ADVANCES IN THE SYSTEMIC THERAPY AND COMBINED MODALITY APPROACHES FOR HEAD AND NECK CANCER

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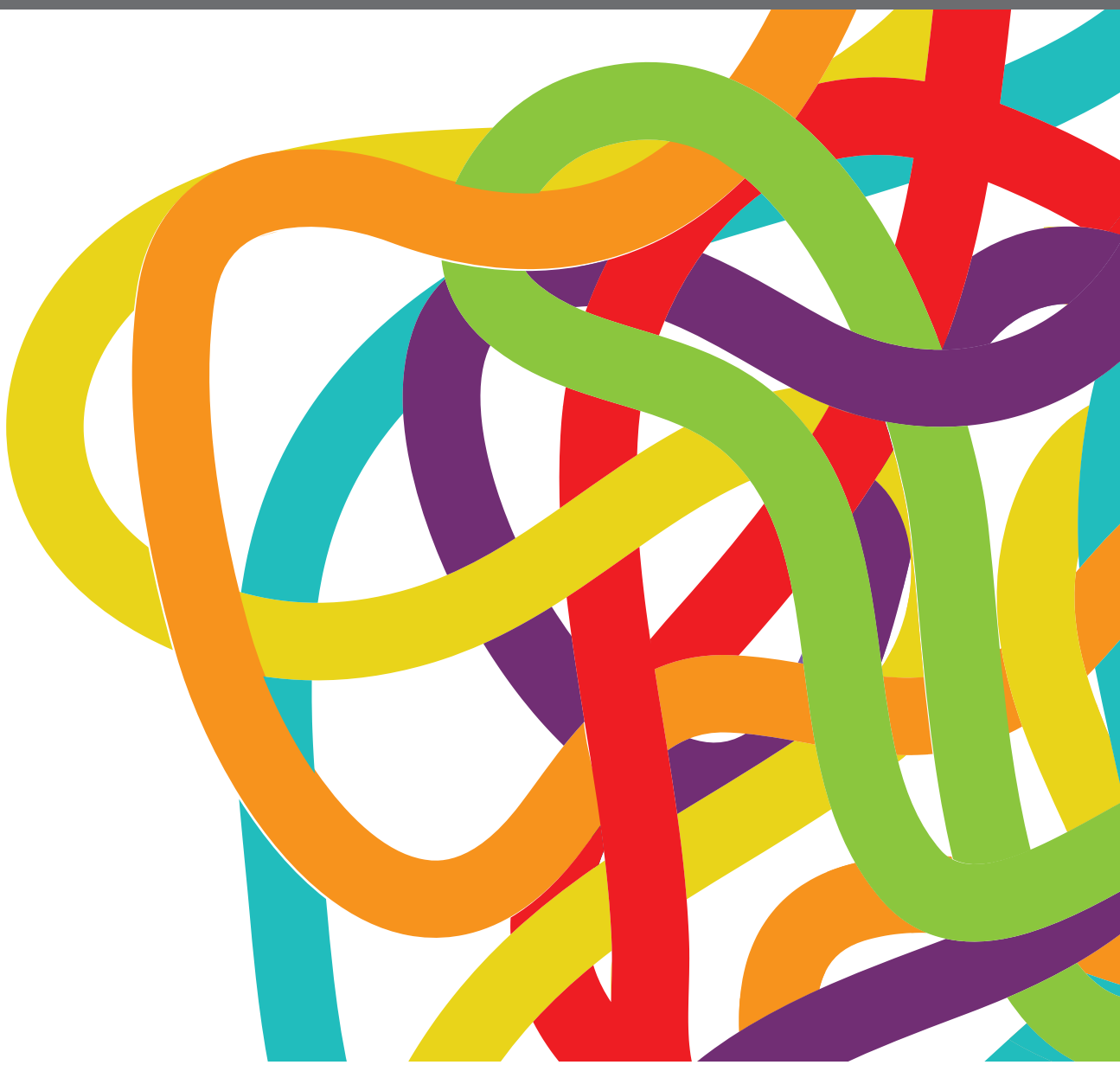

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ADVANCES IN THE SYSTEMIC THERAPY AND COMBINED MODALITY APPROACHES FOR HEAD AND NECK CANCER

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EDITORIAL
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Editorial: Advances in the Systemic Therapy and Combined Modality Approaches for Head and Neck Cancer

Athanassios Argiris[1]* *and Lisa Licitra*[2]

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Keywords: systemic therapy, chemotherapy, cetuximab, head and neck cancer, squamous cell carcinoma of the head and neck, human papillomavirus

Editorial on the Research Topic

Advances in the Systemic Therapy and Combined Modality Approaches for Head and Neck Cancer

In the past few years there have been several developments in the field of head and neck oncology, including major advances in systemic therapy and combined modality treatment. Systemic therapy indeed has been playing an increasing important role in the management of squamous cell carcinoma of the head and neck (SCCHN) in both the locally advanced and the recurrent/metastatic disease settings.

This Special Issue of Frontiers in Oncology focuses on "Advances in the Systemic Therapy and Combined Modality Approaches for Head and Neck Cancer" and was compiled with the main objective of providing a timely overview of emerging concepts in the systemic therapy of head and neck cancer and the integration of systemic agents into multimodality management. We are very thankful to have received the contributions of many prominent experts in head and neck oncology. The Special Issue encompasses reviews on combined modality approaches in locally advanced SCCHN, including cisplatin eligibility issues, postoperative treatment, and laryngeal preservation approaches, an original report of an induction trial with cisplatin, docetaxel, cetuximab followed by radiotherapy and cetuximab, as well as reviews of the current and upcoming role of targeted therapies and immunotherapy in SCCHN. The role of cetuximab in recurrent or metastatic SCCHN is reviewed as well. Combinations of a taxane and cetuximab are active in the first-line setting and have been evaluated in randomized trials. We also cover therapeutic developments in nasopharyngeal cancer and include reviews on prognostic factors in recurrent or metastatic SCCHN and nasopharyngeal cancer that are potentially relevant for patient assessment and treatment decisions. Another interesting review focuses on emerging treatment strategies in human papillomavirus-positive oropharyngeal cancer, an increasing subset of SCCHN with different biology and better treatment outcomes.

We hope that this Special Issue of Frontiers in Oncology succeeded in stimulating the interest of our readers in systemic therapy options for the management of head and neck cancer. As the field is evolving our efforts will continue in order to provide updates with emerging data.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Paclitaxel Plus Cetuximab as 1st Line Chemotherapy in Platinum-Based Chemoradiotherapy-Refractory Patients With Squamous Cell Carcinoma of the Head and Neck

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Purpose: We sought to evaluate the efficacy and safety of the combination of cetuximab (Cmab) and paclitaxel (PTX) in patients with squamous cell carcinoma of the head and neck (SCCHN) who had unresectable recurrent or metastatic (R/M) disease after platinum-based chemoradiotherapy.

Materials and Methods: Data on 23 patients with SCCHN who received paclitaxel and cetuximab (Cmab) for R/M disease no more than 6 months after CRT completion were retrospectively reviewed. PTX and Cmab were given in a 28-day cycle (PTX, 80 mg/m^2 on days 1, 8, and 15; Cmab, loading dose 400 mg/m^2 followed by a weekly 250 mg/m^2). The differences in prognosis between subgroups in different clinical settings were also assessed.

Results: CRT had been delivered as definitive treatment in 13 cases (57%) and as adjuvant treatment in 10 (43%). Median time from CRT completion to disease recurrence or metastasis was 73 days (1–152). The best objective response and disease control rates were 52 and 83%, respectively, with 12 partial responses and seven cases of stable disease by Response Evaluation Criteria in Solid Tumors (RECIST). A total of 17 of 23 patients (74%) achieved a degree of tumor shrinkage. Median progression-free survival (PFS) and overall survival (OS) were 7.0 (95% confidence interval [CI]: 3.7–8.4) and 16.3 months (95% CI: 7.8–23.3), respectively. Patients with a longer duration (≥60 d) from CRT completion to disease progression had a statistically significantly longer OS than the others (median OS 22.3 vs. 8.1 months, log-rank test; $p = 0.034$). Main Grade 3 toxicities included neutropenia (13%), anemia (13%), and hypomagnesemia (13%). No Grade 4 toxicity or treatment-related death was seen.

Conclusion: PTX and Cmab is a tolerable and effective option in SCCHN patients with symptomatic CRT-refractory disease. Its favorable effects on tumor shrinkage will help relieve tumor-associated symptoms.

Keywords: paclitaxel, cetuximab, chemoradiotherapy, platinum-refractory, squamous cell carcinoma of the head and neck

INTRODUCTION

Head and neck cancer is the sixth-most common cancer worldwide, and more than 600,000 new cases of squamous cell carcinoma of the head and neck cancer (SCCHN) are diagnosed annually (1, 2). Optimal management of these patients requires a multidisciplinary approach involving radiation oncologists, medical oncologists, and head and neck surgeons. Chemoradiotherapy (CRT) plays an important role in the treatment of head and neck cancer as both a definitive treatment as well as post-operative adjuvant treatment (3–6). However, the recurrence rate of stage III/IV disease after curative or post-operative adjuvant chemoradiotherapy is about 30–40% in the first 2 years of follow up (5–7). For these patients, treatment options are scarce and survival is dismal. In unresectable recurrent or metastatic (R/M) disease after chemoradiotherapy, palliative chemotherapy is the mainstay of treatment. Patients who progress relatively early in their disease course after the last administered dose of a platinum agent (within 6 months as a general guide) have been referred to as "platinum-refractory." Retreatment with platinum in the setting of platinum-refractory disease has been shown to increase toxicity without improving outcome (8, 9), and it is commonly understood that these patients should be treated with a non-platinum-containing regimen after that date.

As preclinical studies have shown that the combination of cetuximab (Cmab) and taxanes seems to be synergistic (10, 11), paclitaxel (PTX) plus Cmab is a palliative option after failure of platinum-based therapy, offering overall response rates (ORRs)

TABLE 1 | Patient characteristics.

Characteristic	Patients, *n* (%)	
Age [year]		
Median (range)	65 (35–74)	
Gender		
Male	20	(8)
Female	3	(13)
ECOG performance status		
0	6	(26)
1	17	(74)
Primary site		
Oral cavity	10	(43)
Hypopharynx	7	(30)
Oropharynx	3	(13)
Larynx	1	(4)
Unknown primary	2	(9)
Smoking [pack-years]		
Median (range)	30	(0–128)
Clinical setting of chemoradiotherapy		
Definitive chemoradiotherapy	13	(57)
Adjuvant chemoradiotherapry	10	(43)
Cumulative CDDP dose during CRT [mg/m^2] Median (range)		
IV	240	(80–300)
IA	700	(700)
Radiotherapy dose during CRT [Gy]		
Median (range)	66	(50–70)
Time from chemoradiothrerapy to recurrence or metastasis [days]		
Median (range)	73	(1–152)
Disease status at PTX + Cmab initiation		
Loco-regional only	7	(30)
Distant only	7	(30)
Both loco-regional and distant	9	(40)

CRT, chemoradiotherapy; CDDP, cisplatin; PTX, paclitaxel; Cmab, cetuximab; IV, intravenous infusion; IA, intra-arterial infusion.

TABLE 2 | Summary of treatment.

Characteristic	Patients, *n*	
Number of PTX administrations		
Median (range)	12	(4–35)
Number of Cmab administrations		
Median (range)	18.5	(5–46)
Cmab maintenance therapy (%)		
No	15	(65)
Yes	8	(35)
Reason for proceeding to maintenance therapy		
Physicians' decision at the completion of 6 cycles of paclitaxel and cetuximab	4	(17)
PTX induced unacceptable toxicity*	3	(13)
Patient preference	1	(4)
Number of Cmab administrations as maintenance therapy		
Median (range)	6	(3–61)
Reason for discontinuation of PTX+ Cmab† (%)		
Progressive disease	20	(91)
Performance status worsened	1	(5)
Surgery	1	(5)
Subsequent treatment of PTX + Cmab† (%)		
None	3	(14)
Chemotherapy	17	(77)
Radiotherapy	1	(5)
Surgery	1	(5)

*PTX, paclitaxel; Cmab, cetuximab; *Grade 2 malaise in all three patients. †Out of 22 patients who failed treatment of PTX + Cmab at cutoff date.*

TABLE 3 | Best response by treatment†.

Characteristic	Patients, *n* (%)	
CR	0	(0)
PR	12	(52)
SD	7	(30)
PD	4	(17)
Overall response rate (95%CI)	52% (33–71)	
Disease control rate (95%CI)	83% (62–94)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. †RECIST v. 1.1.

of 38–55% and median OS of 7.6–10 months (12–14). Among others, Hitt et al. prospectively showed that PTX and Cmab was active (ORR54%, median PFS 4.2months, median OS 8.1 months) as 1st line treatment in R/M HNSCC patients, for whom platinum is contraindicated (15). Nevertheless, data on PTX and Cmab as 1st line treatment in patients with platinum-based CRT-refractory SCCHN is lacking. This is the first report to focus on the efficacy and safety of PTX and Cmab in patients with highly aggressive disease, who we often experience in daily practice. In addition, several factors have been considered to be potentially prognostic in head and neck cancer patients who relapse after curative treatment [e.g., clinical setting of CRT [definitive vs. adjutant] (16) or recurrence pattern (17)]. Furthermore, Cmab-containing regimens may provide different clinical activity according to the primary site (18). Accordingly, we attempted to evaluate primary site as predictive factor of PTX and Cmab in subgroup analyses.

MATERIALS AND METHODS

Patient Population

To extract a heterogeneous population of platinum-based CRT-refractory patients who received PTX and Cmab as 1st line treatment, we reviewed data for 74 consecutive patients with histologically proven head and neck cancer treated with PTX and Cmab between December 2012 and October 2017 at the National Cancer Center Hospital East, Japan. After the selection process, which included excluding patients with prior exposure to either PTX or Cmab as part of induction or definitive treatment, the final analysis was restricted to those 23 patients with SCCHN who received a combination of PTX and Cmab as 1st line treatment for recurrent or metastatic disease no more than 6 months after platinum-based CRT completion (**Supplementary Figure 1**). They were therefore assumed to be platinum-refractory. Data on patient demographics, tumor characteristics,

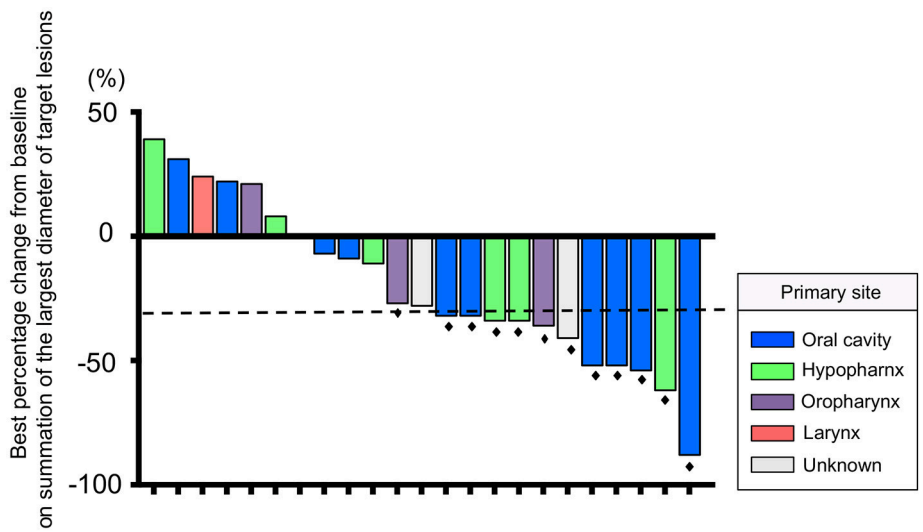

FIGURE 1 | Waterfall plot of the maximum percentage change from baseline on summation of the largest diameter of target lesions for 23 patients. The *dashed line* indicates a 30% reduction in tumor burden in the target lesion. *Black dots* indicate patients who had a response according to RECIST version 1.1.

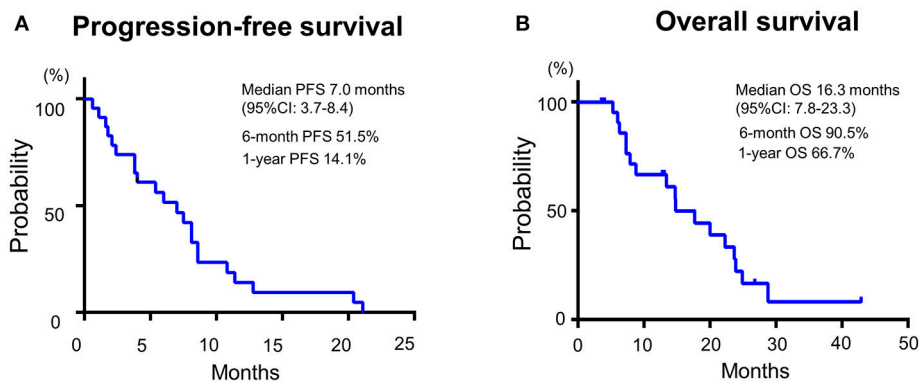

FIGURE 2 | Patient **(A)** progression-free survival and **(B)** overall survival of SCCHN patients with platinum-based CRT-refractory R/M disease treated with the combination of PTX and Cmab in 1st line setting.

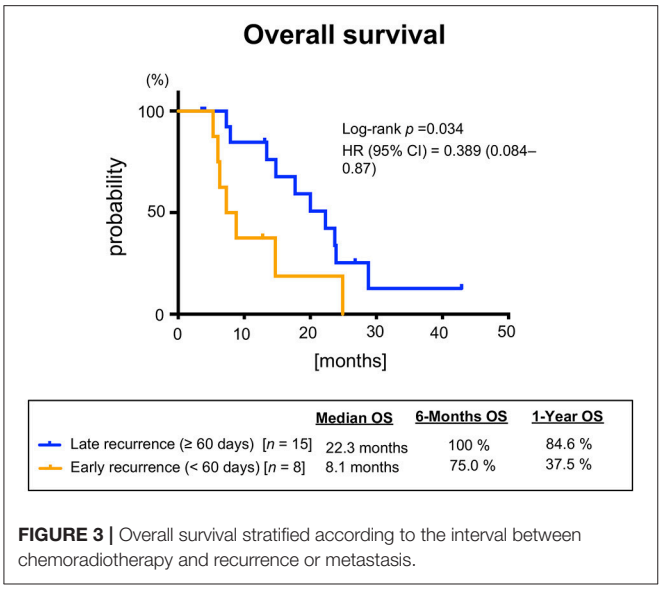

FIGURE 3 | Overall survival stratified according to the interval between chemoradiotherapy and recurrence or metastasis.

treatment-related toxicities, and responses were collected. The study was reviewed and approved by the institutional review board.

Treatment

All patients were required to have adequate hematological, hepatic and renal function before treatment. PTX and Cmab were given in a 28-day cycle, with PTX administered weekly at a dose of 80 mg/m^2 over 1 h on days 1, 8, and 15 of each cycle. Cmab was administered at a loading dose of 400 mg/m^2 during a 2-h infusion, followed by a weekly 1-h infusion of 250 mg/m^2 on days 1, 8, 15, and 22 of the treatment cycle. Some patients were switched at the completion of six cycles of PTX and Cmab to Cmab maintenance therapy at the discretion of the attending physician. Patients received Cmab monotherapy as a maintenance therapy until disease progression or until unacceptable toxic effects. All patients were premedicated with 13.3 mg of dexamethasone, 50 mg of ranitidine, and 8 mg of ondansetron before each dose of PTX and Cmab. Dexamethasone 6.6 mg and chlorpheniramine (H1 blocker) 5 mg were given on the days of Cmab monotherapy.

Evaluation of Efficacy and Toxicity

Clinical response to treatment was evaluated radiographically using computerized tomography imaging approximately every 8 weeks. Anti-tumor activity was retrospectively evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 via the review of imaging results. Toxicity during treatment was graded using the Common Toxicity Criteria for Adverse Event (CTCAE version 4.0).

Statistical Analysis

Progression-free survival (PFS) and Overall survival (OS) were calculated by the Kaplan-Meier product-limit method. The end of PFS was defined as disease progression or death from any cause, while the end of OS was determined as death from any cause. All other events were censored. Hazard ratios (HRs) were calculated by Cox regression analysis. The differences in PFS and OS between patients with oral cavity cancer and others, the differences between patients who received CRT as definitive treatment and as adjuvant treatment, and the differences between patients with and without metastatic disease were assessed using stratified log-rank tests. Statistical analyses were two-tailed and were performed using Prism version 6 software (GraphPad Software, Inc., La Jolla CA, USA). A p-value >0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Characteristics of the 23 eligible patients are summarized in **Table 1.** Most patients were men (87%), and median age was 65 year (range 35–74 year). All patients had undergone radiotherapy and concurrent cisplatin (CDDP), delivered as definitive treatment in 13 cases (57%) and as adjuvant treatment in 10 (43%).

Treatment and Efficacy

The median number of administrations given was 12 (range: 4–35) for PTX and 18.5 (range: 5–46) for Cmab. Eight patients (35%) proceeded to Cmab maintenance therapy. Among them, physicians decided to switch four patients to Cmab maintenance at the completion of six cycles of PTX and Cmab. Three patients experienced unacceptable PTX-induced toxicity, and discontinued PTX at that time, moving to Cmab maintenance. The majority of patients, 77%, began other chemotherapy after discontinuation of PTX and Cmab (**Table 2**). With a median follow up of 12.9 months (range 3.6–42.9), objective overall response (ORR) and disease control rate (DCR) was 52% (95% confidence interval [CI] 33–71%) and 83% (95% CI 62–94%), respectively. Twelve patients had partial responses (PR)(52%) and seven had stable disease (30%) (**Table 3**). Best percent change in tumor diameter (maximum lengths of all target lesions in the patient) were summed and change in tumor burden over time are shown in **Figure 1.**

Median PFS and OS were 7.0 (95%CI: 3.7–8.4) and 16.3 months (95%CI: 7.8–23.3), respectively (**Figure 2**). Additionally, we observed a trend toward improved PFS and a statistically significantly favorable OS in patients with longer duration (≥60 days) from CRT completion to disease recurrence or metastasis (**Figure 3** and **Supplementary Figure 2**). There were no apparent differences in response or prognosis according to clinical setting of CRT (definitive vs. adjuvant), primary site (oral cavity vs. others) or presence or absence of locoregional disease (**Supplementary Figure 3**).

Figure 4 shows scans of a tongue cancer patient with recurrent disease located in the trapezius, mediastinal lymph nodes, and lung, 5 months after completion of post-operative adjuvant chemoradiotherapy (cumulative CDDP dose: 200 mg/m^2 plus radiotherapy: 66 Gy) (**Figures 4A–C**). After one cycle of PTX and Cmab, his tumor-associated occipital pain was significantly relieved. Following three cycles, almost all recurrent lesions

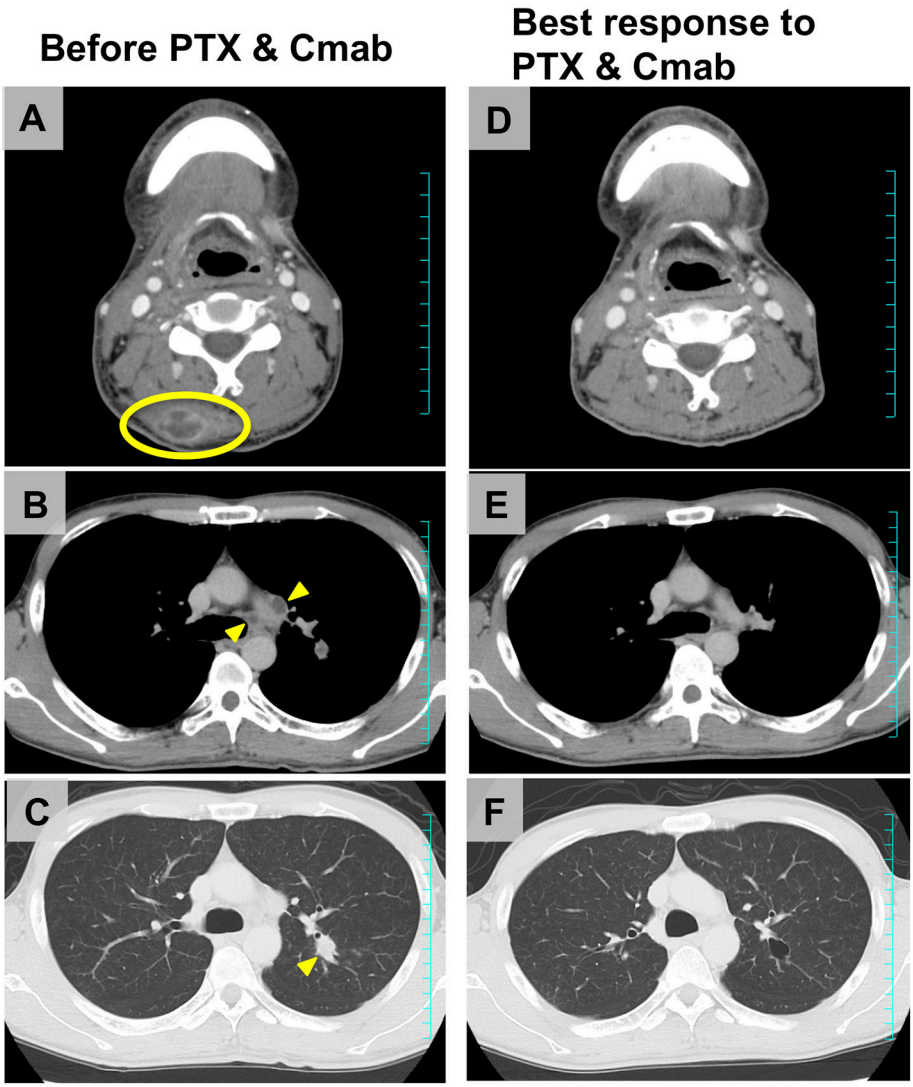

FIGURE 4 | Representative imaging from a tongue squamous cell carcinoma patient who achieved a favorable clinical response after CRT failure, a male initially treated with partial glossectomy and neck dissection and adjuvant CRT. **(A–C)** The tumor recurred in the trapezius (yellow ellipse), mediastinal lymph nodes, and lung (yellow arrowheads) 5 months after completion of CRT. **(D–F)** After four cycles of therapy (PTX 80 mg/m^2, days 1, 8, and 15; and Cmab, 400 mg/m^2 followed by a weekly 250 mg/m^2; 28-day cycle), almost all recurrent lesions had disappeared and occipital pain was completely alleviated.

had disappeared (**Figures 4D–F**). We then switched from PTX and Cmab to Cmab monotherapy according to the patient's preference; vertebral metastases appeared 1 month after. He eventually received PTX and Cmab (6 months) and subsequent Cmab monotherapy (1 month) for a total of 7 months.

Toxicity

Adverse events observed are listed in **Table 4**. Two patients (13%) developed Grade 3 anemia and required blood transfusions. Three patients (13%) developed Grade 3 neutropenia. No patient developed thrombocytopenia or febrile neutropenia of any grade. The most common non-hematological toxicity was skin toxicities (acneiform dermatitis, paronychia, skin cracks, and dry skin), which variously occurred in 20 patients (95%). The second-most common non-hematological toxicity was neuropathy, which was documented in 17 (74%) patients. Prolonged Grade 2 malaise was the stated reason for PTX discontinuation in three patients, who then proceeded to Cmab maintenance therapy. Although one patient developed Grade 3 septicemia and another experienced Grade 3 pulmonary embolism during treatment, they fully recovered. Hypomagnesemia was observed in 14 (67%) patients, and was Grade 3 in 3 patients (13%). No patient experienced Grade 4 toxicity, and no treatment-related deaths were seen.

DISCUSSION

The outcome of patients with recurrent and/or metastatic head and neck cancer refractory to platinum-based chemotherapy

TABLE 4 | Summary of adverse events.

Toxicity	All grades Patients, *n* (%)	Grade 3 Patients, *n* (%)
HEMATOLOGIC		
Leukocytopenia (%)	21 (91)	5 (24)
Neutropenia (%)	17 (74)	3 (13)
Anemia (%)	19 (83)	2 (9)
Thrombocytopenia (%)	0 (0)	0 (0)
Febrile neutropenia (%)	–	–
NONHEMATOLOGIC		
AST increased (%)	3 (13)	0 (0)
ALT increased (%)	7 (30)	0 (0)
Acute kidney injury (%)	1 (5)	0 (0)
Hypomagnesemia (%)	14 (67)	3 (13)
Hyperglycemia (%)	1 (5)	1 (5)
Proteinuria (%)	1 (5)	1 (5)
Peripheral sensory neuropathy (%)	17 (74)	0 (0)
Malaise (%)	12 (57)	0 (0)
Arthralgia (%)	3 (13)	0 (0)
Constipation (%)	3 (13)	0 (0)
Mucositis (%)	7 (33)	0 (0)
Dysgeusia (%)	5 (24)	–
Acneiform dermatitis (%)	14 (67)	3 (13)
Paronychia (%)	12 (57)	1(5)
Skin cracks (%)	15 (71)	0 (0)
Dry skin (%)	16 (76)	0 (0)
Blood stream infection (%)	1 (5)	1 (5)
Thromboembolic event† (%)	1 (5)	1 (5)

†*Pulmonary embolism.*

is unfavorable when treated with conventional chemotherapy alone, with median OS of only around 100 days (19). The results of this study are relatively favorable when compared with other recent studies, which reported median OS of 9.1–10 months (12–14). Reasons for the longer response duration in this study may be that the other studies included patients who received PTX and Cmab as ≥2nd line chemotherapy for recurrence or metastatic disease, and who had had a previous treatment history with PTX, docetaxel (DTX), or Cmab. Moreover, we focused here on platinum-tolerant but platinum-based CRT-refractory patients, who were not a focus of Hitt's study (15). Accordingly, our present study may more accurately reflect the efficacy of PTX and Cmab as 1st line chemotherapy against platinum-based CRT-refractory disease. Values for cumulative CDDP dose during CRT in the present study was sufficient to determine that the cases were truly platinum-refractory.

Until now, there have been few data about the prognosis of patients failing CRT with curative intent. The median overall post-failure survival of patients with loco-regional failure after intensity modulated radiotherapy with/without chemotherapy was 9.37 months (20). Of these patients, a significantly worse prognosis was noted in those unable to undergo salvage surgery (7.4 months vs. 22.6 months; $p = 0.003$). Even though the majority of subjects (95%) in our study had not undergone salvage surgery after CRT failure, median OS was more than double (16.3 months), which suggests the promising efficacy of PTX and Cmab for platinum-refractory SCCHN.

The agent that competes with the treatment regime in our study is the anti-PD-1 antibody, nivolumab. CheckMate 141 was a phase III trial that enrolled 361 patients with R/M SCCHN, of any tumor PD-L1 expression status, who had disease progression within 6 months after platinum-based chemotherapy (21). This trial compared nivolumab to the investigators' selected standard therapy, namely methotrexate, DTX, or Cmab. Nivolumab monotherapy provided a longer OS than standard therapy, with a median OS of 7.5 vs. 5.1 months for standard therapy. Further, ORR was 13.3% for nivolumab vs. 5.8% for standard therapy. Outcomes from Checkmate 141 among patients whose disease was platinum-refractory in the primary or adjuvant setting and who received nivolumab or the investigators' selected treatment as 1st line therapy for R/M have been presented (22). In this situation, ORR, median PFS and OS in the nivolumab arm were 19.2%, 2.3 months, and 7.7 months, respectively. Among Asian patients in the CheckMate 141 study, nine of 23 patients (39%) in the nivolumab group experienced a degree of tumor shrinkage and ORR was 26.1% by RECIST. In contrast, 17 of 23 patients (74%) receiving PTX and Cmab in our study experienced tumor shrinkage and ORR was 52% by RECIST. Our findings suggest that PTX and Cmab may offer comparable or greater anti-tumor activity than nivolumab, especially in terms of tumor shrinkage, which may benefit patients with significant tumor-associated symptoms, as seen in **Table 3** and **Figure 4**. However, we should also note that these are unadjusted non-comparative descriptive data from a small numbers of patients. Further prospective evaluation of this combination within this population is warranted.

An important aspect of palliative chemotherapy includes improvement or maintenance of quality of life (QoL). Although we did not assess the QoL in these patients, three patients (13%) switched to Cmab maintenance therapy from PTX and Cmab combination because of general malaise thought to be due to PTX. Immune checkpoint inhibitors, including nivolumab, generally provide favorable QoL profiles when compared with conventional chemotherapy or molecular targeted drugs (21). It is important that agent selection be appropriate to the situation of the individual patient, such as the necessity or otherwise of prompt tumor shrinkage, in order to achieve maximum benefit with favorable QoL.

Several limitations of this study should be mentioned. First, our study was retrospective and without a control arm. It would therefore be interesting to perform a similar analysis in a cohort of patients treated with other drugs (e.g., Nivolumab) in the same setting as described above. Second, while the eligibility review process indeed provided heterogeneous population, this eventually resulted in a small number of enrolled patients for final analysis. Accordingly, our results should be evaluated with particular care, especially those of the subgroup analysis, which warrant further investigation.

CONCLUSION

In this work, we demonstrated that PTX and Cmab is a tolerable and effective option in SCCHN patients with

platinum-based CRT-refractory disease. Its favorable effects on tumor shrinkage may help relieve tumor-associated symptoms.

AUTHOR CONTRIBUTIONS

TE participated in the study concept and design, interpreted the data, and drafted the manuscript. MT extracted, managed, and analyzed the data. All authors provided critical revisions and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Stewart BW, Kleihues P. *International Agency for Research on Cancer Press.* World cancer report. Lyon (2003).
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebeio M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136:E359–86. doi: 10.1002/ijc.29210
3. Adelstein DJ, Li Y, Adams GL, Wanger H Jr, Kish JA, Enslery JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* (2003) 21:92–8. doi: 10.1200/JCO.2003.01.008
4. Forastiere AA, Goepfert H, Maor M, Pajal TF, Waber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* (2003) 349:2091–8. doi: 10.1056/NEJMoa031317
5. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* (2004) 350:1945–52. doi: 10.1056/NEJMoa032641
6. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Sazman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2004) 350:1937–44. doi: 10.1056/NEJMoa032646
7. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. *Mayo Clin Proc.* (2008) 83:489–501. doi: 10.4065/83.4.489
8. Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortés-Funes H, Hitt R, et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol.* (2005) 23:5568–77. doi: 10.1200/JCO.2005.07.119
9. Vermorken JB, Herbst RS, Leon X, Amellal N, Baselga J. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. *Cancer* (2008) 112:2710–9. doi: 10.1002/cncr.23442
10. Rose WC, Wild R. Therapeutic synergy of oral taxane BMS-275183 and cetuximab versus human tumor xenografts. *Clin Cancer Res.* (2004) 10:7413–7. doi: 10.1158/1078-0432.CCR-04-1045
11. Harada K, Ferdous T, Kobayashi H, Ueyama Y. Paclitaxel in combination with cetuximab exerts antitumor effect by suppressing NF-kappaB activity in human oral squamous cell carcinoma cell lines. *Int J Cancer* (2014) 45:2439–45. doi: 10.3892/ijo.2014.2655
12. Jimenez B, Trigo JM, Pajares BI, Sáez MI, Quero C, Navarro V, et al. Efficacy and safety of weekly paclitaxel combined with cetuximab in the treatment of pretreated recurrent/metastatic head and neck cancer patients. *Oral Oncol.* (2013) 49:182–5. doi: 10.1016/j.oraloncology.2012.09.003
13. Sosa AE, Grau JJ, Feliz L, Pereira V, Alcaraz D, Muñoz-García C, et al. Outcome of patients treated with palliative weekly paclitaxel plus cetuximab in recurrent head and neck cancer after failure of platinum-based therapy. *Eur Arch Otorhinolaryngol.* (2014) 271:373–8. doi: 10.1007/s00405-013-2537-6
14. Peron J, Ceruse P, Lavergne E, Buiret G, Pham BN, Chabaud S, et al. Paclitaxel and cetuximab combination efficiency after the failure of a platinum-based chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma. *Anti Cancer Drugs* (2012) 23:996–1001. doi: 10.1097/CAD.0b013e32835507e5
15. Hitt, R. Irigoyen, A, Cortes-Funes H, Grau JJ, García-Sáenz JA, Cruz-Hernandez JJ, et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Ann Oncol.* (2012) 23:1016–22. doi: 10.1093/annonc/mdr367
16. Chao KS, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. et al. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer *Int J Radiat Oncol Biol Phys.* (2003) 55:312–21. doi: 10.1016/S0360-3016(02)03940-8
17. Liu CH, Chen HJ, Wang PC, Chen HS, Chang YL. Patterns of recurrence and second primary tumors in oral squamous cell carcinoma treated with surgery alone. *Kaohsiung J Med Sci.* (2013) 29:554–9. doi: 10.1016/j.kjms.2013.03.001
18. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* (2008) 359:1116–27. doi: 10.1056/NEJMoa0802656
19. Leon X, Hitt R, Constenla M, ROcca A, Stupp R, Kovács AF, et al. A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. *Clin Oncol.* (2005) 17:418–24. doi: 10.1016/j.clon.2005.02.014
20. De Felice F, Thomas C, Barrington S, Pathmanathan A, Lei M, Urbano TG. Analysis of loco-regional failures in head and neck cancer after radical radiation therapy. *Oral Oncol.* (2015) 51:1051–5. doi: 10.1016/j.oraloncology.2015.08.004
21. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med.* (2016) 375:1856–67. doi: 10.1056/NEJMoa1602252
22. Gillison ML, Blumenschein GR, Fayette J, Guigay J, Dimitrios Colevas A, Licitra L, et al. Nivolumab (Nivo) vs investigator's choice (IC) for platinum-refractory (PR) recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN; Checkmate 141): outcomes in first-line (1L) R/m patients and updated safety and efficacy. *J Clin Oncol.* (2017) 35(Suppl. 15):6019. doi: 10.1200/JCO.2017.35.15_suppl.6019

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REVIEW
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Toxicity Reduction in the Treatment of HPV Positive Oropharyngeal Cancer: Emerging Combined Modality Approaches

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Human papillomavirus positive (HPV+) oropharyngeal squamous cell carcinoma (OPC) is a distinct clinical entity within the head and neck cancers, with a unique epidemiology and, in general, a favorable prognosis. Because of this favorable prognosis, researchers have considered de-intensifying the current standard treatment of HPV+ OPC in order to reduce acute and late treatment related toxicity without compromising outcome. Current ongoing trials can be divided in three main categories: de-intensification of the chemotherapy by replacing concomitant platinum-based chemotherapy with the EGFR-inhibitor cetuximab, or de-intensification of the radiation dose of either the primary radiotherapy of selected, good-responding patients after induction chemotherapy or of the adjuvant radiotherapy based on pathology features after primary surgery. Despite the good prognosis of the majority of HPV+ OPC patients, a proportion of them still have poor prognosis. This unmet need has led clinical research on new treatment strategies focused on influencing the unique micro-environment of HPV+ OPC with for example immunotherapy. This article summarizes the current understanding regarding the optimal treatment of non-metastatic HPV+ OPC. Ongoing and published clinical trials regarding de-intensification strategies, immunotherapy and proton therapy are described focusing on the rationale and underlying evidence of these emerging treatment strategies. Nevertheless, until the results of the ongoing trials are known, the treatment of HPV+ OPC in clinical practice should remain identical to the treatment of HPV negative OPC.

Keywords: head and neck cancer, oropharyngeal cancer, human papillomavirus, HPV, de-intensification trials

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INTRODUCTION

Oropharyngeal squamous cell carcinomas (OPC) are tumors located in the soft palate, the pharyngeal wall, the tonsils or the base of tongue, the latter two being the preferred location of Human Papillomavirus related (HPV+) OPC. The incidence of OPC is increasing in the developed countries, chiefly attributed to the epidemic increase in incidence of HPV+ OPC (1, 2).

HPV+ OPC has a better prognosis than tobacco and alcohol related (HPV–) OPC. They should, therefore, be considered as two distinct clinical entities. This is reflected in the new AJCC/UICC TNM 8th edition (8th Ed) staging system with a different classification for HPV+ and HPV– OPC (3). The new clinical (c) TNM 8th Ed for HPV+ OPC contains adjustments in both T- and N-classification. cT-classification remained unchanged except for the disappearance of the distinction

TABLE 1 | Differences in clinical group staging between the 7th and 8th edition AJCC/UICC TNM classification system (cTNM) for Human Papillomavirus related oropharyngeal squamous cell carcinoma.

Stage	TNM 7th edition	cTNM 8th edition
I	T1N0	T1T2-N0N1
II	T2N0	T3-N0N2; T1T2-N2
III	T3-N0N1; T1T2-N1	$T4N_{any}$; TxN3
IV	IVa: T4a-N0N2c; T1T3-N0N2c IVb: $T4bN_{any}$; T_{any} N3 IVc: $T_{any}N_{any}M1$	$T_{any}N_{any}M1$

of the T4-classification in T4a and T4b. The cN-classification, on the other hand, has changed extensively: N0 is the absence of malignant lymph nodes, N1 is reserved for one or more ipsilateral lymph nodes smaller than 6 cm, N2 is the presence of contralateral or bilateral lymph nodes smaller than 6 cm while N3 is one or more lymph nodes larger than 6 cm. The presence of extranodal extension is not a classification parameter in contrast to the TNM 8th Ed for HPV– OPC. **Table 1** shows the differences in the clinical group staging between the 7th and 8th Ed for HPV+ OPC. In the pathological (p) TNM 8th Ed classification, pT-classification is the same as cT-classification while pN-classification is exclusively defined by the number of pathological lymph nodes.

Although the prognosis of HPV+ OPC is better than that of HPV– OPC, currently, the treatment of these two entities is identical (4). Nevertheless, researchers have attempted to de-intensify the treatment of HPV+ OPC to minimize treatment related toxicity without compromising the oncologic outcome. On the other hand, a part of the HPV+ OPC still have poor prognosis directing clinical research to new treatment strategies focusing on influencing the unique micro-environment of HPV+ OPC with for example immunotherapy. In this paper, we will discuss the current treatment of HPV+ OPC, the ongoing or completed de-intensification trials, their results and underlying rationale. Last, we will briefly describe the potential place of immunotherapy and proton therapy in HPV+ OPC. The review was based on a literature search of PubMed with the Medical Subject Heading term "oropharyngeal cancer" AND "human papillomavirus" combined with the key words "radiotherapy," "toxicity," "de-escalation," "de-intensification," and "dose reduction." The PubMed search was combined with back tracking based on published reference lists.

CURRENT TREATMENT

The treatment of HPV+ OPC depends on patient related characteristics in combination with tumor location, tumor extension, lymph node status and relies, as a result, on accurate staging. The staging and treatment of HPV+ OPC and more generally of head and neck squamous cell carcinoma (HNSCC) can generally be divided in two categories, early vs. locally advanced disease.

Early disease, (T1 or T2 tumor with maximum one ipsilateral malignant lymph node smaller than 3 cm), is treated with a single modality treatment, surgery or radiotherapy (RT). Locally advanced disease is treated with combined modality treatment consisting of either RT with concomitant chemotherapy (CRT) or cetuximab or of surgery followed by adjuvant RT or by adjuvant CRT in case of positive resection margins or extranodal extension (ENE) (5–9). Treatment decisions are made by a multidisciplinary setting, and take into account patient characteristics and the anticipated functional outcomes after surgery.

The added value of concomitant platinum-based chemotherapy in addition of primary RT treatment of locally advanced disease has been demonstrated in a large meta-analysis of 9615 subjects (5). Trials with addition of induction chemotherapy (ICT) to CRT have failed to demonstrate any benefit in overall survival or progression free survival and ICT is therefore not considered standard-of-care (5, 10, 11). Alternatively, the addition of cetuximab, a chimeric epidermal growth factor receptor (EGFR)-inhibitor, in combination with primary radiotherapy has shown improved overall survival, but only in one study including 424 patients (6). Since the two different concomitant systemic therapies, platinum-based chemotherapy and cetuximab, in addition to RT were never compared head-to-head in a randomized controlled trial and the evidence for the use of platinum-based chemotherapy is based on a larger dataset, RT plus concomitant platinum-based chemotherapy is favored, while cetuximab can be given to patients with contra-indications for platinum derivates.

CHANGES IN PRIMARY (CHEMO)RADIOTHERAPY

Radiotherapy induces treatment related toxicities correlated to the RT dose delivered to normal tissues (12, 13). Moreover, concomitant systemic treatment significantly increases the acute and late toxicity (6, 14). This toxicity strongly influences the quality of life of cancer patients (15). The avoidance or diminution of treatment related toxicity becomes more prominent in patients with a good long-term prognosis, such as in HPV+ OPC. For this reason, researchers have attempted to reduce toxicity by changing or leaving out the concomitant therapy or by reducing the RT dose. First, we will discuss the changes in the concomitant systemic therapy. Next, we will discuss the trials with reduced RT dose and with RT dose adaptation after ICT.

Replacement of Cisplatin by Cetuximab

Cisplatin increases the acute and late toxicity with severe mucositis, dermatitis, dysphagia and potential life threatening neutropenic fever, while the use of cetuximab is classically only associated with the typical acneiform rash, hypomagnesemia and infusion reaction (5–7, 14, 16). In addition, a subgroup analysis of the Bonner trial, although underpowered and unplanned, showed that especially younger patients with oropharyngeal cancer, early T stage and advanced N-stage had an improved overall survival with cetuximab-RT compared to RT only (6). The hypothesis rose that these patients for whom cetuximab treatment would

be the most beneficial, were HPV+ OPC, typically presenting at younger age with small primary tumors and multiple lymph nodes.

Several running de-intensification trials hypothesize that treatment with cetuximab-RT is non-inferior to CRT for HPV+ OPC and that cetuximab is associated with a more favorable treatment related toxicity profile and better long-term quality of life. The De-ESCALaTE trial (NCT01874171) and TROG 12.01 trial (NCT01855451) compare the toxicity of both treatments, whereas the largest trial, the RTOG 1016 (NCT01302834), including around 1,000 patients, is currently the only randomized controlled trial with oncologic outcome as primary endpoint (**Table 2**). Although this treatment approach is promising, the efficacy of cetuximab in HPV+ OPC is controversial. Several researchers are convinced that only HPV– OPC can benefit from cetuximab based on several studies demonstrating an inverse relationship between EGFR expression and detection of HPV. In addition, the Cancer Genome Atlas group, examining at the cumulative effect of various mechanisms of biological alterations in HNSCC, suggested EGFR as a relevant oncogenic target but only in HPV– OPC (17–20). In contrast, Rosenthal et al. conducted a retrospective subset analysis of the IMCL-9815 trial of Bonner et al. focusing on the potential impact of p16 status (a surrogate marker of HPV positivity) on the outcome of 182 OPC patients (6, 21). They showed benefit for cetuximab on locoregional control and overall survival in both p16+ and p16– subgroup. Although their data suggested a more pronounced gain from cetuximab in the p16+ subgroup, no significant interaction between treatment group and p16 status was shown, confirming p16 status as a prognostic biomarker, though not a predictive biomarker (21). Interestingly, EGFR expression is also a prognostic biomarker but not predictive for the efficacy of cetuximab (22). Many now believe that the antitumoral activity of cetuximab is mainly an immunologic response on the non-human part of the antibody by potentiating the cytotoxic T-cell antitumor immune response, rather than through EGFR-inhibition (23, 24). This could explain why trials with fully human EGFR-inhibitors, like panitumumab, have failed to demonstrate any survival benefit compared to or in addition to platinum-based chemotherapy (25–28). HPV+ OPC could potentially benefit more of the enhanced immune response by cetuximab than HPV– OPC since HPV+ OPC contains elevated T- and B-lymphocyte infiltration and expresses viral proteins (24). To conclude, despite considerable research devoted to this topic, many questions with respect to the use of EGFR-inhibitors and in particular of cetuximab remain unanswered until now. Results of the afore-mentioned trials will hopefully bring clarification. Interestingly, an interim analysis of the RTOG 1016 trial found that treatment with RT and cetuximab is associated with worse overall and progression-free survival compared to the current standard treatment with RT and cisplatin (29).

Beside treatment efficacy, we must consider other potential pitfalls of these de-intensification trials. The TROG 12.01 trial compares the acute toxicity of radiotherapy (70 Gy) plus weekly cisplatin with radiotherapy (70 Gy) plus weekly cetuximab. A recent systematic review and meta-analysis of Szturz et al. compared two different cisplatin schedules, the traditional 3 weekly high-dose vs. the weekly low-dose regimen, in combination with altered radiotherapy and demonstrated less complications in terms of severe acute mucositis, constipation, toxic deaths and severe late subcutaneous fibrosis in patients receiving the 3 weekly high-dose cisplatin regimen. In addition, the overall survival and compliance differed significantly in favor of the 3-weekly schedule (30). The potential observed toxicity differences in the TROG 12.01 could therefore be not representative of a 3-weekly cisplatin regimen. Furthermore, the toxicity results of the TROG 12.01 trial will be difficult to compare with the results of the De-ESCALaTE trial, examining the toxicity of radiotherapy (70Gy) plus 3-weekly cisplatin vs. radiotherapy (70Gy) plus weekly cetuximab, as their control arms may have a different toxicity profile.

Another concern is the wide inclusion criteria of the RTOG 1016 trial, including T1T2-N2aN3 and T3T4-N_{any} (TNM 7th Ed) and the influence on the distant metastasis rate. Although the MACH-NC group did not demonstrate an influence of concomitant chemotherapy on distant metastasis, O'Sullivan et al. have shown that the benefit of cisplatin on distant metastasis in N0N2a disease is limited, while in N2cN3 disease and in heavy smokers with N2b-disease (7th Ed) chemotherapy has a significant effect (5, 31). In contrast, the Bonner trial has shown improvement by cetuximab of the locoregional control, progression free survival and overall survival but has failed to show an effect on distant metastasis (6). The replacement of cisplatin by cetuximab in N2b heavy smokers or N2c-N3 disease could have detrimental effects on the development of distant metastasis and by consequence on the overall survival. It will be important to keep in mind the O'Sullivan et al. study when interpreting the results of the RTOG 1016 trial.

Lastly, the study design of the RTOG 1016 trial, namely a non-inferiority trial, holds some disadvantages. In non-inferiority trials, minor differences are accepted and demonstration of non-inferiority is therefore not the demonstration of equivalence. A sufficient number of deaths must happen to provide enough statistical power for analysis otherwise potential inferiority might not be ruled out due to wide confidence intervals. Before the start of the trial, the researchers must carefully select the minimum clinically relevant difference, commonly called delta. This delta must be substantially smaller than the estimated benefit of the active treatment, cisplatin, otherwise it could happen that the new treatment, cetuximab, is not better than placebo but gets accepted as non-inferior (32, 33). Interestingly, Brotherston et al. conducted an investigation with questionnaires assessing patients' preferences regarding the acceptable delta for de-intensification cancer treatment. They showed that patients' primary concern was survival with 35% of the patients unwilling to risk any drop in survival probability, even if it implied less treatment related toxicity, and a further 34% of patients willing to accept maximum 5% reduction in survival probability (34). We must therefore be cognizant that the priorities of patients might be different that those of researchers.

Radiotherapy Dose Reduction

HPV+ OPC is believed to be more radiosensitive than the HPV– OPC and may be cured with doses less than 70 Gy (35). A

TABLE 2 | De-intensification trials replacing cisplatin by cetuximab.

Name study	Design	Inclusion TNM 7th	Inclusion TNM 8th	Smoking	Primary endpoint
De-ESCALaTE NCT01874171	70 Gy + 3-weekly cddp vs. 70 Gy + weekly Cetuximab	T3T4-N0; T1N1-T4N3	T3T4-N0; T1N1-T4N3	Exclusion if more than 10 PY and more than one ipsilateral LN, contralateral LN or LN > 6 cm	Acute and late toxicity (2Y)
TROG 12.01 NCT01855451	70Gy + weekly cddp vs. 70 Gy + weekly Cetuximab	T3-N0N2c; T1T2-N2aN2c	T3-N0N2; T1T2-N1N2 (excluding N1 with only one ipsilateral LN < 3 cm)	Exclusion if more than 10 PY and more than one ipsilateral LN or contralateral LN	Symptom severity: acute toxicity
RTOG 1016 NCT01302834	70 Gy + 3-weekly cddp vs. 70 Gy + weekly Cetuximab	T1T2-N2aN3; T3T4-N_{any}	T1T2-N1N2 (excluding N1 with only one ipsilateral LN < 3 cm); T3T4-N_{any}	/	Overall survival
NCT01663259	One arm: 70 Gy + weekly cetuximab	T3-N0N2c; T1T2-N1N2c	T3-N0N2; T1T2-N1N2	<10 PY	Recurrence rate (3Y)

cddp, cisplatin; LN, Lymph nodes; PY, smoking pack years; 2Y,3Y, up to 2 or 3 years after end of treatment.

lower RT dose delivered to the tumor might lead to a lower dose on the surrounding normal tissue and to less toxicity with the same good oncologic outcome. This was first investigated in a prospective, multi-institutional, phase II study in which all patients were treated with RT at 60 Gy at 2Gy per fraction, 5 days a week with weekly low-dose cisplatin, 30 mg/m² (**Table 3**). Four to eight weeks after completion of RT, all patients were evaluated for clinical complete response (cCR), defined as no measurable tumor present on physical and radiologic examination, followed by planned surgical evaluation to asses pathologic complete response (pCR). In patients who had a cCR at the primary site, directed biopsies of the primary site were taken while minimally invasive resection was performed if there was no cCR at the primary site. All patients who had node-positive disease before RT had selective nodal dissection. The pCR rate at the primary site was 86% and in the neck 98% (36). Recently, the long-term follow-up was published with an observed 3 year cause-specific survival of 100% and an OS rate of 95% (37). It is, however, not possible to determine if the planned surgical evaluation was therapeutic because the clonogenic viability of the residual foci could not be determined by microscopic examination. CRT followed by surgery in all patients is probably an overtreatment and an unnecessary enhancement of toxicity, although in this trial the patients' reported long term symptom burden was low to moderate. Patient selection is opportune and is under investigation in the follow-up study (NCT02281955). Patients will receive the same de-intensified CRT regimen, followed by a 12-week post-CRT positron emission tomography/CT to guide the use of surgery (36–38).

Another research group has de-intensified the treatment even further by eliminating the concomitant therapy completely in combination with lowering the RT dose. The NRG HN002 trial (NCT02254278) randomized patients between RT dose of 60 Gy, one fraction a day for 6 weeks, with or without weekly cisplatin. Their inclusion criteria are based on the research of O'Sullivan et al. showing equal effect in terms of distant metastasis of RT, mostly accelerated regimens, and CRT for N0-N2a and N2b disease with less than 10 pack years (31). Notably, the RT regimen of the HN002 trial is significantly different from the regimen of the trial of O'Sullivan. This NRG HN002 trial is set up with a conventional fractionation regimen up to 60 Gy instead of the standard RT dose of 70 Gy or the accelerated RT regimen from the study of O'Sullivan et al. meaning this trial consists of two nonstandard arms. Even more, the time till the primary endpoint, 2 year progression free survival, might be too short to measure the effect of leaving out the concomitant therapy. Several publications have shown that the distant metastasis rate of HPV+ and HPV– OPC is similar but the timing of onset is different with the curve of HPV+ OPC continuing to increase for up to 5 years after treatment in contrast to the rather stable curve of HPV– OPC beyond 2 years (31, 39).

Dose Adaptation After Induction Chemotherapy

A meta-analysis of five randomized trials including over 1,000 patients could not show an OS or PFS benefit of induction chemotherapy (ICT) with docetaxel, cisplatin and 5-FU (TPF) compared to definitive CRT without induction chemotherapy in locally advanced HNSCC (10). The Eastern Cooperative Oncology Group (ECOG) published in 2007 a phase II trial (E2399) of taxane-based induction chemotherapy followed by CRT and obtained high organ preservation rate with low toxicity for OPC (40). Based on these results the ECOG investigated in a phase II trial, E1308, the further use of ICT. The purpose of the ICT was not to improve OS, but to reduce the tumor burden to subclinical disease in patients with HPV+ OPC and to allow in good responders the use of a reduced RT dose, 54 Gy instead of 70 Gy, to eradicate the residual lower tumor burden (40, 41). This lower RT dose to the tumor might lead to lower doses on the surrounding normal tissue and subsequently to less treatment related toxicity, such as dysphagia, feeding tube dependency, and better post-treatment quality of life. Cisplatin, as concurrent

TABLE 3 | De-intensification trials with reduced RT dose.

Name study	Design	Inclusion TNM 7th	Inclusion TNM 8th	Smoking	Primary endpoint
NCT01716195	One arm: ICT (2 cycli paclitaxel-carboplatin) + response adapted RT (54 Gy or 60 Gy) with weekly paclitaxel	T1T2-N2aN3; T3T4-N_{any}	T1T2-N1N2 (excluding N1 with only one ipsilateral LN < 3 cm); T3T4-N_{any}	/	2Y PFS
NCT01530997	One arm: 60Gy + weekly cisplatin	T0T3-N0N2c	T1T3-N0N2	<10PY or <30PY and abstinent >5Y	Pathologic Complete Remission
NRG HN002 NCT02254278	Reduced 60 Gy + weekly cisplatin vs. 60 Gy	T1T2-N1N2b; T3-N0N2b	T1T2-N1; T3-N0N1	<10 PY	2Y PFS grade 3 dysphagia
ECOG 1308 NCT01084083	ICT (3 cycli of cisplatin, paclitaxel, cetuximab), then response adapted RT (54 or 69.3 Gy) with cetuximab	Resectable disease T3T4-N0; T1N1-T4N3	Resectable disease T3T4-N0; T1N1-T4N3	/	2Y PFS
The Quarterback Trial NCT01706939	ICT (TPF), patients with CR/PR randomized between RT (56Gy) with carboplatin vs. RT (70Gy) with carboplatin	T3T4-N0; T1N1-T4N3 OPC/CUP/nasopharynx	T3T4-N0; T1N1-T4N3 OPC/CUP/nasopharynx	Exclusion of active smokers or >20 PY	3Y PFS

ICT, induction chemotherapy; TPF, docetaxel, cisplatin, 5-fluorouracil; CR/PR, complete response / partial response; RT, radiotherapy; OPC, Oropharyngeal carcinoma; CUP, carcinoma of unknown primary; PY, smoking pack years; 2Y, up to 2 years after end of treatment; PFS, progression free survival.

chemotherapy, was in this trial also replaced by cetuximab so the same concerns about the efficacy of cetuximab in HPV+ OPC as described above arise.

There is of course the concern that in patients who do not have a complete response after ICT, ICT will not improve the survival but will delay the start of the potentially curative RT treatment of the radiosensitive HPV+ OPC. In another phase II trial (NCT01716195) with dose adaptation after ICT, 2 cycles of paclitaxel and carboplatin, complete or partial responders received RT 54 Gy with weekly paclitaxel, while less than partial or no responders received RT 60 Gy with weekly paclitaxel. Although all patients in this trial received a lower RT dose than the standard 70 Gy, this treatment approach was associated with a high 2y progression-free survival of 92% (42).

The results of the E1308 trial were published in 2017 showing a high rate of clinical complete response after ICT (70%) with excellent 2y-OS of 94% and good toxicity profile according to the authors. The published acute treatment related toxicity is however worth mentioning, with 2 out of 80 patients only receiving one out of 3 cycles of ICT due to grade 3 or more toxicity. Fourteen patients had dose adaptations of cisplatin during ICT due to grade 3 or more hematologic toxicity, neuropathy or tinnitus and 18 patients had dose modification of cetuximab due to grade 3 or more acneiform rash, mucositis or hypomagnesemia. It is debatable if the reduction of RT dose and of the RT-related toxicity really outweigh the added toxicity of ICT. ICT with TPF was associated with 6.6% treatment-related toxicity in the recently published GORTEC 2007-02 phase III trial randomizing HNSCC patients between RT 70 Gy with carboplatin-5FU vs. 3 cycles of TPF followed by cetuximab-RT 70 Gy (43). The Quarterback trial (NCT01706939), another phase III dose reduction trial after ICT, randomizes patients with good response after ICT between 56 and 70 Gy concomitant with carboplatin. It should be noticed that this trial also includes, besides HPV+ OPC, nasopharyngeal cancers and cancers of unknown primary with p16+ squamous cell carcinoma histology (**Table 3**). To our knowledge the prognostic value of p16+ in HNSCC subsites other than OPC is not proven and trials should therefore only include HPV+ OPC patients to avoid bias and under-treatment of the other tumor subsites.

CHANGES IN PRIMARY SURGERY ± ADAPTIVE (C)RT

Surgery with or without adjuvant RT or CRT is an alternative treatment strategy in HPV+ OPC if the anticipated functional outcome after surgery is acceptable. Retrospective data have shown similar oncologic outcome between open surgery and radiotherapy. However, the rate of severe complications in the surgery group was higher (44). It should be pointed out that the surgical landscape has changed drastically since this published comparison. Minimal invasive surgery such as the transoral laser approach (TLM) or the transoral robotic surgery (TORS), have gained prominence in the last decade. These techniques, when performed by trained surgeons, provide similar oncologic outcome as the classic approaches, while avoiding mandibulotomy (45). As a result, they are associated with fewer complications and functional deficits compared to the classic approaches with mandibular split. To date, a prospective randomized clinical trial concerning oncologic and functional outcome of minimal invasive surgery vs. CRT has not yet been published. Interestingly, two randomized ongoing trials, the

"Best of" EORTC 1420 trial (NCT02984410) and the ORATOR trial (NCT01590355), will compare the treatment related toxicity of TORS and RT or CRT (46, 47).

The extent of benefit from adjuvant treatment after surgery is based on the pathology following resection. Currently, it is unclear if the decision for postoperative (C)RT and the RT dose in HPV+ OPC must be based on the same pathology features as in HPV– OPC. In HPV– OPC, ENE is considered a negative prognostic factor and is now incorporated in the most recent clinical and pathologic nodal staging classification of TNM 8th Ed. In contrast, ENE was not adopted in the clinical nor in the pathological TNM 8th edition for HPV+ OPC, even though a recent analysis from the American national cancer data base, including over 1,000 HPV+ OPC who underwent primary surgery with negative resection margins, showed that ENE was an independent risk factor for worse prognosis in patients with HPV+ OPC. Surprisingly, adjuvant CRT compared with RT was not associated with a better OS in this population (48).

At the moment, there are three de-intensification trials trying to determine the optimal adjuvant treatment for HPV+ OPC after minimal invasive surgery. The ECOG 3311 trial (NCT01898494) tries to determine the optimal RT dose by dividing patients in three risk groups after TORS. The low-risk group without adverse pathology features does not receive adjuvant treatment. The intermediate risk group patients with clear margins, <1 mm ECE, 2-3 positive lymph nodes, perineural invasion or lymphovascular invasion is randomized between RT up to 50 Gy or to 60 Gy. The high risk group with positive margins or >1 mm ECE or ≥4 positive lymph nodes receive standard CRT. The primary endpoint of this trial is 2-year progression free survival. The PATHOS trial (NC02215265) will, in addition, investigate the benefit of concomitant chemotherapy in the high risk group. Patients with positive margins or ECE are randomized between RT 60 Gy with or without concomitant chemotherapy. The ADEPT study (NCT01687413) only focuses on the benefit of chemotherapy in patients with ECE and negative margins and randomizes them between RT 60 Gy with or without concomitant chemotherapy.

OTHER EMERGING TREATMENT STRATEGIES

Immunotherapy

Since the results of the CheckMate-141 study were published, immunotherapy has become standard of care in recurrent or metastatic HNSCC after platinum-based chemotherapy. The OS benefit of nivolumab, a PD-1 monoclonal antibody, was independent of p16 status, although the benefit was more pronounced in the p16+ OPC (49). The Keynote-012 study which investigated the efficacy of a similar PD-1 antibody, pembrolizumab, also observed a higher response to pembrolizumab in patients with recurrent or metastatic HPV+ OPC vs. recurrent or metastatic HPV– HNSCC (50, 51). The role of radiotherapy and the synergy with immunotherapy

TABLE 4 | Running trials with immunotherapy in human papillomavirus related oropharyngeal carcinoma.

