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Managing cisplatin-ineligible patients with resected, high-risk, locally advanced squamous cell carcinoma of the head and neck: Is there a standard of care?

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ABSTRACT

For the past 2 decades, cisplatin-based adjuvant chemoradiotherapy (CRT) has remained the standard of care for patients with resected, locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) who are at high risk of disease recurrence. However, many patients are deemed ineligible for cisplatin-based CRT because of poor performance status, advanced biological age, poor renal function, or hearing loss. Because outcomes with radiotherapy (RT) alone remain poor, patients at high risk of disease recurrence deemed ineligible to receive cisplatin are a population with a significant unmet medical need, and alternative systemic therapy options in combination with RT are urgently needed. Clinical guidelines and consensus documents have provided definitions for cisplatin ineligibility; however, areas of debate include thresholds for age and renal impairment and criteria for hearing loss. Furthermore, the proportion of patients with resected LA SCCHN who are cisplatin ineligible remains unclear. Because of a scarcity of clinical studies, treatment selection for patients with resected, high-risk LA SCCHN who are deemed ineligible to receive cisplatin is often based on clinical judgment, with few treatment options specified in international guidelines. In this review, we discuss considerations related to cisplatin ineligibility in patients with LA SCCHN, summarize the limited clinical evidence for adjuvant treatment of patients with resected high-risk disease, and highlight ongoing clinical trials that have the potential to provide new treatment options in this setting.

Introduction

Head and neck cancer, comprising cancers of the oral cavity, larynx, nasopharynx, salivary gland, sinonasal cavity, oropharynx, and hypopharynx, is the 7th most common cancer worldwide [1]. Each year, >930,000 new cases of head and neck cancer are diagnosed, and nearly 470,000 people die from this disease [1]. This includes approximately 66,000 cases and 15,000 deaths in the United States, 153,000 cases and 69,000 deaths in Europe, and 24,000 cases and 8,000 deaths in Japan [2,3]. The majority of head and neck cancers (~90 %) are squamous cell carcinomas [4], and most patients (~60 %) are diagnosed with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) [5]. The current standard of care (SoC) for patients with LA SCCHN is either surgery followed by adjuvant cisplatin-based chemoradiotherapy (CRT) or radiotherapy (RT), depending on the presence or absence of pathological risk factors, or definitive nonsurgical treatment with CRT with curative intent [5,6]. Based on the results of one phase 3 study, which demonstrated cetuximab + RT improved overall survival (OS) vs

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RT alone, cetuximab + RT may be considered in the definitive setting but has been shown to be inferior to cisplatin-based CRT in human papillomavirus–positive oropharyngeal cancer [5,6]. In real-world studies, approximately 40 % of patients diagnosed with LA SCCHN undergo surgical resection [7–9].

In this article, we review the definitions of cisplatin eligibility and ineligibility in patients with LA SCCHN, summarize data supporting current treatment options for patients with LA SCCHN who are cisplatin ineligible following surgical resection and are at high risk of disease recurrence, and assess the clinical trial landscape in this population, collectively revealing a high unmet need.

Defining cisplatin ineligibility in patients with LA SCCHN

Cisplatin ineligibility can be broadly separated into 2 categories: patients who are ineligible for cisplatin treatment because of secondary resistance (eg, patients with recurrent and/or metastatic SCCHN who have a short disease-free interval following prior platinum treatment) or patients who have absolute or relative contraindications to cisplatin because of a high risk of adverse events (AEs) or other factors. In this review, we focus on cisplatin ineligibility in patients with LA SCCHN who have contraindications to cisplatin due to the risk of development or worsening of an AE or other medical factors. Because of the well-known toxicity profile when cisplatin is given alone or in combination with RT, which includes ototoxicity (any grade, ~10 %; grade ≥ 3, ~0–3 %), renal toxicity (any grade, ~30–67 %; grade ≥ 3, ~0–2 %), and neurotoxicity (any grade, ~10 %; grade ≥ 3, ~0–3 %), a substantial proportion of patients with LA SCCHN are considered ineligible to receive cisplatin [10,11]. To inform treatment decisions, clinical guidelines and consensus documents have attempted to define patients who have no contraindications to cisplatin and those with absolute or relative contraindications due to risk of AEs and potential nonadherence [12–14]. Across these publications, absolute contraindications to cisplatin include a poor performance status (Eastern Cooperative Oncology Group performance status ≥ 3); impaired renal function (creatinine clearance < 50 mL/min); preexisting hearing loss or grade ≥ 2 tinnitus (abnormal audiometry within audible frequency [audiometric criteria: threshold shift > 25 dB averaged at 2 contiguous test frequencies or hearing loss with hearing aid or intervention not indicated]); grade ≥ 2 peripheral neuropathy; severe marrow, hepatic, respiratory, cardiovascular, or metabolic dysfunction; some intercurrent infections; severe psychiatric disorders; poor nutritional status; first trimester of pregnancy; or allergy to platinum [12,14]. Many patients have relative contraindications to cisplatin, which are generally milder or less severe manifestations of the comorbidities or characteristics used to define absolute contraindications; such patients may or may not receive cisplatin-based CRT based on clinical judgment [11,15,16]. No consensus exists regarding criteria indicating absolute or relative contraindications to cisplatin, and wider discussion is needed.

