic therapy.[7] In cases where the NCCN does recommend systemic therapy, it is usually in the context of a clinical trial. For treatment of HNcSCC with incomplete excision of LN disease, and when ≥1 LN has ECE, the NCCN guidelines recommend multidisciplinary consultation and consideration of concurrent systemic therapy with RT (Table 4).[7] In locally advanced cSCC, consideration of immunotherapy (e.g., checkpoint inhibitor) in combination with RT in a clinical trial is recommended for patients with residual disease when further surgery is not an option. In regional recurrence or distant

metastasis, when curative surgery and curative RT are not feasible, immunotherapy with cemiplimab or pembrolizumab is preferred (Table 4), due to recently published clinical trial data and FDA approval of these therapies.[7,94,98,99,101,112] It is important to note that the NCCN indicates that other immune checkpoint inhibitors may also be effective. Additional data will be forthcoming from ongoing clinical trials (see below). When patients are ineligible for checkpoint inhibitors and clinical trials, consideration of EGFR inhibitors and/or chemotherapy is recommended by the NCCN. Also, additional considerations and consultations are necessary for immunosuppressed individuals (e.g., OTRs and immunocompromised patients).

Use of systemic therapy with RT for unresectable, advanced primary lesions for which treatment may need escalation and for inoperable or unresectable LN metastasis is conditionally recommended by the ASTRO task force.[40] The AAD recommends that concurrent systemic therapy may be considered with LN dissection and ART in regional LN metastasis.[79] In advanced locoregional disease or distant metastasis, the AAD recommends consideration of combination systemic therapy (e.g., immunotherapy and/or targeted therapy or chemotherapy), preferably within a clinical trial. Multidisciplinary consultation, especially for immunosuppressed patients, is recommended. As reported by Patel and Chang, further research is needed to understand whether immune-stimulating therapies can be helpful in patients with cSCC with comorbidities (such as immunocompromising diseases) without causing their disease to worsen, and to determine if likelihood to respond to immunotherapy can be predicted in patients with cSCC.[117] It would be advantageous to have prognostic tools that determine which patients would most likely benefit from immunotherapy and/or targeted or other combinatorial therapy. This would help with patient selection for maximizing potential benefits in patients most likely to respond and avoiding potential adverse events in those less likely to respond.

1.4 | Ongoing clinical trials

Several clinical trials are currently underway for cSCC in the adjuvant setting (Table 5). For example, one open-label, phase II clinical trial is comparing IMRT with PBRT in head and neck cancer, including cSCC, and is expected to be completed in 2021 (NCT02923570). Two open-label, phase II studies are investigating ART with cetuximab (NCT01979211) or pembrolizumab (NCT03057613) in HNcSCC with expected completion dates in 2022. Two large, phase III, randomized, placebo-controlled trials of adjuvant therapy with cemiplimab (NCT03969004) or pembrolizumab (NCT03833167, KEYNOTE-630) following surgery and ART in cSCC are estimated for completion in 2026 and 2027, respectively.

Many of the recent and ongoing clinical trials for cSCC are investigating immune checkpoint or EGFR inhibitors in the neoadjuvant setting (Table 5). For example, an open-label, pilot study of cetuximab (NCT02324608) for neoadjuvant treatment in advanced cSCC and an open-label, phase I study of cemiplimab (NCT03889912) for preoperative intralesional treatment in recurrent cSCC were estimated to be completed in 2020. Three open-label, phase II studies of cemiplimab (NCT03565783, NCT04154943, and NCT04315701) given prior to surgery will be completed within the next 3 years. Two studies of cemiplimab given neoadjuvantly and/or adjuvantly in cSCC (NCT03836105 and NCT04428671) are estimated for completion in 2023 and 2030, respectively. Also, many clinical trials in the late-stage/palliative or burden management setting are investigating immune checkpoint and EGFR inhibitors alone or in combination with other novel agents (non-adjuvant trials not shown).[85,95,117,118] The aforementioned phase II, KEYNOTE-629 trial of pembrolizumab (NCT03284424) in recurrent/metastatic or locally advanced cSCC is expected to be completed in 2022.

The NCCN guidelines, ASTRO task force, and AAD recommend clinical trial enrollment and multidisciplinary approaches/consultations when possible, and the ASTRO task force specifically encourages documentation of patient outcomes in clinical trials and registries to increase the quality of data for cSCC (Tables 3 and 4).[7,40,79] Forthcoming data from prospective clinical trials will be invaluable for development of more effective and personalized therapies for high-risk cSCC, particularly in the adjuvant setting and for patients who are no longer candidates for surgery or RT.

2 | CONCLUSIONS

The gold standard treatment for high-risk cSCC remains complete surgical excision of the primary lesion with clear margins when possible. Also, ART is typically considered when certain high-risk features are seen (e.g., PNI, LN metastasis, and/or ECE), the patient is otherwise at high risk for metastasis and/or recurrence, or further surgery is not an option.[7,79,81] The addition of concurrent systemic therapy to ART is not currently recommended for most patients. Depending on the extent of disease, ART with or without systemic therapy may be considered for treating locally advanced disease or regional LN metastasis; however, multidisciplinary consultation is recommended and clinical trial enrollment is

strongly encouraged.[7,40,79] Given the current activity of checkpoint inhibition in this disease, enthusiasm for the addition of cytotoxic chemotherapeutic agents in the adjuvant setting may be on the decline. More prospective, randomized, large cohort, clinical trials are needed for collecting high-quality data from which consensus guidelines can be developed for determining which patients might benefit most from a specific type of adjuvant therapy or combination of therapies. Importantly, this includes prospective studies of prognostic testing, such as GEP testing or SLNB, in patients with high-risk cSCC.[2,23–27] This additional testing would help determine which patients truly need adjuvant therapy and which patients may be managed more appropriately without adjuvant therapy. Multidisciplinary approaches will most likely continue to be recommended in complicated cases, including those involving immunosuppression.[7,79] As previously indicated, there is a critical need to identify patients at early stages of disease who are at high risk for metastasis (such as patients with immunosuppression or other high-risk factors) and who might benefit from adjuvant therapy.[119,120] Early and accurate prognostication could help facilitate timely and risk-appropriate intervention (e.g., prognostic testing of tumors early in disease to identify patients who would likely benefit from adjuvant therapy). Results from ongoing and future clinical trials should help direct patient with high-risk cSCC management decisions with respect to more personalized and effective treatment in the adjuvant and neoadjuvant setting.

CONFLICT OF INTEREST

Dr. Newman is a consultant for Bolder Surgical, Inc. and Medtronic, Inc. Dr. Koyfman receives research funding and consulting fees from Merck, research funding from Bristol Myers Squibb, and honoraria from UpToDate. Drs. Hall, Kurley, and Cook are employees and options holders. Dr. Farberg serves as a consultant. Drs. Newman and Koyfman are investigators for Castle Biosciences, Inc. Dr. Geiger receives research funding from Regeneron, Genentech, and Alkermes; and consulting fees from Regeneron. The 40-gene expression profile (40-GEP) test described in this manuscript was developed by Castle Biosciences, Inc. and is clinically offered as DecisionDx-SCC (Castle Biosciences, Inc., Friendswood, TX).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

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