Name study	Design	Inclusion TNM 7th	Inclusion TNM 8th (for p16+ OPC)	Smoking	Primary endpoint
RTOG 3504 NCT02764593	4 arms: RT 70 Gy + weekly cisplatin + nivolumab 3-weekly cisplatin + nivolumab cetuximab + nivolumab nivolumab	OPC p16+: T1T2-Nb2N3; T4T3-N0N3, OPC p16-;OC, Larynx, HP:T1T2-N2aN3 or T3T4-Nx	OPC p16+: T1T2-N1N3 (excluding N1 with only ipsilateral LN); T3T4-Nx	OPC p16+: >10 PY or <10 PY if T4 or N3	Dose limiting toxicity (DLT)
Keynote-412 NCT03040999	RT 70 Gy + 3-weekly cisplatin + Pembrolizumab vs. placebo	All locally advanced Head and neck squamous cell carcinoma's; independent of p16 status	All locally advanced Head and neck squamous cell carcinoma's; independent of p16 status	/	5Y-Event-free survival
CA209-9TM NCT03349710	Cisplatin eligible patient: RT 70 Gy + cisplatin + nivolumab vs. placebo Cisplatin ineligible patient: RT 70 Gy + Nivo vs. cetuximab	All locally advanced OPC, OC, HP, or larynx; independent of p16 status	All locally advanced OPC, OC, HP, or larynx; independent of p16 status	/	6Y-Event-free survival
CompARE CRUK/13/026	4 arms: RT 70 Gy (OTT: 7 weeks) + cisplatin RT 64 Gy (OTT: 5 weeks) + 3-weekly cisplatin RT 70 Gy (OTT: 7 weeks) + 3-weekly cisplatin + durvalumab surgery + RT + cisplatin	OPC p16+: T1T3-N2bN2c and all T4 or N3 OPC p16–: T1T4-N1N3 or T3T4-N0	OPC p16+: T1T3-N1N2 (excluding N1 with only ipsilateral LN); all T4 or N3	OPC p16+: T1T3-N2bN2c only included if more than 10 PY	Overall survival

RT, radiotherapy; OPC, Oropharyngeal carcinoma; OC, oral cavity; HP, Hypopharynx; PY, smoking pack years; 5 (6)Y, up to 5 (6) years after end of treatment; OTT, Overall Treatment Time; LN, lymph nodes.

as adjuvant or concomitant treatment for advanced HPV + OPC is still under investigation in several running phase I-II [RTOG 3504 (NCT02764593)] and III trials [Keynote-412 (NCT03040999), CA209-9TM (NCT03349710), and CompARE trial (CRUK/13/026)] (**Table 4**).

HPV+ OPC are believed to benefit more from immunotherapy than HPV– OPC because of several factors. First, HPV + tumors express viral antigens which can be recognized as foreign by the patient's immune system leading to immune recognition and activation. Second, the preferred tumor location of HPV+ OPC is situated in the tonsils or base of tongue, two lymphoid tissues. This tumor location leads to the presence of a higher level of CD8+ and PD-1 tumor infiltrating lymphocytes and PDL-1 positive cells which may play a crucial role in the better response of HPV+ OPC to immunotherapy with PD-1 inhibitors such as nivolumab and pembrolizumab, and to cetuximab, as described above (23, 52).

Proton Therapy

Decreased treatment related toxicity by the use of proton therapy instead of photon therapy is still under investigation. The unique energy transfer of proton therapy, with the highest energy transfer at a specific depth inside the tissue, the Bragg peak, makes it possible to spear more healthy tissue located posterior of the tumor. A case matched analysis of 150 OPC, mainly HPV+, treated with proton therapy or photon therapy was performed showing comparable OS and PFS but reduced rate of feeding tube dependency and severe weight loss in patients treated with proton therapy (53). However, prospective multicenter randomized trials, such as the ongoing NCT01893307, are needed to validate such findings.

The proton RT technique is a quite expensive strategy and probably not beneficial for all patients. Therefore, some have proposed patient selection using a model based approach in which a proton and photon treatment plan is made for each patient and the expected reduction of toxicity with proton therapy is calculated. If the toxicity reduction is more than a pre-defined margin, the patient would undergo proton therapy (54). In future, this treatment and selection strategy need to be validated with incorporation of cost-effectiveness analysis as well as patient-reported outcomes.

GENERAL CONCLUSION

In the next decade, the optimal treatment approach for HPV+ OPC will be determined based on the results of several running trials. Sufficient follow up of all these studies is crucial in order to be confident that outcome is not compromised, since HPV+ disease shows a trend for later relapses than HPV– disease. We must emphasize that until the mature results of these trials are known the treatment of HPV+ OPC should remain unchanged and identical to the treatment of HPV– OPC. Furthermore, the result of the trials cannot be generalized to all HPV+ OPC. As described above, most trials have different inclusion criteria in terms of TNM stage and smoking pack years. In addition, there is no consensus on HPV detection method. Whether the future treatment for HPV+ OPC will consist of changes in concomitant therapy, reduction of RT dose, immunotherapy or proton therapy, patient selection will be pivotal.

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Each author has provided substantial contributions to warrant authorship. SD wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

1. Näsman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? *Int J Cancer* (2009) 125:362–6. doi: 10.1002/ijc.24339
2. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* (2011) 29:4294–301. doi: 10.1200/JCO.2011.36.4596
3. Brierley JD, Gospodarowicz MK, Wittekind C. *UICC TNM Classification of Malignant Tumours.* 8th ed. Oxford; Hoboken, NJ: John Wiley & Sons (2017).
4. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* (2010) 363:24–35. doi: 10.1056/NEJMoa0912217
5. Pignon J-P, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17,346 patients. *Radiother Oncol.* (2009) 92:4–14. doi: 10.1016/j.radonc.2009.04.014
6. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2006) 354:567–78. doi: 10.1056/NEJMoa053422
7. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomized trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* (2010) 11:21–8. doi: 10.1016/S1470-2045(09)70311-0
8. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* (2005) 27:843–50. doi: 10.1002/hed.20279
9. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* (2012) 84:1198–205. doi: 10.1016/j.ijrobp.2012.05.008
10. Budach W, Bölke E, Kammers K, Gerber PA, Orth K, Gripp S, et al. Induction chemotherapy followed by concurrent radio-chemotherapy vs. concurrent

radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): a meta-analysis of randomized trials. *Radiother Oncol.* (2016) 118:238–43. doi: 10.1016/j.radonc.2015.10.014

11. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol.* (2014) 25:216–25. doi: 10.1093/annonc/mdt461
12. Dirix P, Abbeel S, Vanstraelen B, Hermans R, Nuyts S. Dysphagia after chemoradiotherapy for head-and-neck squamous cell carcinoma: dose-effect relationships for the swallowing structures. *Int J Radiat Oncol Biol Phys.* (2009) 75:385–92. doi: 10.1016/j.ijrobp.2008.11.041
13. MD Anderson Head and Neck Cancer Symptom Working Group. Beyond mean pharyngeal constrictor dose for beam path toxicity in non-target swallowing muscles: dose-volume correlates of chronic radiation-associated dysphagia (RAD) after oropharyngeal intensity modulated radiotherapy. *Radiother Oncol.* (2016) 118:304–14. doi: 10.1016/j.radonc.2016.01.019
14. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* (2008) 26:3582–9. doi: 10.1200/JCO.2007.14.8841
15. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol.* (2008)26:3770–6. doi: 10.1200/JCO.2007.14.6647
16. Bonner JA, Giralt J, Harari PM, Baselga J, Spencer S, Bell D, et al. Association of human papillomavirus and p16 status with mucositis and dysphagia for head and neck cancer patients treated with radiotherapy with or without cetuximab: assessment from a phase 3 registration trial. *Eur J Cancer* (2016) 64:1–11. doi: 10.1016/j.ejca.2016.05.008
17. Hong A, Dobbins T, Lee CS, Jones D, Jackson E, Clark J, et al. Relationships between epidermal growth factor receptor expression and human papillomavirus status as markers of prognosis in oropharyngeal cancer. *Eur J Cancer* (2010) 46:2088–96. doi: 10.1016/j.ejca.2010.04.016
18. Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, et al. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol.* (2008) 26:3128–37. doi: 10.1200/JCO.2007.12.7662
19. Kim S-H, Koo B-S, Kang S, Park K, Kim H, Lee KR, et al. HPV integration begins in the tonsillar crypt and leads to the alteration of p16, EGFR and c-myc during tumor formation. *Int J Cancer.* (2007) 120:1418–25. doi: 10.1002/ijc.22464
20. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* (2015) 517:576–82. doi: 10.1038/nature14129
21. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J, et al. Association of human papillomavirus and p16 status with outcomes in the IMCL-9815 phase III registration trial for patients with locoregionally advanced oropharyngeal squamous cell carcinoma of the head and neck treated with radiotherapy with or without cetuximab. *J Clin Oncol.* (2016) 34:1300–8. doi: 10.1200/JCO.2015.62.5970
22. Ang KK, Andratschke NH, Milas L. Epidermal growth factor receptor and response of head-and-neck carcinoma to therapy. *Int J Radiat Oncol Biol Phys.* (2004) 58:959–65. doi: 10.1016/j.ijrobp.2003.07.010
23. Partlová S, Bouček J, Kloudová K, Lukešová E, Zábrodský M, Grega M, et al. Distinct patterns of intratumoral immune cell infiltrates in patients with HPV-associated compared to non-virally induced head and neck squamous cell carcinoma. *Oncoimmunology.* (2015) 4:e965570. doi: 10.4161/21624011.2014.965570
24. Schneider K, Marbaix E, Bouzin C, Hamoir M, Mahy P, Bol V, et al. Immune cell infiltration in head and neck squamous cell carcinoma and patient outcome: a retrospective study. *Acta Oncol.* (2018) 57:1165–72. doi: 10.1080/0284186X.2018.1445287
25. Mesía R, Henke M, Fortin A, Minn H, Yunes Ancona AC, Cmelak A, et al. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomized, controlled, open-label phase 2 trial. *Lancet Oncol.* (2015) 16:208–20. doi: 10.1016/S1470-2045(14)71198-2
26. Giralt J, Trigo J, Nuyts S, Ozsahin M, Skladowski K, Hatoum G, et al. Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomized, controlled, open-label phase 2 trial. *Lancet Oncol.* (2015) 16:221–32. doi: 10.1016/S1470-2045(14)71200-8
27. Siu LL, Waldron JN, Chen BE, Winquist E, Wright JR, Nabid A, et al. Effect of standard radiotherapy with cisplatin vs accelerated radiotherapy with panitumumab in locoregionally advanced squamous cell head and neck carcinoma: a randomized clinical trial. *JAMA Oncol.* (2016) 3:220–26. doi: 10.1001/jamaoncol.2016.4510
28. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomized trial. *Lancet Oncol.* (2013) 14:697–710. doi: 10.1016/S1470-2045(13)70181-5
29. *Cetuximab Inferior to Standard Treatment for HPV+ Oropharyngeal Cancer - National Cancer Institute [Internet]*. Available online at: https://www.cancer.gov/news-events/press-releases/2018/oropharyngeal-hpv-cisplatin (Accessed September 11, 2018).
30. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Altered fractionation radiotherapy combined with concurrent low-dose or high-dose cisplatin in head and neck cancer: a systematic review of literature and meta-analysis. *Oral Oncol.* (2018) 76:52–60. doi: 10.1016/j.oraloncology.2017.11.025
31. O'Sullivan B, Huang SH, Siu LL, Waldron J, Zhao H, Perez-Ordonez B, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. *J Clin Oncol.* (2013) 31:543–50. doi: 10.1200/JCO.2012.44.0164
32. Hahn S. Understanding noninferiority trials. *Korean J Pediatr.* (2012) 55:403–7. doi: 10.3345/kjp.2012.55.11.403
33. Pocock SJ. The pros and cons of noninferiority trials. *Fundam Clin Pharmacol.* (2003) 17:483–90. doi: 10.1046/j.1472-8206.2003.00162.x
34. Brotherston DC, Poon I, Le T, Leung M, Kiss A, Ringash J, et al. Patient preferences for oropharyngeal cancer treatment de-escalation. *Head Neck* (2013) 35:151–9. doi: 10.1002/hed.22930
35. Rieckmann T, Tribius S, Grob TJ, Meyer F, Busch C-J, Petersen C, et al. HNSCC cell lines positive for HPV and p16 possess higher cellular radiosensitivity due to an impaired DSB repair capacity. *Radiother Oncol.* (2013) 107:242–6. doi: 10.1016/j.radonc.2013.03.013
36. Chera BS, Amdur RJ, Tepper J, Qaqish B, Green R, Aumer SL, et al. Phase 2 trial of de-intensified chemoradiation therapy for favorable-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* (2015) 93:976–85. doi: 10.1016/j.ijrobp.2015.08.033
37. Chera BS, Amdur RJ, Tepper JE, Tan X, Weiss J, Grilley-Olson JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Cancer* (2018) 124:2347–54. doi: 10.1002/cncr.31338
38. Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol.* (2008) 33:210–22. doi: 10.1111/j.1749-4486.2008.01688.x
39. Trosman SJ, Koyfman SA, Ward MC, Al-Khudari S, Nwizu T, Greskovich JF, et al. Effect of Human Papillomavirus on patterns of distant metastatic failure in oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. *JAMA Otolaryngol Head Neck Surg.* (2015) 141:457–62. doi: 10.1001/jamaoto.2015.136
40. Marur S, Li S, Cmelak AJ, Gillison ML, Zhao WJ, Ferris RL, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx- ECOG-ACRIN cancer research group. *J Clin Oncol.* (2016) 35:490–7. doi: 10.1200/JCO.2016.68.3300
41. Marur S, Cmelak AJ, Burtness B. Purpose of induction chemotherapy in E1308 and importance of patient-reported outcomes in deintensification trials. *J Clin Oncol.* (2017) 35:1968–9. doi: 10.1200/JCO.2017.72.2918
42. Chen AM, Felix C, Wang P-C, Hsu S, Basehart V, Garst J, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. *Lancet Oncol.* (2017) 18:803–11. doi: 10.1016/S1470-2045(17)30246-2

43. Geoffrois L, Martin L, De Raucourt D, Sun XS, Tao Y, Maingon P, et al. Induction chemotherapy followed by cetuximab radiotherapy is not superior to concurrent chemoradiotherapy for head and neck carcinomas: results of the GORTEC 2007-02 phase III randomized trial. *J Clin Oncol*. (2018) doi: 10.1200/JCO.2017.76.2591. [Epubh ahead of print].
44. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. *Cancer* (2002) 94:2967–80. doi: 10.1002/cncr.10567
45. De Almeida JR, Li R, Magnuson JS, Smith RV, Moore E, Lawson G, et al. Oncologic outcomes after transoral robotic surgery: a multi-institutional study. *JAMA Otolaryngol Head Neck Surg*. (2015) 141:1043–51. doi: 10.1001/jamaoto.2015.1508
46. Howard J, Masterson L, Dwivedi RC, Riffat F, Benson R, Jefferies S, et al. Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma. *Cochrane Database Syst Rev*. (2016) 12:CD010963. doi: 10.1002/14651858.CD010963.pub2
47. Nichols AC, Yoo J, Hammond JA, Fung K, Winquist E, Read N, et al. Early-stage squamous cell carcinoma of the oropharynx: radiotherapy vs. trans-oral robotic surgery (ORATOR)–study protocol for a randomized phase II trial. *BMC Cancer* (2013) 13:133. doi: 10.1186/1471-2407-13-133
48. An Y, Park HS, Kelly JR, Stahl JM, Yarbrough WG, Burtness BA, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Cancer* (2017) 123:2762–72. doi: 10.1002/cncr.30598
49. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. (2016) 375:1856–67. doi: 10.1056/NEJMoa1602252
50. Chow LQM, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. (2016) 34:3838–45. doi: 10.1200/JCO.2016.68.1478
51. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. (2016) 17:956–65. doi: 10.1016/S1470-2045(16)30066-3
52. Balermpas P, Rödel F, Krause M, Linge A, Lohaus F, Baumann M, et al. The PD-1/PD-L1 axis and human papilloma virus in patients with head and neck cancer after adjuvant chemoradiotherapy: a multicentre study of the German cancer consortium radiation oncology group (DKTK-ROG). *Int J Cancer* (2017) 141:594–603. doi: 10.1002/ijc.30770
53. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, et al. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. *Radiother Oncol*. (2016) 120:48–55. doi: 10.1016/j.radonc.2016.05.022
54. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol*. (2013) 107:267–73. doi: 10.1016/j.radonc.2013.05.007

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REVIEW
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Postoperative Combined Modality Treatment in High Risk Resected Locally Advanced Squamous Cell Carcinomas of the Head and Neck (HNSCC)

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Patients who undergo upfront curative intent resection for locally advanced squamous cell carcinomas and who have adverse pathologic features benefit from adjuvant therapy. Concurrent cisplatin based chemoradiation is an established standard of care endorsed by national guidelines. Controversy now exists on the applicability of this strategy to the good risk human papilloma virus (HPV) related oropharynx cancer (OPC) patient. Ongoing clinical studies are exploring therapeutic de-escalation in the postoperative setting for this distinct patient population. The introduction of immune checkpoint inhibitors to the therapeutic armamentarium for recurrent/metastatic head and neck cancer patients has led to clinical investigation of incorporation of PD-1 inhibition in the postoperative setting.

Keywords: head and neck cancer, squamous cell carcinoma, HPV, head and neck, oropharyngeal carcinoma, nasopharyngeal carcinoma, sinonasal carcinoma, adjuvant therapy

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INTRODUCTION

Therapeutic standards among patients with locally advanced head and neck cancer who have undergone surgical resection have evolved in the past four decades (1). This is largely a result of intense scientific investigation spurred by poor locoregional disease control and patient outcomes. Early studies conducted in the 1970's and 80's focused on defining the role of postoperative radiation therapy and appropriate dosing in patients with high risk features after surgical resection (2, 3). The activity of cytotoxic agents and their radiation sensitizing properties naturally led to studies investigating the efficacy of this combination in both the definitive and adjuvant settings (4, 5).

This review identified landmark prospective clinical trials that provided the foundation for and established current therapeutic standards for postoperative therapy. Pertinent negative trials in the postoperative setting were also included. Ongoing prospective clinical trials in the adjuvant setting were included and cited according to their NCTN identifier. One primary focus is the appropriate postoperative treatment for the prognostically distinct human papilloma virus (HPV) related oropharynx cancer (OPC) with the advent of robotic surgical procedures and the potential for de-escalation in this cohort. Another area of scientific interest involves the incorporation of novel agents to current adjuvant therapy standards, specifically the anti-PD1 inhibitors which are active in the recurrent/metastatic setting (6, 7). The results of these clinical trials are expected to result in refinements in treatment recommendations in the adjuvant setting and improvements in patient outcomes.

CURRENT GUIDELINES FOR POSTOPERATIVE TREATMENT

1. Definition of high risk features

The majority of patients with newly diagnosed mucosal squamous cell carcinomas of the head and neck present with locally advanced disease. A proportion of these patients are candidates for surgical resection. In general, oral cavity primaries are approached with surgical resection if feasible, due to the success of surgical reconstruction in this location. Although organ preserving definitive chemoradiation is well established for squamous cell carcinomas originating from the larynx, certain disease characteristics make upfront surgical resection the preferred therapeutic approach (such as laryngeal cartilage invasion). The recognition of adverse pathologic features after surgical resection have been extensively described in literature that dates back to the 1950's, where factors such as advanced T stage, primary site location, nodal disease burden, and surgical margin involvement were associated with high rates of locoregional failure. Subsequent clinical trials in the 1970's explored postoperative radiation in high risk patients, albeit with significant heterogeneity in the definition of high risk. These studies revealed a locoregional and survival advantage to postoperative radiation (2). A combined analysis of two cooperative group studies, Intergroup 0034 [or Radiation Therapy Oncology Group (RTOG) 8503] and RTOG 8,824, sought to define the population at highest risk for poor oncologic outcomes after postoperative therapy. Data from these two early prospective studies confirmed that patients with two or more involved regional lymph nodes, positive surgical resection margins and evidence of extracapsular extension (ECE) were characterized by significantly inferior locoregional control and overall survival rates compared to those without these pathologic characteristics (8, 9). These findings are consistent with a multi-institutional phase III experience which risk stratified patients based on primary site and nodal pathologic features. The study reported inferior locoregional control with postoperative radiation doses <63 Gy for patients with ECE, and provided further data supporting inferior outcomes in patients with oral cavity primary sites, perineural invasion, ECE, >2 involved LNs (10). These observations provided the foundation for patient selection in the design of clinical trials exploring intensification of therapy in the adjuvant setting.

Apart from pathologic characteristics, timing of radiation therapy appears to influence the outcome of combined modality treatment. Peters et al. (10) and Ang et al. (11) both observed significantly reduced locoregional control in patients with a longer interval between surgery and the initiation of postoperative therapy (10, 11). Similarly, Rosenthal et al. (12) reported a single institution retrospective experience revealing worse locoregional control rates among patients who completed surgery and postoperative radiation over 100 days versus shorter treatment times. This was confirmed by a multivariable analysis that controlled for potential confounders (12). A more contemporary experience has been described by Graboyes et al. (13) who obtained registry data from the National Cancer Database (NCDB) on ∼41,000 patients who underwent surgery and postoperative radiation treatment from 2006–2014 (13). Their findings indicate that initiation of postoperative therapy beyond 6 weeks from the date of surgery was associated with worse survival, with survival progressively decreasing with increasing delays. Although it is well recognized that the extent of surgical resection, perioperative complications and patient factors such as insurance status and comorbidity often influence the timing of postoperative treatment, these observations support the timely administration of postoperative treatment. The National Comprehensive Cancer Network (NCCN) recommends the initiation of postoperative therapy ≤6 weeks after surgical resection (14).

2. Landmark clinical trials in combined modality postoperative therapy

Recognition of suboptimal outcomes in high risk patients who receive postoperative adjuvant therapy underscored the need for therapeutic intensification in this patient population. Bachaud et al. (15) reported the results of a randomized phase III trial of patients with Stage III–IV resected oral cavity, oropharynx, larynx, or hypopharynx cancers comparing 65–70 Gy postoperative radiation alone to radiation with cisplatin 50 mg/m2 given weekly (15). This phase III trial enrolled 83 patients and revealed superior overall survival and locoregional control in the patients randomized to the cisplatin arm. Similarly, Smid et al. (16) completed a phase III clinical trial examining 56–70 Gy postoperative radiation alone versus radiation with concomitant bleomycin and mitomycin C. The arm with concurrent chemotherapy had superior 2 years locoregional control, disease free, and overall survival (16).

One meta-analyses of chemotherapy in head and neck cancer (MACH-NC) analyzed the results of 63 prospective studies performed from 1965–1993 (17). In the analysis of trials examining postoperative concurrent chemoradiation, chemotherapy administration given during radiation appeared to confer a survival benefit. In contrast, chemotherapy given prior to or after local treatment did not appear to improve survival. These findings paved the way for the design of landmark studies that have established concurrent chemoradiation as a therapeutic standard for high risk resected disease.

The seminal RTOG 9501 trial supported by the Eastern Cooperative Oncology Group (ECOG) R9501 and Southwest Oncology Group (SWOG) 9515 conducted a phase 3 study comparing radiation alone to concurrent chemoradiation with high-dose cisplatin given on days 1, 22, and 43 in patients with squamous-cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx who had undergone a complete resection of their disease and had high-risk characteristics (4). The radiation dose in this trial ranged from 60 to 66 Gy in 30–33 fractions over a period of 6–6.6 weeks. After a median follow-up of nearly 46 months, there was a significantly higher rate of locoregional control in the combined modality arm than in the arm that only had postoperative radiotherapy (HR 0.61; $p = 0.01$). The European Organization for Research and Treatment of Cancer (EORTC) trial 22931 conducted a similar study in which patients

with stage III/IV squamous cell cancer of the head and neck were randomized to postoperative chemoradiation with high-dose cisplatin versus radiation alone (5).

The maximum radiation dose given was 66 Gy in 33 fractions over a period of 6.5 weeks. After a median follow-up of 5 years, the rate of progression-free survival was significantly higher in the group that received combined modality postoperative therapy (HR 0.75; $p = 0.04$) as was overall survival (HR for death 0.70; $p = 0.02$). Furthermore, the cumulative incidence of local or regional recurrences was significantly lower in the combined-therapy group ($p = 0.007$). It is notable, however, that grade 3 or higher toxicities were more frequently observed in the group that received combined modality postoperative therapy (41% vs. 21 %; $p = 0.001$). The RTOG 9501 intergroup trial and the EORTC trial 22931 played a pivotal role in establishing the current North American guidelines for postoperative combined modality treatment.

It is notable that the two aforementioned studies had varying definitions of high-risk disease. The ECOG R9501/SWOG 9515 study defined high-risk as patients with histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, and microscopically involved mucosal margins of resection. The EORTC 22931 study defined high-risk disease as positive margins, extracapsular extension of nodal disease, clinical involvement of lymph nodes at levels 4 or 5 for oral cavity or oropharyngeal cancers, perineural disease, and/or vascular embolism. Given the differing definitions, a comparative retrospective subgroup analysis using pooled data from those two trials was published in 2005 (18). The pooled analysis concluded that outcomes for patients with ECE and/or microscopically involved surgical margins was statistically significantly better with combined modality postoperative treatment compared to radiotherapy alone. The subgroup analysis did reveal a trend toward benefit in patients who had stage III–IV disease, perineural infiltration, and/or clinically enlarged level IV–V lymph nodes secondary to tumors arising in the oral cavity or oropharynx, while patients who had two or more involved lymph nodes without ECE did not benefit from chemoradiation. In a long-term follow-up of patients in the RTOG trial with a median follow-up of 9.4 years, patients with microscopically involved resection margins and/or extracapsular spread of disease who received chemoradiation as opposed to radiation alone had lower local-regional failure rates (21% vs. 33%; $p = 0.02$), higher rates of disease-free survival (18% vs. 125; $p = 0.05$), and trends toward an a higher rate of overall survival (27% vs. 20%; $p = 0.07$) (19).

In summary for patients with locally advanced HNSCC who undergo curative intent surgery and have high-risk features (including but not limited to ECE and positive surgical margins), postoperative chemoradiation with cisplatin is the standard of care for those who can tolerate therapy.

3. Clinical investigation with alternative chemotherapy or radiation regimens

Despite the success of the bolus cisplatin and radiation approach, it is well recognized that further optimization of outcomes in high risk populations is needed. Interest in the incorporation of biological therapy into concurrent chemoradiation seemed an attractive approach to intensifying the systemic therapy component, without the excess toxicity of traditional cytotoxic agents. The epidermal growth factor receptor (EGFr) is nearly universally overexpressed among squamous cell malignancies, and inhibitors appeared to have preclinical synergy with radiation therapy. In the definitive treatment of locally advanced oropharynx, larynx, and hypopharynx cancers, the combination of cetuximab with radiation therapy resulted in superior overall survival, progression free survival, and locoregional control (20).

Harrington et al. (21) reported the results of a multicenter phase III clinical trial which randomized 688 patients with Stage II-IVA resected squamous cell carcinomas of the head and neck to cisplatin based concurrent chemoradiation (to 66 Gy) with either lapatinib, an oral EGFr inhibitor, or placebo (21). Patients continued lapatinib or placebo for a maintenance period lasting 12 months after completion of chemoradiation. This study was terminated early due to findings that there was no difference in the primary endpoint of disease-free survival. The randomized phase II RTOG 0234 trial investigated postoperative concurrent chemoradiation (60 Gy) with cetuximab and the addition of either cisplatin or docetaxel in 238 patients with high risk resected disease defined as positive margins, ECE, or two or more nodal metastases. Although not designed to compare both arms, the 2 years disease-free survival was encouraging in the non-cisplatin containing docetaxel/cetuximab arm, leading to the design of the phase III RTOG 1216 trial (22). It is of note that trials in the definitive setting for locally advanced HNSCC incorporating EGFr inhibition (cetuximab, erlotinib, panitumumab) with chemoradiation have failed to show an advantage in progression-free survival or overall survival over chemoradiation alone (23–25).

Similarly, interest in variations of platinum administration is of particular clinical significance as standard bolus cisplatin based chemoradiation results in significant high grade toxicity. For example, the EORTC 22931 study reported that only 61% of the study patients were able to complete all three planned cisplatin doses in patients randomized to chemoradiation. Argiris et al. (26) conducted a phase III clinical trial comparing postoperative radiation (at least 60 Gy) alone to radiation with concurrent weekly carboplatin 100 mg/m2 (26). This study was terminated early due to poor accrual, and analysis of the 72 patients randomized showed no difference in 5 years disease-free survival and overall survival in the two arms. Noronha et al. (27) reported a phase III trial conducted in India of 300 patients randomized to bolus 100 mg/m2 cisplatin or weekly cisplatin given at 30 mg/m2 given concurrently with radiation (27). The overwhelming majority (90%) of patients enrolled were treated in the postoperative setting for oral cavity primary sites (87%) with the most common high risk feature being ECE. Inferior locoregional control was observed in the arm receiving weekly cisplatin. There was a trend toward superior overall and progression free survival (PFS)in the arm receiving the bolus cisplatin group. It is also notable that this study was criticized for its use of 30 mg/m2 dosing rather than the 40 mg/m2 that is more commonly used in practice. The Japan Clinical Oncology Group is currently conducting a randomized phase II/III study (JCOG1008) of weekly (40 mg/m2) vs. bolus (100

mg/m2) cisplatin given concurrent with postoperative radiation in patients with resected high risk HNSCCs (28). Lastly, one meta-analysis of 52 studies found that there was no difference in OS or response rate between low-dose weekly and high-dose three-weekly cisplatin regimens (29). However, given that this has not been prospectively studied in a randomized clinical trial and the Japanese study results are still pending, the standard of care still remains high-dose cisplatin.

Finally, studies of alternative fractionation in locally advanced HNSCC have failed to show a survival benefit (30, 31). A Phase III study comparing accelerated versus fractionated postoperative radiotherapy for advanced head and neck cancer did show a trend for improved locoregional control for patients who had a delay in starting radiation, but otherwise no significant differences were seen between the control and experimental arms (30). One meta-analysis of six trials involving more than 900 patients with locally advanced HNSCC found that accelerated radiation therapy did not improve loco-regional control, progression-free survival, or overall survival (32). In fact, the meta-analysis found that accelerated radiation therapy schedules were associated with higher rates of acute mucositis.

ONGOING CLINICAL INVESTIGATION

1. HPV-related oropharynx cancer

Increasing recognition of the HPV-related oropharynx squamous cell carcinoma subset has had a tremendous impact on the prospective evaluation of HNSCC. This distinct entity, which carries a superior prognosis both in the locally advanced and the metastatic setting, has led to the design of HPV OPC specific clinical trials and has necessitated stratification for HPV status when studied with non HPV related HNSCC (33). Given the nontrivial toxicities of postoperative chemoradiation, a natural research question in this population is whether de-intensification of therapy would result in similar or better oncologic and quality of life outcomes. One particular controversy is the significance of ECE in patients who have undergone resection for HPV related OPC, since the current therapeutic standard established by RTOG 9501 and EORTC 2291 was studied prior to the recognition of the HPV related OPC as a separate entity. Provocative reports from various single institution studies (34, 35) suggest that in contrast to the previously described experience prior to the HPV era, ECE does not appear to influence outcomes in HPV related OPC patients treated with upfront transoral robotic surgery.

Prospective data is expected from ECOG 3311, a recently completed, randomized, prospective phase II clinical trial for patients with advanced stage HPV associated oropharyngeal squamous cell cancer who have undergone transoral surgery and neck dissection (NCT01898494). In this trial, patients with high-risk features (i.e., positive margins, ECE, or $\geq$5 greater metastatic lymph nodes) were assigned to receive standard of care adjuvant chemoradiation therapy. Patients with no high-risk features were assigned to observation (i.e., no adjuvant therapy); those with intermediate-risk features (close margins, perineural invasion, lymphovascular invasion, or 2–4 metastatic lymph nodes) were randomized between standard- (60 Gy/30 fractions) and reduced-dose radiation (50 Gy/25 fractions). The trial's primary objective will be to evaluate 2 years progression free survival (PFS) in HPV-positive HNSCC patients treated with low-dose radiation therapy, while its secondary end points will be early/late toxicities, quality of life, and swallowing function.

Two other large postoperative de-escalation Phase III trials are ongoing. PATHOS (NCT02215265) is a multi-institutional randomized trial conducted in the United Kingdom similar to ECOG 3311 that will risk stratify HPV related p16+ HNSCC into low, intermediate or high risk groups. Patients with intermediate risk will be randomized to standard or deescalated postoperative radiation. High risk patients will be randomized to postoperative radiation to 60 Gy or postoperative radiation with weekly cisplatin chemotherapy. ADEPT NCT01687413 trial is a study of postoperative adjuvant therapy de-intensification for HPV-related, p16+ oropharynx cancers. In this trial, HPV-related oropharyngeal cancer patients who have undergone surgery and neck dissection and have been found to have high-risk features are randomized to standard-of-care adjuvant chemoradiation versus radiation alone.

In addition, smaller phase II trials are being conducted in North America. The Sinai Robotic Surgery Trial (SIRS - NCT02072148) is a single institution trial which will risk stratify patients to low, intermediate or high risk. Patients with intermediate risk will receive 50 Gy postoperatively, and those with high risk treated with 60 Gy with weekly cisplatin chemotherapy. The Mayo Clinic NCT01932697 is conducting a phase II trial wherein patients with high risk features after resection will be treated with altered fractionation with concurrent docetaxel. The University of Pennsylvania (NCT02159703) has an ongoing clinical trial involving adjuvant radiation to the regional lymph nodes only (sparing the primary sites) in patients with low volume T disease, negative margins and pathologic nodal involvement. Lastly, a large German multi-institutional Phase I study, DELPHI (NCT03396718), is ongoing and is examining deescalated radiation doses in patients with low or intermediate risk pathologic features after resection.

It is notable that in the definitive setting, de-intensification studies for HPV-related oropharyngeal cancers have preliminarily shown negative results. RTOG 1016 (NCT01302834) is an ongoing trial comparing radiation therapy with cisplatin or cetuximab in patients with p16 positive oropharyngeal cancers. For now, the question of whether patients with locally advanced HNSCC which are HPV-positive require the same intensity of adjuvant therapy as those which are HPV-negative remains unanswered. Given the preliminary negative studies reported in the definitive setting, it is important to note that de-escalation still has high-risk and should be tested only within the context of a clinical trial. **Table 1** summarizes the selected de-escalation studies of adjuvant therapies in HPV-positive head and neck cancers.

2. Immunotherapy and other therapeutic strategies in the perioperative setting

Nivolumab and pembrolizumab, two monoclonal antibodies that inhibit PD-1, were approved in 2016 for recurrent/metastatic squamous cell carcinomas of the head and neck previously treated with cisplatin chemotherapy. The encouraging activity of

these agents in the metastatic setting gives merit to investigation in the curative intent setting. Preclinical data suggests synergy between the anti-PD-1 inhibitors and radiation therapy, making this approach an attractive one in the high risk postoperative setting (36).

The NRG has recently completed HN003 (NCT02775812), a phase I experience in high risk resected HPV related squamous cell carcinomas (defined as positive margin and/or ECE), wherein pembrolizumab 200 mg IV every 3 weeks administered with postoperative radiation and weekly cisplatin chemotherapy. The results of this study are expected to provide a basis for future comparison of this regimen to the current therapeutic standard. Another strategy under study is the administration of the anti-PD1 agents in both the neoadjuvant and adjuvant setting. Wise-Draper et al. (37) recently reported the preliminary safety data of an ongoing phase II trial (NCT02641093) wherein patients with locally advanced resectable HNSCC received one dose of pembrolizumab 1–3 weeks prior to surgery (37). All patients received postoperative radiation to 60 Gy with concurrent pembrolizumab 200 mg IV every 3 weeks × 6 doses, or the same regimen with concurrent weekly cisplatin (40 mg/m2) in patients with high risk features. At the time of reporting, 28 patients had been enrolled, and 9 of 19 evaluable patients had evidence of pathological response on examination of the surgical specimen. No dose limiting toxicities were observed. Another phase II trial (NCT02296684) is ongoing with a similar neoadjuvant/adjuvant pembrolizumab design, but with bolus cisplatin 100 mg/m2 given with postoperative radiation in high risk patients. An early report on the first 21 patients enrolled showed encouraging tolerability of the pre-surgical pembrolizumab dose with no patients experiencing delays in surgery or unexpected complications (38). Furthermore, 43% of patients showed a pathologic response on the surgical specimen. **Table 2** summarizes selected immunotherapy trials that are ongoing.

Alongside immunotherapy, a number of other therapeutic strategies are currently under active investigation. The ECOG-ACRIN cancer research group is studying the use of radiation therapy with or without cisplatin in treating patients with p16 negative stage III-IVa HNSCC who have undergone surgery (NCT02734537). This phase II trial mandates central determination of tumor p53 status, and is anticipated to provide valuable information regarding oncologic outcomes based on p53 aberrations, potentially paving the way for genomically driven

TABLE 1 | Summary of selected HPV de-escalation studies in the adjuvant setting.

NCT Identifier	Phase	Intervention
ECOG 3311—NCT0198494	II	Pathologic risk stratification after transoral surgery. Low-risk patients are observed; intermediate-risk patients are randomized between 50 and 60 Gy of radiation; high-risk patients receive 66 Gy with weekly cisplatin
PATHOS—NCT02215265	III	Pathologic risk stratification after transoral surgery and neck dissection. Low-risk patients are observed; intermediate-risk patients are randomized between 50 and 60 Gy; high-risk patients are randomized between 60 Gy +/– concurrent cisplatin
ADEPT—NCT01687413	III	Patients with extracapsular extension are randomized to 60 Gy of radiation +/– concurrent cisplatin
SIRS—NCT02072148	II	Pathologic risk stratification after transoral surgery. Low-risk patients are observed; intermediate-risk patients will receive 50 Gy radiation; high-risk patients will receive 60 Gy of radiation with concurrent cisplatin
Mayo—NCT01932697	II	Patients found to have pathologic high-risk after resection will be treated with altered fractionation with concurrent docetaxel
Penn—NCT02159703	II	Adjuvant radiation to regional lymph nodes in patients with low volume T disease, negative margins, and pathologic nodal involvement
DELPHII—NCT03396718	I	Examines deescalated radiation doses in patients with low or intermediate risk pathologic features after resection

TABLE 2 | Summary of selected immunotherapy trials.

NCT Identifier	Target	Trial
NCT02841748	PD-1	Randomized, Double-Blind Phase II Study of Adjuvant Pembrolizumab Vs. Placebo in Head and Neck Cancers at High Risk for Recurrence
NCT02296684	PD-1	Immunotherapy with MK-3475 in Surgically Resectable Head and Neck Squamous Cell Carcinoma
NCT02775812	PD-1	Cisplatin, Intensity-Modulated Radiation Therapy, and Pembrolizumab in Treating Patients with Stage III–IV Head and Neck Squamous Cell Carcinoma
NCT02641093	PD-1	Phase II Trial of Adjuvant Cisplatin and Radiation with Pembrolizumab in Resected Head and Neck Squamous Cell Carcinoma
NCT03325465	PD-1; IDO1	Neoadjuvant Pembrolizumab + Epacadostat Prior to Curative Surgical Care for Squamous Cell Carcinoma of the Head and Neck
NCT02741570	PD-1; CTLA-4	Study of Nivolumab in Combination with Ipilimumab Compared to the Standard of Care (EXTREME Study Regimen) as First Line Treatment in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

PD-1, Programmed cell death protein 1; IDO1, Indoleamine 2,3-dioxygenase-1; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4.

adjuvant therapy recommendations. Furthermore, translational research is pushing the field toward the development of novel therapeutic strategies, with synthetic lethality proving to be an encouraging avenue for therapy. Increasing preclinical evidence points to the reliance of p53 deficient cells on wee-1, a G2/M checkpoint regulator, to affect DNA repair after exposure to cytotoxic agents. The wee-1 inhibitor—AZD1775—in combination with neoadjuvant weekly docetaxel and cisplatin before definitive therapy in HNSCC had promising findings that may be translated into an innovative therapeutic approach (39). An ongoing trial (NCT03028766) will seek to combine the wee-1 inhibitor with cisplatin and radiotherapy after surgery in patients with HNSCC.

SUMMARY

While concurrent cisplatin based chemoradiation continues to be the standard of care for postoperative management of high risk resected HNSCC, the field is rapidly changing. Improving radiation techniques, checkpoint inhibitors, and novel therapeutic strategies, along with the recognition of HPV status as an important prognostic indicator, may help to increase the probability of cure in patients with advanced head and neck cancers. Ongoing clinical trials will hopefully be able to answer how to rationally combine effective novel therapies in the postoperative setting.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REFERENCES

1. Cognetti DM, Weber RS, Lai SY. Head and neck cancer: an evolving treatment paradigm. *Cancer* (2008) 113:1911–32. doi: 10.1002/cncr.23654
2. Kramer S, Gelber RD, Snow JB, Marcial VA, Lowry LD, Davis LW, et al. Combined radiation therapy and surgery in the management of advanced head and neck cancer: final report of study 73-03 of the Radiation Therapy Oncology Group. *Head Neck Surg.* (1987) 10:19–30. doi: 10.1002/hed.2890100105
3. Marcus RB Jr, Million RR, Cassissi NJ. Postoperative irradiation for squamous cell carcinomas of the head and neck: analysis of time-dose factors related to control above the clavicles. *Int J Radiat Oncol Biol Phys*. (1979) 5:1943–9.
4. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Eng J Med*. (2004) 350:1937–44. doi: 10.1056/NEJMoa032646
5. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Eng J Med*. (2004) 350:1945–52. doi: 10.1056/NEJMoa032641
6. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for platinum-and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol*. (2017) 35:1542–9. doi: 10.1200/JCO.2016.70.1524
7. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Eng J Med*. (2016) 375:1856–67. doi: 10.1056/NEJMoa1602252
8. Laramore G, Scott C, Al-Sarraf M, Haselow R, Ervin T, Wheeler R, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report of intergroup study 0034. *Int J Radiat Oncol Biol Phys*. (1992) 23:705–13.
9. Al-Sarraf M, Pajak TF, Byhardt RW, Beitler JJ, Salter MM, Cooper JS. Postoperative radiotherapy with concurrent cisplatin appears to improve locoregional control of advanced, resectable head and neck cancers: RTOG 88-24. *Int J Radiat Oncol Biol Phys*. (1997) 37:777–82.
10. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys*. (1993) 26:3–11. doi: 10.1016/0360-3016(93)90167-T
11. Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. (2001) 51:571–8. doi: 10.1016/S1278-3218(02)00170-1
12. Rosenthal DI, Liu L, Lee JH, Vapiwala N, Chalian AA, Weinstein GS, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck* (2002) 24:115–26. doi: 10.1002/hed.10038
13. Graboyes EM, Garrett-Mayer E, Ellis MA, Sharma AK, Wahlquist AE, Lentsch EJ, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. *Cancer* (2017) 123:4841–50. doi: 10.1002/cncr.30939
14. National Comprehensive Cancer Network. *Head and Neck Cancers* (Version 2.2018). Available online at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (Accessed September 17, 2018).
15. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys*. (1996) 36:999–1004. doi: 10.1016/S0360-3016(96)00430-0
16. Smid L, Budihna M, Zakotnik B, Soba E, Strojan P, Fajdiga I, et al. Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. *Int J Radiat Oncol Biol Phys*. (2003) 56:1055–62. doi: 10.1016/S0360-3016(03)00207-4
17. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. *Lancet* (2000) 355:949–55. doi: 10.1016/S0140-6736(00)90011-4
18. Bernier J, Cooper JS, Pajak T, Van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (# 22931) and RTOG (# 9501). *Head Neck* (2005) 27:843–50. doi: 10.1002/hed.20279
19. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. (2012) 84:1198–205. doi: 10.1016/j.ijrobp.2012.05.008
20. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Eng J Med*. (2006) 354:567–78. doi: 10.1056/NEJMoa053422
21. Harrington K, Temam S, Mehanna H, D'Cruz A, Jain M, D'Onofrio I, et al. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: a phase III, randomized,

double-blind, placebo-controlled study. *J Clin Oncol*. (2015) 33:4202–9. doi: 10.1200/JCO.2015.61.4370

22. Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. (2014) 32:2486–95. doi: 10.1200/JCO.2013.53.9163
23. Ang KK, Zhang Q, Rosenthal DI, Nguyen-Tan PF, Sherman EJ, Weber RS, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. (2014) 32:2940. doi: 10.1200/JCO.2013.53.5633
24. Mesía R, Henke M, Fortin A, Minn H, Ancona ACY, Cmelak A, et al. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol*. (2015) 16:208–20. doi: 10.1016/S1470-2045(14)71198-2
25. Martins RG, Parvathaneni U, Bauman JE, Sharma AK, Raez LE, Papagikos MA, et al. Cisplatin and radiotherapy with or without erlotinib in locally advanced squamous cell carcinoma of the head and neck: a randomized phase II trial. *J Clin Oncol*. (2013) 31:1415–21. doi: 10.1200/JCO.2012.46.3299
26. Argiris A, Karamouzis MV, Johnson JT, Heron DE, Myers E, Eibling D, et al. Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer. *Laryngoscope* (2008) 118:444–9. doi: 10.1097/MLG.0b013e31815b48f4
27. Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol*. (2017) 36:1064–72. doi: 10.1200/JCO.2017.74.9457
28. Kunieda F, Kiyota N, Tahara M, Kodaira T, Hayashi R, Ishikura S, et al. Randomized phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly cisplatin with weekly cisplatin in high-risk patients with squamous cell carcinoma of head and neck: Japan Clinical Oncology Group Study (JCOG1008). *Jap Journ Clin Oncol*. (2014) 44:770–4. doi: 10.1093/jjco/hyu067
29. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist* (2017) 22:1056–66. doi: 10.1634/theoncologist.2017-0015
30. Sanguineti G, Richetti A, Bignardi M, Gabriele P, Sormani MP, Antognoni P. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. *Int J Radiat Oncol Biol Phys*. (2005) 61:762–71. doi: 10.1016/j.ijrobp.2004.07.682
31. Awwad H, Lotayef M, Shouman T, Begg A, Wilson G, Bentzen S, et al. Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. *Br J Cancer* (2002) 86:517. doi: 10.1038/sj.bjc.6600119
32. Matuschek C, Haussmann J, Bölke E, Gripp S, Schuler PJ, Tamaskovics B, et al. Accelerated vs. conventionally fractionated adjuvant radiotherapy in high-risk head and neck cancer: a meta-analysis. *Radiat Oncol*. (2018) 13:195. doi: 10.1186/s13014-018-1133-8
33. Vokes EE, Agrawal N, Seiwert TY. HPV-associated head and neck cancer. *J Natl Cancer Inst*. (2015) 107:djv344. doi: 10.1093/jnci/djv344
34. Maxwell JH, Ferris RL, Gooding W, Cunningham D, Mehta V, Kim S, et al. Extracapsular spread in head and neck carcinoma: impact of site and human papillomavirus status. *Cancer* (2013) 119:3302–8. doi: 10.1002/cncr.28169
35. Sinha P, Kallogjeri D, Gay H, Thorstad WL, Lewis JS Jr, Chernock R, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol*. (2015) 51:514–20. doi: 10.1016/j.oraloncology.2015.02.098
36. Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* (2015) 520:373–7. doi: 10.1038/nature14292
37. Wise-Draper TM, Old MO, Worden FP, O'Brien PE, Cohen EEW, Dunlap N, et al. Phase II multi-site investigation of neoadjuvant pembrolizumab and adjuvant concurrent radiation and pembrolizumab with or without cisplatin in resected head and neck squamous cell carcinoma. *J Clin Oncol*. (2018) 36(Suppl. 15):6017. doi: 10.1200/JCO.2018.36.15_suppl.6017
38. Uppaluri R, Zolkind P, Lin T, Nussenbaum B, Jackson RS, Rich J, et al. Neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV negative head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol*. (2017) 35(Suppl. 15):6012. doi: 10.1200/JCO.2017.35.15_suppl.6012
39. Mendez E, Rodriguez CP, Kao MC, Raju S, Diab A, Harbison RA, et al. A phase I clinical trial of AZD1775 in combination with neoadjuvant weekly docetaxel and cisplatin before definitive therapy in head and neck squamous cell carcinoma. *Clin Cancer Res*. (2018) 24:2740–8. doi: 10.1158/1078-0432.CCR-17-3796

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Predictive Value of Cetuximab-Induced Skin Toxicity in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and NECK

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Background: Skin toxicity is a common adverse event during cetuximab (Cmab) treatment. However, few reports have investigated the correlation between skin toxicity and the efficacy of Cmab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN).

Methods: We retrospectively reviewed 112 R/M SCCHN patients who received palliative chemotherapy with Cmab. Main eligibility criteria included primary disease in the oral cavity, hypopharynx, nasopharynx, oropharynx, or larynx; no prior history of EGFR-directed therapy; receipt of Cmab plus chemotherapy as first-line therapy for recurrent or metastatic disease; and follow-up for more than 90 days. We analyzed the time to first occurrence and time of maximum grade skin toxicity, and its predictive value with regard to treatment efficacy.

Results: After a median follow-up of 393 days (range 109–1501 days), 105 (94%) and 20 (18%) patients had skin toxicity of any grade and grade 3, respectively. Among them, 8 patients with grade 3 acneiform rash, skin rash, or paronychia within 90 days after treatment initiation ("early skin toxicity") had improved progression-free survival (PFS) (log-rank test, $P = 0.045$; 2-year PFS, 25.0 vs. 2.9%) and overall survival (OS) (log-rank test, $P = 0.023$, 2-year OS, 50.0 vs. 14.4%) compared with those with < grade 3 toxicity. A greater proportion of patients with early skin toxicity than patients without this toxicity could proceed with Cmab maintenance (88 vs. 44%, $P = 0.021$). Multivariate analysis identified early skin toxicity as an independent predictor of better PFS (hazard ratio [HR] = 0.363, 95% confidence interval [CI] 0.142–0.924, $P = 0.034$) and OS (HR = 0.187, 95% CI: 0.045–0.781, $P = 0.022$).

Conclusion: Grade 3 Cmab-induced skin toxicity within 90 days was associated with better survival in R/M SCCHN. Effective rash management therefore seems necessary to realize the benefit of Cmab treatment.

Keywords: skin toxicity, cetuximab, predictive value, head and neck cancer, squamous cell carcinoma, recurrent, metastatic

INTRODUCTION

Head and neck cancer is the sixth-most common cancer, and more than 600,000 new cases are diagnosed annually worldwide (1, 2). In Japan, approximately 20,000 new cases are diagnosed annually (3). Despite optimal treatment, locoregional recurrence will occur in 60% of these patients, often in irradiated areas, and distant metastasis will develop in 20%. The prognosis of patients with recurrent or metastatic disease is poor and their therapeutic options are limited, with most requiring palliative chemotherapy.

Cetuximab (Cmab) is an epidermal growth factor receptor (EGFR) inhibitor which plays an important role in epithelial malignancies, including squamous cell carcinoma of the head and neck (SCCHN). The phase III EXTREME trial reported that the addition of Cmab to platinum/5FU significantly improved overall survival (OS), progression-free survival (PFS) and response compared with platinum/5FU in first-line treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) (4). Accordingly, the regimen has been recognized as a standard care for the disease worldwide, including Japan. One of its major side effects is skin toxicity, manifesting as a skin rash, acneiform rash, paronychia, dry skin, hair growth disorders, pruritus, or nail changes. Studies in multiple malignancies have shown that there is no apparent difference in the incidence or severity of Cmab-induced skin toxicity between races, while, the occurrence of more severe Cmab-induced skin toxicity correlates with better treatment response and longer survival (5–15). However, this correlation of Cmab-induced skin toxicity with efficacy has not been shown for R/M SCCHN. Here, we examined whether Cmab-induced skin toxicity predicts treatment efficacy in patients with R/M SCCHN.

METHODS AND MATERIALS

We have reviewed the medical records of R/M SCCHN patients who received palliative chemotherapy with Cmab in various combination (5-FU + cisplatin; CDDP or carboplatin: CBDCA + Cmab, paclitaxel: PTX + CBDCA + Cmab and PTX + Cmab) at the National Cancer Center Hospital East Japan between December, 2012 and December, 2016 (**Table 1**). Main eligibility criteria were age ≥20 years; primary disease in the oral cavity, hypopharynx, nasopharynx, oropharynx, or larynx; no prior history of EGFR-directed therapy; receipt of chemotherapy plus Cmab as first-line therapy for recurrent or metastatic disease; and follow-up for more than 90 days. All patients received Cmab at a dose of 400 mg/m^2 IV on day 1 and 250 mg/m^2 weekly thereafter. In the Cmab plus platinum agent (cisplatin or carboplatin) group, patients who had at least stable disease received Cmab monotherapy (maintenance therapy) until disease progression or until unacceptable toxic effects occurred after a maximum of six cycles of platinum administration. In the paclitaxel and Cmab group, patients received these agents until paclitaxel-induced toxic effects became unacceptable, after which they continued with Cmab maintenance until disease progression occurred. The patients were not included in a consecutive way. In accordance with the MASCC guidelines (16), we used prophylactic therapy for Cmab-induced skin toxicity, consisting of a skin moisturizer (heparinoid lotion) applied to the body and face twice a day, and oral minocycline 100 mg twice a day, which was started at the beginning of the Cmab-containing regimen. In addition, topical steroids were initiated after the emergence of any skin toxicities. Diflupredate (very strong) 0.05% and hydrocortisone butyrate (mild) 0.1% were applied to the body and face, respectively. The study was approved by the Clinical Research and Ethical Review Board of our institution (task number: 2016-229).

TABLE 1 | Patient characteristics (n = 112).

Characteristic	
Age (years)	
Median (range)	64 (26–78)
Sex, *n* (%)	
Male	94 (84)
Female	18 (16)
ECOG PS, *n* (%)	
0/1/2	54 (48)/54 (48)/4 (4)
Primary site, *n* (%)	
Oral cavity	39 (35)
Hypopharynx	33 (29)
Nasopharynx	15 (13)
Oropharynx	12 (11)
Larynx	13 (12)
Treatment regimen, *n* (%)	
5-FU + CDDP or CBDCA + Cmab	33 (30)
PTX + CBDCA + Cmab	36 (32)
PTX + Cmab	43 (38)

ECOG PS, Eastern Cooperative Oncology Group performance status; 5FU, 5-fluorouracil; CDDP, Cisplatin; CBDCA, Carboplatin; Cmab, Cetuximab; PTX, Paclitaxel.

Skin Toxicity Evaluation and Grading

The Cmab-induced skin toxicity was evaluated and graded using the Common Toxicity Criteria for Adverse Events (CTCAE version 4.0) by the same medical oncologist in charge per patient throughout the treatment. The dermatologist (NA) and registered pharmacist (US) supervised and supported the evaluation to share the same criteria and to reduce inconsistency in observation.

General Principles of Cmab Interruption and Reintroduction

When the grade 3 or worse skin toxicities were observed at the day of Cmab administration, physician omitted Cmab at least one week, and restarted it after the toxicity recovered to Grade 2 or less. In addition, if it is judged that trend of exacerbation was apparent, physician could skip Cmab even in the case of grade 2 skin toxicity, and restarted it as soon as the toxicity recovered to acceptable Grade 2 or less. For patients who experienced Cmab interruption, additional medications (e.g., oral antihistamine and antibiotics, topical antibiotics and a higher-potency topical steroid) were considered at a physician's and dermatologist's discretion. Additionally, when Cmab interruption continued

even though the additional medication was given, dose reduction of Cmab could be applied (e.g. dose level 0: 250mg/m^2, dose level−1: 200mg/m^2, dose level−2: 150mg/m^2). In case that further dose reduction is required after doses of cetuximab reduced by 2 levels, the discontinuation of Cmab was considered.

Statistical Analysis

We analyzed the time to first occurrence and time of maximum grade skin toxicity and its predictive value with regard to treatment efficacy. PFS was defined as the period from the commencement of treatment to the date of confirmation of disease progression or death. OS was determined as the period from the commencement of treatment to the date of death from any cause or the date of the last follow-up. PFS and OS were calculated by the Kaplan–Meier product-limit method. The landmark-time analysis was applied to PFS and OS counted from 90 days after the start of therapy. Hazard ratios (HRs) were calculated by Cox regression analysis. Univariate analyses were undertaken to evaluate the relationship between the pretreatment clinical variables and the risk of development of skin toxicity using the $\chi 2$ test or Fisher's exact test. Multivariate analysis was undertaken using logistic regression to identify significant factors associated with PFS and OS. We used SPSS software (version 17.00, SPSS, Inc., Chicago, IL, USA) for the statistical analysis. $P < 0.05$ were considered to indicate statistical significance.

RESULTS PATIENT CHARACTERISTICS

A total of 112 cases were available for analysis (**Figure 1**). Most patients were men (84%) with a median age of 64 years (range 26–78 years). The main primary disease sites were the oral cavity (35%) and hypopharynx (29%). A total of 33patients (30%) received 5-FU + CDDP or carboplatin: CBDCA + Cmab, while 36 patients (32%) received PTX + CBDCA + Cmab. All other patients were treated with a combination of Cmab and paclitaxel (**Table 1**).

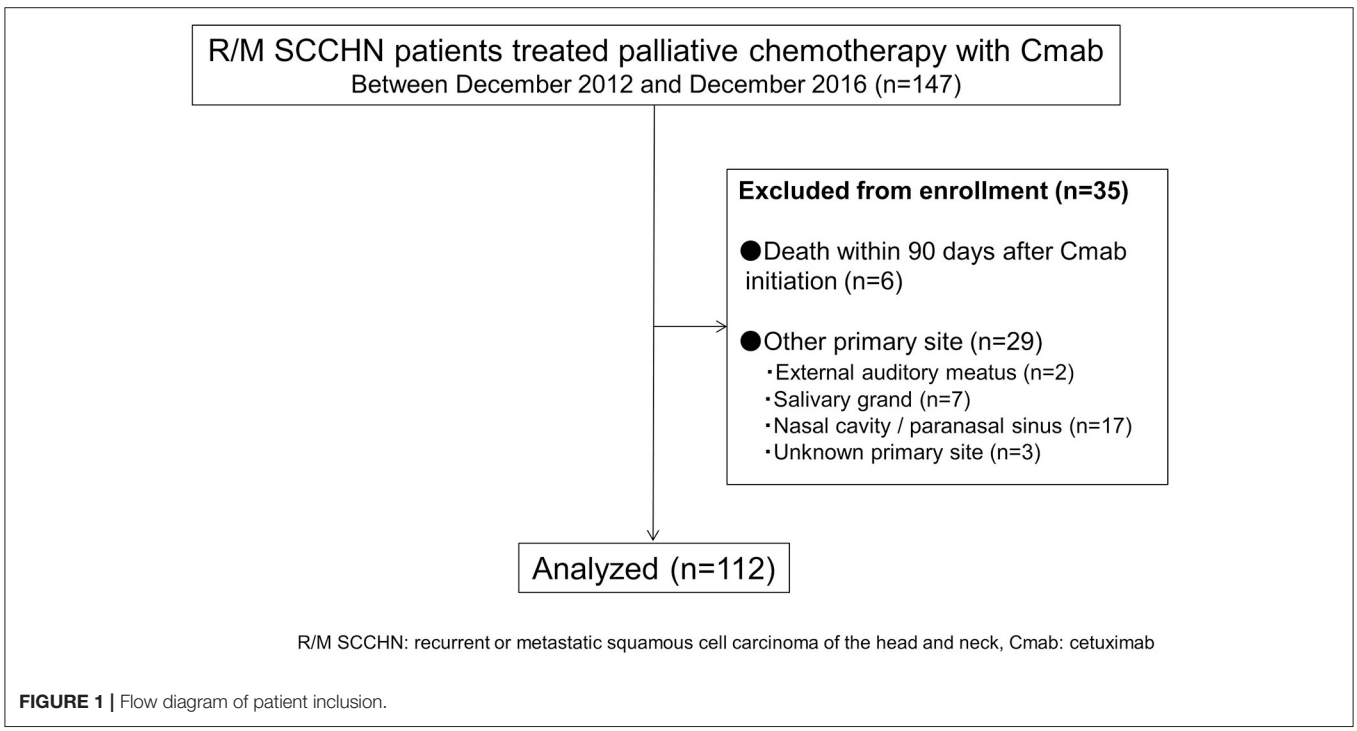


FIGURE 1 | Flow diagram of patient inclusion.

TABLE 2 | Cmab-induced skin toxicity ($n = 112$).

	Grade 1		Grade 2		Grade 3		All Grades	
	≤90days	Overall	≤90days	Overall	≤90days	Overall	≤90days	Overall
Acneiform rash	17 (15)	24 (21)	40 (36)	54 (48)	5 (4)	9 (8)	62 (55)	87 (78)
Paronychia	13 (12)	24 (21)	11 (10)	26 (23)	1 (1)	6 (5)	25 (22)	56 (50)
Skin rash	18 (16)	23 (21)	14 (13)	27 (24)	2 (2)	6 (5)	34 (30)	56 (50)
Fissures	25 (22)	33 (29)	22 (20)	39 (35)	0 (0)	0 (0)	47 (42)	72 (64)
Xerosis	25 (22)	36 (32)	17 (15)	32 (29)	0 (0)	1 (1)	42 (38)	68 (61)
Total with the toxicity*	59 (53)	78 (70)	75 (67)	88 (79)	8 (7)	20 (18)	101 (90)	105 (94)

Data are presented as n (%).

TABLE 3 | Univariate analysis of possible factors related to skin toxicity (≥ Grade 3).

Variable	*n*	≥Grade 3	<Grade 3	*P*-value
(A) OVERALL				
Age				
<70	85	16 (19)	69 (81)	0.636
≥70	27	4 (15)	23 (85)	
Sex				
Male	94	17 (18)	77 (82)	0.886
Female	18	3 (17)	15 (83)	
PS				
0	54	12 (22)	42 (78)	0.244
1 or 2	58	8 (14)	50 (86)	
BSA (m^2)				
<1.62 (median)	56	7 (12)	49 (88)	0.139
≥1.62 (median)	56	13 (23)	43 (77)	
Primary site				
Oral	39	6 (15)	33 (85)	0.618
Non-oral†	73	14 (19)	59 (81)	
Treatment regimen				
5-FU + CDDP or CBDCA + Cmab	33	8 (24)	25 (76)	0.497
PTX + CBDCA + Cmab	36	6 (17)	30 (83)	
PTX + Cmab	43	6 (14)	37 (86)	
Type of combination				
Doublet	43	6 (14)	37 (86)	0.394
Triplet	69	14 (20)	55 (80)	
(B) ≤90 DAYS				
Age				
<70	85	6 (7)	79 (93)	0.951
≥70	27	2 (7)	25 (93)	
Sex				
Male	94	7 (7)	87 (93)	0.775
Female	18	1 (6)	17 (94)	
PS				
0	54	4 (7)	50 (93)	0.916
1 or 2	58	4 (7)	54 (93)	
BSA (m^2)				
<1.62 (median)	56	2 (4)	54 (96)	0.142
≥1.62 (median)	56	6 (11)	50 (89)	
Primary site				
Oral	39	3 (8)	36 (92)	0.869
Non-oral†	73	5 (7)	68 (93)	
Treatment regimen				
5-FU + CDDP or CBDCA + Cmab	33	4 (12)	29 (88)	0.412
PTX + CBDCA + Cmab	36	2 (6)	34 (94)	
PTX + Cmab	43	2 (5)	41 (95)	
Type of combination				
Doublet	43	2 (5)	41 (95)	0.419
Triplet	69	6 (9)	63 (91)	

Data are presented as n (%). BSA, body surface area.
†Hypopharynx, nasopharynx, oropharynx, larynx.

Incidence and Characteristics of Cetuximab-Induced Skin Toxicity

After a median follow-up of 393 days (range 109–1501 days), 105 patients (94%) experienced Cmab-induced skin toxicity. Although no grade 4 toxicity was observed, 20 patients (18%) developed skin toxicity of grade 3. Among these, 8 patients (40%) experienced grade 3 toxicity within 90 days after the start of treatment (**Table 2**).

There were no apparent differences in sex, age, primary site, type of combination, treatment regimen, performance status, or body surface area between patients with and without skin toxicities (**Table 3**.

Interruption and Discontinuation of Palliative Chemotherapy With Cmab

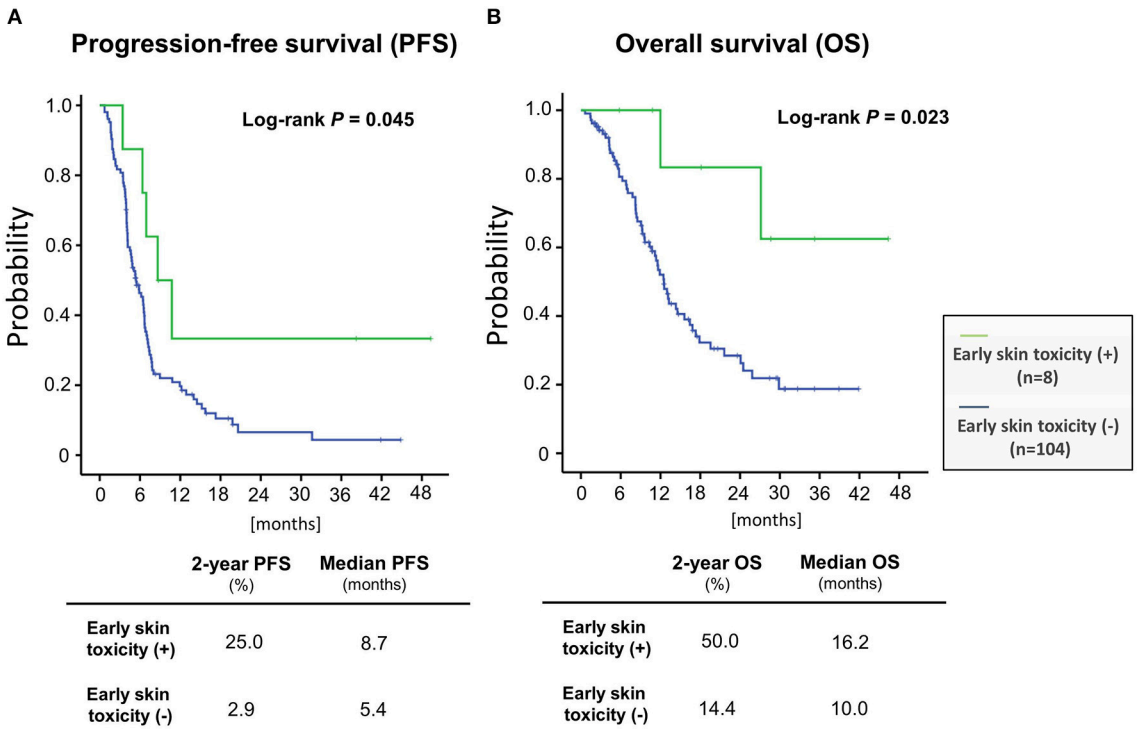
Chemotherapy with Cmab was interrupted because of Cmab-induced skin toxicity in 33 patients (29%). Among these, 16 of 20 patients with grade 3 skin toxicity (acneiform rash in 6, skin rash in 4, paronychia in 6) and 17 of 88 patients with grade 2 skin toxicity (acneiform rash in 8, skin rash in 4, paronychia in 4 cases and others in 7 cases, with some patients having more than one toxicity). The median cumulative duration of interruption of treatment due to skin toxicity was 14 days (7–56 days). During the interruption, additional oral antihistamine and/or antibiotics were given to 14 patients while additional topical antibiotics and/or a higher-potency topical steroid was given to 25 patients (**Table 4**). While, 18 cases experienced Cmab dose reduction because that Cmab interruption continued under the additional medication. Consequently, chemotherapy with Cmab was restarted in almost all cases of treatment interruption, except in one case in which chemotherapy was discontinued at the patient's discretion, despite complete resolution of the skin toxicity.