Authors' perspectives: The most frequently encountered factors to consider regarding cisplatin eligibility in patients with resected LA SCCHN are hearing loss, renal insufficiency, poor performance status, and advanced age. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) for hearing impairment, which are widely used in clinical practice and clinical studies, do not discriminate between changes in frequencies that are critical to daily living and thus may not reflect clinically relevant hearing impairment [17]. Additionally, because hearing impairment is common in older persons, many patients enrolled in clinical studies in LA SCCHN may already have CTCAE grade ≥ 2 hearing loss because hearing difficulty increases with age, starting around 50 years and particularly in those aged ≥ 65 years [18,19]. Definitions of renal function are also an important consideration for cisplatin ineligibility criteria. Many patients with cancer are reported to have impaired renal function. It is generally accepted that patients with a creatinine clearance < 50 mL/min should not receive cisplatin; however, this cutoff is not absolute, and there is no established range for cisplatin dose reductions in patients who have different degrees of renal impairment [20]. Cisplatin ineligibility also varies according to the method used to estimate kidney function. For example, Cockcroft-Gault formula estimates have been reported to exclude approximately 20 % more patients from receiving cisplatin than the Chronic Kidney Disease Epidemiology Collaboration formula, with differences most pronounced in female, elderly, or White patients. Cisplatin eligibility based on Cockcroft-Gault estimates compared with estimated glomerular filtration rate (GFR) has also shown high discordance [20]. Additionally, more patients are deemed ineligible for cisplatin when using estimated creatinine clearance compared with measured creatinine clearance via 12- or 24-hour urine collection [20]. Although other techniques are available to estimate GFR, such as ^{51}Cr-ethylenediaminetetraacetic acid clearance (a reliable indicator of GFR before and during treatment with potentially nephrotoxic drugs), they can be complex, expensive, and time-consuming and therefore less suited to routine clinical practice [21,22]. Age is also a common consideration regarding cisplatin eligibility. Some centers will not offer cisplatin-based CRT to patients with LA SCCHN who are aged > 70 years, largely based on the MACH *meta*-analysis that did not show a benefit with cisplatin in patients aged > 70 years [23]. However, other centers may perform geriatric screening assessments to determine patient eligibility for cisplatin treatment. Chronological age alone should not be a determining factor for cisplatin eligibility because fit older patients have been shown to receive comparable clinical benefits to younger patients when receiving full-dose CRT [24]. Geriatric screening tools should be used to assess the frailty of older patients [12,13]. In the authors' experience, at least 30–40 % of patients with LA SCCHN who are aged < 70 years and undergo surgical resection are ineligible for cisplatin, although estimates vary between centers.

Areas of debate include whether hearing impairment should be based on clinical definitions, such as CTCAE (and if so, grade ≥ 2 or ≥ 3), or audiograms; what approach should be taken for patients who are borderline ineligible based on renal function (creatinine clearance close to 60 mL/min); and whether age > 70 years should be an absolute contraindication to cisplatin or if biological age is more relevant.

Cisplatin-related toxicity is dose dependent, and retrospective analyses suggest that up to half of patients who start cisplatin do not complete the full planned dose [11,15,25]. Furthermore, in the prospective De-ESCALaTE study in patients with unresected, low-risk human papillomavirus–positive oropharyngeal cancer, only 38 % of patients in the cisplatin arm received 3 cycles of cisplatin [26]. A cumulative cisplatin dose of ≥ 200 mg/m^2 has been associated with significantly longer OS than a cumulative dose of < 200 mg/m^2 [16,27]. In a retrospective study of 184 patients, a cumulative cisplatin dose of ≥ 200 mg/m^2 was only achieved in < 40 % of patients [28]. However, in recent randomized phase 3 studies in patients with unresected LA SCCHN receiving CRT, higher proportions of patients have received cumulative doses of ≥ 200 mg/m^2. For example, in the control arm of the JAVELIN Head and Neck 100 study, the median cumulative dose of cisplatin was 278 mg/m^2 (IQR, 201–300 mg/m^2) [29]; in the KEYNOTE-412 study, 88 % of patients who received cisplatin had a total dose of ≥ 200 mg/m^2 [30]. In patients with preexisting relative contraindications to cisplatin, clinicians may consider adjusting the timing of administration with the target of achieving a specific cumulative dose.