Predictive Value of Cetuximab-Induced Skin Toxicity for OS and PFS

We then examined the correlation between skin toxicity and prognosis. Patients with acneiform rash, skin rash and paronychia of grade 3 severity within 90 days after treatment

TABLE 4 | Interruption and discontinuation due to Cmab-induced skin toxicity.

(A) INTERRUPTION AND DISCONTINUATION	
Interruption, *n* (%)	
Median cumulative duration (range)	33 (29%) 14 days (7-56)
Discontinuation, n (%)	1 (0.8%)
(B) ADDITIONAL MANAGEMENT AFTER CMAB INTERRUPTION	
Systemic, *n* (%)	
Antihistamine	11 (33)
Antibiotics	11 (33)
Prednisolone	1 (3)
Topical, *n* (%)	
Escalation of steroid potency	12 (36)
Antibiotics	10 (30)



	2-year PFS (%)	Median PFS (months)
Early skin toxicity (+)	25.0	8.7
Early skin toxicity (-)	2.9	5.4

	2-year OS (%)	Median OS (months)
Early skin toxicity (+)	50.0	16.2
Early skin toxicity (-)	14.4	10.0

FIGURE 2 | Patient prognoses stratified according to the presence or absence of early skin toxicity **(A)** progression-free survival **(B)** overall survival.

initiation ("early skin toxicity") had improved PFS (log-rank test, $P = 0.045$) and OS (log-rank test, $P = 0.023$) compared with those with less than grade 3 toxicity (**Figure 2**). The 2-year PFS and OS rates of patients with early skin toxicity and those without were 25.0 vs. 2.9%, and 50.0 vs. 14.4%, respectively. Multivariate analysis identified early skin toxicity as an independent favorable prognostic factor for PFS (HR = 0.363, 95% confidence interval [CI] 0.142–0.924, $P = 0.034$) and OS (HR = 0.187, 95% CI 0.045–0.781, $P = 0.022$) (**Table 5**). Furthermore, a greater proportion of patients with early skin toxicity could proceed with Cmab maintenance than patients without this toxicity (88 vs. 44%, $P = 0.021$) (**Table 6**).

DISCUSSION

Several reports have indicated a correlation between the severity of Cmab-induced skin toxicity and treatment efficacy, including a retrospective review of Cmab with radiotherapy for SCCHN that showed a better outcome in patients with a G2-4 rash (5–14). However, few studies have focused on the correlation between Cmab-induced skin toxicity and efficacy in R/M SCCHN. Klinghammer et al. observed a trend toward longer PFS and OS in patients who experienced grade 1 rash compared with those with grade 0 among R/M SCCHN patients who were treated with the combination of Cmab and docetaxel (17). In our present study, we found that severe (≥grade 3) Cmab-induced skin toxicity within 90 days ("early skin toxicity") is an independent and more robust predictive factor for a favorable clinical outcome after adjusting for sex, age, primary site and treatment regimen (with HR of 0.363 for PFS and HR of 0.187 for OS). Consistent with this finding, patients with early skin toxicity had a better prognosis than that of the entire Cmab plus chemotherapy group in the EXTREME study (2-year OS: 50 vs. 14%) (18). Furthermore, the majority of patients (88%) with early skin toxicity in the current study proceeded to Cmab maintenance therapy, vs. fewer than half of patients (45%) in the Cmab plus chemotherapy group in the EXTREME study. These findings indicate that early skin toxicity is a promising predictor of outcome in treatment with a Cmab-containing regimen in R/M SCCHN.

When considering the significance of skin toxicity as predictor of outcome of treatment with a Cmab-containing regimen, it is important to avoid treatment interruption and discontinuation due to toxicity in order to achieve maximum benefit. However, the current recommendations for the management of Cmab-induced skin toxicity are generally based on expert opinion and consensus (16, 19). In our study, chemotherapy with Cmab was interrupted in 33 patients (29%) because of skin toxicity; however, almost all of those patients were able to restart chemotherapy with Cmab after the addition of an oral antihistamine, oral antibiotics and/or topical antibiotics. Although it is unclear whether this management was appropriate, these treatments might have enabled continuation of the Cmab-containing regimen. However, one patient discontinued chemotherapy because of skin toxicity, even though the toxicity completely resolved. Cmab-induced skin toxicities, especially

TABLE 5 | Cox regression analysis.

Variable	HR	95% CI	*P*-value
(A) PROGRESSION-FREE SURVIVAL			
Skin toxicity*			
<Grade 3	Referent	0.142–0.924	0.034
≥Grade 3	0.363		
Sex			
Male	Referent	1.039–3.187	0.036
Female	1.819		
Age			
<70	Referent	0.574–1.522	0.787
≥70	0.935		
Primary site			
Oral	Referent	0.631–1.531	0.938
Non-oral†	0.983		
Treatment regimen			
Doublet	Referent	0.565–1.308	0.481
Triplet	0.860		
(B) OVERALL SURVIVAL			
Skin toxicity*			
<Grade3	Referent	0.045–0.781	0.022
≥Grade3	0.187		
Sex			
Male	Referent	0.576–2.235	0.715
Female	1.135		
Age			
<70	Referent	0.751–2.309	0.337
≥70	1.317		
Primary site			
Oral	Referent	0.327–0.940	0.028
Non-oral†	0.554		
Treatment regimen			
Doublet	Referent	0.416–1.201	0.199
Triplet	0.707		

*HR, hazard ratio; CI, confidence interval. *Acneiform rash, skin rash, paronychia. †Hypopharynx, nasopharynx, oropharynx, larynx.*

TABLE 6 | Cmab maintenance therapy ($n = 112$).

Maintenance	*n*	≥Grade 3, *n* (%)	<Grade 3, *n* (%)	*P*-value
Yes	53	7 (88)	46 (44)	0.021
No	59	1 (12)	58 (56)	

rash, paronychia and skin fissures, often compromise quality of life and cause psychological discomfort. A multidisciplinary team comprising medical oncologists, dermatologists, pharmacists and nurses needs to be actively engaged in the management of Cmab-induced skin toxicities. A prospective study is also necessary to investigate and standardize the management of Cmab-induced skin toxicities.

Recently, there has been a focus on identification of patients with increased risk of developing EGFR inhibitor-induced rash. At the basic research phase of SCCHN, an EGFR-R521K genotype (G/G) was reportedly associated with increased Cmab-induced skin toxicity (20). Other reports, which included SCCHN patients, found a significant inverse correlation between the plasma concentration of hepatocyte growth factor and EGFR inhibitor-induced rash (17). On the other hand, identification of clinical factors related to the occurrence of Cmab-induced skin toxicity in SCCHN is still lacking, and we were also unable to identify such factors in the present study (**Table 3**). Men and younger patients with colorectal cancer are considered to be at greater risk of severe Cmab-induced rash (15), but skin toxicity also warrants careful attention in all SCCHN patients who receive Cmab.

CONCLUSIONS

Our present analysis suggested that the occurrence of ≥ grade 3 Cmab-induced skin toxicity within 90 days after the initiation of Cmab was associated with a better prognosis in R/M SCCHN. At the moment, we do not have sufficient clinical knowledge to predict the occurrence of the sing beforehand, which may reflect a different immune status of the patients. However, it is likely important to avoid delays or discontinuation of Cmab, particularly in patients with rapid skin reaction, considering that Cmab appears to play an important role as the mainstay of treatment in this population.

AUTHOR CONTRIBUTIONS

SU and TE participated in the study concept and design, interpreted the data, and drafted the manuscript. SS, TF, and SO participated in the study concept and design and interpreted the data. MT extracted, managed, and analyzed the data. All authors provided critical revisions and approved the final manuscript.

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REFERENCES

1. Stewart BW, Kleihues PE. *World Cancer Report*. Lyon: International Agency for Research on Cancer Press (2003).
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136:E359–86. doi: 10.1002/ijc.29210
3. Cancer Registry and Statistics. *Cancer Information Service, National Cancer Center*. Japan
4. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* (2008) 359:1116–27. doi: 10.1056/NEJMoa0802656
5. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5 year survival data from a phase 3 randomized trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* (2010) 11:21–8. doi: 10.1016/S1470-2045(09)70311-0
6. Saltz LB, Kies M, Abbruzzesse JL, Azarnia N, Needle M, Saltz L, et al. The presence and intensity of the cetuximab-induced acne like rash predicts

increased survival in studies across multiple malignancies. *Proc Am Soc Clin Oncol*. (2003) 21(Suppl.):Abstract817.
7. Orditura M, De Vita F, Galizia G, Lieto E, Vecchione L, Vitiello F, et al. Correlation between efficacy and skin rash occurrence following treatment with the epidermal growth factor inhibitor cetuximab: A single institution retrospective analysis. *Oncol Rep*. (2009) 21:1023–8. doi: 10.3892/or_00000319
8. Gatzemeier U, von Pawel J, Vynnychenko I, Zatloukal P, de Marinis F, Eberhardt WE, et al. First cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. *Lancet Oncol*. (2011) 12:30–37. doi: 10.1016/S1470-2045(10)70278-3
9. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetixumab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. (2009) 360:1408–17 doi: 10.1056/NEJMoa0805019
10. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in inrinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. (2004) 351:337–45. doi: 10.1056/NEJMoa033025
11. Lenz HJ, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinoteacn, oxaliplatin, and fluoropyrimidines. *J Clin Oncol*. (2006) 24:4914–21. doi: 10.1200/JCO.2006.06.7595
12. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. (2007) 357:2040–8. doi: 10.1056/NEJMoa071834
13. Jimenez B, Trigo JM, Pajares BI, Saez MI, Quero C, Navarro V, et al. Efficacy and safety of weekly paclitaxel combined with cetuximab in the treatment of pretreated recurrent/metastatic head and neck cancer patients. *Oral Oncol*. (2013) 49:182–85. doi: 10.1016/j.oraloncology.2012.09.003
14. Bar-Ad V, Zhang QE, Harari PM, Axelrod R, Rosenthal DI, Trotti A, et al. Correlation between the severity of cetuximab-induced skin rash and clinical outcome for head and neck cancer patients: the RTOG Experience. *Int J Radiat Oncol Biol Phys*. (2016) 95:1346–54. doi: 10.1016/j.ijrobp.2016.03.011
15. Jatoi A, Green EM, Rowland KM Jr, Sargent DJ, Alebrt SR. Clinical predictors of severe cetuximab-induced rash: observation from 933 patients enrolled in North Central Cancer Treatment Group study N0147. *Oncology* (2009):77:120–3. doi: 10.1159/000229751
16. Lacoutur M, Anadkat M, Bensadoun RJ, Bryce J, Chan A, Epstein JB, et al. MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* (2011) 19:1079–5. doi: 10.1007/s00520-011-1197-6
17. Hichert V, Scholl C, Steffens M, Paul T, Schumann C, Rudiger S, et al. Predictive blood plasma biomarkers for EGFR inhibitor-induced skin rash. *Oncotarget* (2017) 8:35193–204. doi: 10.18632/oncotarget.17060
18. Vermorken JB, Remenar E, Hitt R, Kawecki A, Rottey S, Knierim L, et al. Platinum –based chemotherapy(CT) plus cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer(R/M-SCCHN):5-year follow-up data for the extreme trial. *J Clin Oncol*. (2014) 32 (Suppl):Abstract 6021. doi: 10.1200/jco.2014.32.15_suppl.6021
19. Brown J, Su Y, Nelleson D, Shankar P, Mayo C. Management of epidermal growth factor receptor inhibitor-associated rash: a systematic review. *J Communitiy Support Oncol*. (2016) 14:21–28. doi: 10.12788/jcso.0193
20. Klinghammer K, Knodler M, Schmittel A, Budach V, Keiholz U, Tinhofer I. Association of epidermal growth factor receptor polymorphism, skin toxicity, and outcome in patients with squamous cell carcinoma of the head and neck receiving cetuximab-docetaxel treatment. *Clin Cancer Res*. (2010):16:304–10. doi: 10.1158/1078-0432.CCR-09-1928

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SYSTEMATIC REVIEW
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The Changing Role of Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma: A Updated Systemic Review and Network Meta-Analysis

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Background and Objective: Both induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT; IC+CCRT) and CCRT plus adjuvant chemotherapy (AC; CCRT+AC) are standard treatments for advanced nasopharyngeal carcinoma (NPC). However, no prospective randomized trials comparing these two approaches have been published yet. We conducted this network meta-analysis to address this clinical question.

Method: We recruited randomized clinical trials involving patients with advanced NPC randomly allocated to IC+CCRT, CCRT+AC, CCRT, or radiotherapy (RT) alone. Pairwise meta-analysis was first conducted, then network meta-analysis was performed using the frequentist approach. Effect size was expressed as hazard ratio (HR) and 95% confidence interval (CI).

Results: Overall, 12 trials involving 3,248 patients were recruited for this study, with 555 receiving IC+CCRT, 840 receiving CCRT+AC, 1,039 receiving CCRT, and 814 receiving radiotherapy (RT) alone. IC+CCRT achieved significantly better overall survival ([HR], 0.69; 95% [CI], 0.51–0.92), distant metastasis-free survival (HR, 0.58; 95% CI, 0.44–0.78), and locoregional recurrence-free survival (HR, 0.67; 95% CI, 0.47–0.98) than CCRT. However, survival outcomes did not significantly differ between IC+CCRT and CCRT+AC, or between CCRT+AC and CCRT arms for all the endpoints. As expected, RT alone is the poorest treatment. In terms of P-score, IC+CCRT ranked best for overall survival (96.1%), distant metastasis-free survival (99.0%) and locoregional recurrence-free survival (87.1%).

Conclusions: IC+CCRT may be a better and more promising treatment strategy for advanced NPC; however, head-to-head randomized trials comparing IC-CCRT with CCRT-AC are warranted.

Keywords: nasopharyngeal carcinoma, concurrent chemoradiotherapy, induction chemotherapy, adjuvant chemotherapy, network meta-analysis

BACKGROUND

Nasopharyngeal carcinoma (NPC) arises from the nasopharynx epithelium and achieves the highest incidence among all head and neck cancers in China (1). Worldwide, NPC exhibits an extremely unbalanced distribution with an incidence of 20–50 per 100,000 in Southern China but <1 per 100,000 in most western countries (2, 3). As constrained by its complicated anatomical location, surgery is not available and radiotherapy (RT) has become the only radical curative treatment for NPC. As NPC is also highly sensitive to chemotherapeutic agents, incorporation of chemotherapy with RT has been established as the standard care for stage II-IVA disease. Notably, patients with early disease usually achieve excellent survival outcomes while prognosis of advanced disease still remains poor (4).

Upon the publishing of Intergroup 0099 trial in 1998, this milestone study has established concurrent chemoradiotherapy (CCRT) plus adjuvant chemotherapy (AC) as the standard regimen for advanced NPC since it could provide a 31% increase in overall survival (OS) (5). However, many subsequent studies demonstrated that AC additional to CCRT may be useless (6–8). More importantly, AC brought severe toxicities and many patients could not complete the assigned cycles, which constrains its wide clinical application. Given this, other intensive treatment strategies should be developed. Recently, there is increasing amount of evidence showing that induction chemotherapy (IC), delivered before radiotherapy, is also an effective and promising treatment strategy as it has better compliance rates and facilitates early eradication of micrometastases (9–12). Based on these findings, the National Comprehensive Cancer Network (NCCN) guidelines recommend IC plus CCRT as one of the standard treatments for stage II-IVA disease. However, it still remains unclear which chemotherapy sequence is better as we lack head-to-head trials comparing IC+CCRT with CCRT+AC. In view of the urgent need for effective and less toxic therapies, we conducted this network meta-analysis to compare IC+CCRT with CCRT+AC through extracting data from published clinical randomized trials.

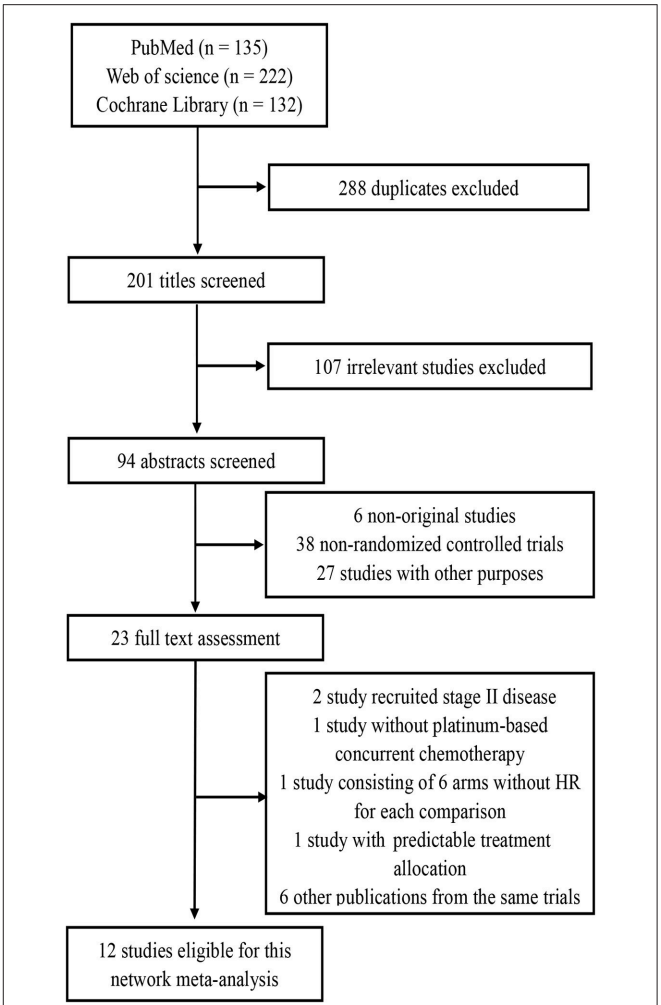

FIGURE 1 | Flow chart of study inclusion.

RESULTS

Baseline Information of Recruited Trials

By the last literature searching (May 2018), we in total identified 24 potentially eligible clinical trials. Flow chart of studies inclusion was presented in **Figure 1**. The study by Lin et al. (13) was not included because HRs and 95% CI was not provided in original text. Two studies involving stage II NPC were excluded (14, 15). Due to the one-side 95% CI reported in the study by Tan et al. (16) and unknown HR for each treatment comparison in the study by Lee et al. (17), we therefore excluded these two studies. We also excluded the study by Kwong et al. (18) because uracil + tegafur was used as the concurrent chemotherapy regimen; however, this study would be included in the sensitivity analysis. Additionally, six studies updated their long follow-up data: Chan et al. (19, 20), Lee et al. (21, 22), Lee et al. (23, 24), Chen et al. (25, 26), Chen et al. (7, 27), and Zhang et al. (28, 29). Finally, 12 studies (5, 9–12, 19, 22, 23, 26–28, 30) were included for the current study. Notably, we excluded two treatment arms receiving accelerated-fraction radiotherapy in the study by Lee et al. (23, 24) because they did not meet the inclusion criterion of conventional-fraction radiotherapy. The basic information of the 12 studies are summarized in **Table 1**. In total, 3,248 patients were randomly allocated with 555 receiving IC+CCRT, 840 receiving CCRT+AC, 1,039 receiving CCRT, and 814 receiving RT alone. Quality assessment of the 12 studies was summarized in **Supplementary Table S1**.

Traditional Pairwise Comparison

Figure 2 presents the results of pairwise meta-analysis. Heterogeneity between treatment arms only existed in CCRT vs. RT for DMFS ($I^2 = 55.9\%$), and a random-effects model was then applied. Compared with CCRT, IC+CCRT was associated with significantly improved OS (HR, 0.65; 95% CI, 0.43–0.83), DMFS (HR, 0.57; 95% CI, 0.39–0.75), and LRFS (HR, 0.63; 95% CI, 0.36–0.89). Undoubtedly, CCRT+AC achieved better

TABLE 1 | Summary of basic information of the 12 studies included in this network meta-analysis.

Study	No. of patients	Study time	Median follow-up duration (months)	Patient stage	Radiotherapy	Chemotherapy		
						Induction	Concurrent	Adjuvant
IC + CCRT vs. CCRT								
Hui et al. (10)	65	2002–2004	51.6	AJCC III-IVB, T1-4, N0-3	66 Gy/33f at 2 Gy/f/day (5f/qw) + additional boost of 20 Gy/10f to parapharyngeal	Docetaxel 75 mg/m^2 d1 + DDP 75 mg/m^2 d1 q3w × 2	40 mg/m^2 d1 qw × 8	None
Frikha et al. (12)	83	2009–2012	43.1	AJCC T2b-4, N1-3	70 Gy/35f at 2 Gy/f/day (5f/qw)	Docetaxel 75 mg/m^2 d1 + Cisplatin 75 mg/m^2 d1+ 5-FU 750 mg/m^2 d1-5 q3w × 3	DDP 40 mg/m^2 weekly for 8 weeks	None
Sun et al. (11)	480	2011–2013	45	AJCC III-IVB, except T3-4N0	≥ 66 Gy at 2.00–2.35 Gy/f/day for 6–7 weeks	Docetaxel 60 mg/m^2 d1 + DDP 60 mg/m^2 d1 + Fu 600 mg/m^2/day d1-5 civ q3w × 3	100 mg/m^2 d1 q3w × 3	None
Cao et al. (9)	476	2008–2015	50	AJCC III-IVB, except T3N0-1	≥ 66 Gy at 2.0-2–33 Gy/f/day	DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1-5 civ q3w × 3	80 mg/m^2 d1 q3w × 3	None
CCRT + AC vs. RT								
Al-Sarraf et al. (5)	193[a]	1989–1995	32.4	AJCC III-IV	66–70 Gy at 1.8–2.0 Gy/f/day (5f/qw)	None	DDP 100 mg/m^2 d1 q3w × 3	DDP 80 mg/m^2 d1 + Fu 1000 mg/m^2/day d1-4 civ q3w × 4
Wee et al. (30)	221	1997–2003	38.4	AJCC III-IV, T3-4Nx or TxN2-3	70 Gy/35f at 2 Gy/f/day (5f/qw) for 7 weeks	None	DDP 25 mg/m^2/day for 4 days or 30/30/40 mg/m^2/day for 3 days q3w × 3	DDP 20 mg/m^2/day for 4 days + Fu 1000 mg/m^2/day d1-4 q3w × 3
Lee et al. (21, 22)	348	1999–2004	70.8	AJCC III-IV, any T, N2-3	≥ 66 Gy at 2.0 Gy/f/day (5f/qw) + additional boosts to parapharyngeal space, primary, or nodal sites when indicated not exceeding 20 Gy	None	100 mg/m^2 d1 q3w × 3	DDP 80 mg/m^2 d1 + 1000 mg/m^2/day d1-d4 civ q4w × 3
Lee et al. (23, 24)	93	1999–2004	75.6	AJCC III-IV, T3-4N0-1	≥ 66 Gy at 2.0 Gy/f/day (5f/qw) + additional boosts to parapharyngeal space, primary, or nodal sites when indicated not exceeding 20 Gy	None	100 mg/m^2 d1 q3w × 3	DDP 80 mg/m^2 d1 + 1000 mg/m^2/day d1-d4 civ q4w × 3
Chen et al. (25, 26)	316	2002–2005	70	AJCC III-IV, T1-4, N0-3	≥ 68 Gy at 2.0 Gy/f/day (5f/qw) for 7 weeks + additional boost in case of parapharyngeal extension, residual neck and/or nasopharyngeal tumor	None	100 mg/m^2 d1 q3w × 3	DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1-5 civ q3w × 3
CCRT+AC vs. CCRT								
Chen et al. (7, 27)	508	2006–2010	68.4	AJCC III-IVB except T3-4N0	≥ 66 Gy at 2.0-2.27 Gy/f/day (5f/qw) for 6–7 weeks	None	DDP 40 mg/m^2 d1 weekly for up to 7 weeks	DDP 80 mg/m^2 d1 + Fu 800 mg/m^2/day d1-5 civ q4w × 3

(Continued)

TABLE 1 | Continued

Study	No. of patients	Study time	Median follow-up duration (months)	Patient stage	Radiotherapy	Chemotherapy		
						Induction	Concurrent	Adjuvant
CCRT vs. RT								
Chan et al. (19, 20)	350	1994–1997	66	Ho's N2-3 or N1 with nodal size ≥ 4cm	66 Gy + additional boost in case of parapharyngeal extension, residual neck, or nasopharyngeal tumor	None	DDP 40 mg/m^2 d1 weekly for 8 weeks	None
Zhang et al. (28, 29)	115	2001–2003	114	AJCC III-IV, any T, N2-3	70-74 Gy at 2 Gy/f/day (5f/qw) + additional boost in case of parapharyngeal extension, residual neck, or nasopharyngeal tumor	None	Oxaliplatin 70 mg/m^2 d1 weekly for 6 weeks	None

CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy; AJCC, American Joint Committee on cancer; f, fraction; DDP, cisplatin; Fu, fluorouracil; civ, continuous i.v.; q3w, every 3 weeks; q4w, every 4 weeks; AUC, area under concentration-time curve. 2D-RT, two-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy.

[a] *193 patients were registered, but only 147 patients were analyzed.*

TABLE 2 | Results of multiple treatment comparison for the three endpoints.

Treatment arm	OS	DMFS	LRFS
P-value of Overall heterogeneity/inconsistency	0.51	0.44	0.55
P-value of heterogeneity (within designs)	0.41	0.35	0.55
P-value of heterogeneity (between designs)	0.82	0.74	0.34
CCRT			
HR	1.00	1.00	1.00
P-score (%)	36.5	37.6	32.7
CCRT+AC			
HR (95% CI)	0.86 (0.69–1.07)	0.85 (0.65–1.12)	0.74 (0.51–1.08)
P-score (%)	67.3	63.4	76.6
IC+CCRT			
HR (95% CI)	0.69 (0.51–0.92)	0.58 (0.44–0.78)	0.67 (0.47–0.98)
P-score (%)	96.1	99.0	87.1
RT			
HR (95% CI)	1.31 (1.08–1.59)	1.47 (1.14–1.89)	1.25 (0.89–1.76)
P-score (%)	0.1	0.4	3.6

OS, overall survival; DMFS, distant metastasis-free survival; LRFS, locoregional recurrence-free survival; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; IC, induction chemotherapy; RT, radiotherapy. HR, hazard ratio; CI, confidence interval.

Fixed-effects model was used for overall survival, distant metastasis-free survival and locoregional recurrence-free survival.

OS (HR, 0.63; 95% CI, 0.53–0.74), DMFS (HR, 0.51; 95% CI, 0.39–0.64), and LRFS (HR, 0.48; 95% CI, 0.32–0.64) than RT alone. Similarly, CCRT could prolong OS (HR, 0.75; 95% CI, 0.58–0.91) and DMFS (HR, 0.61; 95% CI, 0.42–0.81) compared with RT alone. Consistent with the original study, no significant differences between CCRT+AC and CCRT were observed in terms of OS, DMFS and LRFS.

Multiple Network Comparison

Figure 3 presented the network analysis of the four treatment arms (IC+CCRT, CCRT+AC, CCRT, and RT). In the multiple comparison, CCRT arm was treated as the reference group, and results network meta-analysis are summarized in **Table 2**. There is no inconsistency or heterogeneity neither between nor within studies ($P > 0.1$ for all rates). Thus, a fixed-effects model was used. The forest plots of multiple treatment comparisons with different reference groups were presented in **Figure 4**.

Compared to CCRT, IC+CCRT achieved significantly better OS (HR, 0.69; 95% CI, 0.51–0.92), DMFS (HR, 0.58; 95% CI, 0.44–0.78), and LRFS (HR, 0.67; 95% CI, 0.47–0.98). However, no significant survival differences were found between CCRT+AC and CCRT, or CCRT+AC and IC+CCRT (**Supplementary Tables S2–S4**). Notably, RT alone always led to significantly poorer survival outcomes compared with the other three treatments except RT vs. CCRT for LRFS (HR, 1.25; 95% CI, 0.89–1.76).

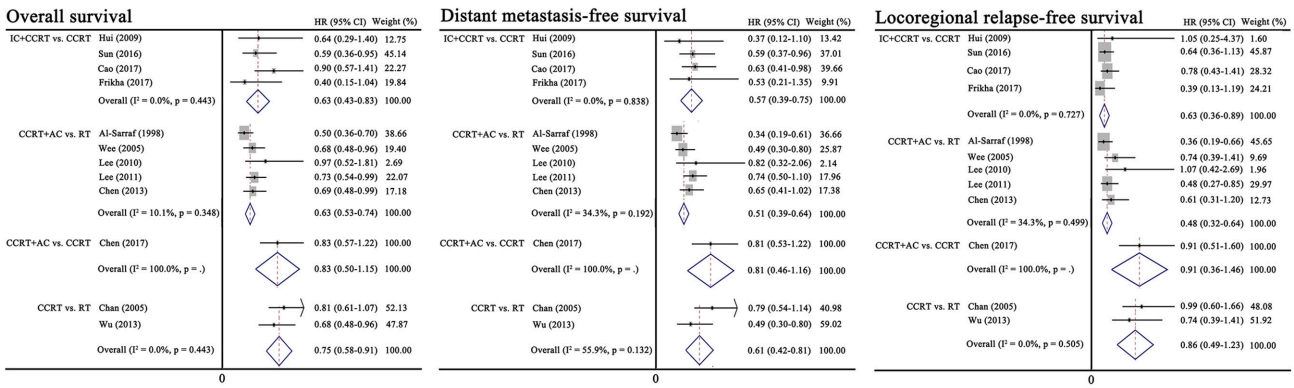

FIGURE 2 | Results of traditional pairwise meta-analysis. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.

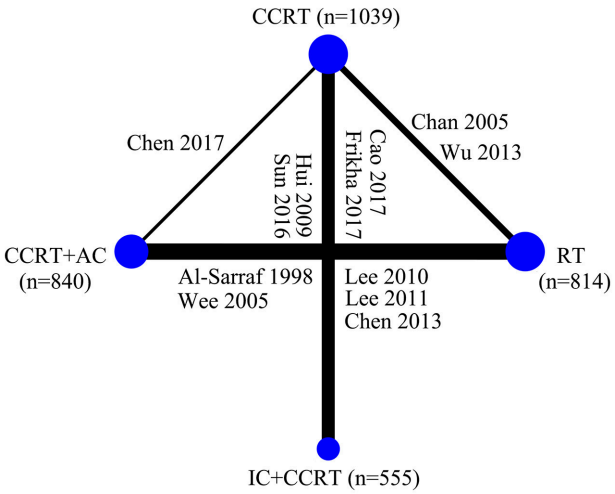

FIGURE 3 | Graphical presentation of the trial network for overall survival. The width of the lines between nodes is proportional to the number of comparisons. Only two treatment arms receiving conventional-fraction radiotherapy in the study by Lee et al. (23) were included in this study. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy.

The corresponding P-scores of IC+CCRT, CCRT+AC, CCRT, and RT treatment arms were 96.1%, 67.3, 36.5, and 0.1% for OS; 99.0, 63.4, 37.6, and 0.4% for DMFS; 87.1, 76.6, 32.7, and 3.6% for LRFS, indicating IC+CCRT has the highest probability of being the best treatment in terms of OS, DMFS, and LRFS.

Sensitivity Analysis

We further performed sensitivity analysis after including the study by Kwong et al. (18) to validate our findings; and the results are shown in the **Supplementary Results** (**Supplementary Figures S1–S3**, **Supplementary Tables S5,S6**). Notably, the conclusions remained valid after including this study. More importantly, IC+CCRT was even found to be superior to CCRT+AC with regard to DMFS (HR, 0.63; 95% CI, 0.43–0.93). Similarly, IC+CCRT still provided the highest benefit on OS, DMFS, and LRFS. These results indicated that IC+CCRT may be better than CCRT+AC.

DISCUSSION

In our current study, we applied frequentist method to conduct multiple treatment comparisons between IC+CCRT, CCRT+AC, CCRT, and RT in advanced NPC based on all available information extracted from the published studies. We found that IC+CCRT was superior to CCRT and RT, and provided the largest OS, DMFS, and LRFS benefits. While no significant difference was observed between IC+CCRT and CCRT+AC. Further sensitivity analysis after including the study by Kwong et al. (18) also yield similar results. Notably, no inconsistency and heterogeneity were observed between these comparisons for all end-points, indicating that our findings are robust.

The role of chemotherapy in managing advanced NPC has changed greatly over the last two decades. Before the Intergroup 0099 study (5), radiotherapy alone is the only care for both early and advanced disease. Later on, CCRT+AC was proven better than RT alone in improving OS and this regimen has deemed the standard treatment for advanced NPC. However, a meta-analysis conducted by Baujat et al. (6) revealed this survival benefit mainly came from concurrent chemotherapy during RT. Moreover, the study by Chen et al. (7) found that AC additional to CCRT may be useless and this conclusion was further proven by long-term follow-up outcomes (27). Consequently, CCRT with or without AC was recommended by the NCCN guidelines. Although this regimen was applied, distant metastasis still remains the main failure pattern for advanced NPC (31). Therefore, novel treatments like IC was introduced. However, we still know little about the efficacy difference between these treatment modalities. In our study, we aimed at addressing this issue.

IC+CCRT achieved significantly better OS, DMFS, and LRFS than CCRT in both the pairwise and network meta-analyses,

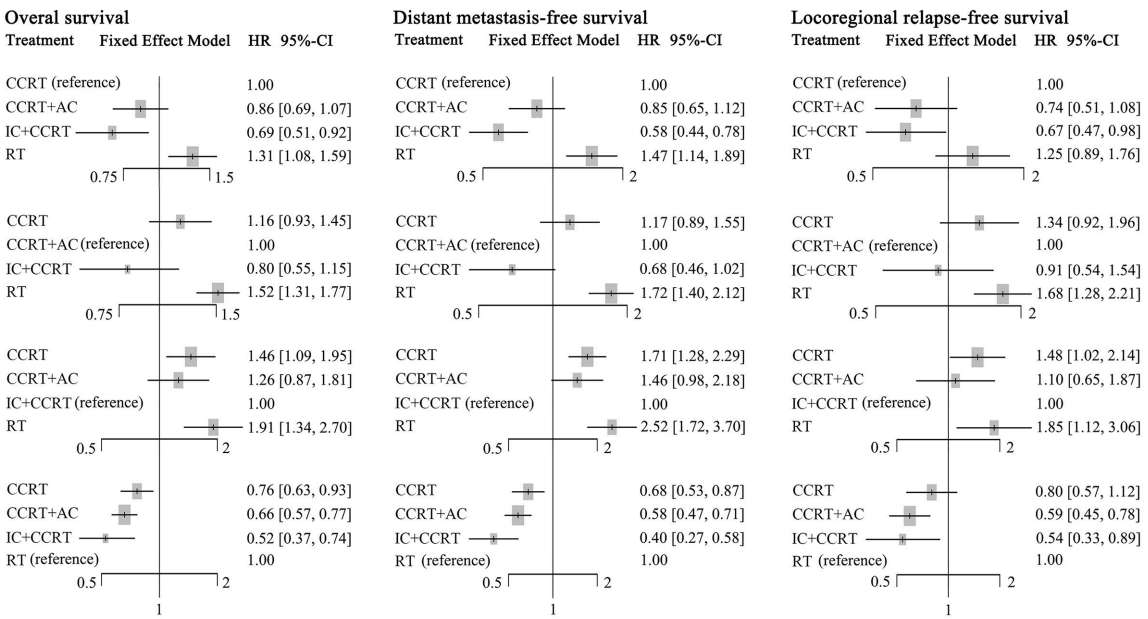

FIGURE 4 | Forest plot of network meta-analysis for overall survival, distant metastasis-free survival, and locoregional recurrence-free survival with different reference groups. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy; RT, radiotherapy.

Which was different from the findings by Ribassin-Majed et al. (32). Undoubtedly, the inclusion of the lastest three IC studies (9, 11, 12) could add the weight of IC+CCRT in the network loop, resulting in better efficacy than CCRT alone. Another possible reason contributing to the survival difference between these two groups may be the difference of radiotherapy technique since almost all patients in IC+CCRT arm received intensity-modulated radiotherapy (IMRT) while some patients in CCRT arm received conventional radiotherapy. Therefore, we could conclude that IC+CCRT is better than CCRT and should be considered prior to CCRT. Although IC+CCRT was not found to be better than CCRT in other head and neck cancers (33), we should not apply this result to NPC because NPC has extremely different biological behaviors and is more sensitive to radiotherapy and chemotherapy compared with other head and neck cancers. It should be noted that the delivery of IC should be selective. Recently, two studies (34, 35) revealed additional IC to CCRT may be useless in T3-4N0-1 patients, indicating that only high-risk patients (defined as patients with N2-3 category, overall stage IVA or high pre-treatment Epstein-Barr virus DAN load) may benefit from IC. Moreover, the IC regimen also plays a key role. Docetaxel plus cisplatin with fluorouracil (TPF) has been proven to be superior to PF in head and neck cancer (36–38). Moreover, gemcitabine with cisplatin (GP) has been proven superior to PF in recurrent or metastatic NPC (39). Therefore, selection of effective IC regimens for high-risk patients should be a priority.

Similar to the results of original studies (7, 27), survival outcomes did not significantly differ between CCRT+AC and CCRT treatment arms, suggesting the value of adding AC to CCRT may be limited. Notably, all the included studies regarding CCRT+AC used the recommended AC regimen, cisplatin with fluorouracil. However, this combined AC regimen did not improve survival outcomes compared with either single-agent regimen individually in head and neck cancer (40). In addition, compliance to three cycles of AC was poor (5, 7, 21, 25, 30) and many patients also require dose reductions. Therefore, it is reasonable to infer the adjuvant PF regimen additional to CCRT is not good enough to further improve survival outcomes. Other regimens like GP or single-agent maintenance therapy should be further investigated.

CCRT may be inadequate for high-risk patients with advanced NPC; additional cycles of chemotherapy are worth being investigated (41). Therefore, either IC+CCRT or CCRT+AC may be a better choice than CCRT alone. However, we lack head-to-head clinical trials comparing IC+CCRT with CCRT+AC. In this study, survival outcomes did not differ significantly between CCRT+AC and IC+CCRT for any end-point. However, after including the study by Kwong et al. (18), IC+CCRT achieved better DMFS than CCRT-AC, which was inconsistent with the finding by Ribassin-Majed et al (32). The main reason as we discuss above is the inclusion of three new trials which achieved positive results and added the weight of IC+CCRT in the network loop. Therefore, IC+CCRT may be a little better than, or at least as efficacious as, CCRT+AC. In light of efficacy, it is reasonable to recommend IC+CCRT as the preferred treatment for advanced NPC. There may be another concern about IC+CCRT that IC may affect compliance with subsequent radiotherapy. Since our study was not based on individualized patient data, we, therefore, could not conclude on this. However, from historical data (9, 11, 12, 16), IC may have no impact on the compliance to radiotherapy. Actually, patients receiving or not receiving IC have same completion rate of radiotherapy at clinical practice. However, it should be pointed that

compliance of concomitant chemotherapy might be impacted by IC.

Undoubtedly, RT was always poorer than IC+CCRT, CCRT+AC, and CCRT for almost all end-points. Thus, RT alone should not be recommended whenever possible. Notably, the rank of each treatment was indicated by the P-score in multiple treatment comparison. Although differences in effect size between different treatment arms were small and non-significant, a treatment ranking probability would still have been generated without definitive statistical meaning. Therefore, we should interpret the P-score discreetly, and clinical treatment strategies should not only refer to it.

Our study also had limitations: HRs and corresponding 95% CIs were mainly extracted from the original studies, which may produce reporting bias. Radiotherapy technique varied between different treatment arms which may affect the results of our study, and this issue should be solved by future individualized study data. Also, the role of hyperfractionated or accelerated hyperfractionated radiotherapy needs further investigation. Moreover, endpoints did not include PFS as the definitions of PFS varied between studies. To minimize these limitations, we set strict inclusion criteria and three investigators independently reviewed and extracted data. Furthermore, sensitivity analysis confirmed the findings were valid.

MATERIALS AND METHODS

Literature Searching Strategy

First, we searched the English datasets including PubMed, Web of Science, and the Cochrane Library using the following items: "nasopharyngeal carcinoma" and "induction chemotherapy" or "neoadjuvant chemotherapy" or "adjuvant chemotherapy" or "concurrent chemoradiotherapy" or "radiotherapy." Study type was restricted to clinical trial. Two investigators (ML and WY) performed the searching independently to identify all potentially eligible studies. Furthermore, we will also retrieve the National Knowledge Infrastructure and WanFang database to include any related Chinese references. **Supplementary Method** showed the detailed process of literature searching. The institutional ethical review board of Zigong NO. 4 People's Hospital approved our current study. All study methods were performed in accordance with our center guidelines.

Study Inclusion Criteria

Brief inclusion criteria of our study were as follow: (1) newly diagnosed advanced NPC without metastasis; (2) randomized controlled phase II/III trials; (3) patients received conventional-fractionation and radical radiotherapy; (4) concurrent chemotherapy should be platinum-based regimens. **Supplementary Method** presented the detailed information on study inclusion criteria. In our present study, we mainly recruited four treatment arms (CCRT+AC, IC+CCRT, CCRT, and RT alone) to conduct multiple network comparisons.

Study Review and Data Acquisition

In order to assess the quality of the recruited trials, the following items were reviewed to score each study according to Jadad/Oxford quality scoring system(42): randomization procedure, blinding principle, intention-to-treat principle, allocation concealment, and patient dropout. The study information such as included patients, study time, radiotherapy, and chemotherapy regimens, follow-up duration, and survival outcomes were extracted. Three investigators (ML, WY, and J-DM) performed the review process and data acquisition separately, and any discrepancies would be resolved by consensus.

Study Endpoints

Survival outcomes were shown as hazard ratios (HRs) and corresponding confidence intervals (CIs) which were extracted from original studies or an individualized data meta-analysis (43) using the method proposed by Parmar et al. (44). Study endpoints included OS, distant metastasis-free survival (DMFS) and locoregional recurrence-free survival (LRFS). Given the different definition of progression-free survival (PFS) in the trials, we did not included it into analysis.

Statistical Method

First, we conducted pairwise meta-analysis comparison between each treatment group was using Stata 12.0 (StataCorp LP, College Station, TX, USA). Treatment effects were presented by HRs and corresponding 95% CIs. Study heterogeneity was determined using the I^2 statistic or χ^2 test. An I^2 statistic $> 50\%$ or the P-value of χ^2 test < 0.1 indicated statistically heterogeneity; otherwise, no heterogeneity exist between studies. Then, we performed network comparisons using the R (version 3.3.3; R Foundation, Vienna, Austria) *netmeta* package (45, 46). The frequentist approach (45) was adopted to carry out the network meta-analysis. Before multiple comparison, heterogeneity or inconsistency between treatment arms was assessed by Q test (45). If no significant heterogeneity existed ($P > 0.1$), fixed-effects model would be employed; otherwise, the random-effects model would be used. Finally, each treatment arm was ranked based on their corresponding P-score (47). A P-score of 100% suggested that treatment is the best, and a P-score of 0% indicated the worst treatment. Toxicity between different arms were compared using the χ^2 test. A two-sided $P < 0.05$ was considered significant. Detailed process of multiple network comparison was shown in **Supplementary Method**.

CONCLUSION

In summary, this network meta-analysis demonstrates IC+CCRT is superior to CCRT and provides highest benefit on OS, DMFS, and LRFS benefits LRFS. Therefore, IC+CCRT may be a better choice for advanced NPC at clinical practice. Head-to-head clinical trials comparing IC+CCRT with CCRT+AC are warranted to validate our findings.

AUTHOR CONTRIBUTIONS

ML and WY conceived and designed the experiments and conducted literature searching. ML, WY, J-DM, X-BZ, and D-KC

extracted study data and performed analysis. ML, WY, LX, and L-FX contributed to reagents, materials, and analysis tools. ML, WY, and Y-BS wrote the paper, WY and YG contributed to quality control and review of the manuscript. All authors approved the final version of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2018.00597/full#supplementary-material

REFERENCES

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. (2016) 66:115–32. doi: 10.3322/caac.21338
2. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet* (2005) 365:2041–54. doi: 10.1016/S0140-6736(05)66698-6
3. Zhang LF, Li YH, Xie SH, Ling W, Chen SH, Liu Q, et al. Incidence trend of nasopharyngeal carcinoma from 1987 to 2011 in Sihui County, Guangdong Province, South China: an age-period-cohort analysis. *Chin J Cancer* (2015) 34:350–7. doi: 10.1186/s40880-015-0018-6
4. Yi JL, Gao L, Huang XD, Li SY, Luo JW, Cai WM, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: ten-year experience of a single institution. *Int J Radiat Oncol Biol Phys*. (2006) 65:161–8. doi: 10.1016/j.ijrobp.2005.12.003
5. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. (1998) 16:1310–7. doi: 10.1200/JCO.1998.16.4.1310
6. Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. (2006) 64:47–56. doi: 10.1016/j.ijrobp.2005.06.037
7. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. (2012) 13:163–71. doi: 10.1016/S1470-2045(11)70320-5
8. Chen YP, Wang ZX, Chen L, Liu X, Tang LL, Mao YP, et al. A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *Ann Oncol*. (2015) 26:205–11. doi: 10.1093/annonc/mdu507
9. Cao SM, Yang Q, Guo L, Mai HQ, Mo HY, Cao KJ, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. *Eur J Cancer* (2017) 75:14–23. doi: 10.1016/j.ejca.2016.12.039
10. Hui EP, Ma BB, Leung SF, King AD, Mo F, Kam MK, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. *J Clin Oncol*. (2009) 27:242–9. doi: 10.1200/JCO.2008.18.1545
11. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol*. (2016) 17:1509–20. doi: 10.1016/S1470-2045(16)30410-7
12. Frikha M, Auperin A, Tao Y, Elloumi F, Toumi N, Blanchard P, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). *Ann Oncol*. (2017) 29:731–6. doi: 10.1093/annonc/mdx770
13. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol*. (2003) 21:631–7. doi: 10.1200/JCO.2003.06.158
14. Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst*. (2011) 103:1761–70. doi: 10.1093/jnci/djr432
15. Fountzilas G, Ciuleanu E, Bobos M, Kalogera-Fountzila A, Eleftheraki AG, Karayannopoulou G, et al. Induction chemotherapy followed by concomitant radiotherapy and weekly cisplatin versus the same concomitant chemoradiotherapy in patients with nasopharyngeal carcinoma: a randomized phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG) with biomarker evaluation. *Ann Oncol*. (2012) 23:427–35. doi: 10.1093/annonc/mdr116
16. Tan T, Lim WT, Fong KW, Cheah SL, Soong YL, Ang MK, et al. Concurrent chemo-radiation with or without induction gemcitabine, Carboplatin, and Paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. (2015) 91:952–60. doi: 10.1016/j.ijrobp.2015.01.002
17. Lee AW, Ngan RK, Tung SY, Cheng A, Kwong DL, Lu TX, et al. Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer* (2015) 121:1328–38. doi: 10.1002/cncr.29208
18. Kwong DL, Sham JS, Au GK, Chua DT, Kwong PW, Cheng AC, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol*. (2004) 22:2643–53. doi: 10.1200/JCO.2004.05.173
19. Chan AT, Leung SF, Ngan RK, Teo PM, Lau WH, Kwan WH, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*. (2005) 97:536–9. doi: 10.1093/jnci/dji084
20. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*. (2002) 20:2038–44. doi: 10.1200/JCO.2002.08.149
21. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol*. (2005) 23:6966–75. doi: 10.1200/JCO.2004.00.7542
22. Lee AW, Tung SY, Chua DT, Ngan RK, Chappell R, Tung R, et al. Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst*. (2010) 102:1188–98. doi: 10.1093/jnci/djq258
23. Lee AW, Tung SY, Chan AT, Chappell R, Fu YT, Lu TX, et al. A randomized trial on addition of concurrent-adjuvant chemotherapy and/or accelerated fractionation for locally-advanced nasopharyngeal carcinoma. *Radiother Oncol*. (2011) 98:15–22. doi: 10.1016/j.radonc.2010.09.023
24. Lee AW, Tung SY, Chan AT, Chappell R, Fu YT, Lu TX, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. (2006) 66:142–51. doi: 10.1016/j.ijrobp.2006.03.054
25. Chen Y, Liu MZ, Liang SB, Zong JF, Mao YP, Tang LL, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma in endemic regions of china. *Int J Radiat Oncol Biol Phys*. (2008) 71:1356–64. doi: 10.1016/j.ijrobp.2007.12.028

26. Chen Y, Sun Y, Liang SB, Zong JF, Li WF, Chen M, et al. Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVB nasopharyngeal carcinoma from endemic regions of China. *Cancer* (2013) 119:2230–8. doi: 10.1002/cncr.28049
27. Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y, et al. Adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase 3 multicentre randomised controlled trial. *Eur J Cancer* (2017) 75:150–8. doi: 10.1016/j.ejca.2017.01.002
28. Wu X, Huang PY, Peng PJ, Lu LX, Han F, Wu SX, et al. Long-term follow-up of a phase III study comparing radiotherapy with or without weekly oxaliplatin for locoregionally advanced nasopharyngeal carcinoma. *Ann Oncol*. (2013) 24:2131–6. doi: 10.1093/annonc/mdt163
29. Zhang L, Zhao C, Peng PJ, Lu LX, Huang PY, Han F, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. *J Clin Oncol*. (2005) 23:8461–8. doi: 10.1200/JCO.2004.00.3863
30. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol*. (2005) 23:6730–8. doi: 10.1200/JCO.2005.16.790
31. Lai SZ, Li WF, Chen L, Luo W, Chen YY, Liu LZ, et al. How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? *Int J Radiat Oncol Biol Phys*. (2011) 80:661–8. doi: 10.1016/j.ijrobp.2010.03.024
32. Ribassin-Majed L, Marguet S, Lee AWM, Ng WT, Ma J, Chan ATC, et al. What is the best treatment of locally advanced nasopharyngeal carcinoma? an individual patient data network meta-analysis. *J Clin Oncol*. (2017) 35:498–505. doi: 10.1200/JCO.2016.67.4119
33. Vidal L, Ben Aharon I, Limon D, Cohen E, Popovtzer A. Role of induction chemotherapy prior to chemoradiation in head and neck squamous cell cancer-systematic review and meta-analysis. *Cancer J*. (2017) 23:79–83. doi: 10.1097/PPO.0000000000000253
34. Lan XW, Xiao Y, Zou XB, Zhang XM, OuYang PY, Xie FY. Outcomes of adding induction chemotherapy to concurrent chemoradiotherapy for stage T3N0-1 nasopharyngeal carcinoma: a propensity-matched study. *Onco Targets Ther*. (2017) 10:3853–60. doi: 10.2147/OTT.S133917
35. Wu LR, Yu HL, Jiang N, Jiang XS, Zong D, Wen J, et al. Prognostic value of chemotherapy in addition to concurrent chemoradiotherapy in T3-4N0-1 nasopharyngeal carcinoma: a propensity score matching study. *Oncotarget* (2017) 8:76807–15. doi: 10.18632/oncotarget.20014
36. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst*. (2009) 101:498–506. doi: 10.1093/jnci/djp007
37. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. (2007) 357:1705–15. doi: 10.1056/NEJMoa070956
38. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. (2007) 357:1695–704. doi: 10.1056/NEJMoa071028
39. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* (2016) 388:1883–92. doi: 10.1016/S0140-6736(16)31388-5
40. Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol*. (1992) 10:257–63. doi: 10.1200/JCO.1992.10.2.257
41. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma–is concurrent chemoradiotherapy adequate? *Int J Radiat Oncol Biol Phys*. (2004) 60:156–64. doi: 10.1016/j.ijrobp.2004.03.002
42. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. (1996) 17:1–12.
43. Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol*. (2015) 16:645–55. doi: 10.1016/S1470-2045(15)70126-9
44. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. (1998) 17:2815–34.
45. Rucker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* (2012) 3:312–24. doi: 10.1002/jrsm.1058
46. Rucker G, Schwarzer G, Krahn U, König J. *Netmeta*: *Network Meta-Analysis Using Frequentist Methods*. Available online at: http://cran.r-project.org/web/packages/netmeta/index.html
47. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. (2015) 15:58. doi: 10.1186/s12874-015-0060-8

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A Multicenter Phase II Trial of Docetaxel, Cisplatin, and Cetuximab (TPEx) Followed by Cetuximab and Concurrent Radiotherapy for Patients With Local Advanced Squamous Cell Carcinoma of the Head and Neck (CSPOR HN01: ECRIPS Study)

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Background: Induction chemotherapy (IC) is a treatment option for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). However, treatment with docetaxel, cisplatin, and 5-FU (TPF) followed by cisplatin and radiotherapy is controversial because of toxicity concerns. The aim of this phase II study was to assess the feasibility of docetaxel, cisplatin, and cetuximab (TPEx) followed by cetuximab and concurrent radiotherapy for LA SCCHN.

Patients and Methods: We enrolled patients with histological evidence of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx without distant metastases. IC comprised cisplatin (75 mg/m^2) and docetaxel (75 mg/m^2) on day 1, repeated every 3 weeks for up to three courses. Cetuximab was initiated at 400 mg/m^2, followed by 250 mg/m^2 doses weekly until the end of radiotherapy. Radiotherapy (70 Gy/35 fr/7 w) was initiated after the last docetaxel administration. The primary endpoint was the rate of treatment completion.

Results: We enrolled 54 patients (median age, 58 years) between August 2013 and October 2015. Our patients were 49 males and 5 females with hypopharyngeal (n = 28), oropharyngeal (n = 19), or laryngeal (n = 7) cancers, and 48 of them had stage IV disease. The overall response rate was 72.2% with a median follow-up of 36.1 months and a 3-year overall survival of 90.7%. The treatment completion rate was 76%; 50

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patients (93%) received ≥2 courses of IC, and 41 (76%) completed radiotherapy. The frequencies of grade ≥3 febrile neutropenia or allergy/infusion reactions were 39% and 11%, respectively. There was one treatment-related death.

Conclusions: IC with TPEx followed by cetuximab with concurrent radiotherapy showed acceptable compliance for the treatment of LA SCCHN. However, high frequency of febrile neutropenia remains a challenge and further improvement in the management of TPEx is necessary.

Trial Registration: UMIN000009928

Keywords: head and neck cancer, induction chemotherapy, cetuximab, clinical trial, endpoint

INTRODUCTION

Induction chemotherapy (IC) is a treatment option for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) and allows for organ preservation. Induction cisplatin and fluorouracil (PF) has been effective for locally advanced head and neck cancers before definitive radiotherapy (1, 2). In the GORTEC 2000–2001 study (3), induction docetaxel, cisplatin, and 5-FU (TPF) was superior to induction PF regimen in terms of the overall response rate. Moreover, in the TAX323 (4) and TAX324 (5) trials, induction TPF improved survival compared with induction PF. A recent meta-analysis of chemotherapy for head and neck cancer suggested that IC may contribute to control of distant metastases (6).

A docetaxel, cisplatin, and cetuximab (TPEx) regimen was tested as a first-line treatment for recurrent/metastatic HNSCC in the GORTEC 2008-03 study and showed good efficacy and compliance (7), suggesting that the TPEx regimen might be useful as IC. The TREMPLIN study comparing the efficacy and safety of IC followed by cisplatin or cetuximab with radiotherapy for larynx preservation (LP) showed that the regimen of cetuximab with radiotherapy achieved higher compliance (even after IC) than the cisplatin regimen, suggesting that it is one of the best options for LP.

We conducted a prospective phase II study to examine the feasibility of docetaxel, cisplatin, and cetuximab (TPEx) followed by cetuximab with concurrent radiotherapy for patients with LA SCCHN.

PATIENTS AND METHODS

This study was a multicenter, single-arm, phase 2 trial. Twenty-two institutions in Japan participated in this study. The study protocol was approved by the National Cancer Center Hospital Institutional Review Board. Written informed consents were obtained from all patients before enrollment in our study. This trial was registered with the UMIN clinical trials registry (UMIN000001439).

Patients

We enrolled 54 patients with stage III-IV resectable locally advanced head and neck cancer fulfilling the following criteria: (1) histologically confirmed squamous cell carcinoma of the oropharynx, hypopharynx, or larynx; (2) age between 20 and 75 years; (3) Eastern Cooperative Oncology Group performance status between 0 and 1; (4) normal organ function; and (5) hope for organ preservation.

Pretreatment Evaluation

Our pretreatment clinical evaluation included upper gastrointestinal and pharyngeal endoscopy; head and neck magnetic resonance imaging; and cervical, thoracic, and abdominal computed tomography (CT) scanning. Radiologists, surgeons, and oncologists evaluated the radiological lesion staging. We used the seventh edition of the International Union Against Cancer TNM classification for tumor staging. We did not routinely use positron emission tomography (PET) because of logistics (routine use of PET CT for staging and response evaluation was not accepted by government-issued health insurance).

Protocol Treatment

The IC comprised intravenous (IV) administration of docetaxel (75 mg/m^2) on day 1 and cetuximab (400 mg/m^2 IV on day 1 of cycle 1, and 250 mg/m^2 IV weekly on subsequent administrations) on days 1, 8, and 15. Cisplatin (75 mg/m^2, IV) was also given on day 1. Cycles were repeated every 21 days thrice, with prophylactic antibiotics on days 5 through 14. We did not administer granulocyte colony-stimulating factor (G-CSF) prophylactically until November 2014, and prescribed it only in cases with febrile neutropenia (150 g/m^2 per day). After a protocol revision on December 2014, we used prophylactic G-CSF for patients considered to be at a high risk for febrile neutropenia (8).

Two weeks after the second IC cycle, patients underwent endoscopies and CT scans of the neck and chest. Those with confirmed progressive disease (PD) stopped receiving the protocol treatment and received surgery or other appropriate treatments instead. Patients with confirmed non-PD status received a third IC cycle. After three IC cycles, all patients

Abbreviations: CI, Confidence intervals; CR, Complete responses; CSPOR, Comprehensive Support Project of the Public Health Research; CT, Computed tomography; CTV, Clinical target volume; GETTEC, Groupe d'Etude des Tumeurs de la Tete et du Cou; GTV, Gross tumor volume; IC, Induction chemotherapy; LEDFS, Laryngo-esophageal dysfunction-free survival; LP, Larynx preservation; ORR, Overall response rate; PD, Progressive disease; PET, Positron emission tomography; PFS, Progression-free survival; PTV, Planning target volume.

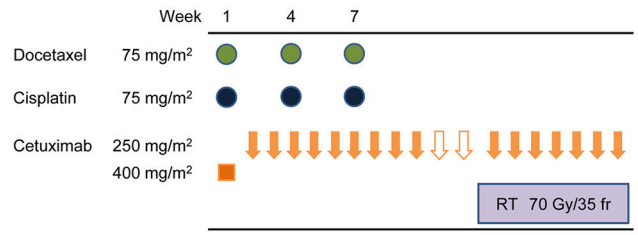

FIGURE 1 | Protocol treatment schematic. Induction therapy comprised docetaxel (75 mg/m^2) intravenously (IV) on day 1, cetuximab on days 1, 8, and 15, then cisplatin (75 mg/m^2 IV) on day 1. Cycles were repeated every 21 days for three cycles. After three induction cycles, patients received standard radiotherapy, a total dose of 70 Gy in 35 fractions over 7 weeks with continued weekly cetuximab (250 mg/m^2).

received standard radiotherapy (total dose of 70 Gy, in 35 fractions over 7 weeks with continued weekly cetuximab 250 mg/m^2) (**Figure 1**).

Regarding the irradiation technique, both three-dimensional multi-beam irradiation (3D-RT) and intensity-modulated radiotherapy (IMRT) were accepted. We determined the gross tumor volume (GTV) by endoscopic or radiographic examination before the IC initiation. Clinical target volume (CTV) was defined as the GTV plus the volumes of all lesions considered at risk of containing microscopic disease. We further categorized the CTVs into two volumes, (1) a therapeutic CTV, including the primary tumor with a 1-cm margin craniocaudally and any metastatic nodes within a 0.5–2-cm margin, and (2) a prophylactic CTV, including a therapeutic CTV plus regional nodes. The planning target volume (PTV) was defined as the CTV plus a 1–3-mm margin that we adjusted as necessary when considering organ risk. The therapeutic and prophylactic PTVs received 70 and 40 Gy, respectively. We used five daily fractions of 2 Gy.

Endpoints and Statistical Analyses

The primary endpoint was the treatment completion rate, which we identified in cases satisfying all of the following criteria: (1) patients received two or more IC courses; (2) irradiation was initiated within 6 weeks between the last IC course and the start of the radiotherapy; (3) full-dose irradiation was completed within 10 weeks; and (4) received cetuximab administration >12 times during their treatment.

In TAX 323 (4) and 324 (5) studies, the complete rates of induction chemotherapy in TPF group were 76 and 73%, respectively. Bonner et al. (9) reported the completion rate of cetuximab with radiotherapy was 90%.

Considering these and on the basis of 5% dropped out because of progressive disease between induction chemotherapy and radiotherapy, with regard to treatment completion rate as the primary endpoint in our phase 2 study, expected and threshold values for exact binomial test were 65 and 40%, respectively, and a total of 50 was required with a power of 90% and one-sided significance level of 2.5%.

TABLE 1 | Patient characteristics ($n = 54$).

Patient characteristics			
Age (years)		Median (range)	58 (35–72)
Sex		Male	49
		Female	5
Performance		0	42
Status		1	12
Primary site		Oropharynx	19
		Hypoparynx	28
		Larynx	7
TNM stage (7th edition)	T		
		1	1
		2	21
		3	12
		4	20
	N	0	8
		1	7
		2a	2
		2b	37
		3	0

We calculated the overall survival times from the date of study registration to the date of death, or the last confirmed survival date. We defined the progression-free survival (PFS) time from the study registration date until the first day of confirmation of PD at any site or of death by any cause.

Events for laryngo-esophageal dysfunction-free survival (LEDFS) included death, local relapse, total or partial laryngectomy or tracheotomy, and chronic enteral nutrition. We estimated binominal confidence intervals (CIs) for the overall response rate (ORR) by using the exact method and assessed the differences in these rates among subgroups using Fisher's exact test. We estimated survival curves using the Kaplan–Meier method.

We conducted primary analysis on the full analysis set population, defined as all registered patients excluding those ineligible after enrollment (i.e., those who did not receive any study treatment). We performed safety analysis for all registered patients who received at least one dose of study treatment. We performed all statistical analyses using the SAS software version 9.4.

RESULTS

Patient Characteristics

Patient characteristics are summarized in **Table 1** and **Table S1**. Total 54 eligible patients with a median age of 58 years participated in the study (49 males and 5 females, 48 with stage IV disease) between August 2013 and October 2015 (**Figure 2**). The numbers of patients with hypopharyngeal, oropharyngeal, and laryngeal cancers were 28, 19, and 7, respectively. Of the 19 patients with oropharyngeal cancer, 14 had p16 positive oropharyngeal cancer.

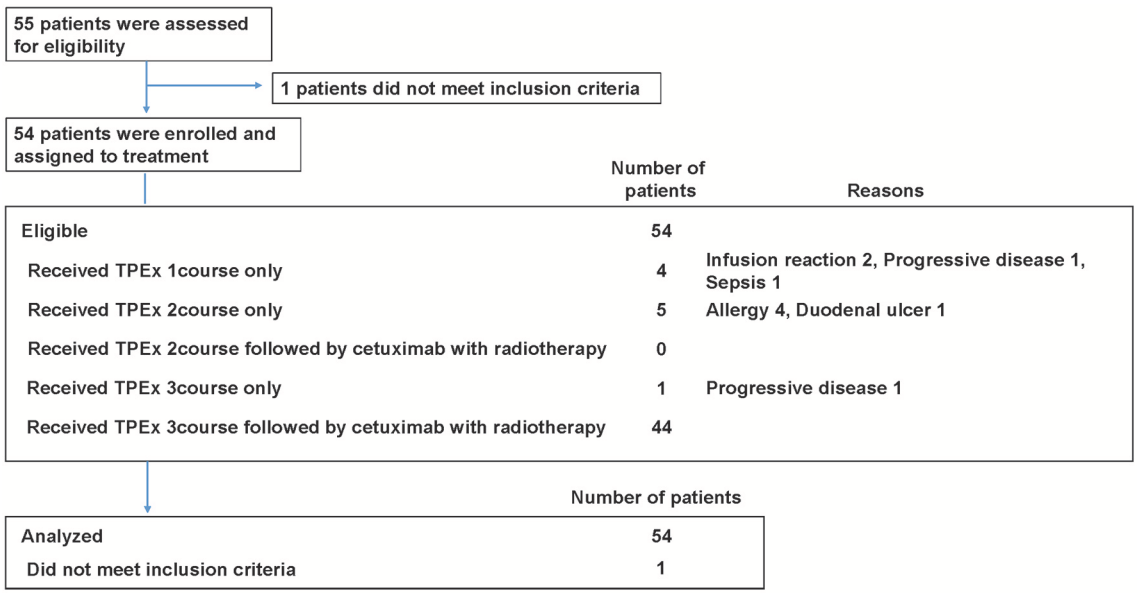

FIGURE 2 | CONSORT diagram. Total 54 patients were analyzed in our study.