Table 1
Summary of recent clinical studies in LA SCCHN enrolling cisplatin-ineligible populations and cisplatin ineligibility criteria used (as of November 2022).

Study (status)	Study number	Phase	Treatment arms	Patients	Cisplatin ineligibility criteria
NRG-HN004 [57] (active, not recruiting)	NCT03258554	2/3	Durvalumab plus RT ± cetuximab vs cetuximab plus RT	Unresected, cisplatin-ineligible LA SCCHN	ECOG PS ≥ 2; renal or hearing impairment; peripheral neuropathy; age ≥ 70 years with moderate/severe comorbidity; or age < 70 years with severe comorbidity
NANORAY-312 [50] (recruiting)	NCT04892173	3	NBTXR3 plus RT ± cetuximab vs RT ± cetuximab	Cisplatin-ineligible, older patients (≥75 years of age) with unresected LA SCCHN	Age ≥ 75 years; estimated CrCl ≥ 30 and < 50 mL/min (per Cockcroft-Gault equation); grade ≥ 2 hearing loss or tinnitus; grade ≥ 2 peripheral neuropathy; ECOG PS > 2; or recent cardiac dysfunction (history of unstable angina pectoris, myocardial infarction, or New York Heart Association class III chronic heart failure < 3 years prior to screening)
PembroRad [58] (completed)	NCT02707588	2	Pembrolizumab + RT vs cetuximab + RT	Unresected LA SCCHN and unfit to receive Q3W cisplatin	Calculated CrCl < 60 mL/min; grade ≥ 2 peripheral neuropathy; grade ≥ 2 sensorineural hearing loss (confirmed by audiogram); cardiac function incompatible with hyperhydration with significant heart disease; age ≥ 75 years; age 71–74 years and ECOG PS 1 and/or G8 score 14; and general clinical status incompatible with Q3W cisplatin and RT, according to the investigator
REACH [59] (active, not recruiting)	NCT02999087	3	Cisplatin unfit*: avelumab + cetuximab and RT followed by avelumab maintenance (12 months) vs RT + cetuximab	Unresected LA SCCHN	Calculated CrCl < 60 mL/min (per modified Cockcroft-Gault equation or EDTA method); absolute neutrophil count < 1,500/μL; platelets < 100,000/μL; hemoglobin < 10 g/dL; AST and ALT > 2 times ULN range; total bilirubin > 1.5 mg/dL; serum albumin ≤ 35 g/L; grade ≥ 2 peripheral neuropathy; clinical hearing loss (confirmed by audiogram); cardiac function incompatible with hyperhydration; or LVEF not within institutional normal range
DHANUSH [49] (active, not recruiting)	CTRI/2017/05/008700	2/3	Docetaxel + RT vs RT alone	Cisplatin ineligible; resected and unresected LA SCCHN	ECOG PS 2; organ dysfunction of grade ≥ 2, such as hearing loss, tinnitus, or neurologic disorders; hypersensitivity to cisplatin; calculated CrCl < 50 mL/min; borderline organ function or comorbidities precluding the use of cisplatin, such as LVEF < 50 % that could preclude cisplatin hydration, renal dysfunction (noncorrectable) with high creatinine even with a CrCl of > 50 mL/min because of high body weight, or uncontrolled or poorly controlled hypertension; loss of > 10 % of baseline body weight in preceding 6 months; malnourished status (BMI < 16 kg/m^2); or requirement for concomitant nephrotoxic drugs for a concurrent medical condition

*The study recruited patients who are cisplatin fit or unfit; criteria to define patients who are cisplatin unfit are listed.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; EDTA, ethylenediaminetetraacetic acid; LA, locally advanced; LVEF, left ventricular ejection fraction; Q3W, every 3 weeks; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; ULN, upper limit of normal.