TABLE 2 | Treatment compliance as the primary endpoint ($n = 54$).

	Achievement rate in each category
Induction chemotherapy (≥2 courses)	92.6%
Interval between the last administration of TPE and start of RT (<6 weeks)	81.5%
Full-dose irradiation within 70 days	75.9%
Cetuximab administration (>12 times)	81.5%

Total treatment compliance (all satisfied): 75.9% (95% CI: 62.4–86.5%).

Treatment Compliance

The mean treatment completion rate was 75.9% (95% CI, 62.4–86.5%). The rate of patients receiving two or more TPEx cycles was 92.6% (50/54). Forty-four patients (44/54, 81.5%) received three TPEx cycles, and of those, 23 completed the planned TPEx.

The relative dose intensities of cisplatin and docetaxel were 0.90 (95% CI, 0.86–0.94) and 0.84 (95% CI, 0.80–0.88), respectively. The reasons for treatment interruption included seven severe adverse events (four allergies, two infusion reactions, and one sepsis), two PD cases, and other reasons (one duodenal ulcer). As a result, 10 patients could not receive radiotherapy with cetuximab within 6 weeks after the last course of TPEx.

Forty-four patients received radiotherapy, and of those, 41 patients (93.2%) completed the planned irradiation. The median radiotherapy duration was 51 days (range, 46–60). Reasons for treatment interruption included sepsis, local infection, and protocol deviation. Through IC and radiotherapy, the median times of cetuximab administration was 17 (range, 2–19), and the rate of patients receiving ≥12 administrations was 81.5% (44/54). **Table 2** summarizes the treatment compliance results.

Toxicities

During the TPEx, the most frequent grade ≥3 toxicities were neutropenia (93%) and febrile neutropenia (39%). We modified our protocol during the study owing to the high frequency of grade ≥3 neutropenia and febrile neutropenia, and thus, initiated the administration of prophylactic G-CSF. The rate of febrile neutropenia dropped from 41.2 (14/34) to 35.0% (7/20) post protocol modification. Toxicity profile in TPEx is shown in **Table 3**. During radiotherapy, the most frequent grade ≥3 toxicities were mucositis (45%) and radiation dermatitis (48%). We did not find any infusion reactions or allergies during the radiotherapy phase, and we did not observe severe late toxicities during the follow-ups. **Table 4** presents all grade toxicities during the radiotherapy phase.

Efficacies

The ORR during the TPEx was 72.2% (95% CI, 58.4–83.5%). We observed complete responses (CR) in nine patients (16.7%), and one patient developed PD. The ORR after the radiotherapy was 75.9% (95% CI, 62.4–86.5%). We observed CR in 26 patients (48.1%), and 1 patient had PD. With a median follow-up period of 36.1 months, the 3-year overall survival and PFS rates were 90.7 and 58.2%, respectively. Twenty-six patients received second-line treatment: 11 patients underwent laryngectomy, 4 underwent neck dissection, 1 underwent surgery for lung metastases, 7 underwent chemoradiotherapy, 2 underwent chemotherapy, and 1 had incomplete data. The 2- and 3-year LEDFS were 64.8 and 60.1%, respectively (**Figure 3**).

DISCUSSION

TPEx followed by cetuximab with concurrent radiotherapy demonstrated an acceptable compliance for the treatment of LA

TABLE 3 | Toxicities at induction phase ($n = 54$).

	Grade (CTCAE Ver 4.0), *n*				Grade 3–4, %
	1	**2**	**3**	**4**	
HEMATOTOXICITY					
Neutropenia	0	2	15	35	93
Platelet	25	4	0	0	0
Anemia	36	11	4	1	9
NON-HEMATOTOXICITY					
Nausea	5	1	0	0	0
Anorexia	17	18	4	0	7
Mucositis	15	11	3	0	6
Skin rush	24	21	2	0	4
Infusion reaction	0	4	2	1	6
Allergy	0	2	4	1	9
Febrile neutropenia*	0	0	20	1	39

CTCAE, Common Terminology Criteria for Adverse Events.
**ABx and G-CSF were allowed after protocol amendment, due to high rate of FN.*

TABLE 4 | Toxicities at radiotherapy phase ($n = 44$).

	Grade (CTCAE Ver 4.0), *n*				Grade 3–4, %
	1	**2**	**3**	**4**	
HEMATOTOXICITY					
Neutropenia	7	2	0	0	0
Platelet	10	0	0	0	0
Anemia	28	11	3	0	7
NON-HEMATOTOXICITY					
Nausea	5	2	0	0	0
Anorexia	15	11	6	0	14
Mucositis	2	22	20	0	45
Skin rush	22	16	2	0	5
Infusion reaction	0	0	0	0	0
Allergy	0	0	0	0	0
Radiation dermatitis	2	18	21	0	48
Febrile neutropenia	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events.

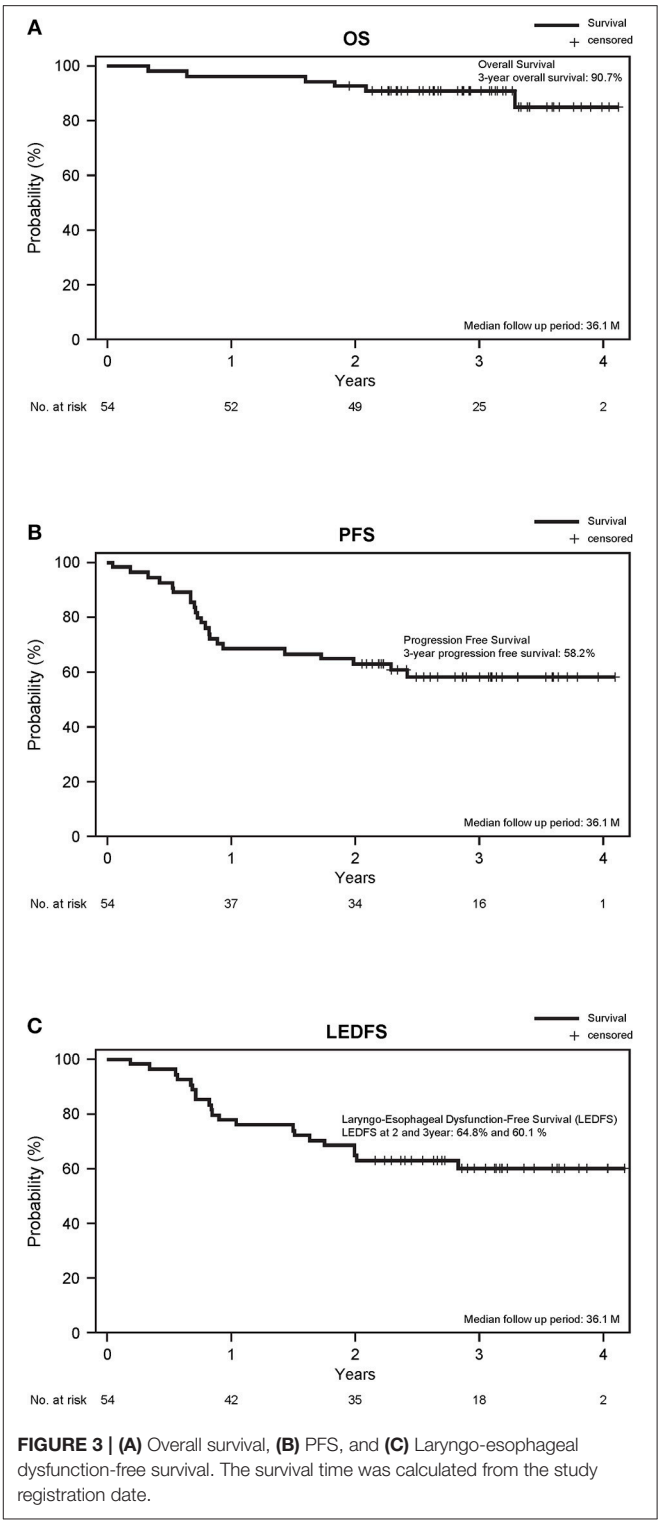

FIGURE 3 | (A) Overall survival, **(B)** PFS, and **(C)** Laryngo-esophageal dysfunction-free survival. The survival time was calculated from the study registration date.

SCCHN. However, high frequency of febrile neutropenia remains a challenge.

We used a cetuximab-based regimen instead of a platinum-based one. Induction TPF followed by chemoradiotherapy (TPF-CRT) seems to be the strongest regimen among the currently available regimens. However, patients have difficulty completing it, and thus, TPF-CRT is not the standard of care in the 2016 National Comprehensive Cancer Network guidelines due to concerns of toxicity and low compliance. Kim et al. (10) reported a meta-analysis of prospective trials (11–14), including TPF IC and chemoradiotherapy, stating that CRT treatment completion rate with this particular regimen was only 63.4% (478/651), and there was no statistically significant overall survival (OS) advantage for TPF prior to CRT (TPF/CRT) over CRT alone (hazard ratio [HR] 0.92; 95% confidence interval [CI], 0.79–1.09; $p = 0.339$).

Induction TPF with cetuximab (TPFE) was tested in the EORTC phase II study (15), showing a severe toxicity profile with only 63.8% (30/47) of patients reaching the radiotherapy phase.

Therefore, the question of which IC is the best for the following chemoradiotherapy remains unanswered.

Considering the results of previous trials, we should consider the treatment compliance before discussing about efficacy.

Thus, the primary endpoint of this study was the treatment completion rate.

In this study, the rate of patients receiving two or more TPEx cycles reached 92.6%, and relative dose intensity of cisplatin and docetaxel were 0.90 (95% CI, 0.86–0.94) and 0.84 (95% CI, 0.80–0.88), respectively.

We observed a high frequency (39%) of febrile neutropenia in our patients, which appears to be one of the most important factors to be considered in a TPEx regimen. Because of this, we modified our protocol during the study and initiated the administration of primary and secondary prophylactic G-CSF. However, considering the small sample size, the frequency of febrile neutropenia appeared to be high even after protocol amendment. Thus, primary prophylactic G-CSF should be considered to manage the TPEx regimen.

Almost all of our patients completed planned irradiation. We encountered frequent cases of severe mucositis and dermatitis that we were able to control with standard oral care (16, 17) and nursing (18–20). We found no cases of infusion reaction or allergy during the radiotherapy phase and believe this may have been due to the gap of 2 months between the initial cetuximab administration and the radiotherapy initiation. The mean treatment completion rate was 75.9% (95% CI, 62.4–86.5%). As a result, seven patients of 10 patients who couldn't receive full dose radiotherapy had some trouble in TPEx section. Then, the management of TPEx section is of upmost importance.

A previous phase II study of TPEx conducted by Argiris et al. (21) showed similar results to ours and reported good compliance. A total of 39 patients were enrolled and of those, 35 patients (90%) received three cycles of cisplatin and docetaxel. A total of 34 patients (87%) received all planned doses of cetuximab during induction TPE, and 33 patients (85%) received full dose radiotherapy.

Several reports suggest that cetuximab with radiotherapy is not less toxic than chemoradiotherapy. However, the toxicity profile of cetuximab with radiotherapy was different from that of CDDP with radiotherapy and this point is important in considering the adjunctive treatment to IC.

The LP Consensus Panel recommended using LEDFS as a composite endpoint in preservation studies (22). In our phase II study, the 2-year LEDFS was 64.8%, greater than that reported in other studies (23, 24).

The 3-year OS and PFS rates were excellent at 90.7 and 58.2%, respectively. However, the efficacy of this regimen couldn't be discussed from these results, because 14 patients with p16 positive oropharyngeal cancer were also included.

Two recent phase III trials showed cetuximab with radiotherapy to be inferior to CDDP with radiotherapy in efficacy (25, 26); therefore, re-evaluation of TPEx followed by cetuximab with radiotherapy in efficacy is mandatory.

In conclusion, IC with TPEx followed by cetuximab with concurrent radiotherapy showed acceptable compliance for the treatment of LA SCCHN. However, high frequency of febrile neutropenia remains a challenge and further improvement in the management of TPEx is necessary.

AUTHOR CONTRIBUTIONS

SZ, NK, MF, TY, and MT: study concept. SZ, NK, TY, and MT: study design. SZ, YO, NK, SO, MF, MK, ST, TU, NM, and MT: acquisition of data. TY: analysis of data. SZ, NK, ST, and MT: interpretation of data. NK, ST, TY, and MT: drafting of the manuscript. SZ, YO, SO, MF, MK, TU, and NM: critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00006/full#supplementary-material

REFERENCES

1. Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). *Br J Cancer* (2000) 83:1594–8. doi: 10.1054/bjoc.2000.1512
2. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst*. (1994) 86:265–72. doi: 10.1093/jnci/86.4.265
3. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst*. (2009) 101:498–506. doi: 10.1093/jnci/djp007
4. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and

neck cancer. *N Engl J Med*. (2007) 357:1695–704. doi: 10.1056/NEJMoa071028
5. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med*. (2007) 357:1705–15. doi: 10.1056/NEJMoa070956
6. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. (2009) 92:4–14. doi: 10.1016/j.radonc.2009.04.014
7. Guigay J, Fayette J, Dillies AF, Sire C, Kerger JN, Tennevet I, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol*. (2015) 26:1941–7. doi: 10.1093/annonc/mdv268
8. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the use of wbc growth factors: american society of clinical oncology clinical practice guideline update. *J Clin Oncol*. (2015) 33:3199–212. doi: 10.1200/JCO.2015.62.3488
9. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *New Engl J Med*. (2006) 354:567–78. doi: 10.1056/NEJMoa053422
10. Kim R, Hahn S, Shin J, Ock CY, Kim M, Keam B, et al. The effect of induction chemotherapy using docetaxel, cisplatin, and fluorouracil on survival in locally advanced head and neck squamous cell carcinoma: a meta-analysis. *Cancer Res Treat*. (2016) 48:907–16. doi: 10.4143/crt.2015.359
11. Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol*. (2014) 32:2735–43. doi: 10.1200/JCO.2013.54.6309
12. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol*. (2013) 14:257–64. doi: 10.1016/S1470-2045(13)70011-1
13. Hitt R, Grau JJ, Lopez-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol*. (2014) 25:216–25. doi: 10.1093/annonc/mdt461
14. Paccagnella A, Ghi MG, Loreggian L, Buffoli A, Koussis H, Mione CA, et al. Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. *Ann Oncol*. (2010) 21:1515–22. doi: 10.1093/annonc/mdp573
15. Specenier PM, Remenar E, Buter J, Schrijvers DL, Bergamini C, Licitra LF, et al. TPF plus cetuximab induction chemotherapy followed by biochemoradiation with weekly cetuximab plus weekly cisplatin or carboplatin: a randomized phase II EORTC trial. *Ann Oncol*. (2017) 28:2219–24. doi: 10.1093/annonc/mdx300
16. Zenda S, Matsuura K, Tachibana H, Homma A, Kirita T, Monden N, et al. Multicenter phase II study of an opioid-based pain control program for head and neck cancer patients receiving chemoradiotherapy. *Radiother Oncol*. (2011) 101:410–4. doi: 10.1016/j.radonc.2011.09.016
17. Yokota T, Tachibana H, Konishi T, Yurikusa T, Hamauchi S, Sakai K, et al. Multicenter phase II study of an oral care program for patients with head and neck cancer receiving chemoradiotherapy. *Supportive Care Cancer* (2016) 24:3029–36. doi: 10.1007/s00520-016-3122-5
18. Zenda S, Ishi S, Akimoto T, Arahira S, Motegi A, Tahara M, et al. DeCoP, a Dermatitis Control Program using a moderately absorbent surgical pad for head and neck cancer patients receiving radiotherapy: a retrospective analysis. *J Clin Oncol*. (2015) 45:433–8. doi: 10.1093/jjco/hyv010
19. Zenda S, Ishi S, Kawashima M, Arahira S, Tahara M, Hayashi R, et al. A Dermatitis Control Program (DeCoP) for head and neck cancer patients receiving radiotherapy: a prospective phase II study. *Int J Clin Oncol*. (2013) 18:350–5. doi: 10.1007/s10147-012-0385-9
20. Zhu G, Lin JC, Kim SB, Bernier J, Agarwal JP, Vermorken JB, et al. Asian expert recommendation on management of skin and mucosal effects of radiation, with or without the addition of cetuximab or chemotherapy, in treatment of head and neck squamous cell carcinoma. *BMC Cancer* (2016) 16:42. doi: 10.1186/s12885-016-2073-z
21. Argiris A, Heron DE, Smith RP, Schrijvers DL, Bergamini C, Licitra LF, et al. Induction docetaxel, cisplatin, and cetuximab followed by concurrent radiotherapy, cisplatin, and cetuximab and maintenance cetuximab in patients with locally advanced head and neck cancer. *J Clin Oncol*. (2010) 28:5294–300. doi: 10.1200/JCO.2010.30.6423
22. Lefebvre JL, Ang KK. Larynx preservation clinical trial design: key issues and recommendations–a consensus panel summary. *Head Neck* (2009) 31:429–41. doi: 10.1002/hed.21081
23. Gorphe P, Matias M, Even C, Ferte C, Bidault F, Garcia G, et al. Laryngo-esophageal dysfunction-free survival in a preservation protocol for T3 laryngeal squamous-cell carcinoma. *Anticancer Res*. (2016) 36:6625–30. doi: 10.21873/anticanres.11269
24. Timme DW, Jonnalagadda S, Patel R, Rao K, Robbins KT. Treatment selection for T3/T4a laryngeal cancer: chemoradiation versus primary surgery. *Ann Otol Rhinol Laryngol*. (2015) 124:845–51. doi: 10.1177/0003489415588130
25. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* (2019) 393:51–60. doi: 10.1016/S0140-6736(18)32752-1
26. Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* (2019) 393:40–50. doi: 10.1016/S0140-6736(18)32779-X

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MINI REVIEW
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Beyond EGFR Targeting in SCCHN: Angiogenesis, PI3K, and Other Molecular Targets

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Although the molecular landscape of squamous cell carcinoma of the head and neck (SCCHN) has been largely deciphered, only one targeted therapy has been approved to date without any molecular selection, namely cetuximab. Cetuximab is a monoclonal antibody targeting EGFR. It has been shown to improve overall survival in the locally advanced setting in combination with radiotherapy and the recurrent and/or metastatic setting in combination with a platinum compound and 5FU. Beside EGFR targeting agents, antiangiogenic agents have been shown to produce antitumor activity but were associated with substantial toxicity. Buparlisib that targets PI3K was also shown to improve survival in combination with paclitaxel in an unselected patient population. Several other targeted therapies have been developed in SCCHN, most of time in all comers, potentially explaining the limited efficacy reported with them. The recent emergence of clinical trials of targeted therapies in enriched patient populations and precision medicine trials such as umbrella trials might boost the clinical development of targeted therapy in SCCHN.

Keywords: head and neck cancer, targeted therapy, biomarker, HPV, genomics, clinical trials

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KEY CONCEPTS

1) EGFR is the only clinically validated target beside PD-1 in SCCHN.
2) Antiangiogenic agents have been shown to produce antitumor activity in SCCHN but are associated with substantial toxicity.
3) Buparlisib has been the only drug targeting the PI3K/AKT/mTOR pathway to show a survival improvement in SCCHN.
4) There is an urgent need to develop targeted therapies in enriched patient populations in SCCHN.

INTRODUCTION

Tobacco smoking and alcohol consumption are the classical main risk factors of squamous cell carcinoma of the head and neck (SCCHN). The human papilloma virus (HPV) infection has been identified as an additional risk factor for oropharyngeal SCCHN (1). HPV-related SCCHN occur in younger patients, more frequently in men than women, and is associated with a better prognosis. HPV-positive smoking SCCHN patients have an intermediate prognostic (1). Locally advanced SCCHN is treated in a curative intent with a multidisciplinary approach that includes surgery, radiotherapy, and chemotherapy. Despite an improvement in the care of SCCHN patients,

almost half of the HPV-negative patients will relapse, most of time within 2 years. Treatment of the relapsing tumors may consist in surgery and/or re-irradiation if possible. Patients with recurrent and/or metastatic (R/M) disease are treated with palliative systemic therapies.

The epidermal growth factor receptor (EGFR) was early on identified as a potential target for the treatment of SCCHN. Indeed, the EGFR protein is almost consistently overexpressed in SCCHN (>90%), and its expression associated with poor prognosis (2, 3). *EGFR* is mutated/amplified in 16% of HPV-negative SCCHN (4). Besides, Cetuximab, a monoclonal targeting the extracellular domain of EGFR, is currently the sole targeted therapy that is approved in combination with a doublet of platinum and 5FU in first-line R/M SCCHN (5). Cetuximab is also approved in combination with radiotherapy for locally advanced SCCHN (6). No predictive biomarker of efficacy of cetuximab has been identified to date in SCCHN, as opposed to colorectal cancer.

We aim to review the main targeted therapies that have been developed beyond cetuximab in R/M SCCHN in light of the molecular landscape of SCCHN.

GENOMIC LANDSCAPE OF SCCHN

The advent of high throughput genomic technologies has enabled to decipher the genomic landscape of SCCHN. SCCHN has a generally high mutational load (7), although this may vary across patients. Several teams reported on the genomic landscape of SCCHN using high throughput technologies (4, 8–11). The Cancer Genome Atlas (TCGA) consortium released the analysis of sequencing data from 279 SCCHN in 2015 (4). The patient population was composed of 243 HPV-negative SCCHN (87%), a majority of men (70%), and mainly heavy smokers. SCCHN of the oral cavity were the most represented tumor location (62%). Following this initial publication, TCGA has reported on more than 500 SCCHN (12).

HPV-positive SCCHN has a rather simple genomic profile (9, 10). HPV-positive SCCHN is characterized by 56% of activating mutations and/or amplifications of the *PIK3CA* gene that encodes for the p100α unit of PI3kinase (PI3K), and a low incidence of tumor suppressor gene (TSG) alterations such as *TP53* mutations (3%) (13), and no *CDKN2A* deletions. HPV-positive SCCHN is also characterized by the dysregulation of transcription factors such as the loss of *TRAF3* (TNF Receptor Associated Factor 3) (22%), and the amplification of *E2F1* (19%). *PIK3CA* mutations were shown to be related to the APOBEC system (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) (14), a family of cytosine deaminases that contributes to DNA mutations (12), in HPV-positive SCCHN. APOBEC related mutations were sub-clonal. HPV-negative SCCHN is a more heterogeneous group, with a higher genomic complexity potentially related to tobacco exposure (14). HPV-negative SCCHN is characterized by deleterious mutations and/or homozygous deletions of TSG such as *TP53* (84%) or *CDKN2A* (58%) (4). *PIK3CA* is activated via mutations or gain/amplifications in 34% of cases. Some oncogenes are amplified and include *CCND1* (31%) which encodes for cyclin D1 and controls the G1/S transition of the cell cycle, and *MYC* (14%) which is a transcription factor that regulates the expression of 15% of all genes. Genes coding for tyrosine kinase receptors (TKR) involved in oncogenesis such as *EGFR*, *FGFR*, *FGFR*, *FGFR3*, *ERBB2*, *IGF-1R, EPHA2*, *DDR2*, and *MET* are inconsistently activated (2–15% of cases), most often via amplifications. Conflicting results were reported regarding genomics of HPV-positive smokers. A recent comparison of HPV-positive tumors according to the smoking status found no significant difference in terms of mutation rate and mutation pattern (15), whereas the use of a larger panel showed that HPV-positive oropharyngeal SCC with a smoking history of more than 10 pack-year had a different profile when compared with HPV-positive non-smokers (16). Mutations more frequently associated with smoking status were mutations in *TP53, CDKN2A*, *KRAS,* and *NOTCH1*. These mutations were associated with poor survival. HLA-A mutations were more common in the non-smokers. These data suggest that smoking history should be taken into account on top of the HPV status, since the biology of HPV-positive HNSCC smoker patients is different than either HPV-positive non-smokers or HPV-negative HNSCC patients.

TARGETING THE ErbB FAMILY

EGFR belongs to the ErbB family of tyrosine kinase receptors (TKRs), along with ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). Binding ligands allow members of the ErbB family to homo- or hetero-dimerize, autophosphorylating the intracellular domain and creating binding sites for signaling proteins. The two primary pathways activated are the RAS/RAF/MEK/ERK and the PI3K/AKT/mTOR pathways. To overcome primary and secondary resistance to EGFR inhibition, a first strategy has been to target other members of the HER (ErbB) family: ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). *ERBB2*, the second member of the HER family, is amplified in 5% of HPV-negative SCCHN. Lapatinib, a tyrosine kinase inhibitor (TKI) targeting EGFR and HER2, was evaluated in R/M SCCHN (17). Among the 45 enrolled patients, no objective response was observed and 49% of patients experienced adverse events (Aes) (15% grade 3). Afatinib, an irreversible pan-HER TKI, was the first to be evaluated in a phase 3 trial in R/M SCCHN (18). Four hundred eighty-three patients were assigned to afatinib or methotrexate in patients who failed platinum therapy. Median progression-free survival (PFS) was significantly longer in the afatinib arm (2.6 vs. 1.7 months, $p = 0.03$). Because of this modest gain of efficacy and the absence of overall survival (OS) gain, afatinib has not been approved in R/M SCCHN. An increased benefit of afatinib over methotrexate was observed in patients with p16-negative, *EGFR* amplified, HER3-low, and PTEN-high tumors (19), which

Abbreviations: Aes, adverse events; EGFR, epidermal growth factor receptor; HPV, Human papilloma virus; ORR, overall response rate; OS, overall survival; PFS, progression free survival; R/M, recurrent metastatic; SCCHN, squamous cell carcinoma of the head and neck; TKR, tyrosine kinase receptor; TKI, tyrosine kinase inhibitor; TSG, tumor suppressor gene.

is being prospectively evaluated in the UPSTREAM umbrella trial (20). Dacomitinib, an oral irreversible pan-HER TKI, was evaluated as first-line treatment in R/M SCCHN (21) in a single-arm phase II trial. Among the 69 enrolled patients, 8 patients achieved a partial response (13%). Median PFS was 3 months, and median OS 7 months. Grade 3/4 diarrhea occurred in 16% of patients leading to frequent dose interruption (41%) and dose reductions (38%). In another phase 2 trial, 10 out of 48 patients (21%) had a partial response (22). Efficacy results were in the same range than the other trial with a median PFS of 3.9 months and a median OS of 6.6 months. The most common AEs were paronychia (65%) and diarrhea (52%). Treatment-related grade 3 AEs occurred in 6 patients. At least one dose interruption and reduction due to treatment-related AEs occurred in 24 patients (50%) and 9 patients (19%), respectively.

Targeting HER3 in SCCHN was also evaluated. Dual-targeting of HER3 and EGFR was evaluated in a randomized phase 2 trial with duligotuzumab, a dual antibody (23). Duligotuzumab was compared to cetuximab in 121 pretreated R/M SCCHN patients. Both drugs were associated with comparable PFS (median: 4.2 vs. 4.0 months), OS (median: 7.2 vs. 8.7 months) and ORR (12 vs. 15%). Patritumab is a fully human anti-HER3 monoclonal antibody. By binding the extracellular domain of HER3, patritumab prevents heregulin-mediated signaling, the dimerization with EGFR or HER2, and promotes the receptor internalization and degradation. A randomized phase 2 study evaluated the combination of cetuximab and platinum chemotherapy with patritumab or placebo in first-line R/M SCCHN (24). AEs were more frequent with patritumab than placebo, leading to discontinuation in 16% of patients treated with patritumab vs. 5% with placebo. The addition of patritumab was not associated with a gain of efficacy in terms of overall response rate (ORR) (36 vs. 28%) or PFS (5.6 vs. 5.5 months).

In summary, cetuximab has been the first and unique approved therapy targeting the ErbB pathway. No validated biomarker has been identified. Targeting other members of the ErbB family is associated with disappointing efficacy probably due to the lack of molecular selection.

TARGETING ANGIOGENESIS

The vascular endothelial growth factor (VEGF) and its receptors VEGFR2 and VEGFR3 are overexpressed in SCCHN (25, 26). VEGF overexpression is associated with poor survival (27). TKIs targeting VEGFR demonstrated limited activity in pre-treated R/M SCCHN with ORR never exceeding 10% (28–30) (**Table 1**). In addition, serious safety issues were frequently reported, including grade 3–4 fatigue in 20–30% of patients, hand foot syndrome and diarrhea with sorafenib (28), and severe bleeding events with sunitinib (4 deaths out of 38 patients) (29). Only 19 out of 30 patients treated with axitinib received the full planned dose (30). Antiangiogenic agents were also combined with other targeted therapies and/or cytotoxic agents (**Table 1**). Although the results of some single arm phase 2 trials with sorafenib as single agent were encouraging (33, 34), the addition of sorafenib to cetuximab did not improve the ORR in randomized phase 2 trials as compared to cetuximab alone (31). The addition of vandetanib to docetaxel did even worse in terms of PFS as compared to docetaxel alone (32). A phase 3 trial assessed the efficacy of the addition of bevacizumab that is a monoclonal antibody targeting VEGF to a doublet of platinum with 5FU or docetaxel. The trial did not reach its primary endpoint with a median OS of 11 months in the control arm vs. 12.6 months in the experimental arm, but showed an improved PFS and ORR with the addition of bevacizumab. Grade 3–5 AEs were more frequent with bevacizumab (67 vs. 82%, $p = 0.0003$), especially for grade 5 bleeding (0 vs. 2.6%, $p = 0.03$). The limited efficacy with substantial toxicity has clearly impacted the clinical development of antiangiogenic agents in SCCHN patients, although combinations of antiangiogenic agents with immunotherapy are ongoing (36).

TABLE 1 | Selected clinical trials evaluating antiangiogenic agents in SCCHN patients.

	Phase	N	ORR (%)	Median PFS (mo)	Median OS (mo)
Sorafenib (28)	II	23	5	3.4	8
Sunitinib (29)	II	38	3	2	3.3
Axitinib (30)	II	42	7	3.7	11
Cetuximab + sorafenib	II	27	8	3	9
Cetuximab (31)		28	8	3.2	5.7
Docetaxel + vandetanib	II	15	13	0.7	6.8
Docetaxel (32)		14	7	2.3	6
Cetuximab + bevacizumab (33)	II	46	16	2.8	7.5
Pemetrexed + Bevacizumab (34)	II	40	30	5	11.3
Platinum + 5FU or docetaxel	III	200	25	4.4	11.0
Platinum + 5FU or docetaxel + bevacizumab (35)		203	36	6.1	12.6

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; mo, months.

TARGETING THE PI3K/AKT/mTOR PATHWAY

Alterations in the PI3K/AKT/mTOR pathway are among the most frequent in SCCHN (13% to 56%), regardless of the HPV status (4). *PIK3CA* amplifications were reported in pre-malignant and cancer lesions, suggesting an early role in SCCHN carcinogenesis (37). The activating mutations of *PIK3CA* are reported in 6–8% of HNSSC, 73% of these mutations being localized in 3 hotspots, namely E542K and E545K coding for the helical domain, and H1047R/L in the kinase domain (38). These three mutations are associated with the overexpression of the protein (39). The function of the other mutations, which are not uncommon, is more uncertain (7, 40). Many other deregulations have been reported in the PI3K/AKT/mTOR pathway including alterations of PTEN, PIK3R1, and mTOR. Preclinical data showed that patient-derived tumorgrafts with *PIK3CA* mutations

were sensitive to PI3K targeting, as opposed to *PIK3CA*-wild-type tumorgrafts (38). Wirtz et al. reported that engineered cell lines harboring the hotspot E545K and H1047R *PIK3CA* mutations were less sensitive to PI3K inhibition (41). In contrast, another study found that the H1047R-expressing cell lines had increased sensitivity to PI3K inhibition, whereas those expressing E545K showed slightly increased sensitivity. These conflicting results open the debate on the actual oncogenic addiction of *PIK3CA* mutations, their actual weight when compared with other driver mutations, and highlight the difficulty of targeting this pathway.

The first results of clinical trials targeting the PI3K/AKT/mTOR pathway with non-selective inhibitors were disappointing (**Table 2**). mTOR inhibitors were first evaluated. In phase 2 trials, no responses were observed with everolimus (42) or temsirolimus (43). The combination of erlotinib with everolimus (44) or temsirolimus (45) resulted in increased toxicity without any additional efficacy. PX-866, an oral, irreversible, pan-isoform inhibitor of PI3K, was evaluated in combination with docetaxel in a phase 2 randomized trial (46). When compared with docetaxel alone, the combination of PX-866 with docetaxel did not improve the PFS, ORR, and OS. PX-866 was also evaluated in combination with cetuximab in another randomized phase 2 trial in pretreated R/M SCCHN (47). The combination again did not improved ORR, PFS, and OS. Buparlisib, a selective PI3K inhibitor of p110α/β/δ/γ subunit was first tested as a single agent in pretreated R/M SCCHN (49). Preliminary results showed a 39% disease control rate at 2 months in patients whose tumor did not have *PIK3CA* mutation (49). Buparlisib was further evaluated in 2nd line R/M SCCHN in combination with weekly paclitaxel in BERIL-1, a randomized placebo controlled phase 2 trial (48). The median PFS was significantly longer in the buparlisib arm (4.6 vs. 3.5 months, $p = 0.01$), as well as OS (10.4 vs. 6.5 months, $p = 0.041$). However, grade 3–4 Aes were more frequent with buparlisib, especially in terms of hyperglycemia (22%), anemia (18%), neutropenia (17%), and stomatitis (9%). Beril-1 was the first randomized trial to demonstrate a significant improvement in PFS and OS with a PI3K inhibitor in R/M SCCHN, but at the price of high toxicity. A preplanned exploratory analysis showed that the combination seemed to benefit a subgroup of patients with *TP53* alterations, HPV-negative status, low mutational load, or high infiltration of tumor infiltrating lymphocytes (TILs) or CD8-positive cells) (50). Importantly, the outcome of patients treated with buparlisib was not associated with deregulation of the PI3K/AKT/mTOR pathway (*PIK3CA* mutation/amplification, PTEN loss). A potential mechanism of action of buparlisib is the promotion of the anti-tumor immune response through the promotion of the INFγ secretion (50). A phase 3 trial is currently planned and will evaluate the predictive value of these biomarkers. To further improve the efficacy of targeting the PI3K pathway, selective PI3K inhibitors are currently developed (51).

TABLE 2 | Selected clinical trials evaluating inhibitors of the PI3K/AKT/mTOR pathway in SCCHN patients.

	Phase	*N*	ORR (%)	Median PFS (mo)	Median OS (mo)
mTOR INHIBITORS					
Everolimus (42)	II	9	0	1.5	4.5
Temsirolimus (43)	II	40	0	2	3.7
Erlotinib + everolimus (44)	II	35	2.8	3	10.2
Erlotinib + temsirolimus (45)	II	12	0	1.9	4
PI3K INHIBITORS					
Docetaxel	II	43	5	2.7	6.5
Docetaxel + PX-866 (46)		42	14	3.1	8.8
Cetuximab	II	41	7	2.7	8.5
Cetuximab + PX-866 (47)		42	4	2.7	7.0
Paclitaxel + placebo	II	79	14	3.5	6.5
Paclitaxel+ buparlisib (48)		79	39	4.6*	10.4*

*$p < 0.05$.

OTHER MOLECULAR TARGETS

Targeting RAS

The proportion of SCCHN having a *KRAS* mutation is low around 5% (52, 53). The activating mutations of *HRAS*, similarly rare in the population of Caucasian HPV-negative SCCHN (5%) (4, 8, 11, 38), are more frequent in the oral cavity SCC of Asian populations because of chewed betel nut (9, 54, 55), and snuff (56). The RAS proteins must undergo a series of post-translational modifications, and in particular a farnesylation, to be functional. Inhibition of farnesyl transferase activity produced antitumor activity in preclinical models of SCC of the skin with *HRAS* mutations, an antitumor effect that was not observed in models with *NRAS* or *KRAS* mutations (57). Tipifarnib, a farnesyl transferase inhibitor is currently tested in a phase 2 study in advanced tumors with activating mutations of *HRAS* (58). Preliminary reports of 7 evaluable SCCHN showed 5 patients (71%) achieving a partial response with a median duration of response of 14.1 months. No *HRAS* mutated SCCHN patients experienced an objective response on their last therapy prior to receiving tipifarnib. If these results are confirmed in the ongoing phase II KO-TIP 007 trial (NCT03719690), tipifarnib could become a standard in this rare and aggressive subgroup of patients.

Targeting the Cell Cycle Regulators

The majority of HPV-negative SCCHN harbors genetic alterations involving the cell cycle such as *TP53* mutations, *CCND1* amplification, *CDKN2A* deletion, and p16 inactivation. These later deregulations enable to circumvent the mitotic checkpoints through aberrant cyclin-dependent kinase activation. *CCND1* is amplified in 31% of HPV-negative SCCHN and is involved in the cell cycle with CDK4/CDK6 in G1 phase, and in G1/S transition (59). Several clinical trials evaluate CDK4/CDK6 inhibitors as monotherapy [palbociclib (NCT03088059), ribociclib (NCT03179956), abemaciclib (NCT03356587)] or in combination with other targeted therapies, such as the combination of palbociclib with cetuximab

(NCT02499120) or the combination of palbociclib with gedatolisib that is a dual PI3K/mTOR inhibitor (NCT03065062). The inclusion in these trials is usually restricted to HPV-negative HNSCC and sometimes to patients whose tumors harbor alterations in the genes involved in cell cycle regulation (amplification of *CCND1* in NCT03088059, intact Rb and genetic alterations in CDK4/CDK6 pathway in NCT03356587). The combination of palbociclib with weekly cetuximab was shown to be safe in a phase I trial (60) with no dose-limiting toxicity. The phase II trial enrolled 30 pretreated HPV-negative R/M SCCHN patients. Among the 28 evaluable reported patients, 3 patients had a complete response (11%), and 8 patients a partial response (29%).The median PFS was 5.4 months and the median OS 9.5 months (61). A randomized phase II trial evaluating this combination (PALATINUS, NCT02499120) is ongoing. Despite encouraging results with CDK4/6 inhibitors in R/M SCCHN, the oral route of these molecules constitutes a significant limit for a development in the treatment of R/M SCCHN, since many patients are no longer able to swallow.

Targeting IGF1 Receptor

IGF-1R is mutated or amplified in 4% of HPV-negative SCCHN (4). Although preclinical data supported IGF-1R inhibition in SCCHN cell lines (62), figitumumab or cixutumumab, monoclonal antibodies targeting IGF-1R, had no efficacy in unselected patient populations (63, 64).

Targeting FGF Receptors

The *FGFR 1, 2,* and *3* (Fibroblast Growth Factor Receptor) activating mutations/amplifications were reported in 14% of the HPV-negative SCCHN (4). *FGFR3* fusion genes have also been reported in HPV-positive SCCHN (4). Specifically, the *FGFR3-TACC3* fusion gene has been evaluated in preclinical models (65). Exposure of carcinoma models carrying *FGFR3* fusion genes after exposure to the FGFR inhibitor PD173074 resulted in significant antitumor activity, an effect that was not observed in cell lines with *FGFR3* activating mutation. Several trials are testing FGFR inhibitors in molecularly selected patients (NCT02706691; NCT03088059).

Targeting MET

The *MET* (Mesenchymal Epithelial Transition) gene encodes a TKR which is activated by binding to its ligand, the Hepatocyte Growth Factor (HGF). The common overexpression of MET in SCCHN is associated with a poor prognosis and resistance to cetuximab (66). Despite a strong rationale to counteract resistance to EGFR inhibitor by targeting MET,results were disappointing in unselected populations. A phase II trial evaluating foretinib (67), a TKI targeting MET, stopped at first interim analysis because no objective response was observed in the first 14 unselected R/M SCCHN patients. A randomized phase II trial that compared the efficacy of tovantinib, another TKI targeting MET, in combination with cetuximab to cetuximab alone failed to show any significant difference in terms of ORR, PFS, or OS (68).

Targeting MYC

The *MYC* gene produces a transcription factor that regulates the expression of 15% of genes by binding to Enhancer Box sequences (E-boxes), and by recruiting enzymes capable of acetylating lysine amino acids from histones such as histone acetyltransferases. *MYC* is amplified in 14% of HPV-negative SCCHN (4). Bromodomain and terminal domain (BET) inhibitors are currently evaluated in cancer patients with *MYC* amplifications (69) (NCT02419417).

Targeting Tumor Suppressor Genes

Oncogene abnormalities that can be targeted with currently available drugs are present in a minority of SCCHN patients. In contrast, the vast majority of SCCHN have a loss of function of tumor suppressor genes (TSGs) such as *TP53* and *CDKN2A*. In HPV-negative SCCHN, this loss is due to inactivating mutations and/or deletions of the genes themselves. In HPV-positive SCCHN, the E6 viral oncoprotein prevents the induction of apoptosis by indirect p53 degradation. The targeting of TSGs is less intuitive than that of oncogenes (70). Unlike oncogene mutations, those of TSGs have to be recessive to result in a loss of function of the protein. Many studies carried out in oncology show that the loss of heterozygosity may be sufficient, by a phenomenon of dosage, to contribute to the cellular transformation. The integration of this information is key since the data from the pan-tumoral sequencing analysis revealed that the majority of chromosome region copy number variations were deletions and that the majority of genes involved were TSGs (71).

Sixty to 100% of HPV-negative SCCHNs have inactivating *TP53* mutations (9–12). These mutations are distributed quite homogeneously along the gene with some hotspots. Several approaches have been developed to target TP53 loss of function (72–74). APR-246 is a small molecule capable of restoring the conformation of mutated p53 proteins in wild conformation (75, 76). In SCCHN, the effect of APR-246 was evaluated in 4 different SCCHN cell lines (77). Reactivation of p53 was observed in PRIMA-1 or CP-31398 treated cell lines, and in wild *TP53*-treated cell lines treated with nutlin-3. Used in combination, these small molecules increased the cytotoxicity of cisplatin, 5-fluorouracil, paclitaxel, and erlotinib (77).

CONCLUSIONS

The characterization of the molecular landscape of SCCHN allowed the identification of actionable and potentially targetable genomic alterations. Despite this undeniable advance, very few targeted therapies have shown a significant efficacy in unselected R/M SCCHN. One potential explanation for this is the lack of clinical trials performed in molecularly enriched patient populations. The UPSTREAM trial is an umbrella biomarker-driven study dedicated to R/M SCCHN patients, sponsored by the European Organization of Research and Treatment of Cancer (20). The UPSTREAM is the first precision medicine trial in SCCHN. In this trial, patients have to undergo a mandatory fresh biopsy in order to establish the molecular profile of patients' tumors. Patients are then allocated to either a targeted therapy or immunotherapy cohort in the absence

of those biomarkers. Tissue of origin agnostic trials, such as NCI-MATCH (NCT02465060) or TAPUR (NCT02693535), are also interesting ways to evaluate targeted therapies in enriched HNSCC patients.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* (2010) 363:24–35. doi: 10.1056/NEJMoa0912217
2. Dassonville O, Formento JL, Francoual M, Ramaioli A, Santini J, Schneider M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol.* (1993) 11:1873–8.
3. Chung CH, Ely K, McGavran L, Varella-Garcia M, Parker J, Parker N, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol.* (2006) 24:4170–6. doi: 10.1200/JCO.2006.07.2587
4. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature* (2015) 517:576–82. doi: 10.1038/nature14129
5. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* (2008) 359:1116–27. doi: 10.1056/NEJMoa0802656
6. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2006) 354:567–78. doi: 10.1056/NEJMoa053422
7. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. *Science* (2013) 339:1546–58. doi: 10.1126/science.1235122
8. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K, Li RJ, et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. *Science* (2011) 333:1154–7. doi: 10.1126/science.1206923
9. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, et al. The mutational landscape of head and neck squamous cell carcinoma. *Science* (2011) 333:1157–60. doi: 10.1126/science.1208130
10. Pickering CR, Zhang J, Yoo SY, Bengtsson L, Moorthy S, Neskey DM, et al. Integrative genomic characterization of oral squamous cell carcinoma identifies frequent somatic drivers. *Cancer Discov.* (2013) 3:770–81. doi: 10.1158/2159-8290.CD-12-0537
11. Seiwert TY, Zuo Z, Keck MK, Khattri A, Pedamallu CS, Stricker T, et al. Integrative and comparative genomic analysis of HPV-positive and HPV-negative head and neck squamous cell carcinomas. *Clin Cancer Res.* (2015) 21:632–41. doi: 10.1158/1078-0432.CCR-13-3310
12. Faden DL, Thomas S, Cantalupo PG, Agrawal N, Myers J, DeRisi J. Multi-modality analysis supports APOBEC as a major source of mutations in head and neck squamous cell carcinoma. *Oral Oncol.* (2017) 74:8–14. doi: 10.1016/j.oraloncology.2017.09.002
13. Westra WH, Taube JM, Poeta ML, Begum S, Sidransky D, Koch WM. Inverse relationship between human papillomavirus-16 infection and disruptive p53 gene mutations in squamous cell carcinoma of the head and neck. *Clin Cancer Res.* (2008) 14:366–9. doi: 10.1158/1078-0432.CCR-07-1402
14. Henderson S, Chakravarthy A, Su X, Boshoff C, Fenton TR. APOBEC-mediated cytosine deamination links PIK3CA helical domain mutations to human papillomavirus-driven tumor development. *Cell Rep.* (2014) 7:1833–41. doi: 10.1016/j.celrep.2014.05.012
15. Mirghani H, Lacroix L, Rossoni C, Sun R, Auperin A, Casiraghi O, et al. Does smoking alter the mutation profile of human papillomavirus-driven head and neck cancers? *Eur J Cancer* (2018) 94:61–9. doi: 10.1016/j.ejca.2018.02.013
16. Zevallos JP, Yim E, Brennan P, Liu AY, Taylor JM, Weissler M, et al. eds. Molecular profile of human papillomaviruse positive oropharyngeal squamous cell carcinoma stratified by smoking status. *Int J Radiat Oncol Biol Phys.* (2016) 94:864. doi: 10.1016/j.ijrobp.2015.12.022
17. de Souza JA, Davis DW, Zhang Y, Khattri A, Seiwert TY, Aktolga S, et al. A phase II study of lapatinib in recurrent/metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res.* (2012) 18:2336–43. doi: 10.1158/1078-0432.CCR-11-2825
18. Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol.* (2015) 16:583–94. doi: 10.1016/S1470-2045(15)70124-5
19. Cohen EEW, Licitra LF, Burtness B, Fayette J, Gauler T, Clement PM, et al. Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. *Ann Oncol.* (2017) 28:2526–32. doi: 10.1093/annonc/mdx344
20. Galot R, Le Tourneau C, Guigay J, Licitra L, Tinhofer I, Kong A, et al. Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach. *Ann Oncol.* (2018) 29:2313–27. doi: 10.1093/annonc/mdy452
21. Abdul Razak AR, Soulieres D, Laurie SA, Hotte SJ, Singh S, Winquist E, et al. A phase II trial of dacomitinib, an oral pan-human EGF receptor (HER) inhibitor, as first-line treatment in recurrent and/or metastatic squamous-cell carcinoma of the head and neck. *Ann Oncol.* (2013) 24:761–9. doi: 10.1093/annonc/mds503
22. Kim HS, Kwon HJ, Jung I, Yun MR, Ahn MJ, Kang BW, et al. Phase II clinical and exploratory biomarker study of dacomitinib in patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Clin Cancer Res.* (2015) 21:544–52. doi: 10.1158/1078-0432.CCR-14-1756
23. Fayette J, Wirth L, Oprean C, Udrea A, Jimeno A, Rischin D, et al. Randomized phase II study of duligotuzumab (MEHD7945A) vs. cetuximab in squamous cell carcinoma of the head and neck (MEHGAN Study). *Front Oncol.* (2016) 6:232. doi: 10.3389/fonc.2016.00232
24. Harrington KJ, Forster MD, Le Tourneau C, Ariza J, Chen S, Greenberg J, et al. eds. Randomized phase 2 trial of patritumab (P) or placebo (PBO) + cetuximab (C) + cisplatin (CIS) or carboplatin (CAR) for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol.* (2018) 36:6045. doi: 10.1200/JCO.2018.36.15_suppl.6045
25. Neuchrist C, Erovic BM, Handisurya A, Steiner GE, Rockwell P, Gedlicka C, et al. Vascular endothelial growth factor receptor 2 (VEGFR2) expression in squamous cell carcinomas of the head and neck. *Laryngoscope* (2001) 111:1834–41. doi: 10.1097/00005537-200110000-00031
26. Neuchrist C, Erovic BM, Handisurya A, Fischer MB, Steiner GE, Hollemann D, et al. Vascular endothelial growth factor C and vascular endothelial growth factor receptor 3 expression in squamous cell carcinomas of the head and neck. *Head Neck* (2003) 25:464–74. doi: 10.1002/hed.10235
27. Kyzas PA, Cunha IW, Ioannidis JP. Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. *Clin Cancer Res.* (2005) 11:1434–40. doi: 10.1158/1078-0432.CCR-04-1870
28. Lalami Y, Garcia C, Flamen P, Ameye L, Paesmans M, Awada A. Phase II trial evaluating the efficacy of sorafenib (BAY 43–9006) and correlating early fluorodeoxyglucose positron emission tomography-CT response to outcome in patients with recurrent and/or metastatic head and neck cancer. *Head Neck* (2016) 38:347–54. doi: 10.1002/hed.23898
29. Machiels JP, Henry S, Zanetta S, Kaminsky MC, Michoux N, Rommel D, et al. Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006–01. *J Clin Oncol.* (2010) 28:21–8. doi: 10.1200/JCO.2009.23.8584
30. Swiecicki PL, Zhao L, Belile E, Sacco AG, Chepeha DB, Dobrosotskaya I, et al. A phase II study evaluating axitinib in patients with unresectable, recurrent or metastatic head and neck cancer. *Invest New Drugs* (2015) 33:1248–56. doi: 10.1007/s10637-015-0293-8
31. Gilbert J, Schell MJ, Zhao X, Murphy B, Tanvetyanon T, Leon ME, et al. A randomized phase II efficacy and correlative studies of

cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma. *Oral Oncol.* (2015) 51:376–82. doi: 10.1016/j.oraloncology.2014.12.011

32. Limaye S, Riley S, Zhao S, O'Neill A, Posner M, Adkins D, et al. A randomized phase II study of docetaxel with or without vandetanib in recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). *Oral Oncol.* (2013) 49:835–41. doi: 10.1016/j.oraloncology.2013.04.010
33. Argiris A, Kotsakis AP, Hoang T, Worden FP, Savvides P, Gibson MK, et al. Cetuximab and bevacizumab: preclinical data and phase II trial in recurrent or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol.* (2013) 24:220–5. doi: 10.1093/annonc/mds245
34. Argiris A, Karamouzis MV, Gooding WE, Branstetter BF, Zhong S, Raez LE, et al. Phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic head and neck cancer. *J Clin Oncol.* (2011) 29:1140–5. doi: 10.1200/JCO.2010.33.3591
35. Argiris A, Li S, Savvides P, Ohr J, Gilbert J, Levine MA, et al. Phase III randomized trial of chemotherapy with or without bevacizumab (B) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): Survival analysis of E1305, an ECOG-ACRIN Cancer Research Group trial. *J Clin Oncol.* (2017) 35(Suppl. 15):6000. doi: 10.1200/JCO.2012.45.4272
36. Taylor MH, Rasco DW, Brose MS, Vogelzang NJ, Richey SL, Cohn AL, et al. A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck. *J Clin Oncol.* (2018) 36(Suppl. 15):6016. doi: 10.1200/JCO.2018.36.15_suppl.6016
37. Singh B, Stoffel A, Gogineni S, Poluri A, Pfister DG, Shaha AR, et al. Amplification of the 3q26.3 locus is associated with progression to invasive cancer and is a negative prognostic factor in head and neck squamous cell carcinomas. *Am J Pathol.* (2002) 161:365–71. doi: 10.1016/S0002-9440(10)64191-0
38. Lui VW, Hedberg ML, Li H, Vangara BS, Pendleton K, Zeng Y, et al. Frequent mutation of the PI3K pathway in head and neck cancer defines predictive biomarkers. *Cancer Discov.* (2013) 3:761–9. doi: 10.1158/2159-8290.CD-13-0103
39. Cai Y, Dodhia S, Su GH. Dysregulations in the PI3K pathway and targeted therapies for head and neck squamous cell carcinoma. *Oncotarget* (2017) 8:22203–17. doi: 10.18632/oncotarget.14729
40. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. *Nat Rev Cancer* (2015) 15:7–24. doi: 10.1038/nrc3860
41. Wirtz ED, Hoshino D, Maldonado AT, Tyson DR, Weaver AM. Response of head and neck squamous cell carcinoma cells carrying PIK3CA mutations to selected targeted therapies. *JAMA Otolaryngol Head Neck Surg.* (2015) 141:543–9. doi: 10.1001/jamaoto.2015.0471
42. Geiger JL, Bauman JE, Gibson MK, Gooding WE, Varadarajan P, Kotsakis A, et al. Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma. *Head Neck* (2016) 38:1759–64. doi: 10.1002/hed.24501
43. Grunwald V, Keilholz U, Boehm A, Guntinas-Lichius O, Hennemann B, Schmoll HJ, et al. TEMHEAD: a single-arm multicentre phase II study of temsirolimus in platin- and cetuximab refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) of the German SCCHN Group (AIO). *Ann Oncol.* (2015) 26:561–7. doi: 10.1093/annonc/mdu571
44. Massarelli E, Lin H, Ginsberg LE, Tran HT, Lee JJ, Canales JR, et al. Phase II trial of everolimus and erlotinib in patients with platinum-resistant recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol.* (2015) 26:1476–80. doi: 10.1093/annonc/mdv194
45. Bauman JE, Arias-Pulido H, Lee SJ, Fekrazad MH, Ozawa H, Fertig E, et al. A phase II study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory head and neck squamous cell carcinoma. *Oral Oncol.* (2013) 49:461–7. doi: 10.1016/j.oraloncology.2012.12.016
46. Jimeno A, Bauman JE, Weissman C, Adkins D, Schnadig I, Beauregard P, et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Oral Oncol.* (2015) 51:383–8. doi: 10.1016/j.oraloncology.2014.12.013
47. Jimeno A, Shirai K, Choi M, Laskin J, Kochenderfer M, Spira A, et al. A randomized, phase II trial of cetuximab with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Ann Oncol.* (2015) 26:556–61. doi: 10.1093/annonc/mdu574
48. Soulieres D, Faivre S, Mesia R, Remenar E, Li SH, Karpenko A, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Oncol.* (2017) 18:323–35. doi: 10.1016/S1470-2045(17)30064-5
49. Fayette J, Digue L, Ferlay C, Treilleux I, Garin G, Wang Q, et al. eds. *PIK-ORL: A Phase II, Multicenter Trial Aiming to Evaluate BKM120 in Monotherapy in Patients With Metastatic/Recurrent Head and Neck Squamous Cell Carcinoma.* Copenhagen: ESMO (2016).
50. Soulieres D, Licitra L, Mesia R, Remenar E, Li SH, Karpenko A, et al. Molecular alterations and buparlisib efficacy in patients with squamous cell carcinoma of the head and neck: biomarker analysis from BERIL-1. *Clin Cancer Res.* (2018) 24:2505–16. doi: 10.1158/1078-0432.CCR-17-2644
51. De Felice F, Guerrero Urbano T. New drug development in head and neck squamous cell carcinoma: the PI3-K inhibitors. *Oral Oncol.* (2017) 67:119–23. doi: 10.1016/j.oraloncology.2017.02.020
52. Prigge ES, Urban K, Stiegler S, Muller M, Kloor M, Mai S, et al. No evidence of oncogenic KRAS mutations in squamous cell carcinomas of the anogenital tract and head and neck region independent of human papillomavirus and p16(INK4a) status. *Hum Pathol.* (2014) 45:2347–54. doi: 10.1016/j.humpath.2014.08.001
53. Tan DS, Wang W, Leong HS, Sew PH, Lau DP, Chong FT, et al. Tongue carcinoma infrequently harbor common actionable genetic alterations. *BMC Cancer* (2014) 14:679. doi: 10.1186/1471-2407-14-679
54. Su SC, Lin CW, Liu YF, Fan WL, Chen MK, Yu CP, et al. Exome sequencing of oral squamous cell carcinoma reveals molecular subgroups and novel therapeutic opportunities. *Theranostics* (2017) 7:1088–99. doi: 10.7150/thno.18551
55. Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups. *Nat Commun.* (2013) 4:2873. doi: 10.1038/ncomms3873
56. Al-Hebshi NN, Li S, Nasher AT, El-Setouhy M, Alsanosi R, Blancato J, et al. Exome sequencing of oral squamous cell carcinoma in users of Arabian snuff reveals novel candidates for driver genes. *Int J Cancer* (2016) 139:363–72. doi: 10.1002/ijc.30068
57. Chen X, Makarewicz JM, Knauf JA, Johnson LK, Fagin JA. Transformation by Hras(G12V) is consistently associated with mutant allele copy gains and is reversed by farnesyl transferase inhibition. *Oncogene* (2014) 33:5442–9. doi: 10.1038/onc.2013.489
58. Ho AL, Chau N, Bauman J, Bible K, Chintakuntlawar A, Cabanillas ME, et al. eds. Preliminary results from a phase 2 trial of tipifarnib in Squamous Cell Carcinomas (SCCs) with HRAS mutations. In: *ESMO Annual Meeting.* Munich (2018).
59. Lechner M, Frampton GM, Fenton T, Feber A, Palmer G, Jay A, et al. Targeted next-generation sequencing of head and neck squamous cell carcinoma identifies novel genetic alterations in HPV+ and HPV- tumors. *Genome Med.* (2013) 5:49. doi: 10.1186/gm453
60. Michel L, Ley J, Wildes TM, Schaffer A, Robinson A, Chun SE, et al. Phase I trial of palbociclib, a selective cyclin dependent kinase 4/6 inhibitor, in combination with cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma. *Oral Oncol.* (2016) 58:41–8. doi: 10.1016/j.oraloncology.2016.05.011
61. Douglas A, PJO, Ley JC, Trinkaus K, Neupane PC, Sacco AG, et al. eds. Multicenter phase II trial of palbociclib, a selective cyclin dependent kinase (CDK) 4/6 inhibitor, and cetuximab in platinum-resistant HPV unrelated (-) recurrent/metastatic head and neck squamous cell carcinoma (RM HNSCC). In: *Asco Annual Meeting.* Chicago (2018).
62. Barnes CJ, Ohshiro K, Rayala SK, El-Naggar AK, Kumar R. Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. *Clin Cancer Res.* (2007) 13:4291–9. doi: 10.1158/1078-0432.CCR-06-2040
63. Glisson BS, Tseng J, Marur S, M Shin D, Murphy BA, Cohen EEW, et al. eds. Randomized phase II trial of cixutumumab (CIX) alone or with cetuximab

(CET) for refractory recurrent/metastatic squamous cancer of head and neck (R/M-SCCHN) In: *ASCO Annual Meeting*. Chicago, IL (2013).
64. Ferrarotto R, William WN Jr, Tseng JE, Marur S, Shin DM, Murphy B, et al. Randomized phase II trial of cixutumumab alone or with cetuximab for refractory recurrent/metastatic head and neck squamous cell carcinoma. *Oral Oncol.* (2018) 82:83–90. doi: 10.1016/j.oraloncology.2018.05.014
65. Wu YM, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov.* (2013) 3:636–47. doi: 10.1158/2159-8290.CD-13-0050
66. Szturz P, Budikova M, Vermorken JB, Horova I, Gal B, Raymond E, et al. Prognostic value of c-MET in head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oral Oncol.* (2017) 74:68–76. doi: 10.1016/j.oraloncology.2017.09.009
67. Seiwert T, Sarantopoulos J, Kallender H, McCallum S, Keer HN, Blumenschein G, Jr. Phase II trial of single-agent foretinib (GSK1363089) in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *Invest New Drugs* (2013) 31:417–24.
68. Vokes EE, Worden FPA, Bauman D, Lim JE, Sukari D, Ammar, Rao KAW, et al. eds. A randomized phase II trial of the MET inhibitor tivantinib + cetuximab versus cetuximab alone in patients with recurrent/metastatic head and neck cancer. In: *ASCO Annual Meeting*. Chicago, IL (2015).
69. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell* (2011) 146:904–17. doi: 10.1016/j.cell.2011.08.017
70. Morris LG, Chan TA. Therapeutic targeting of tumor suppressor genes. *Cancer* (2015) 121:1357–68. doi: 10.1002/cncr.29140
71. Zack TI, Schumacher SE, Carter SL, Cherniack AD, Saksena G, Tabak B, et al. Pan-cancer patterns of somatic copy number alteration. *Nat Genet.* (2013) 45:1134–40. doi: 10.1038/ng.2760
72. Heise C, Sampson-Johannes A, Williams A, McCormick F, Von Hoff DD, Kirn DH. ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents. *Nat Med.* (1997) 3:639–45.
73. Selivanova G, Iotsova V, Okan I, Fritsche M, Strom M, Groner B, et al. Restoration of the growth suppression function of mutant p53 by a synthetic peptide derived from the p53 C-terminal domain. *Nat Med.* (1997) 3:632–8.
74. Martinez LA, Naguibneva I, Lehrmann H, Vervisch A, Tchenio T, Lozano G, et al. Synthetic small inhibiting RNAs: efficient tools to inactivate oncogenic mutations and restore p53 pathways. *Proc Natl Acad Sci USA*. (2002) 99:14849–54. doi: 10.1073/pnas.222406899
75. Mohell N, Alfredsson J, Fransson A, Uustalu M, Bystrom S, Gullbo J, et al. APR-246 overcomes resistance to cisplatin and doxorubicin in ovarian cancer cells. *Cell Death Dis.* (2015) 6:e1794. doi: 10.1038/cddis.2015.143
76. Lehmann S, Bykov VJ, Ali D, Andren O, Cherif H, Tidefelt U, et al. Targeting p53 *in vivo*: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. *J Clin Oncol.* (2012) 30:3633–9. doi: 10.1200/JCO.2011.40.7783
77. Roh JL, Kang SK, Minn I, Califano JA, Sidransky D, Koch WM. p53-Reactivating small molecules induce apoptosis and enhance chemotherapeutic cytotoxicity in head and neck squamous cell carcinoma. *Oral Oncol.* (2011) 47:8–15. doi: 10.1016/j.oraloncology.2010.10.011

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REVIEW
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Combining Radiation and Immune Checkpoint Blockade in the Treatment of Head and Neck Squamous Cell Carcinoma

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Head and neck squamous cell carcinoma (HNSCC) is a significant cause of morbidity and mortality worldwide. Current treatment options, even though potentially curative, have many limitations including a high rate of complications. Over the past few years immune checkpoint inhibitors (ICI) targeting cytotoxic lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) have changed treatment paradigms in many malignancies and are currently under investigation in HNSCC as well. Despite improvements in treatment outcomes and the implementation of combined modality approaches long-term survival rates in patients with locally advanced HNSCC remain suboptimal. Accumulating evidence suggests that under certain conditions, radiation may be delivered in conjunction with ICI to augment efficacy. In this review, we will discuss the immune modulating mechanisms of ICI and radiation, how changing the dose, fractionation, and field of radiation may alter the tumor microenvironment (TME), and how these two treatment modalities may work in concert to generate durable treatment responses against HNSCC.

Keywords: radiation therapy, immunotherapy, immune checkpoint inhibitors, PD1, PD-L1, abscopal effect

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INTRODUCTION

Head and neck cancer is the sixth most common cancer worldwide, with ∼600,000 newly diagnosed cases and 350,000 deaths annually (1). The vast majority of these cancers are squamous cell carcinomas. Most patients with HNSCC present with locally advanced disease and are usually managed with combined modality therapy often incorporating radiation therapy (RT) and chemotherapy. Despite this, ∼50% of patients with high-risk disease experience disease recurrence within 3 years of follow up (2, 3). Those who do develop a recurrence have limited treatment options that are often associated with significant morbidity and poor prognosis, emphasizing the need for alternative treatment options (4).

It is now well-accepted that the immune system plays an important role in preventing tumor development and progression. Our growing understanding of adaptive immune responses has led to the discovery of various checkpoints that are often exploited by cancer to evade immune mediated destruction. Immune checkpoint inhibitors have therefore been developed with the goal of overcoming this form of immune-evasion and are currently in clinical use for various disease sites including those of the head and neck. Indeed, numerous clinical trials have demonstrated

improvement in overall survival (OS) and progression free survival (PFS) with the use of these agents in both the metastatic and locally-advanced disease setting. Unfortunately, only 20–30% of patients typically respond to treatment, and even fewer have responses that persist beyond 6 months (5).

Radiation therapy is a fundamental modality in the treatment of HNSCC. While the immune modulating properties of RT were first reported in the 1970s (6), harnessing this affect to faithfully produce meaningful clinical responses has proven difficult. Recent case reports describing systemic disease responses after combined RT and ICI however has led to the hypothesis that combined therapy may work synergistically to improve treatment outcomes (7, 8).

The goal of this review is thus to discuss the roles of combined ICI and radiation in the treatment of HNSCC. First, we performed a thorough literature search to include peer reviewed preclinical studies and reviews that highlight the current understanding of the immune system's role in tumor development and the importance of checkpoints in curtailing the immune response. Next, we discuss the tumoricidal effects of radiation, how it modulates the immune response, and how dose, fractionation, and field size can potentially affect treatment outcomes. Lastly, we examine the findings of various clinical trials registered on www.clinicaltrials.gov and that have either been published in peer reviewed journals or presented at societal meetings, that investigate combined therapy and their implications for the future management of HNSCC.

IMMUNE CHECKPOINT INHIBITION AND ITS ROLE IN TUMOR IMMUNITY

Initially proposed by Paul Ehrlich over 100 years ago and formally defined by Burnet and Thomas some 50 years later, it is now accepted that the immune system actively protects the host from neoplastic processes, a phenomenon known as cancer immunoediting (9, 10). A full discussion of this hypothesis is reviewed in detail elsewhere (11–15).

Suffice it to say that cluster of differentiation (CD)8^+ cytotoxic T lymphocytes (CTLs) are instrumental to the immunoediting process. These cells have evolved to detect intracellular antigens, including those from viral pathogens, which are displayed on the cell surface by major histocompatability (MHC) class I molecules. Antigenic peptides are recognized by the T cell receptor (TCR) which is specific for a single antigen. Engagement of the TCR by the peptide-MHC class I complex triggers T cell mediated apoptosis of the target cell via release of cytotoxic granules containing perforin and granzymes, release of cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, and direct interactions via Fas-Fas ligand (16, 17).

Given the highly destructive nature of CTLs, their activation and activity are tightly regulated via so-called immune-checkpoints. They first require activation, or priming, by antigen presenting cells (APC)s which consists of three signals and typically occurs in draining lymph nodes (DLN). Signal one is engagement of the TCR with the peptide-MHC class I complex on the surface of the APC. Signal 2 occurs through binding of the co-stimulatory molecules CD80/CD86 (also known as B7-1 and B7-2, respectively) by the APC with CD28 expressed by the T cell. Signal 3 occurs when interleukin (IL)-2 binds to CD25 on the T cell in an autocrine fashion promoting progression through the cell cycle (18, 19).

Modulation of the immune response can occur at signal 2 through the competitive binding of CD28 by CTLA-4, also known as CD152. CTLA-4 has a 500–2,500-fold higher binding affinity compared with CD80/86 and results in decreased IL-2 production, decreased CTL proliferation, and arrest of T cell activation (20). CTLA-4 blockade improves antitumor immunity by shifting the balance back toward immune activation (21). Ipilimumab, a monoclonal antibody that inhibits CTLA-4, has demonstrated improvements in PFS, OS, response rates, and response duration in patients with either metastatic or locally advanced melanoma in two separate Phase III clinical randomized trials and has demonstrated activity in multiple other disease types (22, 23).

Once activated the CTL will circulate in the periphery, searching for any cell expressing its cognate antigen. Recognition of antigen will result in T-cell directed apoptosis as described above. The target cell however can once again evade destruction through the expression of PD-L1. PD-L1 is additionally expressed by monocytes, regulatory T cells (Tregs), B cells, dendritic cells, and other tumor infiltrating lymphocytes. Engagement of PD-L1 with its receptor, PD-1, expressed by CTLs upon activation, triggers an intracellular cascade that interferes with TCR/CD28 signaling. This in turn results in decreased cytokine production and inhibits cell cycle progression. Chronic exposure to PD-1 signaling generates T cell exhaustion and tolerance even in the face of "actionable antigens" (24, 25). While constitutive expression of PD-L1 by healthy cells prevents unintended injury to surrounding bystander cells, its exploitation by cancers, such as melanoma and HNSCC, contributes to evasion of immune-mediated killing. Monoclonal antibodies targeting either PD-1 (nivolumab, pembrolizumab, cemiplimab) or PD-L1 (atezolizumab, avelumab, durvalumab) have therefore been developed to overcome this mechanism of resistance. In early clinical trials, several of these agents have demonstrated efficacy in various disease sites including colorectal cancer, non-small cell lung cancer, melanoma, renal cell carcinoma and will be discussed in greater detail below.

THE MECHANISM OF ACTION OF RADIATION THERAPY

Radiation as a Therapeutic Modality

Radiotherapy is the use of high energy electromagnetic waves (X-rays or γ-rays), charged particles (electrons, protons, or alpha particles), or other modalities to treat both malignant and benign diseases (26). Absorption of ionizing radiation, measured in Gray (Gy), by biologic tissue causes deoxyribonucleic acid (DNA) strand breaks, either directly or indirectly via the generation of reactive oxygen species (ROS), resulting in cell death via autophagy, necrosis, or apoptosis. In order to minimize normal-tissue toxicity, the total dose of radiation needed to achieve tumor

kill is often "fractionated" into smaller doses, typically delivered in a daily fashion (26). While variable depending on the tumor type, location, or presence of gross disease, doses of 50–70 Gy are delivered in 1.5–2.25 Gy per fraction for cancers of the head and neck.

Technological advancements in the delivery of external beam radiation therapy including CT-based inverse planning, multi-leaf collimation, patient immobilization, and active image guidance, have led to the development of techniques such as stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) which allow for the precise delivery of very high doses of radiation in 1 to 5 fractions. These techniques are currently in use for the treatment of brain and bone metastases, early stage non-small cell lung cancer, pancreatic cancer, prostate cancer, and recurrent head and neck cancers (27–30). While these high doses of radiation result in irreversible lethal DNA damage, both preclinical and clinical data now suggest that changes in the TME may also contribute to tumor control (31).

How RT Promotes an Anti-tumor Immune Response

The tumoricidal effects of RT appear to at least in part be dependent on an intact immune system. In 1979, Slone et al. demonstrated that thymectomized mice required twice the dose of radiation to achieve cure compared with mice with intact immune systems (6). Effects of RT on the immune response have been seen in antigen presentation, effector T cell recruitment, creation of an immunosuppressive tumor microenvironment, and the expression of immune checkpoint receptors.

The Importance of Adjuvant Signaling

Similar to how T cells require multiple signals for successful priming, dying cells need to express both exogenous or mutated antigens as well as adjuvant signals in order to elicit an antigen specific immune response. This may in part explain why cells undergoing accidental necrosis, such as that from freeze thawing or osmotic shock, fail to generate protective immunity (32–35). The adjuvant signals in question come in the form of damage-associated molecular pattern (DAMP)s such as adenosine triphosphate (ATP), high mobility group protein 1 (HMGB1), and calreticulin (CRT), which bind to their respective pattern recognition receptors (PRR)s. After RT, CRT is upregulated by irradiated tumor cells which acts as a pro-phagocytic signal via CD91 on activated APCs. Meanwhile, HMGB1, which is also elevated after RT, binds to TLR4 receptors on dendritic cells (DC) resulting in increased activation. These activated APCs begin taking up antigen and promote CTL cross-priming as discussed above (**Figure 1**) (35–38).

Chemotherapies, such as paclitaxel and oxaliplatin, have also been shown to promote immunogenic cell death (ICD) via CRT, ATP, HMGB1, and various heat shock proteins (33). Combined with radiation, Golden et al. demonstrated that platinums and taxanes increase the pro-immunogenic repertoire from dying tumor cells that could facilitate host anticancer immune responses (36). Interestingly cisplatin (CDDP), an alkylating agent commonly used concurrently with RT in treating HNSCC and is in the same drug class as oxaliplatin, fails to induce ICD. This is likely due to cisplatin's inability to trigger CRT translocation from the lumen to the endoplasmic reticulum (ER), a process which is dependent on the phosphorylation of eukaryotic translation initiation factor 2α (eIF2α), the formation of ER stress, and initiation of macroautophagy. The authors however demonstrate that tumor immunogenicity with CDDP is possible through the addition of an ER stress inducer such as tunicamycin (39).

The Importance of Antigenicity

As mentioned earlier, antigenicity, in the form of neo-antigens, in combination with strong adjuvant signals is required to generate a robust adaptive immune response. This has been observed in human malignancies with a high mutational burden due to mismatch repair deficiency. Specifically, patients with mismatch repair deficient colorectal cancers who were treated with pembrolizumab experienced a statistically significant improvement in immune-related progression free survival of 78% compared with 11% in those whose tumors were mismatch repair-proficient (40).

Tumors with a *low* mutational burden however may become antigen rich through the addition of radiation. Reits et al. demonstrated that RT induced the expression of unique proteins involved in DNA repair, cell cycle check-points, apoptosis, and protein degradation, that were subsequently loaded and presented by host MHC class I molecules to effector T cells (41). Similarly, a study by Garnett et al. assessing the responses of 23 human cancer cell lines after non-lytic doses of radiation found that 91% up-regulated one or more surface molecules involved in CTL mediated killing (42).

Of course, immune responses can be provoked against foreign antigens such as viral DNA. As a large subset of HNSCC stem from either human papilloma virus (HPV) or Epstein Barr virus (EBV) infections, these types of antigens may play an important role in immune stimulation. Thus taken together, these studies suggest that radiation may act as an *in situ* vaccine (43).

Once activated CTLs depend on recognition of their cognate antigen presented via MHC class I molecules on the host cell to initiate cell killing. One method used by malignant cells to evade CTL mediated killing is by downregulating and impairing MHC class I peptide presentation (44, 45). Radiation however upregulates MHC expression in various human cancer cell lines (46–48). This process however may be dose dependent as MHC class I expression in a melanoma cell line increased over 2-fold at doses of ionizing radiation of 10–25 Gy but not at doses of 1 or 4 Gy (41).

Radiation Triggers Increased Cytokine and Chemokine Secretion

Radiation also leads to an increased release of cytokines and chemokines which promotes T cell trafficking and priming (49). This is initiated through the detection of DNA damage by cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS). The binding of non-sequence specific DNA to cGAS triggers the synthesis of cyclin GMP-AMP (cGAMP) which in turn acts as a messenger that binds to the ER-membrane adaptor stimulator of interferon genes (STING).

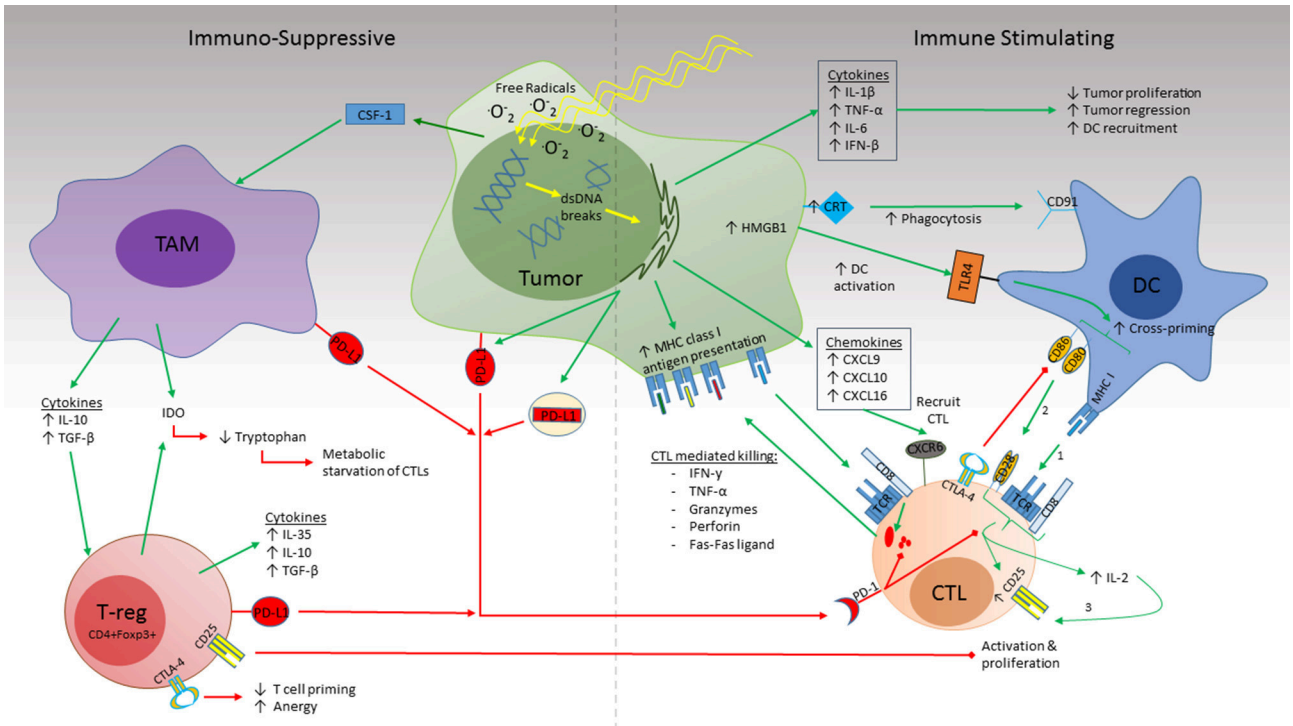

FIGURE 1 | Radiation simultaneously induces immune suppression and immune activation in the TME. RT induces dsDNA damage both directly and indirectly by ROS formation. Activation (**Right**): RT triggers release of the cytokines IL-1β, TNF-α, and IL-6 which promote inflammation and inhibit tumor proliferation while IFN-β promotes DC recruitment. CRT expression by the irradiated tissue binds to CD91 on DCs which promotes phagocytosis. Increased antigen uptake by DCs and activation by HMGB1 binding to TLR4 leads to CTL cross priming in draining lymph nodes. Recognition of cognate antigen by the naïve CTL provides Signal 1 required for CTL maturation. Co-stimulation (signal 2) by CD80/86 on the DC with CD28 on the CTL leads to upregulation of the high-affinity IL-2 receptor, CD25, as well as IL-2 secretion by the CTL which promotes T cell proliferation and survival. Release of the chemokines CXCL9, CXCL10, and CXCL16 recruit activated CTLs to the TME which recognize their cognate antigen via MHC class I molecules on the tumor surface. This in turn initiates cytolysis via release of cytokines (IFN-γ, TNF-α), cytotoxic granules (Granzymes, perforins), and direct cell-cell interactions (Fas-Fas ligand). Suppression (**Left**): CSF-1 promotes recruitment of TAMs to the TME. Production of IL-10 and TGF-β by the TAM promotes Treg recruitment. Together, release of IDO enhances tryptophan consumption resulting in CTL starvation. PD-L1 expression by tumor, TAMs, and Tregs impairs cytotoxicity of activated CTL and promotes exhaustion. Expression of CD25 by Tregs competes with CTL uptake of IL-2 thus indirectly impairing CTL proliferation and survival. CTLA4 expressed by both Tregs and DCs competes with CD80/CD86 for CD28 co-stimulation (signal 2) thus preventing CTL activation and promoting anergy.

Through a series of phosphorylation reactions, STING ultimately leads to the activation of the transcription factors interferon regulatory factor 3 (IRF3) and nuclear factor-kB (NF-kB) (50, 51). These transcription factors then travel to the nucleus where they induce the expression of type 1 interferons, IL-1β, IL-6, and TNF-α up to 6 h after radiation (52, 53) (**Figure 1**). Of these cytokines, the type 1 interferon, IFN-β, is critical in producing the antitumor immunity of RT; type 1 IFN knockout mice exhibited abrogated T cell priming compared with their wild-type controls (54). Furthermore, STING deficient mice fail to reject tumor after local radiation highlighting the importance of the cGAS-STING signaling pathway in RT tumor immunity (55).

Ionizing radiation also upregulates chemokines such as CXC-motif chemokine 9 (CXCL9), and CXCL10, which are involved in the recruitment of activated $CD8^+$ T cells (56). CXCL16, which recruits CXCR6 expressing Th1 and $CD8^+$ effector T cells, is upregulated by both mouse and human breast cancer cells; CXCR6 deficient mice experienced impaired tumor regression and decreased $CD8^+$ T cell infiltration after irradiation (57, 58). IFN-γ produced after RT has also been shown to enhance MHC class I expression and CTL trafficking (38, 59).

How RT May Suppress the Anti-tumor Immune Response

Like a double-edged sword radiation can also create an immunosuppressive environment through the recruitment of tumor associated macrophages (TAMs), myeloid derived suppressor cells (MDSCs), and $CD3^+CD4^+CD25^+Foxp3^+$ Tregs (**Figure 1**). TAM recruitment is dependent on colony stimulating factor (CSF)-1 which is increased after radiation. Once present, TAMs secrete IL-10 and transforming growth factor-β (TGF-β) which inhibits DC maturation and promotes Treg activation, induce T cell anergy via PD-L1 expression, and create metabolic starvation by expression of indoleamine-pyrrole 2,3-dioxygenase (IDO) (60, 61). Meanwhile, Tregs promote immunosuppression by consumption of IL-2 which is necessary for CTL activation, secretion of IL-10, TGF-β, and IL-35, expression of IDO, and upregulation of CTLA-4 which competes

with CD28 binding of B7.1 and B7.2 necessary for T cell priming by APCs (38, 62, 63).

Preclinical models also suggest that Tregs may be radioresistant compared to their CTL counterparts. Using the murine TRAMP C1 model of prostate cancer in mice treated with and without RT, Kachikuwu et al. demonstrated an increased number of Tregs after both local and whole body radiation. In fact these cells persisted in the spleen after doses as high as 20 Gy and maintained their suppressive potential *in vitro* (64, 65). Furthermore, Schaue et al. demonstrated that Treg recruitment may be based on radiation dose. Using a mouse model of melanoma treated with varying doses of radiation revealed that a dose of 15 Gy resulted in a higher proportion of regulatory T cells compared with 5 Gy (66). Fractionation did not appear to have significant effect on Tregs however.

Dovedi et al. showed that radiation at dose of 10 Gy in 5 fractions resulted in upregulation of PD-L1 expression in mouse models of melanoma, colorectal cancer, and triple negative breast cancer. Expression changes were detected as early as 1 day after RT, peaking at 72 h before returning to baseline levels at day 7. This phenomenon was dependent on $CD8^+$ T cell production of IFN-γ (67). RT also has been shown to increase PD-1 expression on $CD8^+$ and $CD4^+$ T cells (68). In humans, PD-L1 expression was significantly increased in patients with previous concurrent chemoradiotherapy for locally advanced esophageal cancer. This was correlated with poorer OS compared to patients with lower PD-L1 levels (69).

THE POTENTIAL IMPORTANCE OF RADIATION DOSE AND FRACTIONATION

In 2009, Lee et al. demonstrated that in a B16 melanoma mouse model, a single ablative dose of 20 Gy led to tumor regression that corresponded to an increase in infiltrating T cells to the TME and lymphoid tissue. In the same study, using a metastatic breast cancer model, single fraction ablative radiation (between 15 and 25 Gy) led to complete resolution of distant lung metastases. The response however was abrogated when the radiation was fractionated, specifically 20 Gy in 4 fractions, over 2 weeks (70). These findings were partially confirmed by Schaue et al. in a study where B16-OVA mice were treated with either 5, 7.5, 10, or 15 Gy delivered in a single fraction. Tumor regression was observed at doses higher than 5 Gy. In contrast to the findings by Lee, fractionating the dose into either 5, 3, or 2 fractions had superior tumor responses (66).

Vanpouille-Box et al. offer a mechanism that may explain this response. Using the TSA mouse breast cancer model, they demonstrated that one or three 8 Gy doses of radiation increases the production of double stranded DNA compared with either 20 or 30 Gy single fraction doses. At these higher single fraction doses, an elevation in the exonuclease, Trex1, which plays an essential role in clearing cytoplasmic DNA, was detected. Knocking down Trex1 expression abrogated the abscopal response. The threshold for Trex1 upregulation ranged from 12 to 18 Gy across various mouse and human carcinoma cell lines. Additionally, increasing amounts of cytoplasmic dsDNA triggered the release of IFN-β, which is involved in DC recruitment. This was significantly increased in the 8 Gy times 3 regimen vs. any of the single fraction schemes and was critical in eliciting anti-tumor T cell responses (71).

COMBINING RADIATION AND IMMUNOTHERAPY

To determine whether immune checkpoint blockade can enhance the response to radiation, Demaria et al. utilized the 4T1 mouse mammary model and treated mice with either a monoclonal antibody against CTLA-4 (9H10) alone, RT (24 Gy in 1 or 2 fractions) to the primary tumor alone, or RT in combination with 9H10. Anti-CTLA4 therapy alone did not delay tumor growth or improve survival whereas RT alone delayed growth of the primary lesion. Combination therapy significantly improved OS and resulted in fewer lung metastases. Depletion of $CD8^+$ and $CD4^+$ T cells confirmed that this process was depended on the presence of $CD8^+$ T cells (72).

PD-1 blockade similarly enhances anti-tumor responses. Using the CT26 murine colon cancer cell line, Dovedi et al. obtained survival rates of 66% and 80% with fractionated RT (10 Gy in 5 fractions) combined with either a PD-1 or PD-L1 inhibitor, respectively. This synergistic response was dependent on the sequencing of therapies. Improvement in OS was only observed when anti-PD-L1 therapy was given concurrently, starting either on day 1 or 5, with fractionated RT as opposed to adjuvantly, 7 days after the completion of RT. Since fractionated RT can induce PD-1 expression in tumor infiltrating $CD4^+$ and $CD8^+$ T cells hours after treatment, checkpoint blockade administered at this time likely blocks the PD-1/L1 signaling axis thereby augmenting T cell responses and preventing T cell anergy (67).

The efficacy of immunotherapy is also affected by radiation dose fractionation. Using the TSA mouse breast cancer model, Dewan et al. implanted tumors at two separate sites. Established tumor at one site was treated with either 20 Gy in a single fraction, 24 Gy in 3 fractions, or 30 Gy in 5 fractions with or without the addition of 9H10. Combination therapy with fractionated radiation, but not single fraction RT, resulted in almost complete tumor regression and significantly delayed growth in the non-irradiated tumor. Interestingly, 24 Gy in 3 fractions was significantly more effective than 30 Gy in 5 fractions at inhibiting tumor growth and generating tumor specific $CD8^+$ CTL responses (73, 74).

Taken together, the preclinical data suggests that 14–24 Gy delivered in 2–3 fractions with concurrent ICI may be the optimal dose and fractionation of radiation, and sequencing of therapies for generating robust anti-tumor CTL responses. Whether this is true in humans as well remains to be elucidated.

THE POTENTIAL IMPORTANCE OF FIELD SIZE AND ELECTIVE NODAL IRRADIATION

Another consideration for the radiation-oncologist, in addition to dose and fractionation, is determination of targets and field size. To aid with target delineation, the international commission

on radiation units (ICRU) developed the concept of gross target volume (GTV), clinical target volume (CTV), and planning target volume (PTV). In brief, the GTV covers all gross disease observed on physical exam and on imaging studies. The CTV encompasses the GTV plus an additional margin ranging from a few millimeters to several centimeters with the goal of covering areas of suspected subclinical disease or disease extension. The PTV is a margin added to the CTV which accounts for errors in daily patient positioning and instrument accuracy which may in turn affect target location (75). As these margins are applied volumetrically, it quickly becomes apparent that their summation leads to a field size that is substantially larger than the tumor.

From an immunologic perspective, the effects of exposing large volumes of healthy tissue to radiation remains unclear. For instance, lymphocytes that traverse through this defined margin of unaffected tissue to reach the tumor may be eradicated by radiation before they are able to illicit an effective anti-tumor response. Injury to the healthy neighboring tissue itself may also promote an anti-inflammatory environment through the secretion of cytokines and the upregulation of immunosuppressive markers such as PD-L1 in an attempt to protect itself from immune mediated killing, thus stifling immune responses even further. SRS and SBRT, techniques which often limit margin sizes to only a few millimeters, may be one way to mitigate these potential complications while preserving the tumoricidal and immune stimulating effects of radiation and is an ongoing area of investigation.

In an attempt to prevent regional disease recurrence, radiation-oncologists will often treat DLN regions that are at high risk for disease based on findings from historical surgical series and analysis of recurrence patterns. This technique is termed elective nodal irradiation (ENI) and when employed, is considered part of the CTV. Given the extensive lymphatic drainage of the head and neck, ENI is commonly used when treating in either the adjuvant or definitive setting despite a surgically negative or clinically negative neck, respectively. The DLN however are one of the major locations where DC priming of CTLs occurs and is therefore essential in generating tumor specific $CD8^+$ T cell responses. In fact, Sharabi et al. demonstrated that the DLN are the primary site for the cross-presentation of MHC class I tumor antigens seen after stereotactic radiation and can be enhanced by either anti-PD-1 therapy or ablation of Tregs (76). Thus, surgical ablation and ENI may actually curtail the efficacy of immunological responses. In fact, Takeshima et al. demonstrated that the generation of tetramer positive tumor specific CTL were significantly reduced after radiation in mice whose DLN were either surgical removed or genetically defective compared with mice whose DLN were intact (77). Recently, Marciscano et al. demonstrated that mice that underwent irradiation of both the tumor and DLNs experienced a statistically significant reduction in the number of intratumoral antigen specific $CD8^+$ effector T cells compared with those receiving irradiation of the tumor alone. This was in part mediated by a decrease in chemokine expression [C-C Motif Chemokine Ligand 5 (CCL5), CXCL10, and CCL3]. Survival was significantly worse in animals receiving radiation to the tumor and DLN compared with those receiving RT to the tumor alone when treated with concurrent immune checkpoint blockade (78). Thus, taken together, these pre-clinical studies suggest that perhaps avoiding both the surgical removal and irradiation of DLN may be necessary to maximize the immunogenic response to combined radiation and immunotherapy. Whether this is true in humans however has yet to be ascertained.

While the immune stimulating potential of these techniques are intriguing, it is important for the reader to bear mind that changes in dose, reduction of margins, and omission of elective lymph node irradiation may come at the cost of local tumor control and thus goes against the current standard of care. These factors however warrant additional investigation and should be considered as evaluable metrics in future clinical trials.

CLINICAL TRIALS EVALUATING IMMUNE MODULATION IN HNSCC

While HNSCCs are most commonly caused by either viral infection (HPV, EBV), tobacco use, and/or alcohol consumption, its progression is closely linked to immune escape. Thus, it stands to reason that mechanisms such as immune checkpoint blockade, which are aimed at overcoming self-tolerance and reengaging the immune system, may lead to tumor eradication and improved long term control. This strategy has already shown promise in clinical trials outside of the head and neck area, (79–81), and as PD-L1 is expressed in anywhere from 46 to 100% of cases depending on cut off for positivity and detection technique, the use of anti-PD-1/L1 therapy also has a biological basis in HNSCCs (82, 83).

Nivolumab, a human IgG4 monoclonal antibody against PD-1, was tested in a phase III open-label clinical trial (CheckMate 141) in 361 patients with recurrent or metastatic HNSCC who experienced disease progression within 6 months of receiving platinum-based chemotherapy. Patients were randomized to receive either nivolumab (at a dose of 3 mg per kilogram of body weight every 2 weeks) or investigator's choice single-agent standard therapy consisting of either methotrexate, docetaxel, or cetuximab. OS was significantly improved in the nivolumab arm: median OS was 7.5 months [95% confidence interval (CI), 5.5 to 9.1] with nivolumab vs. 5.1 months (95% CI, 4.0 to 6.0) with standard therapy. The rate of grade 3 and 4 adverse events was significantly lower with nivolumab (13.1%) compared with the standard arm (35.1%), without deterioration of patient reported quality of life scores (4).

KEYNOTE-040 was a similar open-label, phase III clinical trial including 495 patients with recurrent or metastatic HNSCC after a platinum-based chemotherapy which used pembrolizumab, another PD-1 monoclonal antibody. Patients were randomized to either monotherapy with pembrolizumab or standard of care chemotherapy. While the final publication is still pending at the time of this writing, the results were initially presented at the European Society of Medical Oncology meeting in 2017. Despite a 19% improvement in OS compared with standard of care therapy, the study failed at that time to reach its primary endpoint which was pre-specified to detect significance with a hazard ratio of 0.80. However, patients with

PD-L1 expression levels >50% had significant improvement in OS with the use of pembrolizumab vs. standard chemotherapy, 11.6 vs. 7.9 months, respectively (HR = 0.54; 95% CI = 0.35 to 0.82, $p = 0.0017$). As additional survival data for this patient population was collected, updated information using the same data cutoff date was presented at the American Association for Cancer Research Annual Meeting in 2018. With the more complete dataset, the HR for OS now reached 0.8 ($p = 0.0161$), reinforcing the utility of pembrolizumab for platinum-refractory recurrent or metastatic HNSCC (84).

While nivolumab and pembrolizumab target the PD-1 receptor, durvalumab targets the PD-1 ligand (PD-L1). In an open-label phase I/II multicenter trial, durvalumab was tested in multiple solid tumor subtypes including HNSCC. Specifically, 62 patients with recurrent or metastatic disease were treated with durvalumab at 10 mg/kg every 2 weeks for 12 months. Overall response rate was 12% and as high as 25% in patients with PD-L1 positivity. Again, ICI was well-tolerated, with Grade 3 or higher toxicity being reported in only 7% of patients (85). The HAWK study, an international phase II trial evaluating the objective response rates of durvalumab in 111 immunotherapy-naïve patients with platinum refractory recurrent/metastatic HNSCC with ≥25% PD-L1 expression, revealed a response rate of 16.2% in HPV positive patients and 10.9% in HPV negative patients. PFS and OS were 2.1 and 7.1 months, respectively. Adverse events of any grade was 57.1 and 8% for greater than grade 3 toxicity (86). Lastly, a phase II randomized trial in recurrent or metastatic patients with PD-L1 low or negative tumors (<25% expression on tumor cells) known as CONDOR failed to demonstrate enhanced efficacy of adding the CTLA-4 antibody tremelimumab to single agent durvalumab (ORR 7.8% vs. 9.2% for combination therapy and monotherapy, respectively) (87).

The successes of ICI therapy in the second line metastatic and recurrent setting has spurred significant interest in the use of PD-1 and PD-L1 ICIs in the first line for recurrent and/or metastatic disease as well as in locally advanced disease. Recently, the results from KEYNOTE 048, a 3-arm phase III trial using either pembrolizumab monotherapy, pembrolizumab in combination with platinum and 5-FU, or standard of care platinum and 5-FU plus cetuximab ("EXTREME" regimen) in the first-line treatment of recurrent or metastatic HNSCC, were presented. The primary endpoints included OS and PFS in all patients as well as in patients with positive PD-L1 expression as defined by a combined positive score (CPS), which includes the total number of PD-L1 stained cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells in a field multiplied by 100. For CPS ≥20%, patients treated with pembrolizumab had a median OS of 14.9 months vs. 10.7 months for patients treated with the EXTREME regimen ($p = 0.00007$). In all patients, regardless of CPS, when pembrolizumab was added to a chemotherapy backbone of platinum and 5-fluorouracil patients had longer OS than if they were treated with EXTREME (median OS 13.0 months vs. 10.7 months, $p = 0.0034$). Additional analyses including the efficacy of these treatments in CPS <1 patients, the use of second-line treatments in each arm, and the impact of HPV have not yet been reported (88).

Combining Radiation and Immunotherapy in the Clinic

As discussed above, pre-clinical studies clearly demonstrate that radiation modulates the immune system in ways that, when combined with immunotherapy, has the potential to augment treatment responses. In the clinic, this has been demonstrated through development of what is known as the abscopal ("ab" - away from, "scopus"- target) response. First coined by R H mole in 1953, it describes a phenomenon that can occur when localized radiation therapy induces regression of disease at a distant site. In 2012, Michael Postow published a case report of a patient with metastatic melanoma who demonstrated disease progression after being on treatment with ipilimumab for over a year. She subsequently underwent a course of palliative SBRT, 28.5 Gy in 3 fractions, to a single painful paraspinal lesion, followed by an additional dose of ipilimumab 1 month later. Post treatment imaging at 3 months revealed regression of the irradiated lesion as well as the non-irradiated areas of disease in the hilum and spleen. This corresponded to increased antibody titers for NY-ESO-1, an antigen frequently expressed by melanoma, as well as an increase in effector $CD4^+$ T cells (8). Together these findings suggest that radiation triggered antigen release that with the addition of ipilimumab was able to generate a systemic immune response.

The data on efficacy of combined therapy in the clinical setting is still lacking while many trials are underway. A small retrospective study assessed treatment outcomes of 37 patients on immunotherapy (nivolumab 83.8%, atezolizumab 10.8%, pembrolizumab 5.4%) with brain metastases receiving SRS to a total of 85 lesions. They demonstrated that patients treated with concurrent SRS and ICI had longer OS and reduced rates of distant brain failure (DBF) than those who received SRS either before or after starting ICI (1 year OS, 87.3% vs. 70.0% vs. 0%, $p = 0.008$; 1 year DBF, 38.5% vs. 65.8% vs. 100%, $p = 0.042$). Additionally, local control was significantly improved with combination therapy at 1 year (100% vs. 72.3%, $p = 0.016$) (89).

Despite the excitement generated by this report, concerns about the possibility of increased toxicity with combined therapy exist (90). For instance, a recent retrospective review from the Dana Farber Cancer Institute examined 480 cases of patients with newly diagnosed brain metastases treated with SRS, 115 of whom were also on treatment with checkpoint inhibitors (ipilimumab, pembrolizumab, or nivolumab). Patients who received ICI were 2.5 times more likely to develop radionecrosis; the highest risk (HR 4.7) was in patients with melanoma receiving ipilimumab (91).

Combining Radiation and Immunotherapy in Head and Neck Cancer

With regards to HNSCC, the majority of available clinical data currently focuses on the safety of combining ICI and radiation. Preliminary toxicity results have been published from GORTEC 2015-01 ("PembroRad").This phase II trial randomized patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC) who were unfit to receive cisplatin to either

TABLE 1 | Clinical trials incorporating checkpoint inhibitors and radiation therapy in head and neck squamous cell carcinoma.

NCT ID#	Phase	Title	ICI	Treatment arms
PHASE 1				
NCT03539198	NA	A prospective observational study of study of proton SBRT and immunotherapy for recurrent/progressive locoregional or metastatic head and neck cancer	Nivolumab	Loading dose of Nivolumab on D-14 then concurrently w/RT; Proton SBRT 5 fxs; 35–45 Gy)
NCT02764593	1	Safety Testing of Adding Nivolumab to Chemotherapy in Patients With Intermediate and High-Risk Local-Regionally Advanced Head and Neck Cancer	Nivolumab	Loading dose on D-14 then concurrently w/cisplatin or cetuximab and RT, followed by adjuvant ICI; 70 Gy in 35 fxs; IMRT
NCT03402737	1	SBRT + Immunomodulating Systemic Therapy for Inoperable, Recurrent Head and Neck Cancer	Nivolumab	Concurrently w/RT; 6–8 Gy times 2 fxs 6–8 Gy times 3 fxs 6–10 Gy times 3 fxs 6–12 Gy times 3 fxs
NCT02318771	1	Radiation therapy and MK-3475 for patients with recurrent/metastatic head and neck cancer, renal cell cancer, melanoma, and lung cancer	Pembrolizumab	Arm A: Adjuvant (3–17 days post RT); Arm B: Concurrent; A1 and B1: 8 Gy in 1 fx Arms A2 and B2: 20 Gy in 5 fxs
NCT02586207	1	Pembrolizumab in combination with CRT for LA-SCCHN	Pembrolizumab	Loading dose on D-7 then concurrent q3 weeks with cisplatin-RT; 70 Gy in 35 fxs
NCT02819752	1	Pembrolizumab combined with chemoradiotherapy in squamous cell carcinoma of the head and neck (PEACH)	Pembrolizumab	Concurrently with CRT; Standard therapy
NCT03509012	1	Immunotherapy in combination with chemoradiation in patients with advanced solid tumors (CLOVER)	Durvalumab	Various regimens
NCT02938273	1	Bioimmunoradiotherapy (Cetuximab/RT/Avelumab)	Avelumab	Loading dose D-7 then concurrently w/cetuximab-RT; 70 Gy over 7 weeks
NCT01935921	1	Ipilimumab, cetuximab, and intensity-modulated radiation therapy in treating patients with previously untreated stage III-IVB head and neck cancer	Ipilimumab	Concurrently w/cetuximab-RT; IMRT daily for 7 weeks
NCT01860430	1	A phase Ib trial of concurrent cetuximab (ERBITUX®) and intensity modulated radiotherapy (IMRT) With ipilimumab (YERVOY®) in locally advanced head and neck cancer	Ipilimumab	Concurrently w/cetuximab-RT; 70–74 Gy in 2 Gy daily fxs; IMRT
NCT03162731	1	Nivolumab, ipilimumab, and radiation therapy in treating patients with stage IVA-B head and neck cancer	Nivolumab, Ipilimumab	Loading dose of Nivolumab on D-21 then concurrently w/RT and ipilimumab; 70 Gy in 35 fxs
NCT03529422	1	Durvalumab and Tremelimumab with radiotherapy for adjuvant treatment of intermediate risk SCCHN	Durvalumab, Tremelimumab	Concurrently w/RT; 60 Gy in 30 fxs; IMRT
NCT03317327	1/2	REirradiation and programmed cell death protein 1 (PD-1) blockade on recurrent squamous cell head and neck tumors (REPORT)	Nivolumab	Concurrently w/RT; 60 Gy in 1.5 Gy fxs BID for 4 weeks
NCT03247712	1/2	Neoadjuvant immunoradiotherapy in head and neck cancer	Nivolumab	Concurrently w/RT; Arm 1: 8 Gy times 5 fxs daily Arm 2: 8 Gy times 3 fxs QOD
NCT02759575	1/2	A study of chemoradiation plus pembrolizumab for locally advanced laryngeal squamous cell carcinoma	Pembrolizumab	Loading dose on D-21 then concurrently w/cis-RT; 70 Gy in 35 fxs
NCT03114280	1/2	Pembrolizumab and induction chemotherapy in head and neck squamous cell carcinoma (PICH study) (PICH)	Pembrolizumab	Neoadjuvant with chemotherapy, followed by concurrent chemoradiotherapy with carboplatin; Unknown dose or RT
NCT03051906	1/2	Durvalumab, cetuximab, and radiotherapy in head neck cancer (DUCRO-HN)	Durvalumab	Concurrently w/cetuximab-RT followed by adjuvant therapy; 69.96 Gy in 2.12 Gy fxs
NCT03212469	1/2	A trial of durvalumab and tremelimumab in combination with SBRT in patients with metastatic cancer (ABBIMUNE)	Durvalumab, tremelimumab	SBRT
NCT03283605	1/2	Immunotherapy and SBRT for metastatic head and neck carcinomas	Durvalumab, tremelimumab	Neoadjuvant then concurrently w/RT; SBRT
NCT03522584	1/2	Durvalumab, tremelimumab, and stereotactic body radiation therapy in treating participants with recurrent or metastatic head and neck squamous cell carcinoma	Durvalumab, tremelimumab	Loading dose D-14 then concurrently w/RT; SBRT QOD

(Continued)

TABLE 1 | Continued

NCT ID#	Phase	Title	ICI	Treatment arms
PHASE 2				
NCT02684253	2	Screening trial of nivolumab with image guided, stereotactic body radiotherapy (SBRT) vs. nivolumab alone in patients with metastatic head and neck squamous cell carcinoma (HNSCC)	Nivolumab	Concurrently w/RT; SBRT 27 Gy in 3 fxs QOD
NCT03521570	2	Intensity-modulated radiation therapy and nivolumab for recurrent or second primary head and neck squamous cell cancer	Nivolumab	Loading dose of Nivolumab on D-14 then concurrently with RT; IMRT daily for 6–6.5 weeks
NCT03107182	2	Chemotherapy and locoregional therapy trial (surgery or radiation) for patients with head and neck cancer (OPTIMA-II)	Nivolumab	Induction with chemotherapy followed by adjuvant therapy; Dose de-escalated to 45–50 Gy (Arm 2 and 3) or conventional dose to 70 Gy (Arm 4)
NCT03511391	2	Checkpoint inhibition in combination with an immunoboost of external body radiotherapy in solid tumors (CHEERS)	Pembrolizumab, Nivolumab	Concurrently with RT; SBRT 8 Gy times 3 fxs
NCT03313804	2	Priming immunotherapy in advanced disease with radiation	Pembrolizumab, Nivolumab, Atezolizumab	Concurrently w/RT; SBRT with BED >100 Gy or 30 Gy in 3 Gy fxs
NCT02641093	2	Phase II trial of adjuvant cisplatin and radiation with pembrolizumab in resected head and neck squamous cell carcinoma	Pembrolizumab	Loading dose 1 week prior to surgery then concurrently w/ cis-RT; 60–66 Gy in 2 Gy fxs
NCT02707588	2	Tolerance and efficacy of pembrolizumab or cetuximab combined with RT in patients with locally advanced HNSCC (PembroRad)	Pembrolizumab	Concurrently w/RT; 69.96 Gy in 2.12 Gy daily fxs
NCT02609503	2	Pembrolizumab + radiation for locally Adv SCC of the Head and Neck (SCCHN) Not eligible cisplatin	Pembrolizumab	Concurrently w/RT; IMRT daily for 7 weeks
NCT02296684	2	Immunotherapy with MK-3475 in surgically resectable head and neck squamous cell carcinoma	Pembrolizumab	Arm 1: Neoadjuvant and adjuvant therapy Arm 2: Neoadjuvant;
NCT02289209	2	Reirradiation With pembrolizumab in locoregional inoperable recurrence or second primary squamous cell CA of the head and neck	Pembrolizumab	Concurrently w/RT; 1.2 Gy BID for 5 days a week for 5 weeks
NCT02777385	2	Pembrolizumab in combination with cisplatin and intensity modulated radiotherapy (IMRT) in head and neck cancer	Pembrolizumab	Arm 1: adjuvant 3 weeks post cisplatin-RT Arm 2: concurrently with cisplatin-RT; 70 Gy in 35 fxs; IMRT
NCT03085719	2	Targeting PD-1 therapy resistance with focused high or high and low dose radiation in SCCHN	Pembrolizumab	Concurrently w/RT; High (3 fxs) vs. low dose (2 fxs)
NCT03532737	2	Concomitant immune check point inhibitor with radiochemotherapy in head and neck cancer	Pembrolizumab	Loading dose on D-14 then concurrently w/either cetuximab or cis-RT; 66–70 Gy in 30–35 fxs; IMRT
NCT03057613	2	The addition of pembrolizumab to postoperative radiotherapy in cutaneous squamous cell cancer of the head and neck	Pembrolizumab	Concurrently w/and adjuvantly to post-op RT; 60–66 Gy for 6 weeks; IMRT
NCT03383094	2	Chemoradiation vs. immunotherapy and radiation for head and neck cancer	Pembrolizumab	Concurrently w/and adjuvant to cis-RT; 70 Gy in 33–35 fxs
NCT03546582	2	SBRT +/– pembrolizumab in patients with local-regionally recurrent or second primary head and neck carcinoma (KEYSTROKE)	Pembrolizumab	Adjuvant to RT; SBRT
NCT03386357	2	Radiotherapy with pembrolizumab in metastatic HNSCC	Pembrolizumab	Concurrently w/RT; 12 Gy times 3 fxs
NCT03624231	2	Feasibility and efficacy of Durvalumab+Tremelimumab+RT and Durvalumab+RT in Non-resect. Locally advanced HPVnegativ HNSCC (DURTRE-RAD)	Durvalumab, Tremelimumab	Loading dose D-14 then concurrently w/ RT, followed by adjuvant therapy; 70 Gy in 35 fxs over 7 weeks
NCT03426657	2	Radiotherapy with double checkpoint blockade of locally advanced HNSCC	Durvalumab, Tremelimumab	Concurrently w/RT followed by durva monotherapy; 70 Gy in 35 fxs
NCT03258554	2/3	Radiation therapy with Durvalumab or Cetuximab in treating patients with stage III-IVB head and neck cancer who cannot take cisplatin	Durvalumab	Loading dose D-14 then concurrently w/RT; IMRT

(Continued)

TABLE 1 | Continued

NCT ID#	Phase	Title	ICI	Treatment arms
PHASE 3				
NCT03349710 (closed to slow accrual)	3	Nivolumab or nivolumab plus cisplatin, in combination WITH radiotherapy in patients with cisplatin-ineligible or eligible locally advanced squamous cell head and neck cancer	Nivolumab	RT w/cis and nivo vs. RT w/cis RT w/cetuximab vs. RT w/nivo 70 Gy in 35 fractions over 7 weeks; IMRT
NCT03576417	3	A trial evaluating the addition of nivolumab to cisplatin-rt for treatment of cancers of the head and neck (NIVOPOSTOP)	Nivolumab	Loading dose of Nivolumab on D-21 then concurrently w/cis-RT; 66 Gy over 6.5 weeks; IMRT
NCT03040999	3	Study of pembrolizumab (MK-3475) or placebo with chemoradiation in participants with locally advanced head and neck squamous cell carcinoma (MK-3475-412/KEYNOTE-412)	Pembrolizumab	Loading dose then concurrently w/cis-RT; 70 Gy in 35 fxs over either 6 (accelerated) or 7 (standard) weeks
NCT02952586	3	Study to compare avelumab in combination with standard of care chemoradiotherapy (SoC CRT) vs. SoC CRT for definitive treatment in patients with locally advanced squamous cell carcinoma of the head and neck (Javelin head and neck 100)	Avelumab	Concurrently w/cisplatin-RT; 70 Gy in 35 fxs; IMRT
NCT02999087	3	Randomized trial of avelumab-cetuximab-radiotherapy vs. SOCs in LA SCCHN (REACH)	Avelumab	Concurrently w/cetuximab-RT; 69.96 Gy in 2.12 Gy daily fxs; IMRT
NCT03700905	3	Study of nivolumab alone or in combination with ipilimumab as immunotherapy vs. standard follow-up in surgical resectable HNSCC after adjuvant therapy (IMSTAR-HN)	Nivolumab Ipilimumab	Neoadjuvant Nivolumab followed by surgery, adjuvant cisplatin-RT (66 Gy in 33 fx), and adjuvant Ipilimumab and Nivolumab
NCT03673735	3	Maintenance immune check-point inhibitor following post-operative chemo-radiation in subjects with hpv-negative HNSCC (ADHERE)	Durvalumab	Induction Durvalumab followed by cisplatin-RT (66 Gy in 33 fx), and maintenance Durvalumab
NCT03258554	3	Radiation therapy with durvalumab or cetuximab in treating patients with stage III-IVB head and neck cancer who cannot take cisplatin	Durvalumab	Concurrently with RT (IMRT)

Selected clinical trials incorporating the use of one or more immune checkpoint inhibitor and radiation therapy are included below. When available, the dosing and sequencing for the trials is included. SBRT, Stereotactic Body Radiotherapy; RT, radiation therapy; fxs, fractions; Gy, gray; ICI, immune checkpoint inhibitor; CRT, chemoradiotherapy; IMRT, intensity-modulated radiation therapy; LA-SSCHN, locally advanced squamous cell carcinoma of the head and neck; BED, biologically equivalent dose.

RT with cetuximab or RT with pembrolizumab. Of the 133 accrued patients, 92% completed at least 33 fractions of RT and 87% received 3 courses of ICI. While rates of Grade 3 dermatitis, rash, and mucositis were significantly reduced in the pembrolizumab arm, rates of dysthyroidism were significantly increased compared to those treated with cetuximab. In this study it was somewhat concerning that treatment-related mortality was higher than previous GORTEC studies in both arms, possibly reflecting patient selection (i.e., the inclusion of high risk patients due to age and/or comorbidities that made them cisplatin-ineligible) (92). Efficacy results of the PembroRad trial are still pending.

A smaller phase 2 trial evaluated the safety and efficacy of durvalumab with concurrent palliative RT in 10 patients with either inoperable or metastatic disease with a minimum of 5% PD-L1 expression across multiple disease sites. Five patients reported radiation related adverse events of Grade 1 or 2 severity, and no one experienced grade 3 or greater toxicity. The most common side effect was mucositis which was transient and resolved in <1 week (93).

Other trials have evaluated the combination of ICI with radiotherapy and cisplatin in locally advanced HNSCC. Overall there have been no safety concerns with this approach. Specifically, Powell et al. presented the results of a phase I clinical trial investigating the role of pembrolizumab with cisplatin based chemo-radiation for LA-HNSCC at the national meeting of the American Society of Clinical Oncology (ASCO) (94). Of the 27 patients with AJCC 7th edition stage III or IV oropharyngeal, hypopharyngeal, and laryngeal squamous cell carcinomas, 78% of patients completed all planned doses of ICI while 3 patients discontinued treatment due to either Grade 2 peripheral neuropathy, Grade 1 Lhermitte syndrome, or Grade 3 elevation in liver transaminases. All patients successfully completed radiation to the planned dose of 70 Gy without significant delay, defined as >5 days, and 85% received the target dose of cisplatin. One patient died due to a concurrent illness unrelated to the treatment regimen.

Similarly, the combination of nivolumab with cisplatin in either 3 weekly or weekly dosing was shown to be safe without unexpected toxicities (95). In RTOG 3504 pilot trial, patients with newly diagnosed HNSCC who were considered either intermediate risk (p16+, oropharynx T1-2N2b-N3/T3-4N0-3, >10 pack-years smoking; or T4N0-N3, T1-3N3, ≤10 pack-years) or high-risk (oral cavity, larynx, hypopharynx, or p16-oropharynx, stage T1-2N2a-N3 or T3-4N0-3) were enrolled and treated with nivolumab in addition to cisplatin and radiation.

Cisplatin was given at either a low weekly dose (40 mg/m^2) or high dose (100 mg/m^2 every 3 weeks). Nivolumab was given at a dose of 240 mg every 14 days when in conjunction with the weekly dose cisplatin and as a single dose of 240 mg followed by 360 mg every 21 days with the high dose cisplatin. After the conclusion of concurrent chemoradiotherapy, patients were planned to continue on 480 mg every 28 days for 7 doses. As above, all patients were able to complete the prescribed dose of radiation therapy, 70 Gy in 35 fractions. Of the 17 patients available for analysis at the time interim data was presented, 15 were able to receive at least 70% of their planned platinum dose. Three patients discontinued cisplatin, 2 for an allergic reaction and 1 for cholecystitis. Three patients also discontinued nivolumab for known side-effects related to the drug. One grade 4 AE of elevated amylase was reported but resolved. This trial demonstrated the safety of the combination of nivolumab with chemoradiotherapy as well as the feasibility of adjuvant nivolumab after CRT.

More recently, Wise-Draper et al. reported results from a phase II trial investigating the role of neoadjuvant pembrolizumab followed by surgery and then adjuvant concurrent pembrolizumab-RT or pembrolizumab-cisplatin-RT in patients with LA-HNSCC (96). At interim analysis 16 out of 16 patients in the pembrolizumab-RT arm had no Grade 4 toxicity or delay in care due to dose-limiting toxicity, leading the authors to conclude the combined regimen is safe. The pembrolizumab-cisplatin-RT arm also had no grade 4 events reported in the 19 patients included in their preliminary data.

In order to assess the efficacy of combining ICI with SBRT in metastatic HNSCC, a phase II trial enrolled 56 patient to receive either nivolumab alone ($n = 28$) or nivolumab given with SBRT given as 9 Gy × 3 to a single lesion between the first and second doses of nivolumab ($n = 28$). Non-irradiated index lesions were followed for response. As above, the rates of grade 3 or greater treatment-related toxicities were low, occurring in 14.3% of the nivolumab alone arm and 10.7% of the nivolumab and SBRT arm. The ORR was not significantly different, 30.8% vs. 25.9%, $p = 0.93$, nor were the mPFS (1.9 months vs. 2.4 months, $p = 0.89$) or 1 year OS rates (46% vs. 54%, $p = 0.46$). Thus, they failed to demonstrate an abscopal response in the index lesions. However, subgroup analysis revealed that tumors with a high mutational burden had significantly more responders and that mutational burden predicted response regardless of viral status (97).

Taken together these studies suggest that ICI can be safely administered concurrently with radiation therapy without exacerbation of expected toxicities. Most importantly, however, they highlight the need for additional prospective data looking at efficacy. Fortunately, in addition to the aforementioned trials whose efficacy results are still pending, there are over 40 phase I to III clinical trials aimed at addressing exactly this question in head and neck cancers alone (**Table 1**).

CHALLENGES AND FUTURE DIRECTIONS

It is now evident that radiation, through a plethora of diverse mechanisms, has the ability to generate anti-tumor immune responses which can be potentiated by immune checkpoint inhibition. Despite the progress made over the last few years in our understanding of this response, numerous questions remain. It is unclear as to how ICI should be delivered with RT i.e., neoadjuvant, concurrent, adjuvant, or in some combination of the three. Furthermore, it remains to be seen whether combining anti-CTLA4 and anti-PD-1/L1 therapy, given their non-redundant nature, truly improves responses or whether the toxicity precludes the use of such regimens. Both of these questions are currently being addressed in numerous clinical trials (from phase I to phase III) in HNSCC that are listed in **Table 1**.

For the radiation oncologist, there are also the questions of total dose, fraction size, inter-fraction time, target selection, and field size. Preclinical data appears to support the use of large doses in few fractions in producing optimal immune responses, but this still requires validation in humans. In terms of target, radiation oncologists typically select symptomatic lesions where RT may provide palliative relief. This however may not be the best methodology as it is unknown whether targeting bone vs. soft tissue, or even those located in so-called "sanctuary sites" such as the CNS, may confer better outcomes. Lastly, with improvements in targeting it is unclear what field sizes would improve responses. For instance, if tighter tumor margins reduce unwanted eradication of trafficking CTLs or if larger margins increase antigen exposure allowing for improved DC uptake and CTL priming. Therefore, in order to truly maximize the potential of these therapies, more research in both the preclinical and clinical setting is warranted.

AUTHOR CONTRIBUTIONS

GM produced the original draft of the article with guidance and editing from VB-A, BL, AA, and JJ.

REFERENCES

1. Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. *Oral Maxillofac Surg Clin North Am.* (2014) 26:123–41. doi: 10.1016/j.coms.2014.01.001
2. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* (2004) 350:1945–52. doi: 10.1056/NEJMoa032641
3. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2004) 350:1937–44. doi: 10.1056/NEJMoa032646
4. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2016) 375:1856–67. doi: 10.1056/NEJMoa1602252
5. Pennock GK, Chow LQM. The evolving role of immune checkpoint inhibitors in cancer treatment. *Oncologist.* (2015) 20:812–22. doi: 10.1634/theoncologist.2014-0422

6. Slone HB, Peters LJ, Milas L. Host immune capability transplantability of a effect of subsequent. *J Natl Cancer Inst.* (1979) 63:1229–35.
7. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer.* (2016) 40:25–37. doi: 10.1016/j.currproblcancer.2015.10.001
8. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med.* (2012) 366:925–31. doi: 10.1056/NEJMoa1112824
9. Burnet FM. The concept of immunological surveillance. *Progr Exp Tumor Res.* (1970) 13:1–27. doi: 10.1159/000386035
10. Ehrlich P. Über den jetzigen stand der chemotherapie. *Berichte der Dtsch Chem Gesellschaft.* (1909) 42:17–47.
11. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol.* (2002) 3:991–8. doi: 10.1038/ni1102-991
12. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity.* (2004) 21:137–48. doi: 10.1016/j.immuni.2004.07.017
13. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol.* (2004) 22:329–60. doi: 10.1146/annurev.immunol.22.012703.104803
14. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, et al. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature.* (2007) 450:903–7. doi: 10.1038/nature06309
15. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science.* (2011) 331:1565–70. doi: 10.1126/science.1203486
16. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity.* (2013) 39:1–10. doi: 10.1016/j.immuni.2013.07.012
17. Russell JH, Ley TJ. Lymphocyte-mediated cytotoxicity. *Annu Rev Immunol.* (2002) 20:323–70. doi: 10.1146/annurev.immunol.20.100201.131730
18. Appleman L, Berezovskaya A, Grass I, Boussiotis V. CD28 costimulation mediates T cell expansion via IL-2-independent and IL-2-dependent regulation of cell cycle progression. *J Immunol.* (2000) 164:144–51. doi: 10.4049/jimmunol.164.1.144
19. Kapsenberg ML. Dendritic-cell control of pathogen-driven T-cell polarization. *Nat Rev Immunol.* (2003) 3:984–93. doi: 10.1038/nri1246
20. Peggs KS, Quezada SA, Korman AJ, Allison JP. Principles and use of anti-CTLA4 antibody in human cancer immunotherapy. *Curr Opin Immunol.* (2006) 18:206–13. doi: 10.1016/j.coi.2006.01.011
21. Wolchok JD, Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. *Oncologist.* (2008) 13(Suppl. 4):2–9. doi: 10.1634/theoncologist.13-S4-2
22. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* (2010) 363:711–23. doi: 10.1056/NEJMoa1003466
23. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med.* (2011) 364:2517–26. doi: 10.1056/NEJMoa1104621
24. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, et al. PD-1 and PD-L1 Checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol.* (2017) 8:561. doi: 10.3389/fphar.2017.00561
25. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front Oncol.* (2018) 8:86. doi: 10.3389/fonc.2018.00086
26. Hall E, Giaccia A. *Radiobiology for the Radiologist*. 7th ed. Philadelphia, PA: Lippincott Williams and Wilkins (2012).
27. Baliga S, Kabarriti R, Ohri N, Haynes-Lewis H, Yaparpalvi R, Kalnicki S, et al. Stereotactic body radiotherapy for recurrent head and neck cancer: a critical review. *Head Neck.* (2017) 39:595–601. doi: 10.1002/hed.24633
28. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer.* (2015) 121:1128–37. doi: 10.1002/cncr.29161
29. Meier R, Beckman A, Henning G, Mohideen N, Woodhouse SA, Cotrutz C, et al. Five-year outcomes from a multicenter trial of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *Int J Radiat Oncol.* (2016) 96:S33–4. doi: 10.1016/j.ijrobp.2016.06.094
30. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* (2010) 303:1070–6. doi: 10.1001/jama.2010.261
31. Arnold KM, Flynn NJ, Raben A, Romak L, Yu Y, Dicker AP, et al. The impact of radiation on the tumor microenvironment: effect of dose and fractionation schedules. *Cancer Growth Metastasis.* (2018) 11:1–17. doi: 10.1177/1179064418761639
32. Aaes TL, Kaczmarek A, Delvaeye T, De Craene B, De Koker S, Heyndrickx L, et al. Vaccination with necroptotic cancer cells induces efficient anti-tumor immunity. *Cell Rep.* (2016) 15:274–87. doi: 10.1016/j.celrep.2016.03.037
33. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol.* (2017) 17:97–111. doi: 10.1038/nri.2016.107
34. Kaczmarek A, Vandenabeele P, Krysko DV. Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. *Immunity.* (2013) 38:209–23. doi: 10.1016/j.immuni.2013.02.003
35. Krysko DV, Garg AD, Kaczmarek A, Krysko O, Agostinis P, Vandenabeele P. Immunogenic cell death and DAMPs in cancer therapy. *Nat Rev Cancer.* (2012) 12:860–75. doi: 10.1038/nrc3380
36. Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology.* (2014) 3:e28518. doi: 10.4161/onci.28518
37. Vatner RE, Cooper BT, Vanpouille-Box C, Demaria S, Formenti SC. Combinations of immunotherapy and radiation in cancer therapy. *Front Oncol.* (2014) 4:325. doi: 10.3389/fonc.2014.00325
38. Weichselbaum RR, Liang H, Deng L, Fu Y-X. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol.* (2017) 14:365–79. doi: 10.1038/nrclinonc.2016.211
39. Martins I, Kepp O, Schlemmer F, Adjemian S, Tailler M, Shen S, et al. Restoration of the immunogenicity of cisplatin-induced cancer cell death by endoplasmic reticulum stress. *Oncogene.* (2011) 30:1147–58. doi: 10.1038/onc.2010.500
40. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* (2015) 372:2509–20. doi: 10.1056/NEJMoa1500596
41. Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, et al. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med.* (2006) 203:1259–71. doi: 10.1084/jem.20052494
42. Garnett CT, Palena C, Chakarborty M, Tsang K-Y, Schlom J, Hodge JW. Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. *Cancer Res.* (2004) 64:7985–94. doi: 10.1158/0008-5472.CAN-04-1525
43. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science.* (2015) 348:69–74. doi: 10.1126/science.aaa4971
44. Campoli M, Chang C-C, Ferrone S. HLA class I antigen loss, tumor immune escape and immune selection. *Vaccine.* (2002) 20:A40–5. doi: 10.1016/S0264-410X(02)00386-9
45. Poschke I, Mougiakakos D, Kiessling R. Camouflage and sabotage: tumor escape from the immune system. *Cancer Immunol Immunother.* (2011) 60:1161–71. doi: 10.1007/s00262-011-1012-8
46. Klein B, Loven D, Lurie H, Rakowsky E, Nyska A, Levin I, et al. The effect of irradiation on expression of HLA class I antigens in human brain tumors in culture. *J Neurosurg.* (1994) 80:1074–7. doi: 10.3171/jns.1994.80.6.1074
47. Santin AD, Hiserodt JC, Fruehauf J, DiSaia PJ, Pecorelli S, Granger GA. Effects of irradiation on the expression of surface antigens in human ovarian cancer. *Gynecol Oncol.* (1996) 60:468–74. doi: 10.1006/gyno.1996.0075
48. Santin AD, Hermonat PL, Hiserodt JC, Chiriva-Internati M, Woodliff J, Theus JW, et al. Effects of irradiation on the expression of major histocompatibility complex class I antigen and adhesion costimulation molecules ICAM-1 in human cervical cancer. *Int J Radiat Oncol.* (1997) 39:737–42. doi: 10.1016/S0360-3016(97)00372-6
49. Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor

antigen-specific effector cells that traffic to the tumor. *J Immunol.* (2005) 174:7516–23. doi: 10.4049/jimmunol.174.12.7516
50. Chen Q, Sun L, Chen ZJ. Regulation and function of the cGAS–STING pathway of cytosolic DNA sensing. *Nat Immunol.* (2016) 17:1142–9. doi: 10.1038/ni.3558
51. Li T, Chen ZJ. The cGAS–cGAMP–STING pathway connects DNA damage to inflammation, senescence, and cancer. *J Exp Med.* (2018) 215:1287–99. doi: 10.1084/jem.20180139
52. Hong J-H, Chiang C-S, Tsao C-Y, Lin P-Y, Mcbride WH, Wu C-J. Rapid induction of cytokine gene expression in the lung after single and fractionated doses of radiation. *Int J Radiat Biol.* (1999) 75:1421–7. doi: 10.1080/095530099139287
53. Linard C, Marquette C, Mathieu J, Pennequin A, Clarençon D, Mathé D. Acute induction of inflammatory cytokine expression after γ-irradiation in the rat: effect of an NF-κB inhibitor. *Int J Radiat Oncol.* (2004) 58:427–34. doi: 10.1016/j.ijrobp.2003.09.039
54. Burnette BC, Liang H, Lee Y, Chlewicki L, Khodarev NN, Weichselbaum RR, et al. The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. *Cancer Res.* (2011) 71:2488–96. doi: 10.1158/0008-5472.CAN-10-2820
55. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, et al. STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. *Immunity.* (2014) 41:843–52. doi: 10.1016/j.immuni.2014.10.019
56. Meng Y, Mauceri HJ, Khodarev NN, Darga TE, Pitroda SP, Beckett MA, et al. Ad.Egr-TNF and local ionizing radiation suppress metastases by interferon-β-dependent activation of antigen-specific CD8+ T cells. *Mol Ther.* (2010) 18:912–20. doi: 10.1038/mt.2010.18
57. Barker HE, Paget JTE, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer.* (2015) 15:409–25. doi: 10.1038/nrc3958
58. Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. *J Immunol.* (2008) 181:3099–107. doi: 10.4049/jimmunol.181.5.3099
59. Lugade AA, Sorensen EW, Gerber SA, Moran JP, Frelinger JG, Lord EM. Radiation-induced IFN-gamma production within the tumor microenvironment influences antitumor immunity. *J Immunol.* (2008) 180:3132–9. doi: 10.4049/jimmunol.180.5.3132
60. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol.* (2017) 14:399–416. doi: 10.1038/nrclinonc.2016.217
61. Vatner RE, Formenti SC. Myeloid-derived cells in tumors: effects of radiation. *Semin Radiat Oncol.* (2015) 25:18–27. doi: 10.1016/j.semradonc.2014.07.008
62. Gajewski TF, Schreiber H, Fu Y-X. Innate and adaptive immune cells in the tumor microenvironment. *Nat Immunol.* (2013) 14:1014–22. doi: 10.1038/ni.2703
63. Schmidt A, Oberle N, Krammer PH. Molecular mechanisms of treg-mediated T cell suppression. *Front Immunol.* (2012) 3:51. doi: 10.3389/fimmu.2012.00051
64. Kachikwu EL, Iwamoto KS, Liao Y-P, DeMarco JJ, Agazaryan N, Economou JS, et al. Radiation enhances regulatory T cell representation. *Int J Radiat Oncol.* (2011) 81:1128–35. doi: 10.1016/j.ijrobp.2010.09.034
65. Qu Y, Jin S, Zhang A, Zhang B, Shi X, Wang J, et al. Gamma-ray resistance of regulatory CD4 $^{+}$ CD25 $^{+}$ Foxp3 $^{+}$ T cells in mice. *Radiat Res.* (2010) 173:148–57. doi: 10.1667/RR0978.1
66. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol.* (2012) 83:1306–10. doi: 10.1016/j.ijrobp.2011.09.049
67. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, McKenna C, Jones S, Cheadle EJ, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res.* (2014) 74:5458–68. doi: 10.1158/0008-5472.CAN-14-1258
68. Li D, Chen R, Wang Y-W, Fornace AJ, Li H-H. Prior irradiation results in elevated programmed cell death protein 1 (PD-1) in T cells. *Int J Radiat Biol.* (2018) 94:488–94. doi: 10.1080/09553002.2017.1400192
69. Lim SH, Hong M, Ahn S, Choi Y-L, Kim K-M, Oh D, et al. Changes in tumour expression of programmed death-ligand 1 after neoadjuvant concurrent chemoradiotherapy in patients with squamous oesophageal cancer. *Eur J Cancer.* (2016) 52:1–9. doi: 10.1016/j.ejca.2015.09.019
70. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood.* (2009) 114:589–95. doi: 10.1182/blood-2009-02-206870
71. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun.* (2017) 8:15618. doi: 10.1038/ncomms15618
72. Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res.* (2005) 11:728–34. Available online at: http://clincancerres.aacrjournals.org/content/11/2/728
73. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. *Front Oncol.* (2012) 2:153. doi: 10.3389/fonc.2012.00153
74. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res.* (2009) 15:5379–88. doi: 10.1158/1078-0432.CCR-09-0265
75. Landberg T, Chavaudra J, Dobbs J, Hanks G, Johansson K-A, Möller T, et al. Report 50. *J Int Comm Radiat Units Meas.* (1993) os26. doi: 10.1093/jicru/os26.1.Report50
76. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic radiation therapy augments antigen-specific pd-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res.* (2015) 3:345–55. doi: 10.1158/2326-6066.CIR-14-0196
77. Takeshima T, Chamoto K, Wakita D, Ohkuri T, Togashi Y, Shirato H, et al. Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy. *Cancer Res.* (2010) 70:2697–706. doi: 10.1158/0008-5472.CAN-09-2982
78. Marciscano AE, Ghasemzadeh A, Nirschl TR, Theodros D, Kochel CM, Francica BJ, et al. Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy. *Clin Cancer Res.* (2018) 24:5058–71. doi: 10.1158/1078-0432.CCR-17-3427
79. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N Engl J Med.* (2017) 377:1919–29. doi: 10.1056/NEJMoa1709937
80. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* (2018) 379:2342–50. doi: 10.1056/NEJMoa1809697
81. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob J-J, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* (2017) 377:1345–56. doi: 10.1056/NEJMoa1709684
82. Forster MD, Devlin M-J. Immune checkpoint inhibition in head and neck cancer. *Front Oncol.* (2018) 8:310. doi: 10.3389/fonc.2018.00310
83. Zandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. *Oral Oncol.* (2014) 50:627–32. doi: 10.1016/j.oraloncology.2014.04.003
84. Soulieres D, Cohen E, Tourneau C, Le Dinis J, Licitra L, Ahn M-J, et al. Abstract CT115: updated survival results of the KEYNOTE-040 study of pembrolizumab vs standard-of-care chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma. *Cancer Res.* (2018) 78:CT115. doi: 10.1158/1538-7445.AM2018-CT115
85. Segal NH, Ignatious Ou S-H, Balmanoukian AS, Fury MG, Massarelli E, Brahmer J. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. *J Clin Oncol.* (2015) 33:3011. doi: 10.1200/jco.2015.33.15_suppl.3011
86. Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: results from a single-arm, phase II study in patients with ≥25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. *Eur J Cancer.* (2019) 107:142–52. doi: 10.1016/j.ejca.2018.11.015

87. Siu L, Even C, Mesia R, Daste A, Krauss J, Saba N, et al. A randomized, open-label, multicenter, global phase 2 study of durvalumab (D), tremelimumab (T), or D plus T, in patients with PD-L1 low/negative recurrent or metastatic head and neck squamous cell carcinoma: CONDOR. *Int J Radiat Oncol Biol Phys.* (2018) 100:1307. doi: 10.1016/j.ijrobp.2017.12.021
88. Burtness B, Harrington K, Greil R, Soulieres D, Tahara M, De Castro G, et al. *KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab (P) for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) | OncologyPRO*. ESMO (2018). Available online at: https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/KEYNOTE-048-Phase-3-study-of-first-line-pembrolizumab-P-for-recurrent-metastatic-head-and-neck-squamous-cell-carcinoma-R-M-HNSCC (Accessed November 19, 2018).
89. Schapira E, Hubbeling H, Yeap BY, Mehan WA, Shaw AT, Oh K, et al. Improved overall survival and locoregional disease control with concurrent PD-1 pathway inhibitors and stereotactic radiosurgery for lung cancer patients with brain metastases. *Int J Radiat Oncol Biol Phys.* (2018) 101:624–9. doi: 10.1016/j.ijrobp.2018.02.175
90. Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. *Nat Rev Clin Oncol.* (2018) 15:477–94. doi: 10.1038/s41571-018-0046-7
91. Martin AM, Cagney DN, Catalano PJ, Alexander BM, Redig AJ, Schoenfeld JD, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol.* (2018) 4:1123–4. doi: 10.1001/jamaoncol.2017.3993
92. Sun XS, Sire C, Tao Y, Martin L, Alfonsi M, Prevost JB, et al. A phase II randomized trial of pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN): first results of the GORTEC 2015-01 "PembroRad" trial. *J Clin Oncol.* (2018) 36(Suppl. 15):6018. doi: 10.1200/JCO.2018.36.15_suppl.6018
93. Levy A, Massard C, Soria J-C, Deutsch E. Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: single centre subset analysis from a phase 1/2 trial. *Eur J Cancer.* (2016) 68:156–62. doi: 10.1016/j.ejca.2016.09.013
94. Powell SF, Gitau MM, Sumey CJ, Reynolds JT, Lohr M, McGraw S, et al. Safety of pembrolizumab with chemoradiation (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). *J Clin Oncol.* (2017) 35:6011. doi: 10.1200/JCO.2017.35.15_suppl.6011
95. Gillison M, Ferris R, Zhang Q, Colevas AD, Kell L, Kirsch C, et al. *Safety Evaluations of Nivolumab (Anti-PD1) Added to Chemoradiotherapy Platforms for Patients With Intermediate and High-Risk Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma*. In: *Multidisciplinary Head and Neck Cancers Symposium* (Scottsdale, AZ) (2018).
96. Wise-Draper TM, Old MO, Worden FP, O'Brien PE, Cohen EEW, Dunlap N, et al. Phase II multi-site investigation of neoadjuvant pembrolizumab and adjuvant concurrent radiation and pembrolizumab with or without cisplatin in resected head and neck squamous cell carcinoma. *J Clin Oncol.* (2018) 36(Suppl. 15):6017. doi: 10.1200/JCO.2018.36.15_suppl.6017
97. McBride SM, Sherman EJ, Tsai CJ, Baxi SS, Aghalar J, Eng J, Zhi WI, et al. A phase II randomized trial of nivolumab with stereotactic body radiotherapy (SBRT) versus nivolumab alone in metastatic (M1) head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol.* (2018) 36:6009. doi: 10.1200/JCO.2018.36.15_suppl.6009

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A Nomogram for the Prediction of Prognosis in Patients With Distant Metastases of Nasopharyngeal Carcinoma

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Background: Patients with metastatic nasopharyngeal carcinoma (NPC) have heterogeneous survival outcomes. This study aimed to establish an effective prognostic nomogram for patients with NPC with distant metastases using easily determined factors.