Clinical studies have assessed the efficacy and safety of alternative cisplatin dosing schedules. A phase 3 study conducted in India in 300 patients with resected high-risk or unresected LA SCCHN evaluated the noninferiority of cisplatin 30 mg/m^2 weekly vs cisplatin 100 mg/m^2 every 3 weeks (Q3W) [31]. Most patients (93 %) had undergone tumor resection and received adjuvant CRT, and other patients received CRT as definitive treatment. Locoregional control (primary endpoint) was significantly improved in the Q3W vs weekly arm, and secondary endpoints (progression-free survival [PFS] and OS) also favored the Q3W arm; however, the weekly regimen was associated with less acute toxicity and chronic hearing loss [31]. Importantly, the differences in cumulative dosing between the 2 study arms might explain the study results because the median cumulative cisplatin dose was 210 mg/m^2 (IQR, 180–210 mg/m^2) in the weekly cisplatin arm and 300 mg/m^2 (IQR, 200–300 mg/m^2) in the Q3W arm [31]. In contrast, a randomized phase 2/3 trial conducted in Japan in patients with resected, high-risk LA SCCHN found that adjuvant CRT with weekly cisplatin (40 mg/m^2) was associated with noninferior OS (primary endpoint) compared with CRT including Q3W cisplatin (100 mg/m^2), with some AEs reported more frequently with Q3W cisplatin. Overall proportions of patients with grade ≥ 3 AEs were comparable between the study arms (Q3W, 79.8 %; weekly, 81.1 %), although some toxicities (grade ≥ 3 neutropenia and infection, any-grade renal impairment and hearing impairment) were more prevalent in the Q3W arm [32]. No study of weekly cisplatin in patients with relative contradictions to cisplatin has been conducted.

Until a wider consensus is reached regarding how to define cisplatin eligibility in patients with LA SCCHN, and whether alternative cisplatin regimens to SoC are more suitable for patients with relative contraindications to cisplatin, approaches taken in clinical practice will continue to vary. This lack of consensus is also reflected in clinical trials in cisplatin-ineligible LA SCCHN populations in the definitive treatment setting, with studies having varying eligibility criteria (Table 1).

The evolution of adjuvant treatment for patients with resected, high-risk disease

The treatment landscape for resected LA SCCHN has remained relatively unchanged for approximately 2 decades. Prior to the mid-2000s, most patients received adjuvant RT alone. Based on clinical evidence, no RT fractionation schedule has shown superiority across all types of LA SCCHN; however, RT is typically delivered as a cumulative dose of 60–66 Gy in daily fractions of 1.8–2.0 Gy [5]. Although standard or conventional RT fractionation schedules are still used, alternative schedules, such as hyperfractionation, are becoming increasingly used in clinical practice, with many patients in the United States and Europe now receiving intensity-modulated RT (IMRT) [5,33]. In studies of RT administered alone, IMRT has shown superior efficacy vs 2D RT and comparable locoregional control and OS vs 3D conformal RT [5], although the pivotal studies that compared CRT vs RT published in the early 2000s did not use IMRT. However, the use of IMRT in combination with chemotherapy is recommended in both the adjuvant and definitive LA SCCHN settings due to reductions in the incidence of xerostomia reported in phase 3 studies in patients with early-stage SCCHN [5,34–36].

The introduction of cisplatin-based CRT as SoC for adjuvant treatment of patients at high risk of disease recurrence was based on data from 2 key studies: EORTC-22931 and RTOG 9501 [37,38]. Both studies compared adjuvant RT (EORTC: 66 Gy in 2 fractions over 6.5 weeks; RTOG: 60 Gy in 30 fractions over 6 weeks, with or without a boost of 6 Gy in 3 fractions over a period of 3 days to high-risk sites) with CRT (cisplatin 100 mg/m^2 on days 1, 22, and 43 of RT). However, slightly different criteria were used to define high-risk disease (EORTC: presence of tumor within 5 mm of microscopic tumor margins, extranodal spread, perineural involvement, or vascular tumor embolism; RTOG: presence of microscopic tumor at the mucosal surgical margins, histologic evidence