Methods: The nomogram was based on a retrospective study of 103 patients with metastatic NPC at the First Affiliated Hospital of Xiamen University during January 2009–March 2016. Nomogram performance was evaluated using a concordance index (C-index) and assessed using calibration plot. Bootstraps with 1,000 resamples were applied to these analyses.

Results: In univariate and multivariate Cox proportional hazards model analyses, chemotherapy, metastatic liver involvement, number of tumor metastases, N stage and derived neutrophil–lymphocyte ratio correlated with overall survival (OS). The recurrence probability calibration curve indicated good agreement between nomogram-based predictions and actual observations. For OS predictions, the nomogram had a C-index of 0.824 (95% confidence interval, 0.74–0.91). The stratification by nomogram score of patients into different subgroups showed significant distinction.

Conclusion: This novel nomogram comprises factors that are easily determined at most hospitals and can predict survival in patients with distant metastases of NPC. This model can precisely estimate the survival of individual patients and identify subgroups of patients requiring specific therapeutic strategies.

Keywords: nasopharyngeal carcinoma, distant metastases, prognosis, nomogram, overall survival

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INTRODUCTION

Nasopharyngeal carcinoma (NPC), which is endemic in Southern China and Southeast Asia, has a unique geographical distribution pattern (1). Advances in radiotherapy and the broad application of chemotherapy in recent decades have yielded great improvements in the 5-year overall survival (OS) of affected patients. However, distant metastasis of NPC remains a key treatment obstacle.

Specifically, 17–54% of patients with NPC experience treatment failures due to distant metastases, and these patients have disappointing outcomes (2–4).

The role of chemotherapy for metastases of NPC, a highly chemosensitive malignancy, has been well established. Zhang et al. recently demonstrated that chemotherapy with gemcitabine plus cisplatin could significantly improve progression-free survival (PFS) among patients with metastatic NPC (5), thus establishing this regimen as a standard first-line treatment option for these patients (5). Although the systemic treatment options of patients with metastatic NPC have gradually evolved to include other chemotherapeutic regimens, targeted therapy, and immunotherapy, the outcomes remain heterogeneous.

The American Joint Committee Cancer (AJCC) tumor–node–metastasis (TNM) staging system is currently the most widely used staging strategy and is a fundamental determinant of prognostic predictions. However, the usefulness of this system for patients with metastatic NPC is limited, as the clinical outcomes differ even among patients with the same stage who receive similar treatment regimens (6). Many additional factors affecting the prognosis of NPC have since been identified, including the Epstein–Barr virus (EBV) DNA concentration, miRNAs and the derived neutrophil-lymphocyte ratio (dNLR) (7–9). A scoring system that incorporates several of these factors would likely help to direct individualized patient treatments.

Nomograms are considered reliable for risk quantification. These tools quantify risk by incorporating and illustrating important factors related to oncologic prognosis. Nomograms have been proven to generate more precise predictions for several types of cancers when compared to the conventional TNM staging systems (10, 11). However, few nomograms are available for predicting the long-term survival outcomes of patients with NPC with distant metastases. In this study, we aimed to combine the TNM staging system, metastatic sites, number of metastases, dNLR and other independent factors into a nomogram for NPC patients with distant metastases. Such a nomogram could potentially enable clinicians to precisely calculate the survival outcomes of individual patients with distant metastases of NPC.

PATIENTS AND METHODS

Patients

Between January 2009 and March 2016, 791 patients with newly pathologically diagnosed and previously untreated NPC were retrospectively reviewed. Among them, 120 patients initially presented with or developed metastatic NPC before March 2016. The following enrolment criteria were applied to subjects of this retrospective study: (i) complete sociodemographic data and laboratory test results; (ii) complete imaging data [magnetic resonance (MR)/computed tomography (CT) of the nasopharynx and neck, technetium-99m ($^{99}Tc^{m}$-MDP) bone scans, MR/CT/ultrasound of the liver, chest CT and/or whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT]; (iii) pathologically confirmed World Health Organization (WHO) type II or WHO type III NPC; (iv) pathologically or radiologically confirmed distant metastatic lesion(s) and (v) a Karnofsky performance status (KPS) score $\geq$70. The following exclusion criteria were also applied: (i) brain metastases; (ii) other types of malignancy; and (iii) serious renal or liver disease requiring treatment.

Data were retrieved for 120 patients. Of those, 17 patients were excluded from the total score analysis because of missing laboratory data or a lost to follow-up status. Finally, 103 patients were deemed eligible for risk stratification. The tumors were staged according to the 2009 AJCC staging system. This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Xiamen University.

Treatment and Follow-Up

All patients received multimodal treatment after diagnosis. The first-line regimen comprised platinum-based chemotherapy for 4–6 cycles according to our institutional experience. Patients who could not tolerate or were unwilling to receive additional chemotherapy were administered other therapies, such as palliative radiotherapy, targeted therapy, and surgery. For each patient, treatment was defined according to the experience of our hospital and the wishes of the individual patient.

Follow-up examinations were performed every 3 months during the first and second years after treatment and every 6 months thereafter according to the standard practice of our hospital. These examinations included nasopharyngeal and neck MR imaging, nasopharyngoscopy, chest CT, MR/CT/ultrasonography of the liver, complete blood cell counts, blood biochemical testing, and a $^{99}Tc^{m}$-MPD bone scan. OS was defined as the duration from the date of the most recent metastasis diagnosis to the date of death from any cause or censorship on the last follow-up date (March 31, 2016).

Construction of the Nomogram

Univariate and multivariate analyses were performed using the Cox proportional hazards model. The age at metastasis; sex; chemotherapy ($<$2 vs. $\geq$2 cycles); radiotherapy; targeted therapy; metastases of the liver, lung and/or bone metastasis; number of tumor metastases; synchronous or metachronous status; body mass index (BMI); smoking history; pretreatment dNLR (low vs. high) at the time of metastasis; and stages of the primary tumor (T1 or T2 vs. T3 or T4) and regional lymph nodes (N1–N2 vs. N3) at the initial diagnosis were included in the univariate regression models. Factors identified as significant predictors of OS in the univariate analysis were subsequently entered into the multivariable analyses via the Cox regression model. The cut-off values for continuous variables were determined based on the receiver operating characteristic (ROC) curves. The $\chi 2$, $\chi 2$ continuity correction and Fisher's exact test were used to determine the proportion of independents. Statistical analyses to identify independent prognostic factors were conducted in SPSS 22.0 (IBM, Armonk, NY, USA). On the basis of the results of the multivariable analysis, a nomogram was formulated by R version 3·1.1 statistical analysis software (http://www.r-project.org).

Validation and Calibration of the Nomogram

Following the above analyses, a nomogram was developed based on the multivariate Cox regression results. The final prediction

model used for the nomogram was selected using a backward stepdown procedure with a threshold P of <0.05. The nomogram performance was evaluated using a concordance index (C-index) and assessed using a calibration plot; bootstraps with 1,000 resamples were applied to both analyses. The total points for each patient in the validation cohort were calculated using the established nomogram, after which a Cox regression analysis of the whole cohort was performed using the total points as a factor. The C-index and calibration curves were derived based on the regression analysis.

Risk Stratification Based on the Nomogram Beyond TNM staging

In order to demonstrate the independent discrimination ability of the prognostic nomogram beyond standard TNM staging, we determined the cut-off values by grouping all patients evenly into different risk groups according to the total risk scores in the study cohort. Survival curves for different risk groups were generated using the Kaplan-Meier estimates and were compared using the log-rank test.

RESULTS

Patient Characteristics

The 103 patients included in this analysis comprised 83 men and 20 women with a median age at metastasis of 50 years (range, 23–82 years). All patients had histologically confirmed non-keratinizing undifferentiated or low-keratinizing squamous cell cancer (WHO II or WHO III). Additionally, 66% (68) of patients had stage N1–2 disease, while 34% (35) had stage N3 disease. Forty-three patients (41.7%) presented with liver metastases. The median number of tumor distant metastases was 10 (range, 1–26), and the median pretreatment dNLR at metastasis was 2.33 (range, 0.67–8.52; **Table 1**). Eighty-seven patients (84.5 %) died after a median follow-up of 16 months (range, 1–79 months).

Independent Prognostic Factors

Initially, the covariates listed in **Table 1** were analyzed using a Cox univariate factor regression model, which identified chemotherapy cycles ($P < 0.001$), liver metastasis ($P < 0.001$), number of tumor metastases ($P < 0.001$), N stage($P = 0.045$), and dNLR ($P < 0.001$) as factors significantly associated with OS. By contrast, the age at metastasis ($P = 0.532$), sex ($P = 0.178$), T stage ($P = 0.074$), radiotherapy ($P = 0.202$), targeted therapy ($P = 0.102$), lung metastasis (0.774), bone metastasis ($P = 0.164$), synchronous metastasis ($P = 0.065$), histology ($P = 0.176$), smoking history ($P = 0.878$), and BMI ($P = 0.579$) were not found to correlate with OS (**Table 2**). All significant factors from the univariate analysis were entered into the Cox regression-based multivariate analysis (**Table 3**). Chemotherapy cycles ($P < 0.001$), liver metastasis ($P < 0.001$), number of tumor metastases ($P < 0.001$), N stage($P = 0.001$), and dNLR ($P = 0.011$) remained independent prognostic factors in the Cox model.

Nomogram for Predicting OS in Patients With Distant Metastases of NPC

A nomogram incorporating the significant prognostic factors was established (**Figure 1**). Here, the number of distant metastases and presence of liver metastases made the largest prognostic contribution, followed by the number of chemotherapy cycles and N stage. By contrast, the dNLR level had a moderate impact on survival. Within these variables, each subtype was assigned a score on the point scale. Accordingly, by locating the summed

TABLE 1 | Clinical characteristics of the study patients.

Variable	Number	%
AGE (YEARS)		
Median	50 (23–82)	
<50	48	46.60
≥50	55	53.40
SEX		
Male	83	80.60
Female	20	19.40
T STAGE		
T1/T2	19	18.45
T3/T4	84	81.55
***N* STAGE**		
N1–N2	68	66
N3	35	34
TREATMENT		
Chemotherapy (≥2 cycles)	64	62.10
Radiotherapy	48	46.60
Target therapy	18	17.50
SITE OF METASTASIS		
Liver metastasis	43	41.70
Lung metastasis	41	39.80
Bone metastasis	75	72.80
NUMBER OF METASTASES		
Median	10 (1–26)	
Synchronous	33	32.04
Metachronous	70	67.96
HISTOLOGY, WHO TYPE		
II	30	29.10
III	73	70.90
SMOKING HISTORY		
Non-smoker	64	62.10
Smoker	39	37.90
BMI (kg/m^2)		
<18.5	27	26.20
18.5–23.9	65	63.10
≥23.9	11	10.70
dNLR		
Median	2.33 (0.67–8.52)	

T, tumor; N, node; BMI, body mass index; dNLR, derived neutrophil–lymphocyte ratio.

TABLE 2 | Univariate analysis of the Cox risk ratio model for OS.

Variable	Hazard ratio	95% CI	*P*-value
Age (years)	0.86	0.54–1.38	0.532
<45			
≥45			
Sex	1.43	0.85–2.42	0.178
Male			
Female			
T stage	1.86	1.09–3.18	0.074
T1–2			
T3–4			
N stage	0.64	0.41–0.99	**0.045**
N1–2			
N3			
Chemotherapy	2.21	1.44–3.40	**<0.001**
<2 cycles			
≥2 cycles			
Radiotherapy	1.32	0.86–2.02	0.202
Yes			
No			
Target therapy	1.67	0.90–3.07	0.102
Yes			
No			
Liver metastasis	0.39	0.25–0.61	**<0.001**
Yes			
No			
Lung metastasis	1.07	0.69–1.66	0.774
Yes			
No			
Bone metastasis	0.70	0.43–1.15	0.164
Yes			
No			
Number of metastases	0.26	0.16–0.42	**<0.001**
<8			
≥8			
dNLR	0.46	0.30–0.71	**<0.001**
<2.6			
≥2.6			
Synchronous	0.64	0.40–1.01	0.055
Yes			
No			
Histology, WHO type	1.37	0.87–2.16	0.176
II			
III			
Smoking history	1.04	0.67–1.60	0.878
Yes			
No			
BMI (kg/m^2)	0.87	0.53–1.43	0.579
<18.5			
≥18.5			

OS, overall survival; T, tumor; N, node; BMI, body mass index; dNLR, derived neutrophil-lymphocyte ratio; CI, confidence interval. The bold values indicates p < 0.05.

TABLE 3 | Multivariate analysis of the Cox risk ratio model for OS.

Variable	HR	95% CI	*P*-value
Chemotherapy	2.72	1.73–4.26	<0.001
<2 cycles			
≥2 cycles			
Number of metastases	0.23	0.13–0.40	<0.001
<8			
≥8			
Liver metastasis	0.34	0.21–0.54	<0.001
Yes			
No			
N stage	0.45	0.28–0.71	0.001
N1–2			
N3			
dNLR	0.56	0.36–0.88	0.011
<2.6			
≥2.6			

OS, overall survival; HR, hazard ratio; CI, confidence interval; T, tumor; N, node; dNLR, derived neutrophil-lymphocyte ratio.

total score on the total point scale, we could easily draw a straight line to determine the estimated probability of survival at each time point.

Calibration and Validation of the Nomogram

The constructed nomogram included all independent prognosticators of 1- and 2-year OS identified in the multivariable analysis (**Figure 1**). The C-index for predicting OS was 0.824 [95% confidence interval (CI), 0.74–0.91]. A calibration plot of the survival probabilities at 1 (**Figure 2A**) and 2 years (**Figure 2B**) revealed good agreement between the nomogram-based prediction and the actual observation.

Prognostic Nomogram for Risk Stratification

We determined the cut-off values by grouping all patients in the study cohort into three subgroups based on the tertiles of total scores, each group represents a distinct prognosis. The Kaplan-Meier survival curves were subsequently delineated and were shown in **Figure 3**. Group 1 (total points 0–108, 34 patients) had the highest overall survival as 90.9 % for 1 year and 69.7 % for 2 years, respectively; followed by Group 2 (total points 108–199, 35 patients) as 60.0 and 17.5% for 1 and 2 years, respectively; Group 3(total points 199–338, 34 patients) showed the lowest overall survival as 14.7 and 0% for 1 and 2 years, respectively. The median OS in Group 1–3 are 37 (95%CI, 27.5–46.4), 17 (95%CI, 12.6–21.4), and 6 (95%CI, 3.6–8.4) months, respectively. Significant distinction for survival outcomes was observed between the three groups.

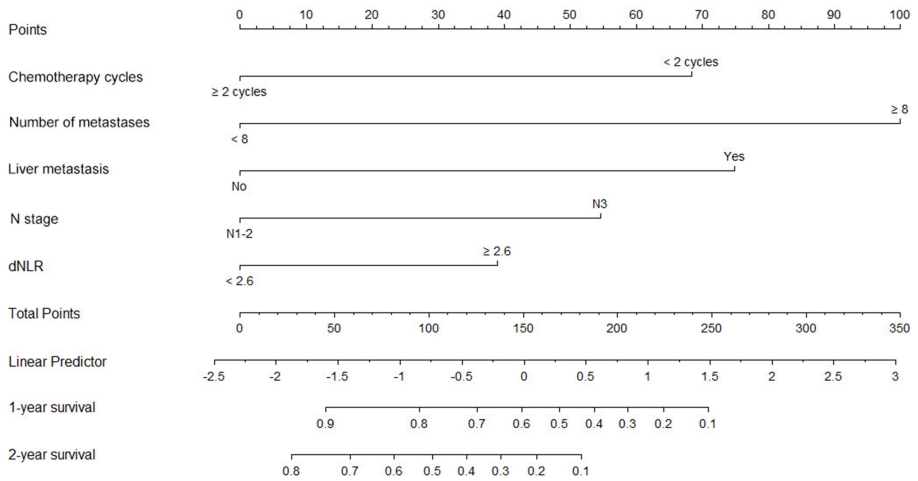

FIGURE 1 | Nomogram A for predictions of 1- and 2-year overall survival (OS) in patients with metastatic nasopharyngeal carcinoma. This nomogram, which includes chemotherapy, the number of metastases, liver metastasis, N stage and dNLR, allows the user to determine the probability of the 1-year and 2-year OS for an individual patient using a combination of covariates. Using the patient's N stage, a line can be drawn straight upward to the "Points" axis to determine the associated score. After repeating the process for each variable, the scores for each variable can be summed and plotted on the "Total Points" axis. Finally, a vertical line can be drawn straight down from the plotted total point axis to the survival axis to determine the 1- and 2-year OS probabilities.

DISCUSSION

Among all head and neck cancers, NPC exhibits the highest propensity for distant metastasis (2). However, far fewer studies have evaluated patients with distant metastases of NPC, compared to their counterparts with non-metastatic advanced NPC. The metastatic NPC patients typically have an OS duration of <15 months (12, 13). Accordingly, many patients diagnosed with metastatic NPC and their clinicians often have negative attitudes regarding treatment. Interestingly, it has been reported that a subset of patients with distant metastases of NPC still experience good OS outcomes in response to an aggressive therapy regimen (14, 15). However, we lack a reliable method of predicting which individuals are likely to get benefit from a more intensive treatment while avoid overtreatment in the unfavorable subgroup. The eighth edition of the AJCC TNM classification represents the most widely used staging system, in which patients with NPC are stratified according to tumor size and invasion, lymph node involvement, as well as distant metastasis. However, survival of patients with metastatic NPC varies widely. This may partly due to the current M staging system is purely based on whether the patient has distant metastasis, and all M1 patients are classified as clinical IVB stage according to the current AJCC staging system. Furthermore, the M classification from the previous AJCC staging system has never been modified for subdividing. As a result, this traditional staging system does not completely reflect the biological heterogeneity of metastatic NPC patients, and other independent risk factors are not taken into account in current AJCC staging systems. Therefore, a reliable prognostic method is needed, as this would enable the administration of individualized therapies to distinct subgroups of patients.

Several studies have attempted to build prognostic models for patients with metastatic NPC. For example, Ong et al. designed a prognostic index score (PIS) system based on liver and lung metastasis, anemia, a poor performance status, distant metastasis at initial diagnosis and the disease-free interval (16). However, that study assessed patients between January 1994 and December 1999 (16), and the availability of chemotherapeutic drugs and approaches to radiotherapy have since been modified during the era of intensity-modulated radiation therapy. In 2012, Jin et al. constructed a prognostic score model (PSM) that incorporated circulating tumor markers of metastatic NPC, performance status, age, hemoglobin level, lactate dehydrogenase (LDH) level, alkaline phosphatase (ALP) level and EBV DNA level (17). However, that scoring system may not be sufficiently precise, as each included factor received a score of 1 or 3 according to the n value (17).

In contrast to other systems, a nomogram can provide a visual representation of the results of a Cox model and facilitate individualized predictions for many cancers (10, 11, 18). However, a nomogram had not previously been developed to include both synchronous and metachronous metastatic NPC. As far as we know, this is the first study to develop a survival prognostic nomogram for this population. Using data from our study cohort, we built a nomogram predictive of OS among patients with metastatic NPC that was based on independent prognostic factors, including the numbers of chemotherapy cycles and metastases, occurrence of liver metastasis, N category and dNLR. Each of these factors is easily obtained at most hospitals. In addition, by stratifying patients into three risk groups from nomogram total score, we separated patients with distinct survival outcomes. We further note that our study cohort comprised patients at the First Affiliated Hospital of Xiamen University in Southern China, a region considered

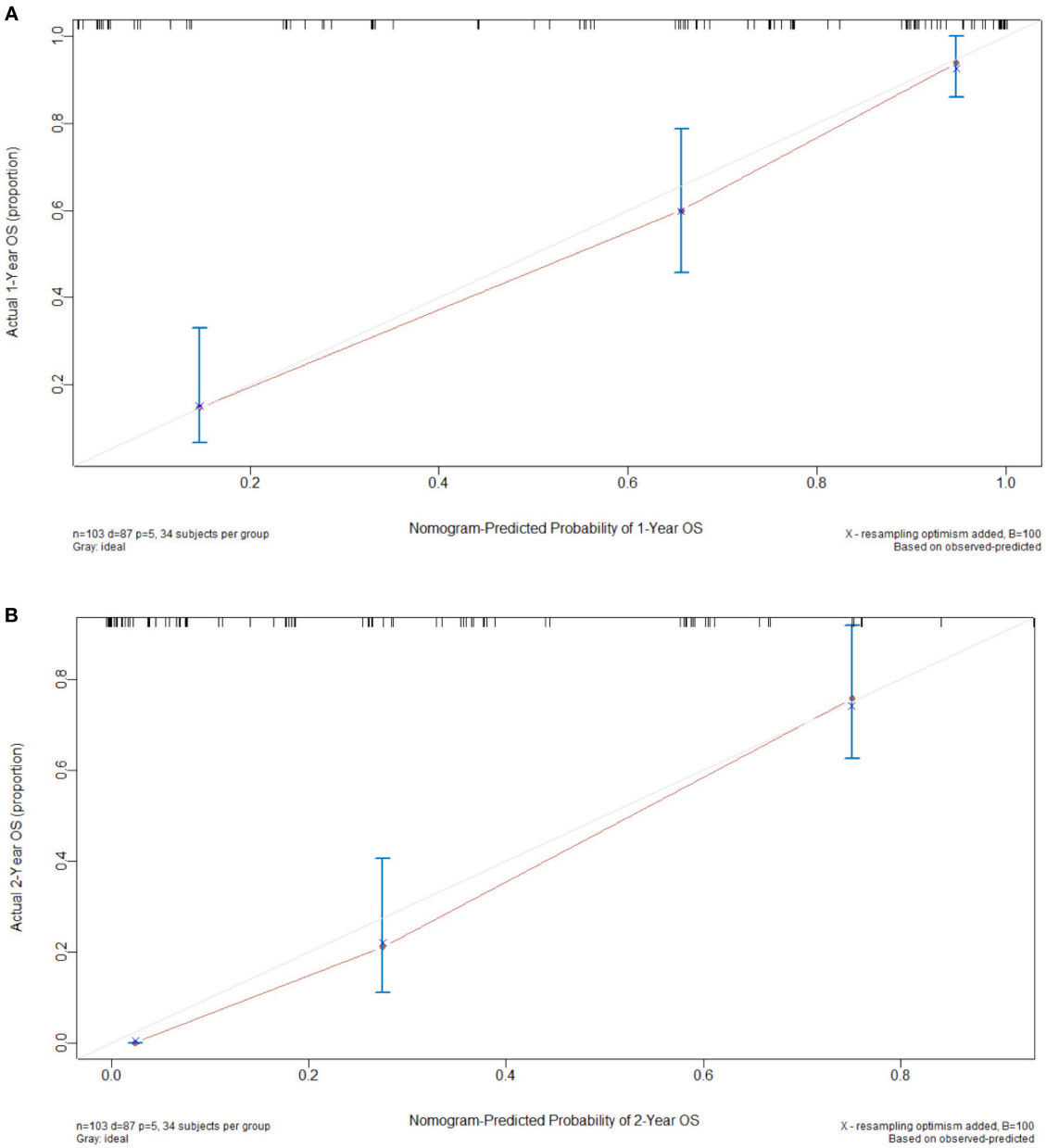

FIGURE 2 | Calibration curves used to compare the nomogram-predicted and actual survival probabilities at 1 **(A)** and 2 years **(B)**. The actual overall survival (OS) is plotted on the y axis, while the nomogram-predicted probability is plotted on the x axis. The dotted line indicates the reference (i.e., ideal prediction).

endemic for NPC. The unique geographic distribution of the patients and the reasonable sample size guarantee that our results are generally representative of Chinese patients with NPC.

We identified the independent prognostic factors for OS that were included in our nomogram through a univariate analysis and subsequent multivariate analysis. In the nomogram we established, the presence of liver metastases and the number of distant metastases made the largest prognostic contribution. Distant metastases of NPC most frequently involved the bone, lung and liver. Some studies have reported an association of hepatic invasion with poor survival in patients with NPC (12, 16, 19). In our study, we identified hepatic involvement as an important predictor of survival, which is consistent with previous reports. Regarding the number of metastatic lesions, most clinicians are only concerned with the distinction between oligometastasis and non-oligometastasis, as the former has been associated with a more favorable OS compared to widespread metastases (17, 20). However, it should be noted that some patients with multiple metastatic lesions still

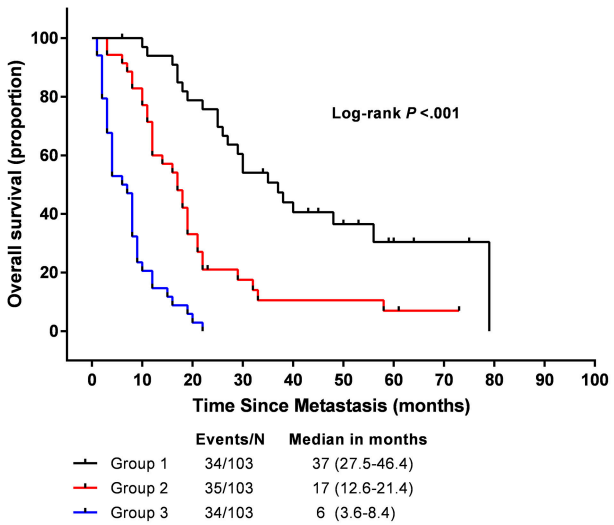

FIGURE 3 | Overall survival in the subgroup according to a tertiles of the total score from nomogram.

achieved relatively good survival outcomes. Therefore, it is important to clarify the relationship between the number of metastases and long-term survival. In our study, we used a ROC analysis to calculate the most discriminative cut-off value of the number of metastatic lesions and found an association of fewer than 8 metastases with better clinical outcomes. A similar study by Tian (21) used a cut-off number of 6 metastatic lesions to further confirm the relationship between a higher number of metastases and poorer survival.

Chemotherapy has also been selected as a candidate factor in this study because it has been recommended as a routine treatment for advanced NPC worldwide. However, the efficacy of chemotherapy regimens remains controversial, and a considerable number of publications have addressed this issue (22–24). In our study, the patients who received more than 2 cycles of chemotherapy were associated with a better OS. Another prognostic factor we selected from metastatic NPC is the N stage, this is because most NPC patients present with neck lymph node metastasis at the time of the initial diagnosis, and emerging evidence suggests that lymph node metastasis increases the risk of metastatic seeding of distant organs and correlates with an unfavorable prognosis (25, 26). Consistent with previous reports, our study further supports the relationship between the higher N stage and the poorer clinical outcome.

In-depth studies of the tumor–inflammation link have identified several blood markers as potential indicators of systemic inflammation and predictors of prognosis in patients with cancer, including the dNLR, C-reactive protein, albumin and LDH. The pretreatment dNLR, which reflects both the neutrophil and lymphocyte counts, can be easily determined in daily clinical practice via peripheral blood testing. A previous study of more than 12,000 patients has also supported the relationship between the higher value of dNLR and poorer OS outcome in different types of cancers (27). One of the possible reasons is that neutrophils can inhibit activated T cells and NK cells to induce immune suppression, while lymphocytes can inhibit tumor cell proliferation and metastasis via anti-tumorigenic responses involving cytokine production and cytotoxic cell death (28).

It should be noted that our nomogram model does not include the plasma EBV DNA concentration. Although this factor has been considered as a potential prognosticator of NPC (29), its significance in terms of metastatic NPC remains uncertain. Additionally, many medical centers do not routinely detect the EBV DNA concentration, for which a globally standardized methodology has not been determined (6). Regarding our study, our hospital began to measure plasma EBV DNA concentrations in 2014; accordingly, this information was not available for roughly half of our cohort. Nonetheless, we admit that the exclusion of plasma EBV DNA is a limitation of our nomogram.

To the best of our knowledge, ours is the first nomogram constructed to estimate the survival of patients with synchronous and metachronous metastases of NPC. This easily used scoring system will allow clinicians and patients to perform individualized survival predictions, and the identification of subgroups of patients with different survival risks may have an impact on the selection of therapeutic regimens or care. Furthermore, our nomogram may help clinicians to address the controversial issue of screening for patients requiring additional or more intensive follow-up and could provide information useful for patient stratification in the context of a clinical investigation. Finally, our nomogram represents a more precise prognostic model when compared with the TNM staging system and some previous prognostic models.

Despite these strengths, our study has some limitations of note. First, this was a retrospective study involving a limited number of patients at a single center. A continue study with a larger patient population and external verified cohort is currently carried out by our team. Second, we used the previous version of the AJCC staging system (2009) in this study. However, in the latest version of AJCC (2017), there has only been moderate changes in the T staging and basically no relevant changes to the N and M staging. Additionally, although the internal calibration indicated a good predictive ability, the C-index for OS prediction was 0.824 (95% CI, 0.74–0.91); in other words, an external cohort is required to validate the usefulness of this model. We encourage additional prospective data collection, broader geographic recruitment and the incorporation of some other factors to improve this model.

In conclusion, we have established a novel nomogram predictive of survival in patients with distant metastases of NPC. Notably, each factor included in our nomogram is easily obtained at most hospitals. Using this model, physicians could precisely estimate the survival of individual patients and identify subgroups of patients requiring specific therapeutic strategies. Prospective randomized studies to validate this nomogram are warranted.

ETHICS STATEMENT

The institutional review board of the First Affiliated Hospital of Xiamen University had approved this study.

AUTHOR CONTRIBUTIONS

LZ: Study concept and design, acquisition and analysis of patient data, drafting of the manuscript; QiuL: Acquisition and analysis of patient data, drafting of the manuscript; JG: Acquisition and analysis of patient data, software; HZ: Formal analysis, software; HC: Conceptualization, writing—review and editing; QinL: Study concept and design, funding acquisition, writing—review.

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REFERENCES

1. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev*. (2006) 15:1765–77. doi: 10.1158/1055-9965.EPI-06-0353
2. Jin Y, Shi YX, Cai XY, Xia XY, Cai YC, Cao Y, et al. Comparison of five cisplatin-based regimens frequently used as the first-line protocols in metastatic nasopharyngeal carcinoma. *J Cancer Res Clin Oncol*. (2012) 138:1717–25. doi: 10.1007/s00432-012-1219-x
3. Liu MT, Hsieh CY, Chang TH, Lin JP, Huang CC, Wang AY. Prognostic factors affecting the outcome of nasopharyngeal carcinoma. *Jpn J Clin Oncol*. (2003) 33:501–8. doi: 10.1093/jjco/hyg092
4. Chiesa F, De Paoli F. Distant metastases from nasopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec*. (2001) 63:214–6. doi: 10.1159/000055743
5. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet*. (2016) 388:1883–92. doi: 10.1016/S0140-6736(16)31388-5
6. Tang LQ, Li CF, Li J, Chen WH, Chen QY, Yuan LX, et al. Establishment validation of prognostic nomograms for endemic nasopharyngeal carcinoma. *J Natl Cancer Inst*. (2016) 108. doi: 10.1093/jnci/djv291
7. Liao LJ, Hsu WL, Wang CT, Lo WC, Cheng PW, Shueng PW, et al. Prognostic impact of pre-treatment neutrophil-to-lymphocyte ratio (NLR) in nasopharyngeal carcinoma: a retrospective study of 180 Taiwanese patients. *Clin Otolaryngol*. (2018) 43:463–9. doi: 10.1111/coa.13222
8. Liu N, Chen NY, Cui RX, Li WF, Li Y, Wei RR, et al. Prognostic value of a microRNA signature in nasopharyngeal carcinoma: a microRNA expression analysis. *Lancet Oncol*. (2012) 13:633–41. doi: 10.1016/S1470-2045(12)70102-X
9. Lin JC, Chen KY, Wang WY, Jan JS, Liang WM, Tsai CS, et al. Detection of Epstein-Barr virus DNA in the peripheral-blood cells of patients with nasopharyngeal carcinoma: relationship to distant metastasis survival. *J Clin Oncol*. (2001) 19:2607–15. doi: 10.1200/JCO.2001.19.10.2607
10. Li YQ, Tian YM, Tan SH, Liu MZ, Kusumawidjaja G, Ong EHW, et al. Prognostic model for stratification of radioresistant nasopharynx carcinoma to curative salvage radiotherapy. *J Clin Oncol*. (2018) 36 891–9. doi: 10.1200/JCO.2017.75.5165
11. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build interpret a nomogram for cancer prognosis. *J Clin Oncol*. (2008) 26:1364–70. doi: 10.1200/JCO.2007.12.9791
12. Bensouda Y, Kaikani W, Ahbeddou N, Rahhali R, Jabri M, Mrabti H, et al. Treatment for metastatic nasopharyngeal carcinoma. *Eur Ann Otorhinolaryngol Head Neck Dis*. (2011) 128:79–85. doi: 10.1016/j.anorl.2010.10.003
13. Razak AR, Siu LL, Liu FF, Ito E, O'Sullivan B, Chan K. Nasopharyngeal carcinoma: the next challenges. *Eur J Cancer*. (2010) 46:1967–78. doi: 10.1016/j.ejca.2010.04.004
14. Pan CC, Wu PH, Yu JR, Li W, Huang ZL, Wang JP, et al. Comparative survival analysis in patients with pulmonary metastases from nasopharyngeal carcinoma treated with radiofrequency ablation. *Eur J Radiol*. (2012) 81 e473–7. doi: 10.1016/j.ejrad.2011.05.037
15. Pan C, Wu P, Yu J, Li W, Huang Z, He N, et al. CT-guided radiofrequency ablation prolonged metastatic survival in patients with liver metastases from nasopharyngeal carcinoma. *Int J Hyperthermia*. (2011) 27:549–54. doi: 10.3109/02656736.2011.593019
16. Ong YK, Heng DM, Chung B, Leong SS, Wee J, Fong KW, et al. Design of a prognostic index score for metastatic nasopharyngeal carcinoma. *Eur J Cancer*. (2003) 39:1535–41. doi: 10.1016/S0959-8049(03)00310-1
17. Jin Y, Cai XY, Cai YC, Cao Y, Xia Q, Tan YT, et al. To build a prognostic score model containing indispensible tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area. *Eur J Cancer*. (2012) 48:882–8. doi: 10.1016/j.ejca.2011.09.004
18. Imai K, Allard MA, Castro Benitez C, Vibert E, Sa Cunha A, Cherqui D, et al. Nomogram for prediction of prognosis in patients with initially unresectable colorectal liver metastases. *Br J Surg*. (2016) 103:590–9. doi: 10.1002/bjs.10073
19. Pan CC, Lu J, Yu JR, Chen P, Li W, Huang ZL, et al. Challenges in the modification of the M1 stage of the TNM staging system for nasopharyngeal carcinoma: a study of 1027 cases review of the literature. *Exp Ther Med*. (2012) 4:334–8. doi: 10.3892/etm.2012.584
20. Khanfir A, Frikha M, Ghorbel A, Drira MM, Daoud J. Prognostic factors in metastatic nasopharyngeal carcinoma. *Cancer Radiother*. (2007) 11:461–4. doi: 10.1016/j.canrad.2007.06.006
21. Tian YH, Zou WH, Xiao WW, Zeng L, Yuan X, Bai L, et al. Oligometastases in AJCC stage IVc nasopharyngeal carcinoma: a subset with better overall survival. *Head Neck*. (2016) 38:1152–7. doi: 10.1002/hed.24345
22. Peng PJ, Lv BJ, Tang C, Liao H, Lin Z, Liu YM, et al. Phase II trial of docetaxel combined with nedaplatin for patients with recurrent metastatic nasopharyngeal carcinoma. *Drug Des Devel Ther*. (2015) 9:6401–5. doi: 10.2147/DDDT.S95946
23. Li YH, Wang FH, Jiang WQ, Xiang XJ, Deng YM, Hu GQ, et al. Phase II study of capecitabine cisplatin combination as first-line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma. *Cancer Chemother Pharmacol*. (2008) 62:539–44. doi: 10.1007/s00280-007-0641-2
24. Chua DT, Sham JS, Au GK. A phase II study of docetaxel cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. *Oral Oncol*. (2005) 41:589–95. doi: 10.1016/j.oraloncology.2005.01.008
25. Pereira ER, Jones D, Jung K, Padera TP. The lymph node microenvironment its role in the progression of metastatic cancer. *Semin Cell Dev Biol*. (2015) 38:98–105. doi: 10.1016/j.semcdb.2015.01.008
26. Pereira ER, Kedrin D, Seano G, Gautier O, E.Meijer FJ, Jones D, et al. Lymph node metastases can invade local blood vessels, exit the node, colonize distant organs in mice. *Science*. (2018) 359:1403–7. doi: 10.1126/science.aal3622
27. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in

patients with cancer. *Br J Cancer*. (2012) 107:695–9. doi: 10.1038/bjc.2012.292

28. Zhao L, Chen H, Hu B, Zhang H, Lin Q. Prognostic significance of Ki67 expression the derived neutrophil-lymphocyte ratio in nasopharyngeal carcinoma. *Cancer Manag Res.* (2018) 10:1919–26. doi: 10.2147/CMAR.S167626
29. Wang WY, Twu CW, Chen HH, Jan JS, Jiang RS, Chao JY, et al. Plasma EBV DNA clearance rate as a novel prognostic marker for metastatic/recurrent nasopharyngeal carcinoma. *Clin Cancer Res.* (2010) 16:1016–24. doi: 10.1158/1078-0432.CCR-09-2796

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REVIEW
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Cetuximab-Containing Combinations in Locally Advanced and Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Cetuximab remains to date the only targeted therapy approved for the treatment of head and neck squamous cell carcinoma (HNSCC). The EGFR pathway plays a key role in the tumorigenesis and progression of this disease as well as in the resistance to radiotherapy (RT). While several anti-EGFR agents have been tested in HNSCC, cetuximab, an IgG1 subclass monoclonal antibody against EGFR, is the only drug with proven efficacy for the treatment of both locoregionally-advanced (LA) and recurrent/metastatic (R/M) disease. The addition of cetuximab to radiotherapy is a validated treatment option in LA-HNSCC. However, its use has been limited to patients who are considered unfit for standard of care chemoradiotherapy (CRT) with single agent cisplatin given the lack of direct comparison of these two regimens in randomized phase III trials and the inferiority suggested by metanalysis and phase II studies. The current use of cetuximab in HNSCC is about to change given the recent results from randomized prospective clinical trials in both the LA and R/M setting. Two phase III studies evaluating RT-cetuximab vs. CRT in Human Papillomavirus (HPV)-positive LA oropharyngeal squamous cell carcinoma (De-ESCALaTE and RTOG 1016) showed inferior overall survival and progression-free survival for RT-cetuximab combination, and therefore CRT with cisplatin remains the standard of care in this disease. In the R/M HNSCC, the EXTREME regimen has been the standard of care as first-line treatment for the past 10 years. However, the results from the KEYNOTE-048 study will likely position the anti-PD-1 agent pembrolizumab as the new first line treatment either alone or in combination with chemotherapy in this setting based on PD-L1 status. Interestingly, cetuximab-mediated immunogenicity through antibody dependent cell cytotoxicity (ADCC) has encouraged the evaluation of combined approaches with immune-checkpoint inhibitors in both LA and R/M-HNSCC settings. This article reviews the accumulated evidence on the role of cetuximab in HNSCC in the past decade, offering an overview of its current impact in the treatment of LA and R/M-HNSCC disease and its potential use in the era of immunotherapy.

Keywords: head and neck cancer, head and neck squamous cell carcinoma, HPV-positive head and neck cancer, head and neck cancer treatment, anti-EGFR therapy, cetuximab

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INTRODUCTION

The role of the epidermal growth factor receptor (EGFR) in the development and progression of head and neck squamous cell carcinoma (HNSCC) has been widely studied (1). EGFR is a transmembrane glycoprotein member of the tyrosine kinase growth factor receptor family that regulates cell growth and proliferation (2). This receptor is overexpressed in up to 90% of HNSCC and has been associated with decreased survival (2–4). The accumulating evidence led to the evaluation of agents targeting the EGFR pathway in this tumor type.

Cetuximab is the only anti-EGFR agent that has been proven effective for the treatment of HNSCC thus far (5, 6). Cetuximab is a chimeric IgG1-subclass monoclonal antibody that binds to the extracellular domain of the EGFR with higher affinity than the natural ligands EGF and TGFα, blocking the activation of its intracellular domain and subsequent tyrosine kinase-dependent signal transduction pathway (7). Cetuximab also stimulates the internalization of EGFR, removing the receptor from the cell surface and thus preventing its interaction with the ligand (8). Additionally, as an IgG1 molecule, it stimulates antibody dependent cell cytotoxicity (ADCC) (9, 10). Several preclinical studies demonstrated that EGFR inhibition by cetuximab increases the efficacy of radiotherapy (RT) (11) since it decreases the proportion of cells in S phase and increases that of G1 phase, facilitates apoptosis, decreases the capacity of DNA repair, and has an antiangiogenic effect (12, 13). Moreover, cetuximab enhanced the antitumor activity of several chemotherapeutic drugs in mouse xenograft models (14).

Cetuximab reached the clinics a decade ago at a time where treatment options for HNSCC were very limited. Chemo-RT (CRT) or RT alone depending on patients' functional status and comorbidities were the only available conservative treatment options in the locally-advanced (LA) setting. Cetuximab improved the variability of choice (5) although the clinical practice finally positioned its use in combination with RT (RT-Cx) to those patients unfit to receive high dose cisplatin or those who had previously received three cycles of cisplatin-based induction chemotherapy (ICT) and had significant residual toxicity. In recurrent/metastatic (R/M) HNSCC, we had to choose between monotherapy and polychemotherapy until the results from the EXTREME trial. The addition of cetuximab to first-line chemotherapy significantly improved disease control and overall survival (OS) when compared to chemotherapy alone becoming the new standard of care in this patient population (6). However, despite the EXTREME regimen has remained the recommended first-line as per the clinical guidelines for the past 10 years, its use has been limited outside Europe. Nevertheless, the results of the KEYNOTE-048 clinical trial (NCT02358031) evaluating the activity of pembrolizumab (anti-PD-1 therapy) with or without chemotherapy will likely lead immunotherapy to the first line treatment for the majority of R/M HNSCC patients (15).

Besides cetuximab, several anti-EGFR monoclonal antibodies have been tested in HNSCC, including panitumumab, zalutumumab and nimozutumab (1, 16–18). Among all these, panitumumab is the only one that has been evaluated in randomized phase III clinical trials in both LA and R/M disease, failing to show any improvement in LRC or survival when compared to the standard of care (16, 19). Some authors argued that, unlike cetuximab (IgG1), the inability of panitumumab (IgG2) to produce antitumor activity through ADCC and natural killer (NK) cell activation might have explained the lack of benefit from this agent in HNSCC (7, 20). To date, cetuximab is the only anti-EGFR antibody with proven efficacy and survival gain in HNSCC.

In this article, the authors review the evidence accumulated on the role of cetuximab in HNSCC in the past decade, offering an overview of its current impact in the treatment of LA and R/M disease and its potential use in the era of immunotherapy.

LOCALLY-ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Has Cetuximab Reached a Plateau in the Treatment of LA-HNSCC?

Cetuximab is the only targeted therapy that has been proven effective for the treatment of LA-HNSCC (5). The implications of EGFR overexpression in resistance to RT has been reported in several studies (2, 13). Preclinical models showed that EGFR blockade by cetuximab increases radiation-induced apoptosis and blocks secondary repair mechanisms dependent on PI3K/AKT/MAPK and JAK/STAT3 downstream signaling pathways, indicating a synergistic effect of the RT-Cx combination (21, 22). In 2006, the Bonner randomized phase III study evaluated the addition of cetuximab to RT in over 400 patients with LA-HNSCC showing a significant improvement in locoregional control (LRC) (24.4 vs. 14.9 months, $p = 0.005$) and OS (49 vs. 29 months, $p = 0.006$) with the combination (5). These results led to the FDA approval of cetuximab for the treatment of LA-HNSCC and RT-Cx was incorporated in the clinical guidelines as a validated alternative to standard chemoradiotherapy (CRT) in this setting (23, 24).

The survival benefit obtained by the addition of cetuximab to RT was confirmed by the 5-year update of the Bonner trial (5-year OS of 45.6% for the combination vs. 36.4% for RT alone, $p = 0.018$). However, the lack of a direct comparison with standard of care CRT in randomized phase III trials and the differential toxicity profile of both drugs contributed to limit the use of RT-Cx to patients considered "unfit" for cisplatin-based CRT despite this patient population was not represented in the Bonner trial (25, 26). Whether both treatments are equivalent in terms of efficacy has remained unclear over the years as several retrospective series and meta-analysis had showed mixed results (27–30). The meta-analysis conducted by Huang et colleagues in 2016 including up to 31 studies and over 4,000 patients showed no differences in disease control or survival beyond the 2-year threshold between both treatment combinations, although the overall pooled HR for OS, progression-free survival (PFS) and LRC were significantly inferior in the arm of RT-Cx (31). However, the intrinsic limitations of the retrospective analyses including unmatched patient characteristics and biased treatment selection based on

patient's baseline condition difficulted the interpretation of these data. The prospective randomized phase II trial evaluating CRT vs. RT-Cx conducted by Magrini et al. failed to show any significant differences in treatment outcome between both arms, despite the 2-year LRC and 2-year cancer specific survival rates were lower among patients treated with RT-Cx (53 vs. 80%; and 68 vs. 81%, respectively) (32). Since the study was stopped prematurely, with only 35 patients per arm, it was underpowered for its primary endpoint, hence definitive conclusions could not be drawn from its results. In HPV-positive LA oropharyngeal cancer (OPC), two randomized phase III studies evaluating RT-Cx vs. CRT (CDDP) in HPV-positive LA-OPC (De-ESCALAaTE and RTOG 1016) have recently reported significantly worse survival and disease control rates in the RT-Cx arm (33, 34). A phase III randomized prospective study comparing RT-Cx vs. CRT in LA-HNSCC with OS as primary endpoint is currently on-going and might provide a more definitive answer (NCT01969877).

The positive results obtained by the addition of cetuximab to platinum-based chemotherapy in the first line R/M HNSCC led to its evaluation in combination with CRT and ICT in the LA setting (35–39). Few publications have reviewed the studies conducted to date indicating that intensification therapy with cetuximab given concurrently with CRT does not seem to improve patient outcome but adds significant toxicity (1, 40, 41). The only phase III randomized trial evaluating cetuximab plus standard CRT with single agent cisplatin vs. CRT failed to show any improvement in LRC, distant control nor survival in the cetuximab arm but did show higher rate of grade 3/4 toxicity (36). Recently, the GORTEC 2007-01 phase III study that evaluated RT-Cx plus carboplatin and 5-FU vs. RT-Cx alone showed no OS benefit despite better PFS and LRC, with again significantly grade 3–4 toxicity increment (42).

The addition of cetuximab to different ICT regimens appeared to improve response rates and extend survival when compared to historical controls, especially when combined with taxane-based chemotherapy regimens (43–45). The role of ICT in LA-HNSCC has been widely debated since it has not demonstrated a sustained survival benefit when compared to standard CRT in randomized trials (44, 46–49). Overall, the lack of control arms allowing direct comparison in the studies evaluating cetuximab-based ICT combinations and the severe toxicity increased in some of the trials, particularly when using the TPF regimen, has precluded a widespread use of this treatment modality among the head and neck community (49–51). However, RT-Cx given sequentially to ICT does seem to offer similar results in terms of efficacy when compared to standard CRT, with an overall acceptable toxicity, which is particularly relevant in patients who previously received cisplatin as part of the ICT (37, 39, 52, 53).

To date, no randomized phase III trials have evaluated the role of cetuximab vs. cisplatin in the adjuvant treatment of resected LA-HNSCC. The phase II study RTOG-0234 did investigate the addition of cetuximab to weekly docetaxel or cisplatin and RT in patients with resected HNSCC and high risk features (positive margins and/or extranodal extension) (54). Despite both regimens were tolerable, and the combination with docetaxel showed promising disease-free survival, these regimens were never compared against standard post-operative high-dose cisplatin and RT in a randomized study, and therefore its use was not widespread. Similarly, the ACCRA-HN phase 2 study compared post-operative RT-Cx vs. RT-Cx plus cisplatin and 5-FU (NCT00791141), although the results of these study have not been published yet.

Overall, with the current available data, RT-Cx remains a valid treatment option for the treatment of LA-HNSCC, although standard of care CRT (cisplatin 100 mg/m^2 every 3 weeks) should be pursued when feasible. Sequential RT-Cx following ICT as part of organ-preservation strategy is a reasonable alternative to avoid acute and late toxicity, but other treatment combinations should be avoided. There is no evidence to support the use of cetuximab in the adjuvant setting.

Other Cetuximab Containing Combinations in LA-HNSCC

Cetuximab has also been investigated in combination with a variety of chemotherapy agents and targeted therapies in multiple clinical trials for LA-HNSCC although none of them has reached the clinics yet. Based on the good results observed in combination with taxanes in the R/M setting and within ICT regimens in the LA disease above mentioned, a few trials evaluated the combination of cetuximab with taxanes concurrent with RT. A phase I/II study investigated nab-paclitaxel plus cetuximab and low-dose cisplatin (20 mg/m^2) showing similar 2-year PFS compared to historical controls (60%) and tolerable toxicity, but no further evaluation of this regimen is on-going (55). A separate phase II randomized study is evaluating docetaxel plus cetuximab concurrent with RT vs. standard CRT, but results are yet to be presented (NCT02128906). Other chemotherapy combinations, such as pemetrexed plus cetuximab and RT have also been tested in phase II studies with similar efficacy and tolerability, but have not been further investigated in phase III randomized trials (56). In regards to targeted therapies, Bevacizumab, an anti-VEGF monoclonal antibody, has been investigated in combination with cetuximab in the LA-HNSCC based on preclinical data suggesting a key role for VEGF pathway in the resistance to RT and Cetuximab (57, 58). Given the promising activity and tolerability seen in early studies performed in the R/M setting, two phase II studies evaluated bevacizumab in combination with RT plus pemetrexed and RT plus cisplatin (59, 60). Despite positive results in terms of efficacy, the increased toxicity and the lack of comparative arms precluded further investigation of bevacizumab in this setting. Other antiangiogenic agents, such as sunitinib, have been combined with cetuximab (NCT00906360) but results are still pending.

The inhibition of other molecular targets including the Src family kinase, the Poly (ADP-Ribose) Polymerase (PARP), Cyclin Dependent Kinase complex (CDK) has shown to have a synergistic effect in combination with EGFR blockade by cetuximab and overcome resistance to this agent according to several studies using preclinical models (61–64). Dasatinib (SRC inhibitor), olaparib (PARP inhibitor), and pablociclib (selective CDK 4/6 Inhibitors) are currently subject of investigation in combination with cetuximab and RT in the LA setting (NCT00882583, NCT01758731, NCT03024489, respectively). Despite preliminary results from early trials have showed a safe toxicity profile with the combination, their efficacy is yet to

be determined (65, 66). Noteworthy, preclinical studies using xenograft models suggested that dasatinib might be detrimental for tumor control when combined with cetuximab and RT (61). Therefore, we must remain cautious while awaiting the results from the ongoing clinical trials.

A summary of published phase II/III studies evaluating cetuximab combinations in LA-HNSCC is provided (**Supplementary Table 1**).

Patient Selection: Are the Bonner Trial Results Reproducible in Daily Practice?

Besides the severity of cetuximab-induced skin rash no other biomarkers have shown to predict clinical activity of cetuximab (67). Several biological and molecular candidates have been tested including EGFR protein expression, truncated receptor variants, such as EGFRvIII, or mutations at the level of EGFR gene or downstream, such as KRAS, but thus far none of them has been proven effective in predicting response (or resistance) to cetuximab in HNSCC (68–71). Therefore, treatment selection between standard CRT and RT-Cx in patients with LA-HNSCC has been often based on patient baseline condition and comorbidities, taking into consideration the differential toxicity profile between cetuximab and cisplatin. Patients with significant comorbidities and/or poor ECOG performance status and the elderly are usually ineligible for cisplatin and as such, they tend to be treated with cetuximab (72). Cetuximab's acute side effects mainly include infusion reactions, skin rash and mucositis, with no major organ-specific or chronic toxicity described, making it a suitable option for this patient population (29). However, the majority of patients enrolled in the Bonner study were under 70 years old, with no significant comorbidities and a Karnofsky index $\geq$80 (5). In this regard, an exploratory *post-hoc* analysis published in the 5-year update of the Bonner trial suggested that younger patients with good performance status were more likely to benefit from this combination (25). Several studies have reported increased risk of local and systemic toxicity from cetuximab in patients at older age, with significant baseline comorbidities or with poor performance status, including cytopenia, bloodstream infections and sepsis (73). Some authors have postulated that fragile patients might be more susceptible to toxicity due to local and systemic inflammatory responses triggered by cetuximab-induced antibody-dependent cellular cytotoxicity (74).

Altogether these data suggest that the expected efficacy and toxicity from RT-Cx might differ when compared to the Bonner trial in our daily practice given our biased patient selection for this treatment. Hence, the need for prospective trials focusing on this frail population is timely.

RECURRENT OR METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA

Cetuximab in R/M HNSCC

In 2006, a phase I/II study investigating cetuximab in combination with cisplatin/carboplatin and 5-FU in R/M HNSCC showed promising activity and acceptable tolerability (75). The subsequent phase III randomized study evaluating the addition of cetuximab to cisplatin/carboplatin and 5-FU for a total of 6 cycles followed by maintenance cetuximab (EXTREME regimen) vs. chemotherapy alone in the first-line R/M setting conducted by Vermorken and colleagues demonstrated the superiority of the combination in terms of OS and response rate (6). The combined regimen improved both OS and PFS from 7.4 to 10.1 months; and from 3.3 to 5.6 months, respectively, when compared to chemotherapy alone. The overall response rate (ORR) was also increased from 20 to 36% with the combination. The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19 and 13%, respectively), neutropenia (23 and 22%), and thrombocytopenia (11% in both groups). Of 219 patients receiving cetuximab, 9% had grade 3 skin reactions (6). The results from this study set the EXTREME regimen as the new standard of care for the first-line treatment of R/M HNSCC (24, 76), which has remained unchanged since 2008. Noteworthy, subsequent observational studies (SOCCER, DIRECT, ENCORE) endorsed the results from the EXTREME study in the daily clinical practice (76–78). In addition, about 14% of the patients treated with the EXTREME regimen have been reported to have long-term responses (35).

Several randomized trials are currently evaluating immune-checkpoint inhibitors (ICI) alone or in combination with chemotherapy against the EXTREME regimen in an attempt to improve patients' survival and quality of life. The main phase III randomized clinical trials are keynote-048 (NCT02358031), Kestrel (NCT02551159), and Checkmate-651 (NCT02741570) (**Figure 1**).

The preliminary results of the Keynote 048 trial have been recently presented. This phase III study evaluated the efficacy of pembrolizumab (anti-PD-1) alone and in combination with cisplatin/carboplatin plus 5FU vs. the EXTREME regimen as first-line therapy for R/M-HNSCC based on PD-L1 expression by CPS (combined positive score) (15). The study showed better OS in the pembrolizumab monotherapy arm vs. EXTREME when PD-L1 expression $\geq$1 and $\geq$20% by CPS (HR 0.78 [0.64–0.96], $p = 0.0086$ and HR 0.61 [0.45–0.83], $p = 0007$, respectively) and in the pembrolizumab plus chemotherapy arm vs. EXTREME regardless of PD-L1 expression (10.7 vs. 13 months, HR 0.77 IC 95% 0.63–0.93, $p = 0.0034$). With these results, pembrolizumab monotherapy and the combination of pembrolizumab-chemotherapy will likely become the new first line treatment for R/M-HNSCC based on CPS PD-L1 expression. However, the complete results of the study are still to be published, and full biomarker analyses are awaited.