of invasion of ≥ 2 regional lymph nodes, or extracapsular extension of nodal disease). In the primary analysis of both studies, CRT was found to be superior to RT alone for the primary endpoints (EORTC: PFS; RTOG: locoregional control), and OS was improved in the EORTC study but not in the RTOG study [37,38]. Unlike contemporary studies in LA SCCHN, both studies included patients with oropharyngeal cancer, but no human papillomavirus testing was conducted. In a combined exploratory analysis of both studies reported in 2005, the most significant prognostic factors for poor outcome were microscopically involved resection margins (the analysis did not differentiate between positive and close margins used in EORTC and RTOG) and extracapsular spread of disease from neck nodes; adjuvant CRT was found to improve outcomes in patients with 1 or both of these factors [39]. Furthermore, a long-term analysis of the RTOG study (median follow-up, 9.4 years) was reported in 2012. Consistent with the primary publication, no difference in OS was observed between the treatment arms in the overall population; however, improved outcomes were seen with CRT for high-risk patients (patients who had microscopically involved resection margins and/or extracapsular spread of disease) [40]. Based on data from the EORTC and RTOG studies, the National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and European Society for Medical Oncology (ESMO) guidelines recommend cisplatin-based CRT for adjuvant treatment of patients with LA SCCHN who are at high risk of disease recurrence (defined as those with positive or close margins [< 5 mm] or extracapsular spread of disease). These features must not be confused with other high-risk features in patients without close margins and without extracapsular spread of disease (pT3, pT4, pN2, pN3, perineural, vascular, or lymphatic invasion), which guide the use of adjuvant RT alone [5,6].

A phase 3 study reported in 2015 provided more contemporary data for outcomes in patients with resected high-risk LA SCCHN receiving adjuvant CRT (defined as a surgical margin of ≤ 5 mm and/or extracapsular extension). This study found that the addition of lapatinib to CRT (cisplatin 100 mg/m^2 Q3W) provided no efficacy benefit vs placebo plus CRT. In the placebo plus CRT arm, disease-free survival (DFS) rates at 3 and 5 years were 62.2 % and 57.1 %, and OS rates at 3 and 5 years were 66.2 % and 57.3 %, respectively. The most common grade 3/4 AEs in this arm were lymphopenia (21 %), mucosal inflammation (17 %), leukopenia (13 %), dysphagia (12 %), and neutropenia (11 %) [41].

While criteria for adjuvant CRT in patients at high risk of disease recurrence following resection are established (microscopically involved resection margins and extracapsular spread of disease from neck nodes), no consensus exists regarding the margins. For most head and neck cancers, 5 mm of surrounding tissue with no involvement of cancer is accepted as a "clear" margin [5,6,42]; however, this may not be achievable if surgery is limited by close proximity to critical anatomical features [43]. Additionally, tissue samples often contract during formalin fixation, causing a reduction in the observed margins [43]. Although 1–4 mm is widely considered as a close margin, this remains an area of debate, with some publications suggesting that a smaller margin, such as 1 mm, does not result in significantly shorter OS [43–46].

Authors' perspectives: Adjuvant cisplatin-based CRT should be used when margins are < 5 mm and if there is extracapsular spread in the lymph nodes. Several other factors may indicate a higher risk of recurrence, including tumor cells infiltrating near the margin, lymphovascular space invasion, perineurial space invasion, and T stage of tumor (≥ T3); however, they are not absolute indications of a high risk of disease recurrence. In patients with a margin ≥ 5 mm and absence of extracapsular extension, adjuvant RT alone should be used.

What are the adjuvant treatment options for patients with high-risk disease who are ineligible to receive cisplatin?

For patients with resected LA SCCHN who are ineligible for cisplatin, clinical data are scarce, and few adjuvant treatment options are supported by guidelines. The NCCN Guidelines list docetaxel plus cetuximab plus RT as a potential treatment option for adjuvant treatment in patients with positive margins and/or extranodal extension who are ineligible for cisplatin, with level of evidence 2B [5]. This option is based on data from the phase 2 RTOG 0234 study, which randomized 238 cisplatin-eligible patients with stage III/IV resected LA SCCHN who had positive margins, extracapsular nodal extension, or ≥ 2 nodal metastases [47]. Patients received cetuximab (400 mg/m^2 loading dose followed by 6 weekly infusions of 250 mg/m^2) plus RT (60 Gy) with either cisplatin (30 mg/m^2 weekly) or docetaxel (15 mg/m^2 weekly). The combination of cetuximab, RT, and docetaxel compared with cetuximab, RT, and cisplatin significantly increased DFS (primary endpoint; 31 % vs 24 %) and OS (2-year OS, 79 % vs 69 %) rates. Additionally, patients with p16-positive oropharyngeal tumors had markedly improved OS relative to patients with p16-negative oropharyngeal tumors [47]. One limitation for interpreting the results of this study is that the population included patients with ≥ 2 involved lymph nodes without the presence of other adverse features, in addition to patients with the highest risk of recurrence (ie, patients with positive margins and/or extracapsular nodal extension). Notably, cisplatin was administered at a dose of 30 mg/m^2 rather than 40 mg/m^2, and the majority of patients in both arms received non-IMRT (61.6 %), further limiting the generalizability of these results. Taken together, a confirmatory phase 3 study is needed to substantiate these findings. ESMO guidelines do not recommend any specific treatment for patients with resected LA SCCHN ineligible to receive cisplatin [6]. The American Society of Clinical Oncology guidelines for the management of squamous cell carcinomas of the oral cavity and oropharynx recommend enrollment in clinical trials for patients with resected tumors who are ineligible to receive cisplatin and note that absolute and relative contraindications to cisplatin are common in clinical practice, but alternative regimens have little evidence-based support [48].

A recent phase 3 study explored docetaxel plus RT in patients with LA SCCHN who were ineligible to receive cisplatin [49], defined as meeting ≥ 1 criterion established by Ahn et al [12] (Table 1). In this study, 356 patients were randomized 1:1 to receive docetaxel 15 mg/m^2 weekly for a maximum of 7 cycles plus RT vs RT alone as either definitive (66–70 Gy) or adjuvant (60 Gy) treatment. Most patients (61 %) received treatment in the definitive setting, and the remainder (39 %) received adjuvant treatment [49]. Docetaxel plus RT improved DFS (primary endpoint) vs RT alone; the 2-year DFS rate was 42 % (95 % CI 34.6–49.2 %) vs 30.3 % (95 % CI 23.6–37.4 %), respectively (hazard ratio [HR], 0.673; 95 % CI 0.521–0.868; $P = 0.002$). OS was also improved with docetaxel plus RT vs RT alone; median OS was 25.5 months (95 % CI 17.6–32.5 months) vs 15.3 months (95 % CI 13.1–22 months), respectively ($P = 0.035$). However, a subgroup analysis of the adjuvant population alone showed no significant improvements in DFS and OS with the addition of docetaxel to RT (2-year DFS [HR, 0.82; 95 % CI 0.52–1.28; $P = 0.396$]; 2-year OS [HR, 0.84; 95 % CI 0.53–1.33; $P = 0.478$]). In addition, data were not presented for risk groups (high and intermediate), and 2D RT was used, which is not SoC in most countries [49].

Overall, no consensus exists on the best adjuvant treatment for cisplatin-ineligible patients with resected LA SCCHN who are at high risk of disease recurrence. Given the lack of clinical data showing improved efficacy in this population, RT alone remains a reasonable and acceptable SoC option. The lack of available data also means that OS in

Table 2
Summary of active phase 3 trials of neoadjuvant treatment for LA SCCHN (as of November 2022).

Neoadjuvant treatment	NCT number	Study name	Cisplatin eligibility	Sponsor	Primary endpoint	Number of patients	Estimated primary completion date	Status
Neoadjuvant tislelizumab + cisplatin and nab-paclitaxel, then surgery, followed by tislelizumab + CRT (high risk) or tislelizumab + RT (low risk) vs surgery (high-risk CRT; low-risk RT)	NCT05582265	REDUCTION-I	Cisplatin eligible only	Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University	EFS	588	October 2028	Recruiting
Neoadjuvant toripalimab + nab-paclitaxel and cisplatin vs docetaxel, cisplatin, and 5-FU	NCT05125055	Illuminate-2	Cisplatin eligible only	Shanghai Jiao Tong University School of Medicine	Major pathological response	80	September 2023	Recruiting
Neoadjuvant pembrolizumab + SoC adjuvant therapy vs no neoadjuvant treatment and SoC adjuvant therapy	NCT03765918	KEYNOTE-689	Cisplatin eligible only	MSD	EFS, major pathological response	704	July 2025	Recruiting

5-FU, 5-fluorouracil; CRT, chemoradiotherapy; EFS, event-free survival; LA, locally advanced; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard of care.

this population is unclear; however, based on the greater comorbidity in cisplatin-ineligible patients, it is likely that this population will have a shorter median OS than that seen in a cisplatin-eligible population, irrespective of treatment. Thus, cisplatin-ineligible patients with resected high-risk LA SCCHN are a population with a high unmet need, and new clinical studies are needed.

Which future studies might impact the treatment landscape?

In the definitive setting, there is one active, phase 3 study in patients who are platinum-ineligible; NANORAY-312 is investigating the combination of the radioenhancer NBTXR3, given as an intratumoral or intranodal injection, plus investigators' choice of RT ± cetuximab vs investigators' choice of RT ± cetuximab in elderly patients with unresected LA SCCHN [50].