Improving the EXTREME Regimen With Other Chemotherapy Agents

Within the 3 drugs of the EXTREME regimen, 5-FU is the most difficult one to be administered in terms of logistics, as it requires 24-h continuous infusion for a total of 4 days. Furthermore, 5-FU is associated with increased rate of mucositis and diarrhea, and its use is not recommended in patients with cardiovascular diseases or with dihydropyrimidine dehydrogenase deficiency. Therefore,

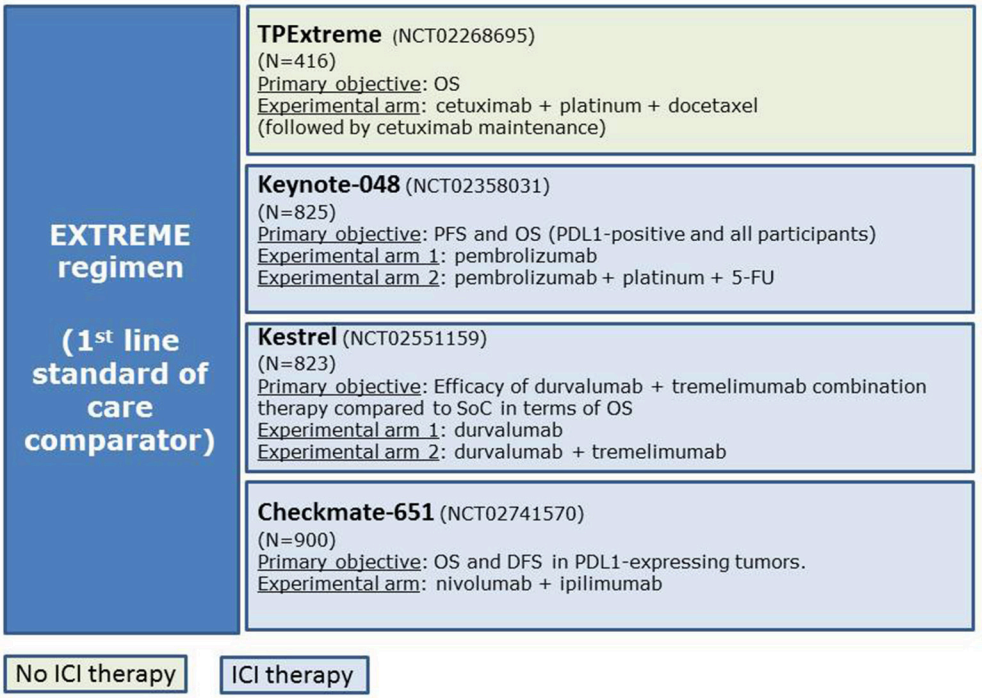

FIGURE 1 | Main clinical trials evaluating the efficacy of new schemes of treatments compared with the EXTREME regimen.

the substitution of 5-FU with a taxane is being investigated as a potentially new scheme for R/M-HNSCC. Preclinical data have suggested a synergistic effect when combining taxanes with cetuximab (79). Bossi et al. demonstrated in a phase IIb clinical trial (B409) that the cetuximab-cisplatin regimen was non-inferior to the cetuximab-cisplatin-paclitaxel regimen in terms of PFS [HR for cetuximab-cisplatin vs. cetuximab-cisplatin-paclitaxel [0.99; 95% CI: 0.72–1.36, $P = 0.906$; margin of non-inferiority (90% CI of 1.4) not reached] (80). Interestingly, the ORR achieved by the three drugs regimen was >50%. Grade 4 toxicities were reported in 14% of patients receiving cetuximab-cisplatin and 33% of those receiving cetuximab-cisplatin-paclitaxel ($P = 0.015$), but by substituting 5-FU for paclitaxel, the rates of grade_3 cardiac toxicity appeared lower in both arms and no sepsis was described compared to EXTREME regimen (80). Argiris et al. introduced for the first time the combination of cisplatin-docetaxel-cetuximab in a phase II clinical trial for LA-HNSCC (81). The GORTEC group developed this combination (named "TPEx") in a phase II study (GORTEC 2008-03) for R/M disease (82). They demonstrated that 4 cycles of docetaxel combined with cisplatin (75 mg/m^2 both at day 1) and weekly cetuximab (250 mg/m^2) followed by maintenance cetuximab (500 mg/m^2, every 2 weeks) were feasible, active, and with a manageable safety profile in fit patients with R/M HNSCC. ORR at week 12 was 44.4%; median OS and PFS were 14.0 and 6.2 months, respectively. In addition, the ORR increased to, 16.8 and 7.1 months in the population of patients with disease control after the initial 4 cycles of complete TPEx regimen. The European TPEx randomized phase II study evaluating the TPEx regimen vs. the EXTREME regimen is currently ongoing and will contribute in determining which one might be the best treatment option for the first-line treatment in this patient population (NCT02268695). Other taxane-based combinations in first-line R/M-HNSCC are also being currently evaluated, such as the phase II study CACTUX trial investigating nab-paclitaxel and cetuximab (NCT02270814).

From the Clinical Trial to an Outpatient Clinic: Treatment for Unfit Patients.

In daily clinical practice, a considerable number of patients with HNSCC have significant comorbidities and/or a frail functional status that makes them unfit to receive the EXTREME regimen. This patient population is usually underrepresented in clinical trials. Despite the lack of prospective randomized data, the combination of taxanes with cetuximab or a single agent (paclitaxel, docetaxel, cetuximab, methotrexate, 5-FU, capecitabine…) have been suggested as alternative treatment options for these patients. (83). The combination of docetaxel/paclitaxel with cetuximab appears to have a manageable safety profile and good response rates. Few prospective single-arm phase II studies have investigated this combination: the first study was conducted by Hitt et al. and evaluated cetuximab plus paclitaxel as first-line treatment showing an ORR of 54% (95% CI: 39–69) (84). Interestingly, 61% of the population included in the trial had a Karnofky Index of 70–80%. The Knoedler et al. study evaluated cetuximab plus docetaxel in patients who failed a platinum-based therapy, achieving an overall disease control rate of 51% (85). Recently, a retrospective study showed that the combination of paclitaxel

and cetuximab could be a suitable treatment option in HNSCC patients with platinum-based CRT-refractory disease (86).

In addition, based on the keynote 048 preliminary results (15), pembrolizumab monotherapy might represent an option in patients unfit for cisplatin-based chemotherapy.

Cetuximab Containing Combinations in R/M HNSCC

The combination of cetuximab with different chemotherapy regimens and with other targeted agents against key pathways involved in HNSCC tumorigenesis and progression has been investigated in several clinical trials.

Besides the EXTREME regimen and taxane-based chemotherapy combinations, cetuximab has been also been evaluated in combination with other chemotherapies, such as pemetrexed or methotrexate. A phase III study comparing pemetrexed plus cisplatin vs. cisplatin alone in R/M HNSCC did not significantly improve survival for the intent-to-treat population (87). Despite this result, a phase II study evaluated the addition of cetuximab to this regimen. However, the study did not reach its primary end-point (PFS) and was considered negative (88). The Dutch Head and Neck Society is currently investigating cetuximab in combination with methotrexate in a Phase Ib-II study (NCT02054442).

Phosphatidylinositol 3-kinase (PI3-K) inhibitors were one of the most promising targeted therapies for cetuximab-based combinations given the relevance of the PI3K pathway in proliferation, apoptosis and cell differentiation of HNSCC. Two phase Ib/II studies are investigating the combinations of cetuximab and PI3K inhibitors, the first one with BKM 120 (NCT01816984), and the second one with BYL719 (NCT01602315). A randomized phase II study evaluated the addition of PX-866 to cetuximab in patients with advanced R/M-HNSCC; PX-866 addition did not show any significant improvement in PFS nor OS (89).

Cilengitide, an integrin inhibitor, has also been investigated in the ADVANTAGE phase I/II study. The phase II part was a multicenter, open-label, randomized and controlled study investigating cilengitide 2,000 mg once or twice weekly plus chemotherapy based on EXTREME regimen vs. EXTREME regime alone. Neither of the cilengitide-containing regimens demonstrated a PFS benefit over EXTREME regimen alone in R/M-SCCHN patients (90).

Preclinical studies had also suggested that mammalian target of rapamycin (mTOR) inhibitors might overcome the resistance to EGFR blockade and augment cetuximab efficacy. The combination of everolimus (RAD001) with cetuximab and carboplatin was explored in a phase I study showing encouraging antitumor activity in a selected group of patients (91). The currently on-going MAESTRO study is evaluating temsirolimus with or without cetuximab for previously treated R/M-HNSCC patient (NCT01256385).

Based on pre-clinical data, Argiris et al. conducted a phase II study to evaluate the efficacy of bevacizumab and cetuximab in patients with R/M SCCHN refractory to first-line treatment. The modest median PFS and OS (2.8 and 7.5 months, respectively) did no lead to further development of this regimen (59).

Other agents, such as patritumab (U3-1287), an anti-HER3 monoclonal antibody, in combination with platinum-based therapy and cetuximab has been studied in a double-blind phase 2 study, but no results have been released yet (NCT02633800). Cyclin-dependent-kinase-inhibitors, such as palbociclib are also been tested in combination with avelumab and cetuximab for R/M-HNSCC (NCT03498378).

A summary of published phase II/III studies evaluating cetuximab combinations in RM-HNSCC is provided (**Supplementary Table 2**).

CETUXIMAB IN HPV-POSITIVE OPC

HPV-positive OPC represents a biologically distinct disease characterized by increased radiosensitivity and improved overall survival when compared to HPV-negative OPC (92, 93). Retrospective subgroup analyses from randomized trials had reported better outcome in patients with HPV-positive disease, regardless of treatment (94–96). Given the acute and potential long-term side-effects associated to CRT (97), many on-going clinical trials are currently evaluating de-escalation treatment strategies to reduce long-term toxicity without compromising survival in this subgroup of patients (98). Chemo-sparing approaches to replace cisplatin by other agents, such as cetuximab or immune checkpoint inhibitors (ICI) given concurrent with radiation are the most attractive options (NCT02254278, NCT01874171, NCT03410615). Main de-escalation clinical trials ongoing evaluating cetuximab in combination with RT are summarized on **Table 1**.

TABLE 1 | Main de-escalation clinical trials ongoing evaluating cetuximab in combination with RT for HPV-related OPSCC.

Strategy	Country	Trial	Phase	*N*	HPV diagnosis technic	Primary objective	Comments
Cetuximab with IMRT radiation (in comparison with IMRT-cisplatin)	US	RTOG 1016 NCT01302834	Phase III	987	$p16^{INK4a}$ IHC	OS (non-inferiority)	Cisplatin day 1 and 22
	Australia	TROG 1201 NCT01855451	Phase III	189	$p16^{INK4a}$ IHC	Symptom severity	Weekly cisplatin Evaluate smoking history
	UK	De-ESCALaTE NCT01874171	Phase III	334	$p16^{INK4a}$ IHC	Overall severe (acute and late) toxicity (Grade 3–5)	Cisplatin day 1, 22, and 43 Bulky disease with >10 p/y smoking history excluded

The role of cetuximab in HPV-positive OPC has been extensively debated (99, 100). The exploratory subgroup analysis from the 5-year survival update of the Bonner study seemed to favor the use of cetuximab in young patients (<65 years old), with primary OPC and high Karnofsky index (25). The *post-hoc* analysis published by Rosenthal et al. evaluating the differential effect of RT-Cx in p16-positive vs. p16-negative patients treated within the Bonner trial showed higher OS gain in the p16-positive subgroup (HR 0.38 vs. 0.93, respectively) (101). However, no significant interaction was observed between p16 positivity and treatment effect. Similarly, the exploratory subgroup analysis from the EXTREME trial in the recurrent/metastatic setting reported increased survival in HPV-positive vs. HPV-negative patients (102). Conversely, in the CONCERT-2 and SPECTRUM clinical trials evaluating panitumumab in the LA and R/M setting, respectively, patients with p16-positive tumors had significantly lower survival when compared to p16-negative disease (16, 45). The fact that both studies were negative for their primary endpoints and that the threshold used for p16 positivity was lower than the standard recommendations (10% staining instead of 70%) made interpretation of these results difficult.

The accumulating evidence on the biological rationale behind the use of cetuximab in HPV-positive disease had been inconsistent with the abovementioned subgroup analysis. Several studies had highlighted the absence of EGFR protein overexpression and EGFR/HER pathway activation in HPV-driven tumors (103–106). Moreover, a comprehensive analysis of the genomic landscapes of HPV-positive and negative HNSCC confirmed the lack of EGFR aberrations in HPV-positive tumors and an increased frequency of RAS mutations when compared to HPV-negative tumors (107). Noteworthy, anti-EGFR therapies are not currently recommended for treatment of anogenital HPV-positive cancer (108, 109) highlighting the lack of sense of targeting EGFR in HPV-related tumors.

In concordance with these data, latter studies did show decreased efficacy of RT-Cx in HPV-positive disease (27, 110). The interim subgroup analysis from a prospective phase II trial evaluating RT-cetuximab vs. CRT with weekly cisplatin in LA-HNSCC showed a trend favoring the cisplatin arm

TABLE 2 | Summarized of clinical data investigating anti-EGFR therapy on HPV-positive HNSCC.

References (Study)	Treatment	HPV positivity analysis	Result
Recurrent and metastatic HNSCC			
Vermorken et al. (45) (SPECTRUM)	Cisplatin and fluorouracil ± panitumumab	Prospective	Addition of panitumumab to cisplatin-based chemotherapy significantly improves OS and PFS only in HPV negative HNSCC patients
Vermorken et al. (90) (EXTREME)	Cisplatin and fluorouracil ± cetuximab	Retrospective	Survival benefit of adding cetuximab to platinum-based chemotherapy was independent of p16 status
Fayette et al. (111) (MEHGAN)	Cetuximab vs. cetuximab-duligotuzumab.	Prospective	HPV-negative HNSCC but not HPV-positive are most likely to respond to EGFR blockage by cetuximab or duligotuzumab.
Seiwert et al. (112) (BIBW 2992 trial)	Afatinib vs. cetuximab	Prospective	HPV positive HNSCC patients had a lower response rate to EGFR inhibitors compared with HPV negative patients
Locally advanced HNSCC			
Pajares et al. (113) (Restrospective series)	Cisplatin-RT vs. cetuximab-RT	Retrospective series	p16-positive patients may benefit more from RT combined with EGFR inhibitors than with cisplatin
Koutcher et al. (114) (Retrospective series)	Cisplatin-RT vs. cetuximab-RT	Retrospective series	Treatment with cisplatin not cetuximab predict for better OS, FFS and locoregional control
Ang et al. (36) (RTOG 0522 study)	Cisplatin ± cetuximab with AFX RT	Prospective	The addition of cetuximab produce no benefit in PFS or OS in patient with p16 positive or negative HNSCC
Rosenthal et al. (101) (IMCL-9815 phase III Study)	RT vs. cetuximab-RT	Retrospective	Better outcomes in both groups p16-positive and p16-negative when treated with cetuximab and RT in comparison with RT alone
Mesía et al. (115) (CONCERT-1)	Cisplatin-RDT ± panitumumab	Prospective	No benefit was noted with the addition of panitumumab in either PFS or OS in the patients with p16-postive tumors
Giralt et al. (16) (CONCERT-2)	Panitumumab-RT vs. cisplatin-RT	Prospective	Better outcomes for cisplatin-RT (few p16 positive patients included)
Ou et al. (116) (Retrospective series)	Cisplatin-RT vs. cetuximab-RT	Restrospective series	Better outcomes in patients receiving concurrent cisplatin over cetuximab regardless of HPV/p16 status
Mena et al. (117) (Retrospective series)	Cisplatin-RT vs. cetuximab-RT vs. surgery/RT vs. ICT/RT	Retrospective series	Improved OS for all treatment schemes with the exception of those who underwent cetuximab-RT

AFX RT, Accelerated fractionation radiotherapy; HNSCC, Head and neck squamous cell carcinoma; FFS, failure free survival; OS, overall survival; PFS, progression free survival; RT, radiotherapy.

in all outcome parameters including LRC, PFS and OS in the p16-positive group (NCT01216020) (110). Unfortunately, this study was terminated due to slow recruitment and the sample was limited and therefore unpowered to show significant differences. Summarized clinical data investigating anti-EGFR therapies on HPV-positive OPC are presented on **Table 2**. It is important to highlight that most of these studies based the HPV positivity on p16 staining exclusively. Recently published data suggest that p16 expression alone may not be accurate to classify OPC as HPV-positive, and other biomarkers, such as HPV DNA might be required to characterize these tumors (117–119).

The results from three de-escalation randomized phase III clinical trials (**Table 1**) evaluating RT-Cx vs. standard CRT with cisplatin provided a definitive answer regarding the role of cetuximab in HPV-positive OPC patients. The RTOG 1016, a phase III non-inferiority study showed inferior OS in the RT-Cx arm [5 years OS 84.6 (95% CI 73.4–82.5) vs. 77.9% (95% CI 73.4–82.5)] (34). The De-SCALaTE phase III clinical trial revealed the same rate of severe and all-grade toxicities when compared to CRT and worse OS in the RT-Cx arm (2 years OS 97.5 vs. 89.4%; HR = 4.99; 95% CI: 1.70–14.67 (33). Therefore, CRT will remain the standard of care for HPV-positive LA-OPC while awaiting results from other on-going de-escalation clinical trials.

FUTURE PERSPECTIVES: CETUXIMAB AND ICI

The efficacy of cetuximab has been partly attributed to its immunologic activity through ADCC, which is thought to link innate and adaptive antitumor immune responses via NK cells and antigen presenting cells that ultimately lead to EGFR-specific T cells (120, 121). Long-term survivorship described in patients with R/M HNSCC treated with cetuximab might be explained by sustained antitumor specific immune responses (122). The immunologic activity of cetuximab is of relevance in the era of immunotherapy. ICI will shortly become a backbone in the treatment of R/M HNSCC, and are already being investigated in the LA setting in combination with CRT or RT alone (NCT02952586, NCT03040999) (123, 124). Safety data from a phase I study combining ipilimumab (anti-CTLA-4 monoclonal antibody) with cetuximab and IMRT in LA-HNSCC (NCT01935921) was presented at ESMO meeting in 2016 by Bauman et al. (125). While dermatologic side-effects were the main dose-limiting toxicity of this combination, they were manageable, and treatment was felt to be overall well-tolerated. Results on efficacy are waiting. Growing evidence supports the investigation of antiPD-1/PD-L1 agents in combination with cetuximab and RT in LA-HNSCC (126, 127). The immunostimulatory effects attributed

TABLE 3 | Main clinical trials evaluating cetuximab combinations with ICI in HNSCC.

	N	Treatment	Phase/status	Comments
LOCALLY-ADVANCED HNSCC				
NCT02999087	688	Experimental arm: Avelumab + cetuximab + IMRT	Phase III/recruiting	Comparative arm: standard CRT with high dose cisplatin D1,22,43
NCT03349710	1046	Cohort 1: Experimental arm A: Nivolumab + cetuximab/placebo + IMRT Experimental arm B: Cetuximab + nivolumab/placebo + IMRT	Phase III/recruiting	Comparative double-blind, placebo-controlled, Phase 3 study. The study includes a 2nd cohort (cohort 2) with experimental arms C and D involving cisplatin + nivolumab/placebo
NCT03051906	69	Experimental arm: Cetuximab + durvalumab + IMRT followed by mainteinance durvalumab	Phase II/III/active, pending recruitment	Excludes oral cavity and HPV-positive oropharynx when T1-2, N0-N2a (AJCC, 7th ed.) or any T, any N with smoking history of <10 pack/years
NCT0193592	18	Experimental arm: Ipilimumab ± Cetuximab ± IMRT	Phase Ib/active, finished recruitment	Safety data presented at ESMO 2016 (125).
R/M HNSCC				
NCT02643550	100	Experimental arm: Monalizumab + cetuximab	Phase Ib-II	One arm for patients with prior exposure to PD-(L)1 ICI
EACH NCT03493322	130	Experimental arm: Avelumab + cetuximab Experimental arm: avelumab monotherapy	Phase II	
NCT03498378	24	Experimental arm: Avelumab + cetuximab + palbociclib	Phase I	
NCT00397384	83	Experimental arm: Pembrolizumab + cetuximab	Phase II	Four arms: cetuximab-naive, PD-(L)1-refractary-cetuximab-naive, PD-(L)1-refractary-cetuximab-refreactary and cutaneous HNSCC.
NCT01836029	175	Comparator arm: EXTREME Experimental arm: EXTREME + motolimod (VTX-2337, TLR8)	Phase II	Randomized

to RT, the increased antitumor immune infiltration induced by cetuximab and the blockade of inhibitory checkpoint receptors by ICI are hypothesized to act in a synergistic manner and ultimately revert the immune suppression of the HNSCC tumor microenvironment. As such, this triple combination is already being investigated in several clinical trials with different anti-PD-1/PD-L1 agents including avelumab (NCT02999087), durvalumab (NCT03051906) or nivolumab (NCT03349710) (128).

In R/M HNSCC disease, ICI are also being investigated in combination with cetuximab. Anti-PD-1, such as pembrolizumab or anti-PD-L1, such as avelumab in combination with cetuximab are being evaluated in phase II clinical trials [NCT03082534 and REACH study (NCT03082534), respectively]. Furthermore, preliminary data from an ongoing Phase I/II trial evaluating the safety and efficacy of the combination of monalizumab, a first-in-class monoclonal antibody targeting NK checkpoint receptor NKG2A, with cetuximab in previously treated R/M HNSCC patients reported increased response rates with the combination without potentiating the side effects of cetuximab (129).

Apart from ICI, other immunotherapies, such as motolimod (VTX-2337), a Toll-like receptor 8 agonist, are being investigated in combination with cetuximab (130) (NCT01836029). The addition of motolimod to the EXTREME regimen has been recently evaluated. Despite it was overall well-tolerated, it did not improve survival. However, in the subgroup analysis, patients with HPV-positive disease and those with injection site reactions seemed to benefit from the combination, suggesting that TLR8 stimulation may be useful in biomarker-selected patients (131).

Main clinical trials evaluating cetuximab combinations with ICI HNSCC are summarized on **Table 3**.

CONCLUSIONS

Cetuximab is the only targeted therapy that has been proven effective for the treatment of HNSCC in both the LA and R/M settings. The incorporation of cetuximab not only expanded the range of treatment options in the past decade but also encouraged the investigation of many other targeted therapies in this tumor type. Particularly in LA-HNSCC, cetuximab has been crucial for the treatment of a subset of patients unfit for standard CRT due to baseline comorbidities or poor clinical condition. Despite this population was under-represented in the Bonner trial, RT-Cx has been the cornerstone in this subgroup of patients given its superiority when compared to RT alone. However, the lack of a direct comparison with CRT and the absence of predictive biomarkers of response to cetuximab have conditioned its widespread use in this setting. Results from the on-going clinical trials will hopefully shed light into this matter. In patients with HPV-positive OPC, the results from the RTOG-1016 and De-ESCALaTE phase III clinical trials have confirmed the inferiority of RT-Cx compared to standard CRT (cisplatin) in this disease, indicating that cetuximab is not an equivalent treatment option for de-escalation approaches in this patient population. The EXTREME regimen has remained the standard of care for the first line treatment of R/M-HNSCC in patients with PS 0–1. However, its use was not widespread likely due to the considerable toxicity and the logistics of managing 3 concomitant drugs including 5-FU. In the light of the recent results from the Keynote 048 study, the antiPD-1 agent pembrolizumab will likely become the new standard either alone or in combination with chemotherapy as first-line treatment for R/M HNSCC based on CPS PD-L1 expression. On-going trials evaluating cetuximab combinations with ICI and other immunotherapies might offer soon new treatment options in both LA and R/M HNSCC.

AUTHOR CONTRIBUTIONS

MT, MO, and RM: review concept, review design, interpretation, manuscript preparation, and manuscript review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00383/full#supplementary-material

REFERENCES

1. Agulnik M. New approaches to EGFR inhibition for locally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN). *Med Oncol*. (2012) 29:2481–91. doi: 10.1007/s12032-012-0159-2
2. Ang K, Berkey B, Tu X, Zhang H, Katz R, Hammond E, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res*. (2002) 62:7350–6.
3. Grandis JR, Melhem MF, Gooding WE, Day R, Holst VA, Wagener MM, et al. Levels of TGF-α and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst*. (1998) 90:824–32. doi: 10.1093/jnci/90.11.824
4. Maurizi M, Ferrandina G, Almadori G, Scambia G, Cadoni G, D'Agostino G, et al. Prognostic significance of methyl-p-hydroxy-phenyllactate-esterase activity in laryngeal squamous cell carcinoma. *Br J Cancer*. (1998) 77:1253–9. doi: 10.1038/bjc.1998.210
5. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus Cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. (2006) 354:567–78. doi: 10.1056/NEJMoa053422
6. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus Cetuximab in head and neck cancer. *N Engl J Med*. (2008) 359:1116–27. doi: 10.1056/NEJMoa0802656
7. Goldstein NI, Prewett M, Zuklys K, Rockwell P, Mendelsohn J. Biological efficacy of a chimeric antibody to the epidermal growth factor receptor in a human tumor xenograft model. *Clin Cancer Res*. (1995) 1:1311–8.
8. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *N Engl J Med*. (2008) 358:1160–74. doi: 10.1056/NEJMra0707704
9. Kimura H, Sakai K, Arao T, Shimoyama T, Tamura T, Nishio K. Antibody-dependent cellular cytotoxicity of Cetuximab against tumor cells with wild-type or mutant epidermal growth factor receptor. *Cancer Sci*. (2007) 98:1275–80. doi: 10.1111/j.1349-7006.2007.00510.x

10. Patel D, Guo X, Ng S, Melchior M, Balderes P, Burtrum D, et al. IgG isotype, glycosylation, and EGFR expression determine the induction of antibody-dependent cellular cytotoxicity *in vitro* by cetuximab. *Hum Antibodies*. (2010) 19:89–99. doi: 10.3233/HAB-2010-0232
11. Balaban N, Moni J, Shannon M, Dang L, Murphy E, Goldkorn T. The effect of ionizing radiation on signal transduction: antibodies to EGF receptor sensitize A431 cells to radiation. *Biochim Biophys Acta*. (1996) 1314:147–56. doi: 10.1016/S0167-4889(96)00068-7
12. Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. *J Clin Invest*. (1995) 95:1897–905. doi: 10.1172/JCI117871
13. Akimoto T, Hunter NR, Buchmiller L, Mason K, Ang KK, Milas L. Inverse relationship between epidermal growth factor receptor expression and radiocurability of murine carcinomas. *Clin Cancer Res*. (1999) 5:437–43.
14. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. *Int J Radiat Oncol Biol Phys*. (2001) 49:427–33. doi: 10.1016/S0360-3016(00)01488-7
15. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, De Castro G Jr., et al. Keynote-048: phase III study of firts-line pembrolizumab for recurrent/metastatic head and neck squemous cell carcinoma. In: *ESMO Conference, LBA8-PR*. Munich (2018).
16. Giralt J, Trigo J, Nuyts S, Ozsahin M, Skladowski K, Hatoum G, et al. Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial *Lancet Oncol*. (2015) 16:221–32. doi: 10.1016/S1470-2045(14)71200-8
17. Reddy BKM, Lokesh V, Vidyasagar MS, Shenoy K, Babu KG, Shenoy A, et al. Nimotuzumab provides survival benefit to patients with inoperable advanced squamous cell carcinoma of the head and neck: a randomized, open-label, phase IIb, 5-year study in Indian patients. *Oral Oncol*. (2014) 50:498–505. doi: 10.1016/j.oraloncology.2013.11.008
18. Schick U, Gujral DM, Richards TM, Harrington KJ, Nutting CM. Zalutumumab in head and neck cancer. *Expert Opin Biol Ther*. (2012) 12:119–25. doi: 10.1517/14712598.2012.643864
19. Siu LL, Waldron JN, Chen BE, Winquist E, Wright JR, Nabid A, et al. Effect of standard radiotherapy with cisplatin vs accelerated radiotherapy with panitumumab in locoregionally advanced squamous cell head and neck carcinoma a randomized clinical trial. *JAMA Oncol*. (2017) 3:220–6. doi: 10.1001/jamaoncol.2016.4510
20. López-Albaitero A, Ferris RL. Immune activation by epidermal growth factor receptor-specific monoclonal antibody therapy for head and neck cancer. *Arch Otolaryngol Head Neck Surg*. (2007) 133:1277–81. doi: 10.1001/archotol.133.12.1277
21. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res*. (2000) 6:2166–74.
22. Bonner JA, Raisch KP, Trummell HQ, Robert F, Meredith RF, Spencer SA, et al. Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation head and neck cancers. *J Clin Oncol*. (2000) 18(Suppl. 21):47S–53S.
23. Cetuximab approved by FDA for treatment of head and neck squamous cell cancer. *Cancer Biol Ther*. (2006) 5:340–2. doi: 10.4161/cbt.5.4.2666
24. Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, et al. NCCN Guidelines® insights: head and neck cancers, version 1.2018 featured updates to the NCCN guidelines. *J Natl Compr Cancer Netw*. (2018) 16:479–90. doi: 10.6004/jnccn.2018.0026
25. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus Cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*. (2010) 11:21–8. doi: 10.1016/S1470-2045(09)70311-0
26. Garden AS, Asper JA, Morrison WH, Schechter NR, Glisson BS, Kies MS, et al. Is concurrent chemoradiation the treatment of choice for all patients with stage III or IV head and neck carcinoma? *Cancer*. (2004) 100:1171–8. doi: 10.1002/cncr.20069
27. Riaz N, Sherman E, Koutcher L, Shapiro L, Katabi N, Zhang Z, et al. Concurrent chemoradiotherapy with cisplatin versus Cetuximab for squamous cell carcinoma of the head and neck. *Am J Clin Oncol Cancer Clin Trials*. (2016) 39:27–31. doi: 10.1097/COC.0000000000000006
28. Ley J, Mehan P, Wildes TM, Thorstad W, Gay HA, Michel L, et al. Cisplatin versus Cetuximab given concurrently with definitive radiation therapy for locally advanced head and neck squamous cell carcinoma. *Oncology*. (2013) 85:290–6. doi: 10.1159/000355194
29. Ho C, Ye A, Hay J, Laskin J, Wu J. Toxicity and outcomes in combined modality treatment of head and neck squamous cell carcinoma: cisplatin versus cetuximab. *J Cancer Res Ther*. (2013) 9:607–12. doi: 10.4103/0973-1482.126455
30. Petrelli F, Coinu A, Riboldi V, Borgonovo K, Ghilardi M, Cabiddu M, et al. Concomitant platinum-based chemotherapy or Cetuximab with radiotherapy for locally advanced head and neck cancer: a systematic review and meta-analysis of published studies. *Oral Oncol*. (2014) 50:1041–8. doi: 10.1016/j.oraloncology.2014.08.005
31. Huang J, Zhang J, Shi C, Liu L, Wei Y. Survival, recurrence and toxicity of HNSCC in comparison of a radiotherapy combination with cisplatin versus cetuximab: a meta-analysis. *BMC Cancer*. (2016) 16:689. doi: 10.1186/s12885-016-2706-2
32. Magrini SM, Buglione M, Corvò R, Pirtoli L, Paiar F, Ponticelli P, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J Clin Oncol*. (2016) 34:427–35. doi: 10.1200/JCO.2015.63.1671
33. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or Cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. (2019) 393:51–60. doi: 10.1016/S0140-6736(18)32752-1
34. Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus Cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. (2019) 393:40–50. doi: 10.1016/S0140-6736(18)32779-X
35. Vermorken JB, Remenar E, Hitt R, Kawecki A, Rottey S, Knierim L, et al. Platinum-based chemotherapy (CT) plus Cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M-SCCHN): 5-year follow-up data for the extreme trial. *J Clin Oncol*. (2014) 32:6021. doi: 10.1200/jco.2014.32.15_suppl.6021
36. Ang KK, Zhang Q, Rosenthal DI, Nguyen-Tan PF, Sherman EJ, Weber RS, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without Cetuximab for stage III to IV head and neck carcinoma: RTOG. (0522) *J Clin Oncol*. (2014) 32:2940–50. doi: 10.1200/JCO.2013.53.5633
37. Mesía R, Garcia-Saenz JA, Lozano A, Pastor M, Grau JJ, Martínez-Trufero J, et al. Could the addition of Cetuximab to conventional radiation therapy improve organ preservation in those patients with locally advanced larynx cancer who respond to induction chemotherapy? an organ preservation spanish head and neck cancer cooperative group phase 2 study. *Int J Radiat Oncol Biol Phys*. (2017) 97:473–80. doi: 10.1016/j.ijrobp.2016.11.016
38. Merlano M, Russi E, Benasso M, Corv R, Colantonio I, Vigna-Taglianti R, et al. Cisplatin-based chemoradiation plus Cetuximab in locally advanced head and neck cancer: a phase II clinical study. *Ann Oncol*. (2011) 22:712–7. doi: 10.1093/annonc/mdq412
39. Lefebvre JL, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. *J Clin Oncol*. (2013) 31:853–9. doi: 10.1200/JCO.2012.42.3988
40. Numico G, Franco P, Cristofano A, Migliaccio F, Spinazzé S, Silvestris N, et al. Is the combination of Cetuximab with chemo-radiotherapy regimens worthwhile in the treatment of locally advanced head and neck cancer? A review of current evidence. *Crit Rev Oncol Hematol*. (2013) 85:112–20. doi: 10.1016/j.critrevonc.2012.05.005
41. Peddi P, Bhi R, Nair B, Ampil F, Mills GM, Jafri SH. Cisplatin, cetuximab, and radiation in locally advanced head and neck squamous cell cancer: a retrospective review. *Clin Med Insights Oncol*. (2015) 9:1–7. doi: 10.4137/CMO.S18682

42. Tao Y, Auperin A, Sire C, Martin L, Khoury C, Maingon P, et al. Improved outcome by adding concurrent chemotherapy to Cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. *J Clin Oncol*. (2018) 36:3084–90. doi: 10.1200/JCO.2017.76.2518
43. Kies MS, Holsinger FC, Lee JJ, William WN, Glisson BS, Lin HY, et al. Induction chemotherapy and Cetuximab for locally advanced squamous cell carcinoma of the head and neck: results from a phase II prospective trial. *J Clin Oncol*. (2010) 28:8–14. doi: 10.1200/JCO.2009.23.0425
44. Zhang L, Jiang N, Shi Y, Li S, Wang P, Zhao Y. Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis. *Sci Rep*. (2015) 5:10798. doi: 10.1038/srep10798
45. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomised trial. *Lancet Oncol*. (2013) 14:697–710. doi: 10.1016/S1470-2045(13)70181-5
46. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*. (2007) 357:1695–704. doi: 10.1056/NEJMoa071028
47. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol*. (2014) 25:216–25. doi: 10.1093/annonc/mdt461
48. Haddad RI, Posner M, Hitt R, Cohen EEW, Schulten J, Lefebvre JL, et al. Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck: role, controversy, and future directions. *Ann Oncol*. (2018) 29:1130–40. doi: 10.1093/annonc/mdy102
49. Mesía R, Vázquez S, Grau JJ, García-Sáenz JA, Lozano A, García C, et al. A phase 2 open label, single-arm trial to evaluate the combination of Cetuximab plus taxotere, cisplatin, and 5-flurouracil as an induction regimen in patients with unresectable squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. (2016) 94:289–96. doi: 10.1016/j.ijrobp.2015.10.019
50. Strojan P, Kuhar CG, Žumer B, Kadivec M, Karner K, Fajdiga I, et al. TPF induction chemotherapy and concomitant irradiation with cisplatin and Cetuximab in unresectable squamous cell carcinoma of the head and neck. *Head Neck*. (2014) 36:1555–61. doi: 10.1002/hed.23506
51. Specenier PM, Remenar E, Buter J, Schrijvers DL, Bergamini C, Licitra LF, et al. TPF plus Cetuximab induction chemotherapy followed by biochemoradiation with weekly Cetuximab plus weekly cisplatin or carboplatin: a randomized phase II EORTC trial. *Ann Oncol*. (2017) 28:2219–24. doi: 10.1093/annonc/mdx300
52. Fayette J, Bonnin N, Ferlay C, Lallemant B, Ramade A, Favrel V, et al. Neoadjuvant TPF in locally advanced head and neck cancer can be followed by radiotherapy combined with cisplatin or cetuximab: a study of 157 patients. *Anticancer Drugs*. (2013) 24:623–9. doi: 10.1097/CAD.0b013e328360b9d6
53. Marur S, Li S, Cmelak AJ, Gillison ML, Zhao WJ, Ferris RL, et al. E1308: Phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly Cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx- ECOG-ACRIN cancer research group. *J Clin Oncol*. (2017) 35:490–7. doi: 10.1200/JCO.2016.68.3300
54. Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and Cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. (2014) 32:2486–95. doi: 10.1200/JCO.2013.53.9163
55. Chun SG, Hughes R, Sumer BD, Myers LL, Truelson JM, Khan SA, et al. A Phase I/II study of nab-paclitaxel, cisplatin, and Cetuximab with concurrent radiation therapy for locally advanced squamous cell cancer of the head and neck. *Cancer Invest*. (2017) 35:23–31. doi: 10.1080/07357907.2016.1213275
56. Argiris A, Bauman JE, Ohr J, Gooding WE, Heron DE, Duvvuri U, et al. Phase II randomized trial of radiation therapy, cetuximab, and pemetrexed with or without bevacizumab in patients with locally advanced head and neck cancer. *Ann Oncol*. (2016) 27:1594–600. doi: 10.1093/annonc/mdw204
57. Tabernero J. The role of VEGF and EGFR inhibition: implications for combining anti-VEGF and anti-EGFR agents. *Mol Cancer Res*. (2007) 5:203–20. doi: 10.1158/1541-7786.MCR-06-0404
58. Wachsberger P, Burd R, Dicker AP. Tumor response to ionizing radiation combined with antiangiogenesis or vascular targeting agents: exploring mechanisms of interaction. *Clin Cancer Res*. (2003) 9:1957–71.
59. Argiris A, Kotsakis AP, Hoang T, Worden FP, Savvides P, Gibson MK, et al. Cetuximab and bevacizumab: preclinical data and phase II trial in recurrent or metastatic squamous cell carcinoma of the head and neck cancer. *Ann Oncol*. (2013) 24:220–5. doi: 10.1093/annonc/mds245
60. Fury MG, Xiao H, Sherman EJ, Baxi S, Smith-Marrone S, Schupak K, et al. Phase II trial of bevacizumab + Cetuximab + cisplatin with concurrent intensity-modulated radiation therapy for patients with stage III/IVB head and neck squamous cell carcinoma. *Head Neck*. (2016) 38(Suppl. 1):E566–70. doi: 10.1002/hed.24041
61. Baro M, de Llobet LI, Figueras A, Skvortsova I, Mesia R, Balart J. Dasatinib worsens the effect of Cetuximab in combination with fractionated radiotherapy in FaDu- and A431-derived xenografted tumours. *Br J Cancer*. (2014) 111:1310–8. doi: 10.1038/bjc.2014.432
62. Nowsheen S, Bonner JA, LoBuglio AF, Trummell H, Whitley AC, Dobelbower MC, et al. Cetuximab augments cytotoxicity with poly (ADP-Ribose) polymerase inhibition in head and neck cancer. *PLoS ONE*. (2011) 6:e24148. doi: 10.1371/journal.pone.0024148
63. Güster JD, Weissleder SV, Busch CJ, Kriegs M, Petersen C, Knecht R, et al. The inhibition of PARP but not EGFR results in the radiosensitization of HPV/p16-positive HNSCC cell lines. *Radiother Oncol*. (2014) 113:345–51. doi: 10.1016/j.radonc.2014.10.011
64. Kalish LH, Kwong RA, Cole IE, Gallagher RM, Sutherland RL, Musgrove EA. Deregulated cyclin D1 expression is associated with decreased efficacy of the selective epidermal growth factor receptor tyrosine kinase inhibitor gefitinib in head and neck squamous cell carcinoma cell lines. *Clin Cancer Res*. (2004) 10:7764–74. doi: 10.1158/1078-0432.CCR-04-0012
65. Marur S. A phase I (Ph1) study of dasatinib (D) with Cetuximab (Cet)/radiation (IMRT) ± cisplatin (P) in stage II, III/IV head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol*. (2015) 33(Suppl. 15):e17036. doi: 10.1200/jco.2015.33.15_suppl.e17036
66. Karam SD, Reddy K, Blatchford P, Waxweiler T, DeLouize AM, Oweida A, et al. Final report of a phase I trial of olaparib with Cetuximab and radiation for heavy smoker patients with locally advanced head and neck cancer. *Clin Cancer Res*. (2018) 24:4949–59. doi: 10.1158/1078-0432.CCR-18-0467
67. Abdel-Rahman O, Fouad M. Correlation of cetuximab-induced skin rash and outcomes of solid tumor patients treated with cetuximab: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. (2015) 93:127–35. doi: 10.1016/j.critrevonc.2014.07.005
68. Rabinowits G, Haddad RI. Overcoming resistance to EGFR inhibitor in head and neck cancer: a review of the literature. *Oral Oncol*. (2012) 48:1085–9. doi: 10.1016/j.oraloncology.2012.06.016
69. Boeckx C, Weyn C, Vanden Bempt I, Deschoolmeester V, Wouters A, Specenier P, et al. Mutation analysis of genes in the EGFR pathway in head and neck cancer patients: implications for anti-EGFR treatment response. *BMC Res Notes*. (2014) 7:337. doi: 10.1186/1756-0500-7-337
70. Argiris A, Lee SC, Feinstein T, Thomas S, Branstetter BF IV, Seethala R, et al. Serum biomarkers as potential predictors of antitumor activity of cetuximab-containing therapy for locally advanced head and neck cancer. *Oral Oncol*. (2011) 47:961–6. doi: 10.1016/j.oraloncology.2011.07.034
71. Sok JC, Coppelli FM, Thomas SM, Lango MN, Xi S, Hunt JL, et al. Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. *Clin Cancer Res*. (2006) 12:5064–73. doi: 10.1158/1078-0432.CCR-06-0913
72. Ahn MJ, D'Cruz A, Vermorken JB, Chen JP, Chitapanarux I, Dang HQT, et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: a literature review. *Oral Oncol*. (2016) 53:10–6. doi: 10.1016/j.oraloncology.2015.11.019
73. Marin M, Gudiol C, Castet F, Oliva M, Peiró I. Bloodstream infection in patients with head and neck cancer: a major challenge in the Cetuximab era. *Clin Transl Oncol*. (2018) 21:187–96. doi: 10.1007/s12094-018-1905-5

74. Formenti SC, Demaria S. Effects of chemoradiation on tumor-host interactions: the immunologic side. *J Clin Oncol*. (2008) 26:1562–3. doi: 10.1200/JCO.2007.15.5499
75. Bourhis J, Rivera F, Mesia R, Awada A, Geoffrois L, Borel C, et al. Phase I/II study of Cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. (2006) 24:2866–72. doi: 10.1200/JCO.2005.04.3547
76. Grégoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. (2010) 21:v184–6. doi: 10.1093/annonc/mdq185
77. Tourneau C, Ghiani M, Cau M. The observational ENCORE study: Cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). *Ann Oncol*. (2017) 28(Suppl. 28):v372–94. doi: 10.1093/annonc/mdx374.024
78. Hetch M, Hahn D, Beutner D, Reichert D, Göhler T, Wurm R, et al. Cetuximab in combination with platinum-based chemotherapy or radiotherapy in recurent and/or metastatic SCCHN in a non-selected patient cohort (interim analysis of the phase IV SOCCER trial). *Ann Oncol*. (2016) 27:994P. doi: 10.1093/annonc/mdw376.46
79. Rose WC, Wild R. Therapeutic synergy of oral taxane BMS-275183 and Cetuximab versus human tumor xenografts. *Clin Cancer Res*. (2004) 10:7413–7. doi: 10.1158/1078-0432.CCR-04-1045
80. Bossi P, Miceli R, Locati LD, Ferrari D, Vecchio S, Moretti G, et al. A randomized, phase 2 study of Cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol*. (2017) 28:2820–6. doi: 10.1093/annonc/mdx439
81. Argiris A, Heron DE, Smith RP, Kim S, Gibson MK, Lai SY, et al. Induction docetaxel, cisplatin, and Cetuximab followed by concurrent radiotherapy, cisplatin, and Cetuximab and maintenance Cetuximab in patients with locally advanced head and neck cancer. *J Clin Oncol*. (2010) 28:5294–300. doi: 10.1200/JCO.2010.30.6423
82. Guigay J, Fayette J, Dillies AF, Sire C, Kerger JN, Tennevet I, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol*. (2015) 26:1941–7. doi: 10.1093/annonc/mdv268
83. Argiris A, Harrington KJ, Tahara M, Schulten J. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Front Oncol*. (2017) 7:72. doi: 10.3389/fonc.2017.00072
84. Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, García-Sáenz JA, Cruz-Hernandez JJ. Phase II study of the combination of Cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Ann Oncol*. (2012) 23:1016–22. doi: 10.1093/annonc/mdr367
85. Knoedler M, Gauler TC, Gruenwald V, Matzdorff A, Schroeder M, Dietz A, et al. Phase II study of Cetuximab in combination with docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck after platinum-containing therapy: a multicenter study of the Arbeitsgemeinschaft Internistische Onkologie. *Oncology*. (2013) 84:284–9. doi: 10.1159/000345453
86. Ekonnida T, Tahara M, Uozumi S, Okano S, Ueda Y. Paclitaxel plus Cetuximab as 1st line chemotherapy in platinum-based chemoradiotherapy-refractory patients with squamous cell carcinoma of the head and neck. *Front Oncol*. (2018) 8:338. doi: 10.3389/fonc.2018.00339
87. Urba S, van Herpen CM, Sahoo TP, Shin DM, Licitra L, Mezei K, et al. Pemetrexed in combination with cisplatin versus cisplatin monotherapy in patients with recurrent or metastatic head and neck cancer: final results of a randomized, double-blind, placebo-controlled, phase 3 study. *Cancer*. (2012) 118:4694–705. doi: 10.1002/cncr.27449
88. Vermorken JB, Licitra L, Stöhlmacher-Williams J, Dietz A, Lopez-Picazo JM, Hamid O, et al. Phase II study of pemetrexed in combination with cisplatin and Cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck. *Eur J Cancer*. (2013) 49:2877–83. doi: 10.1016/j.ejca.2013.05.002
89. Jimeno A, Bauman JE, Weissman C, Adkins D, Schnadig I, Beauregard P, et al. A randomized, phase 2 trial of docetaxel with or without PX-866, an irreversible oral phosphatidylinositol 3-kinase inhibitor, in patients with relapsed or metastatic head and neck squamous cell cancer. *Oral Oncol*. (2015) 51:383–8. doi: 10.1016/j.oraloncology.2014.12.013
90. Vermorken JB, Peyrade F, Krauss J, Mesía R, Remenar E, Gauler TC, et al. Cisplatin, 5-fluorouracil, and Cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part). *Ann Oncol*. (2014) 25:682–8. doi: 10.1093/annonc/mdu003
91. Saba NF, Hurwitz SJ, Magliocca K, Kim S, Owonikoko TK, Harvey D, et al. Phase 1 and pharmacokinetic study of everolimus in combination with Cetuximab and carboplatin for recurrent/metastatic squamous cell carcinoma of the head and neck. *Cancer*. (2014) 120:3940–51. doi: 10.1002/cncr.28965
92. Taberna M, Mena M, Pavón MA, Alemany L, Gillison ML, Mesía R. Human papillomavirus related oropharyngeal cancer. *Ann Oncol*. (2017) 28:2386–98. doi: 10.1093/annonc/mdx304
93. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. *J Clin Oncol*. (2015) 33:3235–42. doi: 10.1200/JCO.2015.61.6995
94. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Eng J Med*. (2010) 363:24–35. doi: 10.1056/NEJMoa0912217
95. Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, et al. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. *Lancet Oncol*. (2011) 12:153–9. doi: 10.1016/S1470-2045(10)70279-5
96. Rischin D, Young RJ, Fisher R, Fox SB, Le Q-T, Peters LJ, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. *J Clin Oncol*. (2010) 28:4142–8. doi: 10.1200/JCO.2010.29.2904
97. Taberna M, Rullan AJ, Hierro C, Navarro V, Vazquez S, Lozano A, et al. Late toxicity after radical treatment for locally advanced head and neck cancer. *Oral Oncol*. (2015) 51:795–9. doi: 10.1016/j.oraloncology.2015.05.002
98. Kelly JR, Husain ZA, Burtness B. Treatment de-intensification strategies for head and neck cancer. *Eur J Cancer*. (2016) 68:125–33. doi: 10.1016/j.ejca.2016.09.006
99. Wirth LJ. Cetuximab in human papillomavirus-positive oropharynx carcinoma. *J Clin Oncol*. (2016) 34:1289–91. doi: 10.1200/JCO.2015.65.1414
100. Bonner JA, Mesia R, Giralt J, Psyrri A, Keilholz U, Rosenthal DI, et al. p16, HPV, and cetuximab: what is the evidence? *Oncologist*. (2017) 22:811–22. doi: 10.1634/theoncologist.2016-0433
101. Rosenthal DI, Harari PM, Giralt J, Bell D, Raben D, Liu J, et al. Association of human papillomavirus and p16 status with outcomes in the IMCL-9815 phase III registration trial for patients with locoregionally advanced oropharyngeal squamous cell carcinoma of the head and neck treated with radiotherapy with or without C. *J Clin Oncol*. (2016) 34:1300–8. doi: 10.1200/JCO.2015.62.5970
102. Vermorken JB, Psyrri A, Mesía R, Peyrade F, Beier F, De Blas B, et al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III extreme trial. *Ann Oncol*. (2014) 25:801–7. doi: 10.1093/annonc/mdt574
103. Reimers N, Kasper HU, Weissenborn SJ, Stützer H, Preuss SF, Hoffmann TK, et al. Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. *Int J Cancer*. (2007) 120:1731–8. doi: 10.1002/ijc.22355
104. Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, et al. EGFR, p16, HPV titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. *J Clin Oncol*. (2008) 26:3128–37. doi: 10.1200/JCO.2007.12.7662
105. Troy JD, Weissfeld JL, Youk AO, Thomas S, Wang L, Grandis JR. Expression of EGFR, VEGF, and NOTCH1 suggest differences in tumor angiogenesis in HPV-positive and HPV-negative head and neck squamous cell carcinoma. *Head Neck Pathol*. (2013) 7:344–55. doi: 10.1007/s12105-013-0447-y

106. Keck MK, Zuo Z, Khattri A, Stricker TP, Brown CD, Imanguli M, et al. Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes. *Clin Cancer Res*. (2015) 21:870–81. doi: 10.1158/1078-0432.CCR-14-2481
107. Seiwert TY, Zuo Z, Keck MK, Khattri A, Pedamallu CS, Stricker T, et al. Integrative and comparative genomic analysis of HPV-positive and HPV-negative head and neck squamous cell carcinomas. *Clin Cancer Res*. (2015) 21:632–41. doi: 10.1158/1078-0432.CCR-13-3310
108. Nogueira-Rodrigues A, Moralez G, Grazziotin R, Carmo CC, Small IA, Alves FVG, et al. Phase 2 trial of erlotinib combined with cisplatin and radiotherapy in patients with locally advanced cervical cancer. *Cancer*. (2014) 120:1187–93. doi: 10.1002/cncr.28471
109. Schilder RJ, Sill MW, Lee YC, Mannel R. A Phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix. *Int J Gynecol Cancer*. (2009) 19:929–33. doi: 10.1111/IGC.0b013e3181a83467
110. Buglione M, Maddalo M, Corvò R, Pirtoli L, Paiar F, Lastrucci L, et al. Subgroup analysis according to human papillomavirus status and tumor site of a randomized phase II trial comparing Cetuximab and cisplatin combined with radiation therapy for locally advanced head and neck cancer. *Int J Radiat Oncol Biol Phys*. (2017) 97:462–72. doi: 10.1016/j.ijrobp.2016.10.011
111. Fayette J, Wirth L, Oprean C, Udrea A, Jimeno A, Rischin D, et al. Randomized phase II study of duligotuzumab (MEHD7945A) vs. cetuximab in squamous cell carcinoma of the head and neck (MEHGAN study). *Front Oncol*. (2016) 6:232. doi: 10.3389/fonc.2016.00232
112. Seiwert TY, Fayette J, Cupissol D, del Campo JM, Clement PM, Hitt R, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. *Ann Oncol*. (2014) 25:1813–20. doi: 10.1093/annonc/mdu216
113. Pajares B, Trigo JM, Toledo MD, Alvarez M, González-Hermoso C, Rueda A, et al. Differential outcome of concurrent radiotherapy plus epidermal growth factor receptor inhibitors versus radiotherapy plus cisplatin in patients with human papillomavirus-related head and neck cancer. *BMC Cancer*. (2013) 13:26. doi: 10.1186/1471-2407-13-26.
114. Koutcher L, Sherman E, Fury M, Wolden S, Zhang Z, Mo Q, et al. Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. (2011) 81:915–22. doi: 10.1016/j.ijrobp.2010.07.008
115. Mesía R, Henke M, Fortin A, Minn H, Yunes Ancona AC, et al. Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial. *Lancet Oncol*. (2015) 16:208–20. doi: 10.1016/S1470-2045(14)71198-2
116. Ou D, Blanchard P, Rosellini S, Levy A, Nguyen F, Leijenaar RTH, et al. Predictive and prognostic value of CT based radiomics signature in locally advanced head and neck cancers patients treated with concurrent chemoradiotherapy or bioradiotherapy and its added value to Human Papillomavirus status. *Oral Oncol*. (2017) 71:150–5. doi: 10.1016/j.oraloncology.2017.06.015
117. Mena M, Taberna M, Tous S, Marquez S, Clavero O, Quiros B, et al. Double positivity for HPV-DNA/p16ink4ais the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients. *Oral Oncol*. (2018) 78:137–44. doi: 10.1016/j.oraloncology.2018.01.010
118. Rietbergen MM, Braakhuis BJM, Moukhtari N, Bloemena E, Brink A, Sie D, et al. No evidence for active human papillomavirus (HPV) in fields surrounding HPV-positive oropharyngeal tumors. *J Oral Pathol Med*. (2014) 43:137–42. doi: 10.1111/jop.12123
119. Prigge ES, Arbyn M, von Knebel Doeberitz M, Reuschenbach M. Diagnostic accuracy of p16INK4a immunohistochemistry in oropharyngeal squamous cell carcinomas: a systematic review and meta-analysis. *Int J Cancer*. (2016) 140:1186–98. doi: 10.1002/ijc.30516
120. Lee SC, Srivastava RM, López-Albaitero A, Ferrone S, Ferris RL. Natural killer (NK):dendritic cell (DC) cross talk induced by therapeutic monoclonal antibody triggers tumor antigen-specific T cell immunity. *Immunol Res*. (2011) 50:248–54. doi: 10.1007/s12026-011-8231-0
121. Lattanzio L, Denaro N, Vivenza D, Varamo C, Strola G, Fortunato M, et al. Elevated basal antibody-dependent cell-mediated cytotoxicity (ADCC) and high epidermal growth factor receptor (EGFR) expression predict favourable outcome in patients with locally advanced head and neck cancer treated with Cetuximab and radiotherapy. *Cancer Immunol Immunother*. (2017) 66:573–9. doi: 10.1007/s00262-017-1960-8
122. Linares J, Rullan A, Taberna M, Vazquez S, Mesia R. Emergence of long-term surviving patients with the introduction of Cetuximab in recurrent/metastatic disease of squamous cell carcinoma of head and neck. *Oral Oncol*. (2016) 55:e4. doi: 10.1016/j.oraloncology.2016.02.006
123. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncol*. (2018) 81:45–51. doi: 10.1016/j.oraloncology.2018.04.008
124. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. (2016) 2045:1–10. doi: 10.1016/S1470-2045(16)30066-3
125. Bauman JE. Phase I trial of cetuximab, intensity modulated radiotherapy (IMRT), and ipilimumab in previously untreated, locally advanced head and neck squamous cell carcinoma. *Ann Oncol*. (2016) 27:1–36. doi: 10.1093/annonc/mdw435.31
126. Melero I, Berman DM, Aznar MA, Korman AJ, Gracia JLP, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer*. (2015) 15:457–72. doi: 10.1038/nrc3973
127. Jie H-B, Srivastava RM, Argiris A, Bauman JE, Kane LP, Ferris RL. Increased PD-1 + and TIM-3 + TILs during Cetuximab therapy inversely correlate with response in head and neck cancer patients. *Cancer Immunol Res*. (2017) 5:408–16. doi: 10.1158/2326-6066.CIR-16-0333
128. Bonomo P, Desideri I, Loi M, Mangoni M, Sottili M, Marrazzo L, et al. Anti PD-L1 DUrvalumab combined with Cetuximab and RadiOtherapy in locally advanced squamous cell carcinoma of the head and neck: a phase I/II study (DUCRO). *Clin Transl Radiat Oncol*. (2018) 9:42–7. doi: 10.1016/j.ctro.2018.01.005
129. Fayette J, Lefebvre G, Posner MR, Bauman J, Salas S, Even C, et al. Phase II study evaluating monalizumab + Cetuximab in previously treated R/M SCCHN. In: *ESMO Conference*. Munich (2018).
130. Chow LQM, Morishima C, Eaton KD, Baik CS, Goulart BH, Anderson LN, et al. Phase Ib trial of the toll-like receptor 8 agonist, motolimod (VTX-2337), combined with Cetuximab in patients with recurrent or metastatic SCCHN. *Clin Cancer Res*. (2017) 23:2442–50. doi: 10.1158/1078-0432.CCR-16-1934
131. Ferris RL, Saba NF, Gitlitz BJ, Haddad R, Sukari A, Neupane P, et al. Effect of adding motolimod to standard combination chemotherapy and Cetuximab treatment of patients with squamous cell carcinoma of the head and neck. *JAMA Oncol*. (2018) 4:1583–8. doi: 10.1001/jamaoncol.2018.1888

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REVIEW
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Laryngeal Preservation Strategies in Locally Advanced Laryngeal and Hypopharyngeal Cancers

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For long, the treatment of locoregionally advanced laryngeal and hypopharyngeal squamous cell cancers (SCC) consisted of either total laryngectomy (TL) or definitive radiotherapy (RT). The development of induction cisplatin plus 5-fluorouracil (PF) and the correlation between chemosensitivity and radiosensitivity in previously untreated patients opened a new era of treatment aiming at laryngeal preservation (LP). The fundamental concept was to employ induction PF in order to select patients for subsequent treatment with either TL or RT according to tumor response to PF. The first two trials (VALGSG for laryngeal SCC and EORTC 24891 for hypopharyngeal SCC) concluded that such an approach could preserve nearly 60% of larynx without deleterious impact on survival. The EORTC 24954 trial compared 4 cycles of induction PF followed by RT in good responders vs. alternating PF-RT in laryngeal and hypopharyngeal SCC. There was no significant difference in 5-year overall survival with a functional larynx between the two arms (31 vs. 35%). The GORTEC 2000-01 trial compared induction PF to induction PF plus docetaxel (TPF) both followed by RT in good responders in larynx and hypopharynx SCC. The 5-year LP was significantly higher in the TPF arm (60 vs. 39%) but without a difference in survival. The RTOG 91-11 trial compared induction PF followed by RT in good responders vs. concurrent chemoradiotherapy (chemo-RT) vs. RT alone in laryngeal SCC. There was no significant difference in 5-year laryngectomy-free survival between the patients treated with induction chemotherapy (44%) vs. those treated with chemo-RT (47%), both being superior to RT alone (34%). At 5 years, LP was superior with chemo-RT: 84 vs. 71% with induction PF. Two phase II trials explored the role of cetuximab (E) in LP in laryngeal and hypopharyngeal SCC. The TREMPLIN trial compared RT+E or chemo-RT (RT + P) after TPF. The DeLOS-II trial compared TPE followed by RT+E vs. TP followed by RT. However, these trials failed to indicate an advantage for the incorporation of E in the treatment paradigm. To date, two approaches for LP have been validated: induction TPF followed by RT for laryngeal and hypopharyngeal SCC and concurrent chemo-RT for laryngeal SCC. An ongoing trial (SALTORL) is comparing these two approaches, induction TPF and chemo-RT, in laryngeal/ hypopharyngeal SCC.

Keywords: laryngeal preservation, surgery, radiotherapy, chemotherapy, biotherapy

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INTRODUCTION

Since the beginning of the twentieth century two major options were available for the treatment of locally advanced laryngeal and hypopharyngeal squamous cell carcinomas (SCC): definitive radiation therapy (RT) with salvage surgery reserved in case of local failure or total laryngectomy with postoperative RT. The indications for each approach varied according to institutional policies. Since no randomized trials with these two approaches were available at that time and results were derived from retrospective analyses comparisons of outcomes and the merits of each treatment strategy were highly debatable.

For long, clinical investigations aimed at extending the indications of partial laryngectomy or exploring different protocols of RT using altered fractionation schedules or concurrent radiosensitizers. These efforts did not notably alter the main treatment approaches (i.e., surgical vs. non-surgical) in laryngeal and hypopharyngeal SCC. At that time chemotherapy was mainly used for the palliative treatment of head and neck SCC.

An important milestone was the publication in 1983 by the Wayne State University of its experience with induction chemotherapy using cisplatin and 5-fluorouracil (PF) in previously untreated patients with head and neck cancers. In a series of 35 patients treated with three cycles of induction chemotherapy with PF, 94% demonstrated a tumor reduction of at least 50 and 63% had a complete clinical disappearance of the disease (1). In another report on 60 patients treated by induction cisplatin-based chemotherapy it appeared that the 42 patients who had demonstrated a tumor response over 50%, 97% of them were controlled by a subsequent RT opposite to 6% of the 18 patients with a tumor reduction below 50% who were controlled by a subsequent RT (2). For the first time, induction chemotherapy was shown to have a potential role in curative intent treatment and could assist in selecting good candidates for subsequent definitive RT. These data re-opened the discussion on the treatment of advanced laryngeal and hypopharyngeal cancers. Two approaches were under discussion: (a) induction PF followed by RT in good responders (tumor regression of at least 50%) or by surgery in other patients and (b) upfront surgery and postoperative RT. Later on, the results of a large meta-analysis showed that concurrent chemoradiotherapy (CRT), in particular with cisplatin-based regimens, achieved better results in terms of survival than induction PF followed by RT (3). Finally, the introduction of induction PF plus docetaxel (TPF protocol) and the use of cetuximab enriched the potential clinical research questions. Several clinical protocols explored induction chemotherapy, concurrent CRT, and the combination of these two approaches.

THE FIRST TRIALS WITH INDUCTION CHEMOTHERAPY

The main objective of these phase III trials was to compare upfront total laryngectomy with postoperative RT with an experimental approach with induction PF followed in responders by RT (with salvage surgery if required for failures after RT) or by a total laryngectomy with postoperative RT in non-responders.

Each cycle of chemotherapy consisted of cisplatin 100 mg/m^2 on day 1 followed by 5-fluorouracil 1,000 mg/m^2 /day for 5 days and was delivered every 3 weeks. Definitive RT was administered to a total dose of 70 Gy and postoperative RT to a total dose of 60 Gy. "Responders" to chemotherapy were defined as patients with a tumor regression of at least 50%.

The primary end-point was under discussion as these first trials were designed. Published data from surgical series provided good results in terms of survival and locoregional control but on selected patients (operable patients with resectable disease). The reported survival rates after definitive RT were lower but included patients with worse prognosis (e.g., unresectable or inoperable). To validate the concept of laryngeal preservation the prerequisite was to assure that there was no deleterious impact on disease control and survival. Therefore, the two first trials had survival as their primary end-point. However improving overall survival has not been a primary objective given the impact of salvage surgery on overall survival.

The Veterans Administration Larynx Cancer Study Group (VALCSG) Trial

In the United States, the department of VALCSG conducted this randomized trial in 332 laryngeal cancer patients (166 in the surgical control arm and 166 in the experimental arm) (4). The experimental treatment consisted of two cycles of PF followed in responders by a third cycle and RT or surgery and postoperative RT in non-responders). Overall survival was the primary endpoint. At a median follow-up of 33 months, the 2-year survival was 68% in both treatment arms (95% Confidence Interval [CI]: 60–75% in the surgery arm vs. 60–76% in the chemotherapy arm, $P = 0.9846$) and the larynx was preserved in 64% of the patients in the experimental arm. In the chemotherapy arm, salvage laryngectomies were indicated significantly more often in patients with T4 diseases vs. those with T3 disease ($P = 0.001$). Of note distant metastases were observed less frequently in the chemotherapy arm (4).

The European Organization for Research and Treatment of Cancer (EORTC) 24891 Trial

In Europe, the EORTC Head and Neck Cooperative Group conducted a similar trial in patients with advanced hypopharyngeal and lateral epilarynx tumors requiring a total laryngectomy (5). In this EORTC 24891 trial, 194 previously untreated patients were enrolled.

Chemotherapy consisted of 100 mg/m^2 given intravenously over a 1-h period followed by fluorouracil 1,000/m^2 /day given as a 120-h infusion over 5 days (total dose 5,000 mg/m^2). A partial response (PR) after two or three cycles of chemotherapy was required to receive RT. The primary endpoint was overall survival in terms of non-inferiority in the experimental arm with a hazard ratio (HR) $\leq$ 1.43. In the first evaluation the median duration of survival was 25 months in the immediate-surgery arm and 44 months in the induction-chemotherapy arm

and, since the observed hazard ratio was 0.86 (log-rank test, $P = 0.006$), which was significantly <1.43, the two treatments were judged to be equivalent. The 3- and 5-year estimates of retaining a functional larynx in patients treated in the induction-chemotherapy arm were 42% (95% CI: 31–53%) and 35% (95% CI: 22–48%), respectively (5).

These results were confirmed by long-term evaluation. At a median follow-up of 10.5 years, the 5-year and 10-year overall survival rates were, respectively, 32.6% (95% CI: 23.0–42.1%) and 13.8% (95% CI: 6.1–21.6%) in the surgery arm vs. 38.0% (95% CI: 28.4–47.6%) and 13.1% (95% CI: 5.6–20.6%) in the chemotherapy arm. In 37 patients still alive at 5 years in the chemotherapy arm, 22 (59.5%) had retained a normal larynx (6). It is noteworthy that distant metastases were less frequent in the chemotherapy arm as in the American trial.

Conclusions After These Trials

These two trials showed that the concept could be validated, both for laryngeal and hypopharyngeal cancers, as the larynx could be preserved in about two-thirds of the patients without compromising survival or disease control. This clinical research paradigm, therefore, could continue with the primary end-point being laryngeal preservation. However, the definition of "laryngeal preservation" had to be clearly defined.

Laryngeal preservation may be defined by only one parameter: larynx in place (i.e., no laryngectomy). A more comprehensive one is to consider both the organ and its function: no laryngectomy, no long-term tracheotomy, and no long-term feeding tube, which implies also that local control is obtained. As survival is an important issue, it may also be integrated in the definition of laryngectomy-free survival or survival with a functional larynx in place.

In 2009, a group of experts fine-tuned the definition of laryngeal preservation taking into account all parameters participating to the real benefit for the patients. They elaborated the "laryngoesophageal dysfunction-free survival" that combined as events: death, local failure, salvage laryngectomy, and tracheotomy or feeding tube at 2 years or later (7, 8).