Active phase 3 studies of neoadjuvant or adjuvant treatment for LA SCCHN, irrespective of cisplatin eligibility or risk status, are summarized in Table 2 and Table 3. In the neoadjuvant setting, 3 phase 3 studies are ongoing, all of which are enrolling only cisplatin-eligible patients. All 3 trials are assessing immune checkpoint inhibitor–based treatment in combination with different chemotherapy and RT regimens, and 2 trials (REDUCTION-I and KEYNOTE-689) involve both neoadjuvant and adjuvant treatment.

In the postoperative adjuvant setting, 6 studies are ongoing, including 1 in an intermediate-risk population and 5 in high-risk populations. In these trials, different classes of agents are being combined with either CRT or RT, including immune checkpoint inhibitors, RT/chemotherapy sensitizers, an epidermal growth factor receptor inhibitor (cetuximab), and nonplatinum cytotoxic chemotherapies. In terms of cisplatin eligibility, 3 studies are enrolling cisplatin-eligible patients only, and 2 are enrolling patients regardless of cisplatin eligibility. Of the studies that do not consider cisplatin eligibility, 1 phase 3 study, RTOG 0920 (NCT00956007), is investigating cetuximab plus IMRT vs IMRT alone in patients who have undergone surgical resection and are at intermediate risk of disease recurrence. The primary study endpoint is OS, and data are expected at the end of 2024. The second phase 3 study, RTOG 1216 (NCT01810913), is comparing 4 treatments (CRT; docetaxel plus IMRT; cetuximab plus docetaxel and IMRT; and CRT plus atezolizumab) in high-risk patients. The primary study endpoints are DFS and OS, and primary data are expected in 2027.

One phase 3 study is exclusively enrolling patients who are ineligible to receive cisplatin: the XRay Vision study (NCT05386550), which is investigating xevinapant plus IMRT. Xevinapant is a potent, oral, small-molecule IAP (inhibitor of apoptosis protein) inhibitor that is thought to restore cancer cell sensitivity to apoptosis and thereby enhance the efficacy of chemotherapy and RT. Xevinapant inhibits X-linked IAP and cellular IAP 1 and 2 (cIAP1/2), releasing the blockade on downstream caspase activity, which is crucial for apoptosis and anticancer activity of chemotherapy and RT [51–53]. Inhibition of cIAP1/2 may also amplify immune cell activation by activating noncanonical nuclear factor–κB signaling, which induces the production of inflammatory cytokines in response to tumor necrosis factor receptor signaling [51,52].

Xevinapant has demonstrated synergistic/additive activity with RT in preclinical SCCHN models [51,54]. In a randomized phase 2 study of patients with unresected LA SCCHN, xevinapant plus CRT significantly increased the rate of locoregional control at 18 months after the end of CRT (primary endpoint) [55], markedly improved PFS and prolonged duration of response after 3 years of follow-up, and halved the risk of death after 5 years of follow-up [56]. Xevinapant's novel mode of action, preclinical anticancer activity in combination with RT, and promising clinical data in combination with CRT provide the rationale for evaluating xevinapant in combination with RT. XRay Vision (NCT05386550) is an international, randomized, double-blind, placebo-controlled, phase 3 trial evaluating xevinapant plus IMRT vs placebo plus IMRT in patients with resected, high-risk LA SCCHN ineligible to receive cisplatin. The primary endpoint is DFS, and secondary endpoints include OS, time to subsequent anticancer treatment, safety, and QoL. The trial started enrolling patients in 2022.

Conclusions

The landscape for adjuvant treatment of patients with resected LA SCCHN has not seen any major improvements since trials demonstrating the benefits of cisplatin-based CRT in the mid-2000s. In particular, patients with resected, high-risk LA SCCHN ineligible to receive cisplatin have limited treatment options and are a population with high unmet need. Because of a lack of clinical studies, evidence to guide treatment in this population is very limited, and treatment selection is often based on clinical judgment and data extrapolated from different settings. Other data gaps include the lack of a universally agreed definition of cisplatin ineligibility, a lack of clarity in the proportion of patients with resected LA SCCHN who are cisplatin ineligible, and no data to determine

Table 3
Summary of active phase 3 clinical trials of adjuvant treatment for LA SCCHN (as of November 2022).

Adjuvant treatment	Placebo controlled	NCT number	Study name	Cisplatin eligibility	Risk of recurrence	Sponsor	Primary endpoint	Number of patients	Estimated primary completion date	Status
Docetaxel + RT vs cisplatin + RT	No	NCT02923258	2016HNRT004	Cisplatin eligible only	High*	Shanghai Ninth People's Hospital	DFS	387	December 2020	Unknown
Cetuximab + RT vs RT	No	NCT00956007	RTOG 0920	Any	Intermediate†	RTOG	OS	703	December 2024	Active, not recruiting
Nimotuzumab + CRT vs CRT	Yes	NCT00957086	IHN01	Cisplatin eligible only	High‡	National Cancer Centre, Singapore	DFS	710	January 2024	Active, not recruiting
CRT vs docetaxel + IMRT§ vs cetuximab + docetaxel + IMRT vs atezolizumab + CRT	No	NCT01810913	RTOG 1216	Any	High¶	NCI	DFS, OS	613	January 2027	Recruiting
Nivolumab + CRT vs CRT	No	NCT03576417	NIVOPOSTOP	Cisplatin eligible only	High**	GORTEC	DFS	680	August 2027	Recruiting
Xevinapant + RT vs RT	Yes	NCT05386550	XRay Vision	Cisplatin ineligible only††	High‡‡	Merck KGaA	DFS	700	October 2027	Recruiting

* ≥ 1 of the following: histologic extracapsular nodal extension; histologic involvement of ≥ 2 regional lymph nodes; invasive cancer seen on microscopic evaluation of the resection margin, with no evidence of gross tumor residual.

† ≥ 1 of the following: perineural invasion; lymphovascular invasion; single lymph node > 3 cm or ≥ 2 lymph nodes (all < 6 cm; no extracapsular extension); close margin(s) of resection, defined as cancer extending to within 5 mm of a surgical margin, and/or an initially focally positive margin that is subsequently superseded by intraoperative negative margins (similarly, patients whose tumors had focally positive margins in the main specimen but negative margins from re-excised samples in the region of the positive margin are eligible); pathologically confirmed T3 or T4a primary tumor; T2 oral cavity cancer with > 5 mm depth of invasion.

‡ ≥ 1 of the following: pT3 or pT4 and any nodal stage, except T3N0 of the larynx, with negative resection margins, or a tumor stage of 1 or 2 with a nodal stage of 2 or 3 and no distant metastasis (M0); patients with stage T1 or T2 and N0 or N1 who had unfavorable pathological findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) are also eligible, as are those with oral cavity or oropharyngeal tumors with involved lymph nodes at level IV or V.

§ Arm closed March 2020.

¶ Extracapsular nodal extension or invasive cancer at the primary tumor resection margin.

** ≥ 1 of the following criteria: extracapsular extension; multiple perineural invasion; multiple nodal extension without extracapsular extension (≥ 4 nodes); positive margins (R1 or close margin ≤ 1 mm), where R1 is microscopic residual disease and close margin is R0 with a minimum margin ≤ 1 mm in any direction.

†† ≥ 1 of the following criteria: estimated glomerular filtration rate < 60 mL/min/1.73 m^2; history of hearing impairment, defined as grade ≥ 2 audiometric hearing loss or grade ≥ 2 tinnitus. An audiogram is not required if 1 of the other criteria meets unfitness to receive high-dose cisplatin; grade ≥ 2 peripheral neuropathy; and if age ≥ 70 years, unfit according to G8 questionnaire (score ≤ 14).

‡‡ One or 2 of the following criteria, confirmed by local histopathology: nodal extracapsular extension; positive resection margins (R1 or close margin ≤ 1 mm).

CRT is cisplatin-based chemoradiotherapy.

CRT, chemoradiotherapy; DFS, disease-free survival; IMRT, intensity-modulated radiation therapy; LA SCCHN, locally advanced squamous cell carcinoma of the head and neck; OS, overall survival; RT, radiotherapy.

expected OS in this population. Cisplatin-free treatment regimens that have superior antitumor activity vs RT alone in cisplatin-ineligible patients are urgently needed. XRay Vision is the only ongoing phase 3 study that has the specific objective of improving outcomes in patients with resected, high-risk LA SCCHN who are ineligible to receive cisplatin.

Statement of literature search

This review is based on previously published studies and does not contain novel data. This narrative review included publications identified from a series of PubMed searches. References detailing information on LA SCCHN, cisplatin ineligibility, and adjuvant treatment of resected LA SCCHN were included. Based on the authors' judgement, publications determined to be irrelevant were excluded from consideration. Any relevant references cited within the publications discussed in this review and articles known by the authors were also considered. Clinical studies were identified from searches of ClinicalTrials.gov. The authors (Robert I. Haddad, Kevin Harrington, Makoto Tahara, Petr Szturz, Christophe Le Tourneau, Satu Salmio, Marcis Bajars, and Nancy Y. Lee) are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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