The EORTC 24954 Trial

The EORTC Head and Neck and Radiotherapy Oncology Cooperative Groups designed a randomized trial in order to compare two different schedules for delivering more cycles of chemotherapy: a sequential schedule like the one used in the previous EORTC 24891 trial vs. an alternating one as described by Merlano (9). The sequential arm consisted of two cycles of PF with the same doses and administration as in the 24891 trial. After 2 cycles responders received two additional cycles of PF and were then treated with RT at a dose of 70 Gy. The non-responders were treated by total laryngectomy and postoperative RT. In the alternating arm, patients received on weeks 1, 4, 7, and 10 a cycle of chemotherapy consisting of cisplatin at a dose of 20 mg/m^2 per day on days 1–5 (for a total dose of 100 mg/m^2) and 5-fluorouracil by bolus infusion at a dose of 200 mg/m^2 per day on days 1–5 (for a total of 1,000 mg/m^2). During the three 2-week intervals patients were treated by RT at a dose of 20 Gy per course for a total of 60 Gy. As a result, the total doses of 5-fluorouracil and of RT were lower in the alternating arm. A total of 450 patients were enrolled in this trial (224 to the sequential arm and 226 to the alternating arm).

For the first evaluation the median follow-up was 6.5 years. Survival with a functional larynx was similar in the sequential and alternating arms (hazard ratio of death and/or event = 0.85, (95% CI: 0.68–1.06), as were median overall survival (4.4 and 5.1 years, respectively). Grade 3 or 4 mucositis occurred in 64 (32%) of the 200 patients in the sequential arm who received radiotherapy and in 47 (21%) of the 220 patients in the alternating arm. Late severe oedema and/or fibrosis was observed in 32 (16%) patients in the sequential arm and in 25 (11%) in the alternating arm (10).

For the long-term evaluation, the median follow-up was 10.2 years. Ten-year survival with a functional larynx (primary end-point) and overall survival were similar in the sequential and alternating arms (18.7 and 33.6% vs. 18.3 and 31.6%, respectively). Late toxicity was also similar even if there was a trend for higher laryngeal preservation and better laryngeal function in the alternating arm (11). The lower doses of chemotherapy and RT in the alternating arm may explain the better tolerance to treatment. However, due to the organizational difficulties when delivering such an alternating schedule in daily practice, it is rarely used.

The Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC) 2000-01 Trial With Cisplatin, 5-FU, Docetaxel

Two large randomized trials (12, 13) had shown that adding docetaxel to cisplatin fluorouracil (the so-called TPF regimen) before RT (or CRT) resulted in a significantly higher survival compared to that observed with the doublet regimen (PF).

In France, in order to assess whether induction TPF could provide better results than induction PF in the frame of laryngeal preservation, the GORTEC conducted a two-arm randomized trial in 220 patients with a locally advanced laryngeal or hypopharyngeal cancer eligible for a total laryngectomy. Patients were randomized between an experimental arm starting with TPF (docetaxel at 75 mg/m^2 on day 1, cisplatin at 75 mg/m^2 on day 1, and 5-fluorouracil at a dose of 750 mg/m^2 by 120-h continuous infusion over 5 days) compared with the classical PF one (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil given at a dose of 1,000 mg/m^2 by 120-h continuous infusion over 5 days). Three cycles at a 3-week interval were planned in the two arms and responders were treated by RT while non-responders had total laryngectomy and postoperative RT. Laryngeal preservation (larynx in place without tumor, tracheostomy or feeding tube) was the primary end-point. Overall survival and progression-free survival were secondary endpoints. two hundred twenty patients were enrolled, of whom 213 were eligible (110 in the TPF arm and 103 in the PF arm).

The first evaluation revealed that in the TPF arm 69 patients (62.7%) could receive the complete treatment without delay or dose reduction vs. 33 patients (32%) in the PF arm. The response rates were 80% with TPF arm and 59.2% with PF ($P = 0.002$). As a result, laryngeal preservation was offered to 78.8% of patients

in the TPF arm vs. 55.3% in the PF arm. With a median follow-up of 36 months, the 3-year actuarial laryngeal preservation rate was 70.3% in the TPF arm vs. 57.5% in the PF arm ($P = 0.002$) (**Table 1**). However, there were no significant differences in terms of survival (14).

The long-term evaluation confirmed the initial results. The 5-year and 10-year laryngeal preservation rates were 74.0% (95% CI: 64–82%) vs. 58.1% (95% CI: 47–68%) and 70.3% (95% CI: 58–80%) vs. 46.5% (95% CI: 31–63%, $P = 0.01$) with TPF and PF, respectively. There was no significant difference in 5-year and 10-year overall survival, or disease-free survival. Of note there were fewer grade 3–4 late toxicities in the TPF arm (9.3%) than in the PF arm (17.1%, $P = 0.038$) (15).

Of note, in this trial it was left to institutional policies to deliver either radiotherapy alone or concurrent chemoradiotherapy in responders. Seventeen patients in the TPF arm and 9 patients in the PF arm received concurrent chemo-radiation. The impact of this on the overall study results is unknown.

THE RADIATION THERAPY ONCOLOGY GROUP (RTOG) 91-11 TRIAL WITH CONCURRENT CHEMORADIOTHERAPY

In the Unites States, the RTOG and the Head and Neck Intergroup conducted a three-arm randomized trial comparing the standard alternative to total laryngectomy validated by previous trials (induction PF chemotherapy followed by radiotherapy) vs. radiotherapy with concurrent cisplatin vs. radiotherapy alone in 547 previously untreated patients with locally advanced larynx cancer (16). Laryngectomy-free survival was the primary endpoint while laryngeal preservation (larynx in place) and survival were secondary endpoints. This study excluded patients with large-volume stage T4 disease defined as tumor penetrating through the cartilage or extending more than 1 cm into the base of tongue. In total only 10% of patients enrolled in 91–11 trial had stage T4 tumors.

In the first report no difference was found in acute toxicity during the radiotherapy between the induction chemotherapy and the radiotherapy alone arm. The 2-year and the 5-year estimates for laryngectomy-free survival were, respectively, 59 and 43% in the induction arm, 66 and 45% in the concurrent arm, and 53 and 38% in the radiotherapy alone arm. The difference was not significant between the induction and the concurrent arms. The 2-year and 5-year overall survival did not differ significantly according to the treatment arm. The rate of laryngeal preservation at a median follow-up of 3.8 years was significantly higher in the concurrent arm (84%) when compared with the induction arm (72%, $P = 0.005$) or with the radiotherapy alone arm (67%, $P < 0.001$) (16).

The long-term analysis with a median follow-up of 10.8 years in surviving patients confirmed that there was no significant difference in late toxicity between the three arms. The two chemotherapy arms significantly improved laryngectomy-free survival compared with radiotherapy alone without significant difference between these two arms. Overall survival did not differ significantly between the treatment arms, although there was a trend for a higher survival in the induction arm. However the rate of deaths not related to the study cancer was significantly higher in the concurrent arm compared with the induction one (69.8 vs. 52.8%, respectively, at 10 years, $P = 0.03$). With regards to laryngeal preservation, the difference favoring the concurrent arm with regards to the laryngeal preservation persisted at 10 years 67.5% (95% CI: 60.4–74.6%) in the induction arm, 81.7% (95% CI: 75.9–87.6%) in the concurrent arm, and 63.8% (95% CI: 56.5–71.1%) in the radiotherapy alone arm (17) (**Table 1**). Again, there were fewer distant metastases in the two arms with chemotherapy when compared with radiotherapy alone.

Long-term results of 91–11 confirm that CRT is a standard treatment option but also raise concerns about late effects from CRT leading to increased number of non-cancer related deaths.

TRIALS INTEGRATING CETUXIMAB AND COMBINING INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIOTHERAPY

A randomized trial had shown that adding cetuximab to RT significantly provided higher survival and loco-regional control over RT alone (18). Therefore, further study of cetuximab in combined modality regimens was worth exploring.

The GORTEC "TREMPLIN Trial"

An experimental approach with induction chemotherapy followed by concurrent CRT was tested in the laryngeal preservation setting. Anticipating an overall toxicity that could compromize the larynx function, and taking into account the results of the radiotherapy plus cetuximab trial (18), the GORTEC conducted a randomized phase II study to assess what could be the best post-induction protocol in 153 patients with laryngeal or hypopharyngeal cancer amenable to a total laryngectomy (19).

Patients received 3 cycles of TPF and responders were randomized between RT plus cisplatin (100 mg/m^2 on day 1, 22, and 43 of RT) and RT plus cetuximab (a loading dose of 400 and 250 mg/m^2 per week during RT. The primary endpoint was laryngeal preservation (no residual disease justifying immediate salvage laryngectomy) 3 months after the end of treatment. The secondary endpoints were larynx function preservation and overall survival 18 months after the end of treatment.

Of the 153 enrolled patients, 116 were randomized (60 in the cisplatin arm, and 56 in the cetuximab arm). Substantial acute toxicity was observed in both arms, in particular in-field skin toxicity in the cetuximab arm and renal, hematological, and performance status alteration in the cisplatin arm. Limiting acute toxicity led to protocol modification in more patients in the cisplatin arm than in the cetuximab arm (71 and 43 vs. 71%, respectively). Except for grade 1 renal toxicity, late toxicity did not differ significantly between both arms. At last examination, there were fewer local recurrences in the cisplatin arm (8 patients) compared with 12 patients in the cetuximab arm, but successful salvage surgery could be performed only in the cetuximab arm.

TABLE 1 | Key phase III trials of laryngeal preservation strategies.

Study	Patients enrolled	Investigational regimen(s)	Control regimen	Primary endpoint(s)	Results	Comments
RTOG 91-11	547 (larynx 100%)	a) CRT c) RT	b) PF followed by RT	Laryngeal preservation Laryngectomy-free survival	Laryngeal preservation rates at 5 years (a vs. b vs. c): 84% vs. 71% vs. 66% Laryngectomy-free survival at 5 years (a vs. b vs. c): 47% vs. 44% vs. 34% Overall survival at 5 years (a vs. b vs. c): 55% vs. 58% vs. 54%	CRT and PF followed by RT are superior to RT alone
GORTEC 2000-01	213 (larynx, 46%; hypopharynx, 54%)	TPF followed by RT*	PF followed by RT*	Laryngeal preservation	Laryngeal preservation rates (actuarial) at 3 years: 70.3 vs. 57.5% No difference in overall survival (60% at 3 years in both arms)	TPF is more effective than PF

**16% of patients in the PF arm and 20% of patients in the TPF arm received concurrent chemotherapy during RT. CRT, chemoradiotherapy; RT, radiotherapy; TPF, cisplatin, docetaxel, 5-fluorouracil; PF, cisplatin, 5-fluorouracil.*

There was no significant difference in laryngeal preservation at 3 months: 95% (95% CI: 86–98%) in the cisplatin arm vs. 93% (95% CI: 83–97%) in the cetuximab arm. There was no obvious difference in secondary endpoints at 18 months as well. The larynx function preservation was 87% (95% CI: 76–93%) in the cisplatin arm vs. 82% (95% CI: 70–90%) in the cetuximab arm. The overall survival was 92% in the cisplatin arm (95% CI: 82–96%) and 89% (95% CI: 79–95%). At a median follow-up of 36 months overall survival was 75% (95% CI: 62–85%) and 73% (95% CI: 60–84%) in the cisplatin arm and cetuximab arm, respectively. These data must be considered with caution as they related to the population selected after induction chemotherapy (i.e., 75% of the overall population).

As the composite end-point of laryngoesophageal dysfunction-free survival had been described after the trial was initiated and had been published at the time of the trial evaluation, this end-point was tested. Two years after the end of treatment there was no significant difference in that end-point: 79% (95% CI: 67–89%) with cisplatin vs. 72% (95% CI: 65–89%) with cetuximab (19).

The conclusion was that there was no signal that one arm was superior over the other one, and none appeared to be superior to induction TPF followed by RT alone as found in the above-mentioned GORTEC 2000-01 trial.

After induction TPF it is difficult to administer high-dose cisplatin due to cumulative toxicities. RT plus carboplatin or cetuximab have been explored but we do not have any data coming from trials specifically designed for laryngeal preservation. However, whether the addition of a systemic agent to RT after TPF induction is superior to RT alone is unproven.

The German "DeLOS-II Trial"

The German Larynx Organ preservation Study group (DeLOS) conducted another randomized phase II study assessing the place of cetuximab in laryngeal preservation for patients with larynx or hypopharynx cancer (20). The initial trial design was to compare induction TPF followed by RT with TPF plus cetuximab (E) followed by RT plus cetuximab. Due to 4 treatment-related deaths among the first 64 patients, the protocol was amended and fluorouracil was omitted from induction chemotherapy in both arms. There were no further treatment-related deaths thereafter. The evaluation was made after one cycle and responders continued the protocol while non-responders went to laryngectomy. The primary objective was a 2-year functional laryngectomy-free survival (fLFS) above 35%.

Of the 180 patients randomized in the trial, 173 fulfilled the intent to treat criteria. At final examination, the objective response rates in the arm without cetuximab were 79.1% in patients who had received PF, and 94.7% in patients who had received TP. In the arm with cetuximab they were 80% in patients who had received TPFE, and 94.9% in patients with TPE, 94.9% (i.e., similar to TPF). The primary objective was similarly met in both arms: 44.7% in the arm without cetuximab and 46.6% in the cetuximab arm (OR:0.9268, 95% CI:0.5094–1.6863). There was no difference in 2-year overall survival: 68.2% in the arm without cetuximab, and 69.3% in the cetuximab arm (OR:0.9508, 95% CI:0.4997–1.8091).

The conclusions were that despite being accompanied by an elevated frequency in adverse events, the induction chemotherapy with TPF/TP plus cetuximab was feasible but showed no superiority to induction chemotherapy with TPF/PF alone regarding LFS and OS at 24 months (20).

CONCLUSIONS

To date, only two strategies for laryngeal preservation in previously untreated patients with locally advanced laryngeal

and hypopharyngeal cancers have been validated: induction TPF followed by RT alone (GORTEC 2000-01) and RT with concurrent cisplatin (RTOG 91-11). Whereas, both approaches have been assessed in laryngeal cancers, only induction chemotherapy-based protocols have been evaluated in hypopharyngeal cancers. The RTOG 91–11 trial did not contain an arm with TPF induction as this trial was initiated before the TPF induction regimen was proved to be superior to PF in the GORTEC 2000-01 trial. As a result, there is a need to compare the RTOG concurrent arm and the TPF arm of the GORTEC trial. The ongoing French phase III trial (GORTEC 2014-03-SALTORL, clinicaltrials.gov NCT03340896) is comparing induction TPF followed by RT in responders vs. concurrent cisplatin-based chemoradiotherapy with the composite end-point of laryngoesophageal dysfunction-free survival as primary end-point. Eligible are patients with stage T2-3, N0-2 laryngeal, or hypopharyngeal SCC requiring total laryngectomy. Patients with pretreatment poor laryngo-esophageal function (in particular those requiring a pre-treatment tracheostomy) should be treated by upfront TL.

The decision of enrolling a patient in a laryngeal preservation protocol must be taken by a multidisciplinary tumor board. We acknowledge that there is significant variability between centers worldwide regarding the applicability of clinical trial results on laryngeal preservation approaches. In general, patients eligible for a laryngeal preservation strategy are patients with advanced larynx and hypopharynx cancers who are not eligible for partial surgery. Of importance, bulky T4 tumors extending to the post-cricoid area are not eligible for laryngeal preservation. Also, patients who are not candidates to receive cisplatin should not be generally be considered for a laryngeal preservation approach given the low success rates with RT alone. Treatment with RT plus cetuximab is not a validated approach for laryngeal preservation and may result in inferior outcomes compared to RT plus cisplatin.

To transition the outcomes of these trials into clinical practice it is important to strictly follow the study protocols with respect to initial work-up and eligibility criteria, chemotherapy protocols, prophylaxis/management of treatment-induced toxicity, response to treatment evaluation, as well as schedule and tools for post-treatment follow-up. Such approaches require experienced multidisciplinary teams.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Decker DA, Drelichman A, Jacobs J, Hoschner J, Kinzie J, Loh JJ, et al. Adjuvant chemotherapy with cis-diamminodichloroplatinum II and 120-hour infusion 5-fluorouracil in Stage III and IV squamous cell carcinoma of the head and neck. *Cancer.* (1983) 51:1353–5. doi: 10.1002/1097-0142(19830415)51:8<1353::AID-CNCR2820510805>3.0.CO;2-I
2. Ensley JF, Jacobs JR, Weaver A, Kinzie J, Crissman J, Kish JA, et al. Correlation between response to cisplatinum-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. *Cancer.* (1984) 54:811–4. doi: 10.1002/1097-0142(19840901)54:5<811::AID-CNCR2820540508>;3.0.CO;2-E
3. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet.* (2000) 355:949–55. doi: 10.1016/S0140-6736(00)90011-4
4. Department of Veterans Affairs Laryngeal Cancer Study Group, Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med.* (1991) 324:1685–90.
5. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst.* (1996) 88:890–9.
6. Lefebvre JL, Andry G, Chevalier D, Luboinski B, Collette L, Traissac L, et al. Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. *Ann Oncol.* (2012) 23:2708–14. doi: 10.1093/annonc/mds065
7. Lefebvre JL, Ang KK. Larynx Preservation Consensus P: Larynx preservation clinical trial design: key issues and recommendations–a consensus panel summary. *Int J Radiat Oncol Biol Phys.* (2009) 73:1293–303. doi: 10.1016/j.ijrobp.2008.10.047
8. Lefebvre JL, Kian Ang K. Larynx Preservation Consensus P: Larynx preservation clinical trial design: key issues and recommendations–a consensus panel summary. *Head Neck.* (2009) 31:429–41. doi: 10.1002/hed.21081
9. Merlano M, Grimaldi A, Benasso M, Bacigalupo A, Toma S, Scarpati D, et al. Alternating cisplatin-5-fluorouracil and radiotherapy in head and neck cancer. *Am J Clin Oncol.* (1988) 11:538–42. doi: 10.1097/00000421-198810000-00006
10. Lefebvre JL, Rolland F, Tesselaar M, Bardet E, Leemans CR, Geoffrois L, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs. alternating chemotherapy and radiotherapy. *J Natl Cancer Inst.* (2009) 101:142–52. doi: 10.1093/jnci/djn460
11. Henriques De Figueiredo B, Fortpied C, Menis J, Lefebvre JL, Barzan L, de Raucourt D, et al. Long-term update of the 24954 EORTC phase III trial on larynx preservation. *Eur J Cancer.* (2016) 65:109–12. doi: 10.1016/j.ejca.2016.06.024
12. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* (2007) 357:1695–704. doi: 10.1056/NEJMoa071028
13. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* (2007) 357:1705–15. doi: 10.1056/NEJMoa070956
14. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C, Tortochaux J, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst.* (2009) 101:498–506. doi: 10.1093/jnci/djp007
15. Janoray G, Pointreau Y, Garaud P, Chapet S, Alfonsi M, Sire C, et al. Long-term Results of a Multicenter Randomized Phase III Trial of Induction Chemotherapy With Cisplatin, 5-fluorouracil, +/- Docetaxel for Larynx Preservation. *J Natl Cancer Inst.* (2016) 108. doi: 10.1093/jnci/djv368
16. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* (2003) 349:2091–8. doi: 10.1056/NEJMoa031317
17. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical

treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* (2013) 31:845–52. doi: 10.1200/JCO.2012.43.6097
18. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* (2006) 354:567–78. doi: 10.1056/NEJMoa053422
19. Lefebvre JL, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, et al. Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. *J Clin Oncol.* (2013) 31:853–9. doi: 10.1200/JCO.2012.42.3988
20. Dietz A, Wichmann G, Kuhnt T, Pfreundner L, Hagen R, Scheich M, et al. Induction chemotherapy (IC) followed by radiotherapy (RT) versus cetuximab plus IC and RT in advanced laryngeal/hypopharyngeal cancer resectable only by total laryngectomy-final results of the larynx organ preservation trial DeLOS-II. *Ann Oncol.* (2018) 29:2105–14. doi: 10.1055/s-0038-1640003

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REVIEW
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Cisplatin Eligibility Issues and Alternative Regimens in Locoregionally Advanced Head and Neck Cancer: Recommendations for Clinical Practice

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Well-designed randomized trials provide the highest level of scientific evidence to guide clinical decision making. In chemoradiotherapy of locally advanced squamous cell carcinoma of the head and neck (SCCHN), data support the use of three cycles of 100 mg/m^2 cisplatin given every 3 weeks concurrently with conventionally fractionated external beam radiotherapy, although a full compliance with all three cycles is reserved to only about two thirds of initially eligible cases. On an individual patient level, practicing oncologists have to determine whether the patient is a suitable candidate for this treatment or whether contraindications exist. In the latter case, an adequate alternative has to be offered. In this regard, to facilitate triaging of medical information, we reviewed available publications on this topic and prepared practice-oriented recommendations for systemic treatment concurrent to definitive and post-operative radiotherapy. Even if no contraindications for the standard-of-care cisplatin apply, clinicians may opt for alternative regimens by adjusting the peak dose, cumulative dose, or timing of cisplatin. Relative contraindications pose the major issue in clinical practice, as very limited data is available in the literature and final decisions are usually based on an expert opinion or retrospective cohort studies. In the case of absolute interdiction of cisplatin, several alternative regimens incorporating carboplatin, 5-fluorouracil, cetuximab, and docetaxel are available. At the same time, it should be kept in mind that radiotherapy alone represents a viable option with hyperfractionation being particularly beneficial in the definitive management of limited nodal disease. Ideally, all treatment propositions should be discussed within multidisciplinary tumor boards taking into account the patient- and disease-related characteristics as well as local logistics and reimbursement policies.

Keywords: head and neck cancer, chemoradiotherapy, cisplatin, cetuximab, targeted therapy, immunotherapy, clinical trials, practice recommendations

INTRODUCTION

Locoregionally advanced disease is still the most frequent clinical manifestation in patients with squamous cell carcinoma of the head and neck (SCCHN). In this setting, chemoradiotherapy offers an effective non-surgical approach as primary treatment, or alternatively, it can be delivered with adjuvant intent after a curative resection (1). Whether being part of bimodality or trimodality management, chemoradiotherapy usually comes at the cost of substantial acute and late toxicity, and it has been subject of numerous clinical trials to establish a treatment schedule with a reasonable compromise between its tumoricidal activity on the one hand and dose-limiting side effects on the other (2). This paper sets out to present the current standard-of-care chemoradiotherapy regimen in non-nasopharyngeal mucosal head and neck cancer along with other commonly used protocols for which a lower level of clinical evidence applies. Based on this theoretical framework, practice-oriented recommendations were conceptualized focusing primarily on systemic treatment. The different treatment options were categorized by clinical settings (definitive or post-operative) and by the presence or absence of contraindications to the standard-of-care treatment (absolute or relative). In addition, to rate the quality of evidence and strength of recommendations of each schedule mentioned here, the European Society for Medical Oncology (ESMO) grading consensus system was adopted (**Table 1**) (3). However, precise clinical, radiological, and pathological criteria used to select cases suitable for definitive or adjuvant chemoradiotherapy are not covered in this article. Furthermore, enrolment of patients in clinical research is highly recommended whenever a well-designed randomized trial opens for recruitment.

DEFINING THE STANDARD OF CARE

The findings from four large randomized phase III trials established cisplatin-based chemoradiotherapy as the reference treatment both in the definitive and adjuvant treatment settings (3–8). The regimen consists of three infusions of 100 mg/m^2 cisplatin given every 3 weeks concurrently with conventionally fractionated external beam radiotherapy. It represents a cost-effective, broadly available, and accessible treatment option (9, 10). The growing interest in de-intensification strategies investigated primarily in human papillomavirus (HPV)-positive oropharyngeal cancer has recently been dampened by the results of two phase III trials confirming the primacy of high-dose cisplatin against cetuximab (11, 12). Mounting evidence suggests that HPV-associated oropharyngeal cancer in men should be regarded as a separate entity with different biology and clearly a better prognosis (13). In economically developed countries, the prevalence of HPV-associated oropharyngeal cancer in men has been sharply increasing over the past three decades (14). At the same time, these regions have been the major force of clinical trial recruitment, enhancing their influence in academic communities (15). Thus, a notion may inadvertently be acquired that the changing epidemiologic landscape is uniform worldwide. However, the majority of patients with head and neck cancer still present with HPV-negative disease in which outcomes have been unsatisfactory calling for preservation of a sufficient treatment intensity. At present, HPV status has no predictive value in locoregionally advanced head and neck cancer.

Enrolling altogether 842 patients during the 1990s, two of the aforementioned trials were conducted in the definitive setting (4, 5). In a Head and Neck Intergroup trial, Adelstein et al. tested the benefit of chemotherapy as an adjunct to concurrent radiotherapy in patients with (mainly) unresectable squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx. The Radiation Therapy Oncology Group (RTOG) 91-11 trial, coordinated by Forastiere et al. was designed to compare the rates of larynx preservation between two chemoradiotherapy regimens (with induction or concurrent chemotherapy) and radiotherapy alone. Adelstein et al. (4) demonstrated a clear improvement of overall survival, the primary endpoint of the study (median: from 12.6 to 19.1 months, 5 year rates: from 14 to 26%). In the RTOG 91-11 trial, concurrent chemoradiation with 3 weekly cisplatin emerged as the optimal approach for larynx preservation, locoregional and distant controls, and disease-free survival. However, these benefits did not translate into overall survival advantage with 5 year rates being almost identical across all three treatment arms (about 55%). What is more, results of an updated publication after a median follow-up of 10.8 years caused a stir in the oncology community, suggesting a worse outcome in the concomitant chemoradiation treatment arm compared with the sequential treatment arm ($p = 0.08$) (16). Being attributed to an increase of deaths from non-cancer related causes probably due to unrecognized late toxicity, the correct interpretation is still a matter of debate. In this respect, it should be mentioned that RTOG 91-11 included only patients with glottic and supraglottic larynx cancer, in contrast to about 10% of such cases in the Intergroup study population. Therefore, subsite-specific impact on the results cannot be excluded.

In the post-operative setting, the RTOG 9501 and the European Organization for Research and Treatment of Cancer (EORTC) 22931 trials enrolled 793 patients with high-risk features in the pathology specimens between 1994 and 2000 (6, 7). The primary objectives were locoregional control and progression-free survival, respectively. In both trials, the addition of cisplatin to radiotherapy was associated with a significant enhancement of 5 year locoregional control and disease- or progression-free survival, but the prolongation of overall survival reached statistical significance only in EORTC 22931, being 53% vs. 40% (hazard ration [HR] 0.70, 95% confidence interval [CI]: 0.52–0.95, p = 0.02) at 5 years. In this context, special attention should be paid to patient selection criteria. An exploratory pooled analysis implied that a significant advantage of combined modality treatment was limited to patients with extracapsular spread and/or positive surgical margins. Importantly, the EORTC inclusion criteria defined microscopically involved margins as the presence of tumor at 5 mm or less, while RTOG 9501 did not allow such tolerance. Hence, it could be speculated to what extent this difference influenced the outcomes, above all its impact on overall survival. In any case, patients with close margins should

TABLE 1 | Grading of the level of clinical evidence and strength of recommendation for clinical practice according to the ESMO consensus guidelines (3).

Level of evidence	
I	≥1 large well-conducted randomized control trial or meta-analyses of such trials
II	Randomized control trials with a suspicion of bias or meta-analyses of such trials
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, and experts opinions
Strength of recommendation	
A	Strongly recommended
B	Generally recommended
C	Optional
D	Generally not recommended
E	Never recommended

be considered for adjuvant chemoradiotherapy. Of note, systemic treatment had no meaningful impact on distant control in these two trials, with rates varying between 80 and 75% irrespective of treatment cohort in the adjuvant, but also definitive settings.

Of further evidence has been the individual patient-based meta-analysis of 87 randomized trials, performed between 1965 and 2000 (17). This meta-analysis demonstrated that adding chemotherapy to locoregional treatment in locally advanced SCCHN was associated with an absolute survival advantage of 4.5% at 5 years ($p < 0.0001$). The conclusions on this benefit did not differ significantly between post-operative radiotherapy and definitive curative radiotherapy and with using either conventional or altered fractionation. However, chemotherapy protocols varied largely in this meta-analysis in that different drugs and different dose levels were applied. No preference for poly-chemotherapy including platin or 5-fluorouracil over mono-chemotherapy with cisplatin or vice-versa was noted. Single agent cisplatin appeared, therefore, to be one of the standard treatments in combination with radiotherapy. Most of the randomized trials in the analysis used a dose of cisplatin of 100 mg/m^2 three times throughout the course of radiotherapy (cumulative dose of 300 mg/m^2), and this came forward as the preferred and recommended option.

Two further variables remain to be addressed, i.e., toxicity and compliance. Adding cisplatin to radiotherapy was found to be associated with an increase in acute adverse events, both in terms of toxicity related primarily to the systemic treatment (gastrointestinal, hematological, neurological, and renal side effects) and toxicity owing mainly to radiotherapy (mucositis, dysphagia, and skin adverse events). Data on ototoxicity were not available. As an example, with the addition of high-dose cisplatin, the rate of severe acute mucositis almost doubled in EORTC 22931 (from 21 to 41%) and more than one third of patients developed severe acute dysphagia in RTOG 91-11. Unfortunately, in general, late toxicity reporting often suffers from inaccuracy and inconsistency (2). With that in mind, the cumulative incidence of late toxicity ranged between 20 and 40%, without a statistical correlation with the systemic treatment (6, 7, 16, 18). It was not surprising that the high rate of acute side effects came at the cost of decreased compliance. In fact, the proportion of patients who could receive all planned cycles of chemotherapy was between 61 and 85%.

DECISION-MAKING PROCESS

The cisplatin-based concurrent chemoradiation protocol presented above is generally accepted as the reference for the definitive non-surgical and post-operative approaches in selected patients with locoregionally advanced SCCHN. At the same time, the efficacy is far from being satisfactory and toxicity is one of the major drawbacks. Nevertheless, the four randomized trials established level I evidence for its use supported by the individual patient-based meta-analysis, and no other regimen has proven to outperform this. The decision-making process gets complicated in the presence of patient-related characteristics hindering the employment of cisplatin. In their 2016 seminal work, Ahn et al. (largely opinion leaders from the Asia-Pacific region) summarized criteria for absolute contraindications and high-risk cases (19). Subsequently, these criteria were adopted for the purpose of the present work as absolute and relative contraindications. The original Ahns' criteria did not differentiate between palliative and curative settings. Herein, we focus on locally advanced disease where the addition of 3 weekly high-dose cisplatin to radiotherapy may save further patients' lives, and the absolute overall survival benefit at 5 years may be even higher than 10% (17). In this respect, the following modifications were made (**Table 2**).

First, the age limit of 70 years (calendar age) was removed because fit elderly individuals receiving full-dose treatment were shown to derive the same magnitude of clinical benefit as their younger counterparts (20). Thus, where applicable, our decisions should implement geriatric screening tools and if necessary complex geriatric assessment (21). Frailty as a surrogate marker for biological age represents a crucial factor in decision making related to older cancer patients. About 10% of the general senior population are expected to be frail. However, in the context of an oncologic disease, this proportion rises to over one half, comprising also vulnerable individuals, with not more than one third being fit. According to recently published clinical recommendations for systemic therapy of head and neck cancer in the elderly, fit patients should primarily be considered for high-dose 3 weekly cisplatin with curative intent, while treatment in those who are frail will rather consist of palliative measures such as palliative irradiation and/or palliative surgical interventions (e.g., tracheostomy, gastrostomy). In the intermediate group characterized by vulnerability, management follows the recommendations pertinent to the intermediate group with relative contraindications to high-dose cisplatin as explained further in this paper (22).

Next, pre-existing hearing impairment grade II was moved from absolute to relative contraindications. This condition

TABLE 2 | Absolute and relative contraindications to cisplatin in definitive or post-operative treatment of locally advanced head and neck cancer, modified from Ahn et al. (19).

Clinical condition	Relative contraindications	Absolute contraindications
Performance status	ECOG score = 2	ECOG score ≥ 3
Biological age	According to geriatric assessment and screening tools	ND
Renal dysfunction	Creatinine clearance 50–60 ml/min	Creatinine clearance <50 ml/min
Hearing impairment	Hearing loss or tinnitus grade = 1 or 2[a,b]	Hearing loss or tinnitus grade = ≥ 3[a]
Neuropathy	Grade = 1[a]	Grade = ≥ 2[a]
Marrow, hepatic, respiratory, and cardiovascular, dysfunctions	Grade 2[a] or Child-Pugh score = B[c]	Grade ≥ 3[a] or Child-Pugh score = C[c]
Other comorbidities	Insulin-dependent diabetes mellitus, recurrent (pulmonary) infections, severe psychiatric disorders interfering with treatment compliance	Life-threatening conditions such as uncontrolled systemic infection or autoimmune disease
HIV/AIDS	CD4 count 200–350/μl[d]	CD4 count < 200/μl[d]
Nutritional status	Involuntary weight loss ≥ 20%	ND
Pregnancy and lactation	ND	First trimester of pregnancy[e], lactation not recommended
Hypersensitivity to platinum agents	ND	Allergy to agents that contain platinum[f] or mannitol
Previous platinum therapy	>200 mg/m^2 or >3 cycles of TPF induction	ND
Drug interactions	Concomitant use of nephrotoxic drugs	ND
Socioeconomic status	Impaired social and economic support	ND

[a] *Based on the National Cancer Institute Common Toxicity Criteria version 4.0.*
[b] *Repeated audiometry exams may be indicated during the treatment.*
[c] *For hepatic impairment.*
[d] *World Health Organization definition.*
[e] *Fetal exposure to radiation, irrespective of the duration of pregnancy, increases the risk on developing malignancies in childhood and in addition is associated with abortion and intra-uterine death. Therefore, radiotherapy is preferably postponed until after delivery.*
[f] *If a skin test does not rule out cross-reactions among platinum agents.*
HIV/AIDS, human immunodeficiency virus infection/acquired immune deficiency syndrome; ECOG, Eastern Oncology Cooperative Group; TPF, docetaxel, cisplatin, 5-fluorouracil; ND, not defined.

belongs to the class-specific adverse events of cisplatin and can indeed be accelerated by such treatment. However, according to two large meta-analyses of 59 prospective trials, severe ototoxicity has not been common even with high cumulative doses of cisplatin, and the risk-benefit ratio on an individual patient basis can ultimately favor the standard, high-dose treatment (23, 24). Still, periodic audiometry exams might be indicated throughout the treatment course leading eventually to cisplatin interruption in some cases. Further modifications relative to the Ahn's criteria concerning organ dysfunctions, other comorbid conditions, and pregnancy are listed in **Table 2**.

The bottom line is that patient and disease characteristics are crucial in decision making which should preferably be consensual within the frame of a multidisciplinary tumor board. To facilitate this task, we have elaborated a decision tree algorithm separately for the definitive and post-operative treatment settings available in **Figures 1**, **2** together with an overview of studies supporting the resulting level of evidence and grade of recommendation provided in the **Tables S1, S2**.

DEFINITIVE TREATMENT SETTING

No Contraindications to High-Dose Cisplatin

The standard of care should be pursued whenever patients are in good general condition with few and/or mild comorbidities and are willing to adhere to the treatment program [I, A]. Alternatively, two cycles of 100 mg/m^2 of cisplatin given in a 3–4 week interval concomitantly with altered fractionation radiotherapy may be considered [I, B] (12, 24, 25). On the other hand, current evidence is insufficient to prioritize weekly low-dose cisplatin protocols (26). Up to now, three prospective trials comparing survival outcome with weekly low-dose cisplatin-based chemoradiotherapy vs. radiotherapy alone have been published. The first two studies, enrolling a total of 275 patients, were conducted in the 1980s. Quon et al. chose a relatively low cumulative dose of cisplatin (7 × 20 mg/m^2) being very probably responsible for the disappointing results. Median overall survival was even numerically worse in the combined modality arm (11.8 months vs. 13.3 months) (27). Sharma et al. doubled the target cumulative dose (7 × 40 mg/m^2) leading apparently to better outcomes with a significant separation of overall survival curves (median: 27 months vs. no reached, $p = 0.02$). Nevertheless, the median follow-up period did not exceed 2 years and no information on late toxicity was provided (28). The third prospective study, a three-arm trial comparing two radiotherapy fractionation schedules with chemoradiation using up to 8 cycles of 30 mg/m^2 cisplatin, was underpowered and had to be terminated prematurely due to poor accrual (199 out of 750 patients planned). The small improvement in locoregional control ($p = 0.049$) did not translate into significant overall survival improvement and the difference was only numerical (5 year rates: 56% vs. 36%) (29). Other prospective and retrospective trials exploring the weekly schedule are available but the data have been conflicting [II, C] (23). For further information regarding a comparison between the weekly and 3 weekly regimen please see below in a separate chapter.

Finally, retrospective observations in patients intended to receive three cycles of high-dose cisplatin suggest that a cumulative dose of 200 mg/m^2 produces an adequate anti-tumor effect in terms of overall survival, especially in the prognostically favorable low-risk group of HPV positive oropharyngeal cancer, with higher doses possibly further improving locoregional control (11, 25, 30–32). At present, it is unclear whether dose escalation up to 300 mg/m^2 brings additional survival advantage or whether this is offset by excessive toxicity responsible for an increase in non-cancer

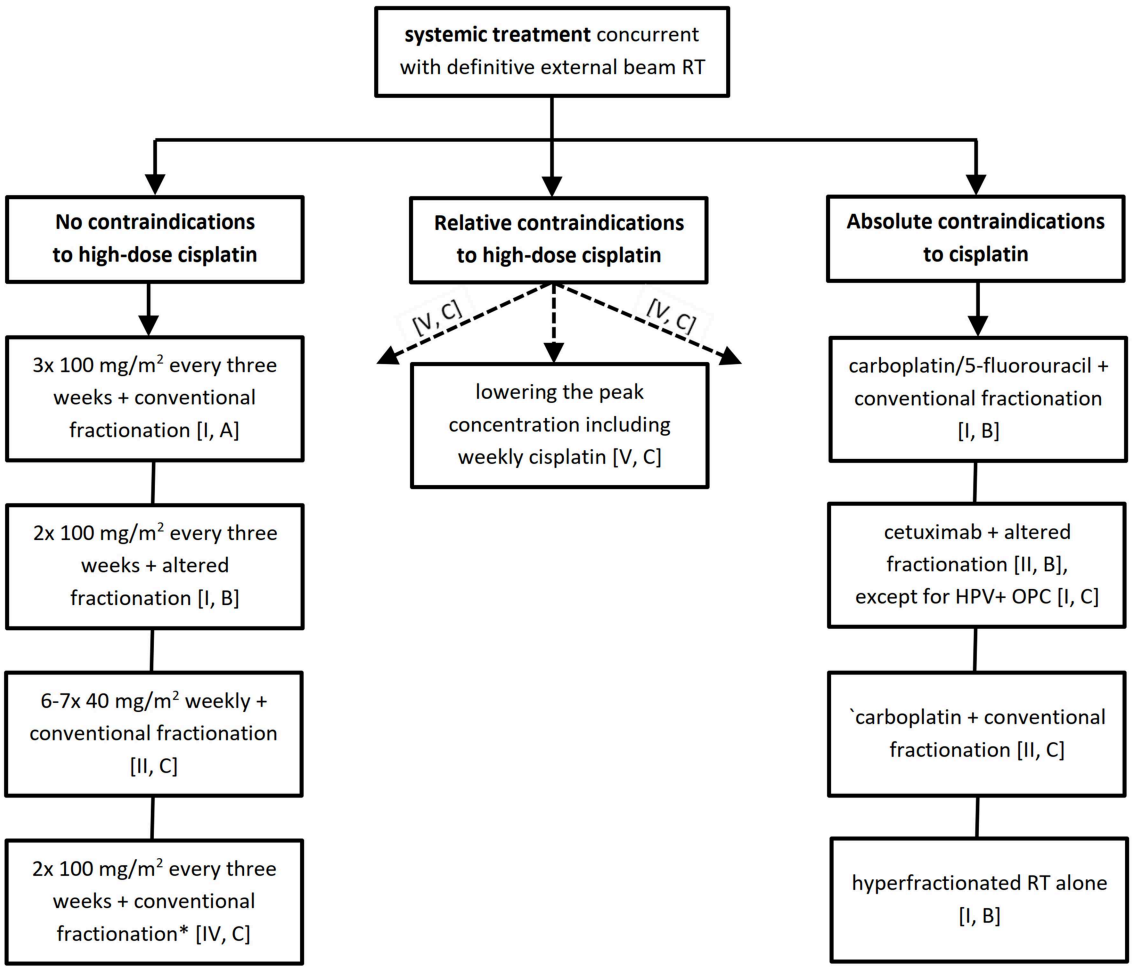

FIGURE 1 | Systemic treatment recommendations for definitive chemoradiotherapy. *Particularly in human papillomavirus positive low risk or intermediate risk oropharyngeal cancer. RT, radiotherapy; HPV+ OPC, human papillomavirus positive oropharyngeal cancer.

related deaths. Similarly, it remains unknown whether the progressively extending survival associated with 10 mg/m^2 cisplatin increments in a range between 140 and 270 mg/m^2, as demonstrated in a model based on 6 phase III trials, is due to the higher dose itself or to healthier patients better tolerating additional cisplatin delivery (33). Thus, even if two doses of 100 mg/m^2 cisplatin given concurrently with conventional fractionation may be considered by some experts sufficient in the context of drug exposition [IV, C], clinicians should always ensure maximal comfort and supportive care for their patients and if toxicity permits, administration of the third cycle is indicated.

Relative Contraindications to High-Dose Cisplatin

Owing to the high prevalence of comorbid conditions in patients with head and neck cancer, many cases fall into this category (34). Here, more than in any of the two alternative clinical scenarios, physicians have to rely on local medical expertise including multidisciplinary tumor board meetings with an emphasis on patient engagement and shared decision making. Consequently, some practitioners opt for the standard of care, while others consider treatment plans recommended in the case of absolute contraindications to cisplatin (see below) [V, C]. Under such circumstances, lowering the peak concentration of cisplatin, as an important determinant for acute toxicity (nausea, vomiting, transaminase elevations, ototoxicity, serum creatinine increase), by either prolonging the infusion time (e.g., for 24 h) or reducing the single dose (e.g., weekly or daily administration or the 3 weekly schedule with a reduced dose) is justifiable as well (19, 35–38) [V, C]. If preference is given to weekly cisplatin, single doses of 40 mg/m^2 are recommended to ensure that the majority of patients receive a cumulative dose of at least 200 mg/m^2 (28). The latter proved difficult to be attained with lower single doses, and this could negatively impact on survival (27, 29). A split administration of 4 × 25 mg/m^2 on 4 consecutive days instead of the standard 100 mg/m^2 infusion is currently under investigation in the GORTEC 2015-02 trial.

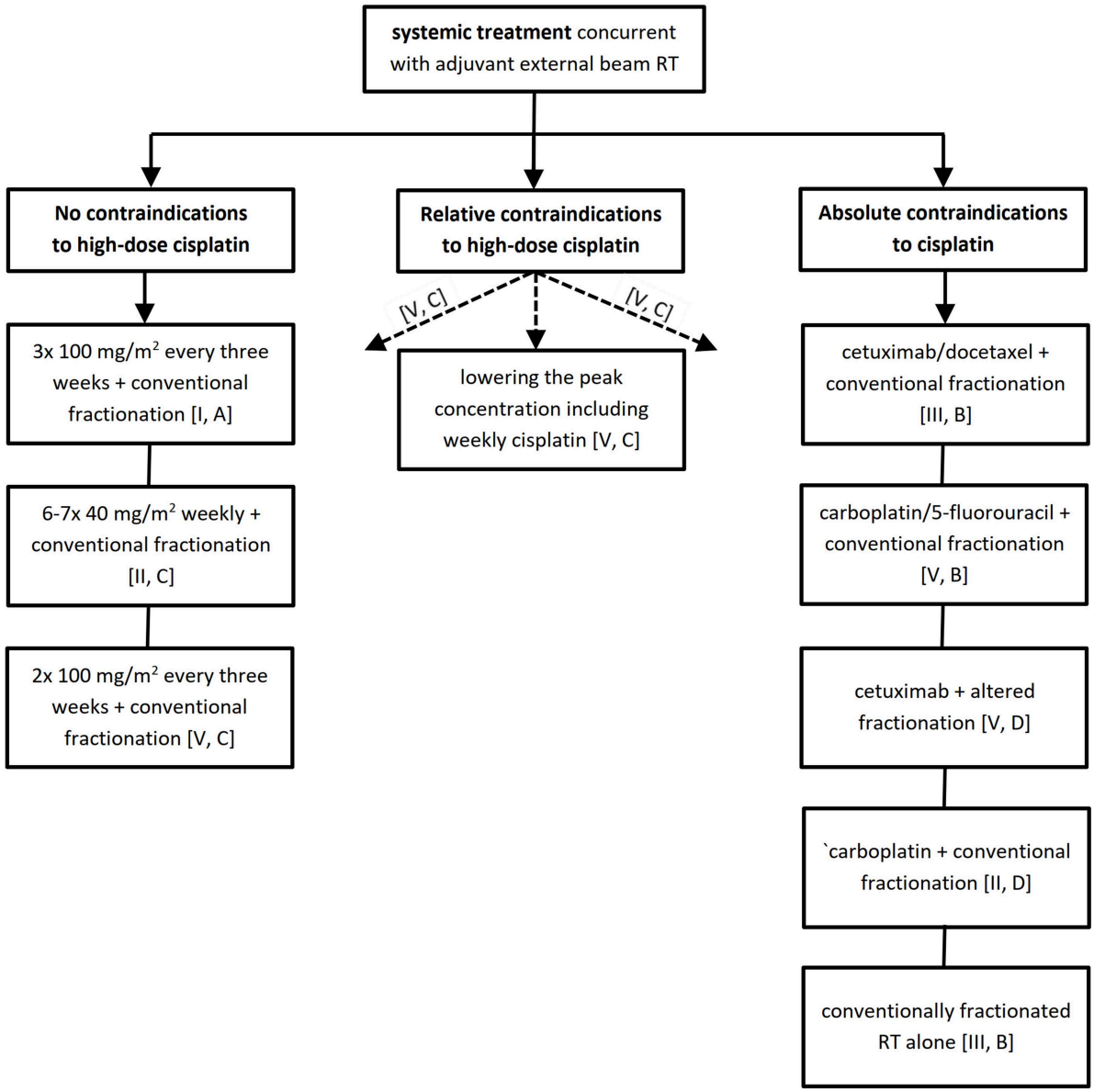

FIGURE 2 | Systemic treatment recommendations for adjuvant (post-operative) chemoradiotherapy. RT, radiotherapy.

Absolute Contraindications to Cisplatin

This situation precludes both high-dose and low-dose cisplatin regimens. Combining carboplatin 70 mg/m^2 and fluorouracil 600 mg/m^2 daily for 4 days three times every 3 weeks, the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) regimen was explored in two large randomized trials. Between 1994 and 1997, the GORTEC 94-01 trial randomly allocated 226 oropharyngeal cancer patients to receive either carboplatin/5-fluorouracil chemotherapy with conventionally fractionated radiotherapy or radiotherapy alone. The combined modality arm managed to significantly enhance overall survival and this benefit was maintained even after a median follow-up of 5.5 years (5 year rates: 22.4% vs. 15.8%) (39, 40). The GORTEC 99-02 recruited 840 patients between 2000 and 2007, distributing them evenly between conventional chemoradiotherapy with the same carboplatin/5-fluorouracil regimen as described above, accelerated radiotherapy with a slightly modified systemic treatment, and very accelerated radiotherapy alone. Compared with the latter approach, conventional chemoradiotherapy induced superior 3 year PFS (37.6% vs. 32.2%; HR 0.82, 95% CI 0.67–0.99, $p = 0.041$) and overall survival (42.6% vs. 36.5%; HR 0.81, 95% CI 0.67–0.99, $p = 0.04$), while the use of accelerated radiation did not provide any benefit in this trial. Importantly, giving all three cycles vs. less amount of chemotherapy seemed to generate better survival and distant control, and this could not be compensated by acceleration (41, 42). In both GORTEC 94-01 and GORTEC 99-02, the acute toxicity was the major downside of this type of conventional

chemoradiotherapy. The rate of severe acute mucositis of about 70% was at the limit of clinical acceptance. In GORTEC 94-01, it almost doubled compared with the standard arm (71% vs. 39%). In summary, patients with a history of neurological, hearing, or renal comorbidities as the sole factors precluding cisplatin administration should be primarily considered for carboplatin/5-fluorouracil doublet [I, B].

Cetuximab is an immunoglobulin G1 chimeric monoclonal antibody against epidermal growth factor receptor (EGFR) and the only approved targeted agent in locoregionally advanced SCCHN. It is usually administered at an initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. Serving as a possible alternative to platinum derivatives, the IMCL-9815 trial showed survival advantage with the addition of cetuximab to radiotherapy alone, primarily integrating altered fractionation and excluding oral cavity primaries (43). However, as suggested by several retrospective observations and recently confirmed by the De-ESCALaTE and RTOG 1016 trials, bioradiation with cetuximab should not be prioritized over the conventionally or altered fractionation cisplatin-based chemoradiation either in terms of efficacy or in terms of acute and late toxicity [II, B] (11, 12, 44–46). A similar conclusion has recently been suggested for the anti-tumor activity of the carboplatin/5-fluorouracil (vs. cetuximab) in patients who were not eligible for high-dose cisplatin, based on GORTEC 2007-01, showing superiority of this regimen plus cetuximab vs. cetuximab alone when combined with radiation (47). Moreover, since the publication of De-ESCALaTE and RTOG 1016, the recommendation for cetuximab as an adjunct to definitive radiotherapy has been weaker in patients with HPV-positive oropharyngeal cancer where it remains optional in the case of a contraindication for platinum-based chemotherapy [I, C]. In this situation, hyperfractionated radiotherapy alone might be a reasonable choice also (please see below).

Supported by limited scientific evidence, many practicing oncologist have been using single agent carboplatin as a less toxic substitute for cisplatin in these circumstances. Between 1988 and 1991, Jeremic et al. tested conventional radiotherapy (arm I) with or without daily administration of cisplatin (6 mg/m^2, arm II) or carboplatin (25 mg/m^2, arm III) (48). Fountzilas et al. utilized a similar three-arm design but with high-dose cisplatin (100 mg/m^2) or carboplatin (area under the curve 7) administered every 3 weeks for a total of three infusions (49). In both studies, carboplatin had a significantly positive impact on overall survival with an acceptable toxicity profile most frequently in the form of bone marrow suppression. Nonetheless, the results should be interpreted with caution in view of the clearly insufficient number of patients treated with carboplatin in each of these trials (53 and 38, respectively) and its differing dose. Of note, according to the previously mentioned individual patient-based meta-analysis, only concomitant monochemotherapy with cisplatin or polychemotherapy including a platinum derivate or 5-fluorouracil gave a survival advantage when combined with radiotherapy, and this was not the case when carboplatin alone was used alone as a radiosensitizer [II, C] (17).

In selected cases where patient-related factors impede systemic treatment, altered fractionation radiotherapy alone should be pursued. The greatest survival gain can be achieved by hyperfractionation, especially in limited nodal disease (N0 and N1). This came forward in a large meta-analysis of 15 randomized trials comparing conventional radiotherapy with altered fractionation schedules in definitive treatment of non-metastatic SCCHN [I, B] (50). A recently published update corroborated its conclusions (51).

POST-OPERATIVE TREATMENT SETTING

No or Only Relative Contraindications to High-Dose Cisplatin

With the exception of altered fractionation radiotherapy which should preferably not be delivered in the post-operative setting and the fact that data supporting a cumulative dose of 200 mg/m^2 cisplatin in combination with conventional fractionation are extrapolated from the definitive setting [V, C], the remaining recommendations are equivalent to those pertinent to definitive treatment intent (52). Only one small randomized trial explored the outcome of adding weekly cisplatin to conventional radiotherapy in a sample of 88 participants. The statistically significant improvement of 5 year overall survival (13% vs. 36%), disease-free survival (23% vs. 45%), and locoregional control (55% vs. 70%) was accompanied by an increase in severe acute adverse events (16% vs. 41%). Of note, the used single (50 mg/m^2) and cumulative (350–450 mg/m^2) cisplatin doses exceeded those employed in current protocols, limiting thus the applicability of this weekly regimen in daily practice (53, 54). Data from other prospective and retrospective studies do not permit substituting the 3 weekly for a weekly schedule on a routine basis (23). For more on this subject, please refer to a separate chapter below.

Absolute Contraindications to Cisplatin

In case the risk/benefit ratio strongly discourages from exposing patients to cisplatin, there is no adequate systemic replacement. In this context, patients with a high risk for recurrence should routinely receive conventional radiotherapy alone despite a paucity of randomized trials of post-operative radiotherapy vs. observation, originating from the fact that the concept of adjuvant therapy developed empirically [III, B] (55). Nevertheless, addressing the clinical need to potentiate treatment outcomes above all in patients in good clinical condition without other contraindications, several systemic agents have been recommended in combination with conventional radiotherapy in this setting. In the randomized RTOG 0234 phase II trial, 238 patients treated with post-operative radiotherapy were evenly divided into the following two arms, cetuximab with weekly cisplatin 30 mg/m^2 or cetuximab with weekly docetaxel 15 mg/m^2. With a median follow-up of 4.4 years, the latter regimen augmented overall survival relative to historical controls from the RTOG 9501 trial (2 year rates: 79% vs. 65%) with a 54% rate of severe acute mucositis [III, B] (56). Although some advantage has been suggested with the use of paclitaxel in definitive chemoradiation de-escalation trials in HPV-positive oropharyngeal cancer, this has not been tested in the post-operative setting (57, 58).

On the contrary, for single-agent cetuximab as an adjunct to post-operative radiotherapy no prospective evidence exists, and a recently published report on a small series of patients discouraged from its use here (59). Therefore, with the additional negative results of cetuximab/radiation in comparison with cisplatin/radiation in the definitive setting (see earlier) we do not recommend this approach [V, D]. Similarly, carboplatin/5-fluorouracil doublet has never been tested prospectively after curative resection. Nevertheless, it has been generally accepted as an adequate surrogate for high-dose cisplatin concurrent with definitive radiotherapy, and we assume comparable activity when extrapolated to the adjuvant setting [V, B]. However, for single-agent carboplatin, the rationale is weak at present. The only randomized trial in mucosal SCCHN was closed prematurely due to slow accrual and did not demonstrate any benefit with the addition of weekly carboplatin to adjuvant radiotherapy [II, D] (60). This is in line with another negative phase III trial performed in 321 patients with cutaneous SCCHN. The Trans-Tasman Radiation Oncology Group (TROG) 05.01 study provided high-quality data with a median follow-up of 60 months showing that potentiation by weekly low-dose carboplatin had no effect on survival or toxicity (61).

WEEKLY VS. 3 WEEKLY CISPLATIN

As alluded to above, 3 weekly high-dose cisplatin delivered concurrently with external beam radiotherapy remains the standard of care. This is in line with the results of a composite meta-analysis of 59 prospective trials enrolling altogether 5,582 patients (23, 24, 26). Although the weekly schedule produced less severe acute adverse events than three cycles of the standard regimen when combined with conventionally fractionated radiotherapy, no benefit could be observed in survival and late toxicity analyses. Of note, only two thirds of patients allocated to the high-dose arm could receive all three cycles (23). On the other hand, altered fractionation was associated with a significant advantage of two high-dose cisplatin cycles not only in terms of overall survival but in acute and late side effects. Here, the compliance with the standard regimen surpassed 90% (24). Moreover, in patients treated with adjuvant intent, two prospective trials comparing weekly vs. 3 weekly cisplatin are available. The first has been reported by Tsan et al. Among 55 randomly assigned patients followed for a median of 12 months, the 3 weekly regimen produced less acute toxicity, particularly severe mucositis, than weekly 40 mg/m^2 cisplatin and proved also superiority in terms of reaching cumulative doses of at least 200 mg/m^2 (62). Another proof against the routine use of weekly cisplatin was recently furnished by a single-center phase III trial from the Tata Memorial Cancer Centre in Mumbay, India, comparing weekly 30 mg/m^2 vs. 3 weekly 100 mg/m^2 cisplatin. Non-inferiority of the low-dose regimen could not be confirmed. The standard, high-dose group, showed significant gain in locoregional control, the primary objective (73.1% vs. 58.5% at 2 years, $p = 0.014$), albeit at the cost of an increased incidence of acute (84.6% vs. 71.6%, $p = 0.006$), but not late side effects (63).

In summary, the enhanced short-term tolerance of weekly cisplatin (i.e., less acute nausea, vomiting, transaminase elevations, ototoxicity, serum creatinine increase, and myelotoxicity) may be outweighed by compromised survival and a lack of improvement in late toxicity.

CONCLUSIONS

With the advent of novel targeted drugs, particularly immunotherapy, the landscape of head and neck cancer management has been undergoing profound changes affecting the recurrent and/or metastatic setting in the first place. In locoregionally advanced disease, the limited efficacy and unfavorable safety profile of the standard cisplatin-based chemoradiation has prompted many attempts at improving or even substituting this regimen. Now, 15 years after the publication of the four seminal articles, there is finally some reason for optimism. The activity of the immune checkpoint inhibitors nivolumab and pembrolizumab has been demonstrated in at least three large phase III trials in recurrent/metastatic SCCHN and in 2019, the efficacy results of the first studies performed in the locoregionally advanced disease setting will be presented as well, including the PembroRad trial (NCT02707588) randomizing patients between definitive radiotherapy with pembrolizumab or cetuximab and the RTOG 3504 trial (NCT02764593) exploring different combinations of definitive radiotherapy, nivolumab, cisplatin, and cetuximab.

Recommendations presented in this review paper should not be understood as a dogmatic system of rules but rather a frame to guide clinical decision making in which we underscore an individual approach allowing for patient- and disease-related factors. The relevance of these instructions should pertain at least for some time even in the era of modern immunotherapy because the availability and accessibility of immunomodulating antibodies will unfortunately be restricted in many countries worldwide. In this situation, cisplatin will retain its significance and continue to represent a cost-effective and feasible modality saving patients' lives.

AUTHOR CONTRIBUTIONS

PS and JV drafted the manuscript. CS and JB contributed to writing of the manuscript. VC and RH contributed to the conception and reviewed the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2019.00464/full#supplementary-material

REFERENCES

1. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet*. (2008) 371:1695–709. doi: 10.1016/S0140-6736(08)60728-X
2. Vermorken JB. Patient and treatment factors in concurrent chemoradiotherapy. In: Vermorken JB, Budach V, Leemans CR, Machiels JP, Nicolai P, O'Sullivan B, editors. *Critical Issues in Head and Neck Oncology: Key Concepts From the Fifth THNO Meeting*. Cham: Springer International Publishing AG (2017). p. 189–201.
3. Grégoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. (2010) 21(Suppl. 5):v184–6. doi: 10.1093/annonc/mdq185
4. Adelstein DJ, Li Y, Adams GL, Wagner H Jr., Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. (2003) 21:92–8. doi: 10.1200/JCO.2003.01.008
5. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. (2003) 349:2091–8. doi: 10.1056/NEJMoa031317
6. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med*. (2004) 350:1937–44. doi: 10.1056/NEJMoa032646
7. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. (2004) 350:1945–52. doi: 10.1056/NEJMoa032641
8. National Comprehensive Cancer Network. *Head and Neck Cancers* (Version 1.2019). Available online at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed March 6, 2019).
9. Brentani A, de Castro G Jr., Federico MH. Cost-effectiveness analysis of cisplatin-based chemoradiation to treat patients with unresectable, nonmetastatic head and neck cancer in Brazil. *Head Neck*. (2011) 33:1199–205. doi: 10.1002/hed.21601
10. Atun R, Jaffray DA, Barton MB, Bray F, Baumann M, Vikram B, et al. Expanding global access to radiotherapy. *Lancet Oncol*. (2015) 16:1153–86. doi: 10.1016/S1470-2045(15)00222-3
11. Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet*. (2019) 393:51–60. doi: 10.1016/S0140-6736(18)32752-1
12. Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet*. (2019) 393:40–50. doi: 10.1016/S0140-6736(18)32779-X
13. O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol*. (2016) 17:440–51. doi: 10.1016/S1470-2045(15)00560-4
14. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol*. (2014) 50:380–6. doi: 10.1016/j.oraloncology.2013.12.019
15. Drain PK, Parker RA, Robine M, Holmes KK. Global migration of clinical research during the era of trial registration. *PLoS ONE*. (2018) 13:e0192413. doi: 10.1371/journal.pone.0192413
16. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol*. (2013) 31:845–52. doi: 10.1200/JCO.2012.43.6097
17. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. (2009) 92:4–14. doi: 10.1016/j.radonc.2009.04.014
18. Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys*. (2012) 84:1198–205. doi: 10.1016/j.ijrobp.2012.05.008
19. Ahn MJ, D'Cruz A, Vermorken JB, Chen JP, Chitapanarux I, Dang HQ, et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: a literature review. *Oral Oncol*. (2016) 53:10–6. doi: 10.1016/j.oraloncology.2015.11.019
20. Ward MC, Reddy CA, Adelstein DJ, Koyfman SA. Use of systemic therapy with definitive radiotherapy for elderly patients with head and neck cancer: a National Cancer Data Base analysis. *Cancer*. (2016) 122:3472–83. doi: 10.1002/cncr.30214
21. Szturz P, Vermorken JB. The role of chemoradiotherapy in elderly patients with locoregionally advanced head and neck cancer. *Belg J Med Oncol*. (2018) 12:110–7.
22. Szturz P, Bossi P, Vermorken JB. Systemic treatment in elderly head and neck cancer patients: recommendations for clinical practice. *Curr Opin Otolaryngol Head Neck Surg*. (2019) 27:142–50. doi: 10.1097/MOO.0000000000000526
23. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist*. (2017) 22:1056–66. doi: 10.1634/theoncologist.2017-0015
24. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Altered fractionation radiotherapy combined with concurrent low-dose or high-dose cisplatin in head and neck cancer: a systematic review of literature and meta-analysis. *Oral Oncol*. (2018) 76:52–60. doi: 10.1016/j.oraloncology.2017.11.025
25. Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol*. (2014) 32:3858–66. doi: 10.1200/JCO.2014.55.3925
26. Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V, et al. Low-dose versus high-dose cisplatin: lessons learned from 59 chemoradiotherapy trials in head and neck cancer. *Front Oncol*. (2019) 9:86. doi: 10.3389/fonc.2019.00086
27. Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). *Int J Radiat Oncol Biol Phys*. (2011) 81:719–25. doi: 10.1016/j.ijrobp.2010.06.038
28. Sharma A, Mohanti BK, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. *Ann Oncol*. (2010) 21:2272–7. doi: 10.1093/annonc/mdq219
29. Ghosh-Laskar S, Kalyani N, Gupta T, Budrukkar A, Murthy V, Sengar M, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: results of a prospective randomized trial. *Head Neck*. (2016) 38:202–7. doi: 10.1002/hed.23865
30. Otty Z, Skinner MB, Dass J, Collins M, Mooi J, Thuraisingam K, et al. Efficacy and tolerability of weekly low-dose cisplatin concurrent with radiotherapy

in head and neck cancer patients. *Asia Pac J Clin Oncol*. (2011) 7:287–92. doi: 10.1111/j.1743-7563.2011.01405.x

31. Spreafico A, Huang SH, Xu W, Granata R, Liu CS, Waldron JN, et al. Impact of cisplatin dose intensity on human papillomavirus-related and -unrelated locally advanced head and neck squamous cell carcinoma. *Eur J Cancer*. (2016) 67:174–82. doi: 10.1016/j.ejca.2016.08.013
32. Ang K, Zhang Q, Wheeler RH, Rosenthal DI, Nguyen-Tan F, Kim H, et al. A phase III trial (RTOG 0129) of two radiation-cisplatin regimens for head and neck carcinomas (HNC): impact of radiation and cisplatin intensity on outcome. *J Clin Oncol*. (2010) 28:5507. doi: 10.1200/jco.2010.28.15_suppl.5507
33. Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz M Jr., Bossi P, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. *Head Neck*. (2016) 38(Suppl. 1):E2151–8. doi: 10.1002/hed.24026
34. Paleri V, Wight RG, Silver CE, Haigentz M Jr., Takes RP, Bradley PJ, et al. Comorbidity in head and neck cancer: a critical appraisal and recommendations for practice. *Oral Oncol*. (2010) 46:712–9. doi: 10.1016/j.oraloncology.2010.07.008
35. Vermorken JB, van der Vijgh WJ, Klein I, Gall HE, Pinedo HM. Pharmacokinetics of free platinum species following rapid, 3-hr and 24-hr infusions of cis-diamminedichloroplatinum (II) and its therapeutic implications. *Eur J Cancer Clin Oncol*. (1982) 18:1069–74. doi: 10.1016/0277-5379(82)90085-2
36. Vermorken JB, Kapteijn TS, Hart AA, Pinedo HM. Ototoxicity of cis-diamminedichloroplatinum (II): influence of dose, schedule and mode of administration. *Eur J Cancer Clin Oncol*. (1983) 19:53–8. doi: 10.1016/0277-5379(83)90398-X
37. Vermorken JB, van der Vijgh WJ, Klein I, Gall HE, van Groeningen CJ, Hart GA, et al. Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. *Clin Pharmacol Ther*. (1986) 39:136–44. doi: 10.1038/clpt.1986.24
38. Kurihara N, Kubota T, Hoshiya Y, Otani Y, Ando N, Kumai K, et al. Pharmacokinetics of cis-diamminedichloroplatinum (II) given as low-dose and high-dose infusions. *J Surg Oncol*. (1996) 62:135–8.
39. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. (1999) 91:2081–6. doi: 10.1093/jnci/91.24.2081
40. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. (2004) 22:69–76. doi: 10.1200/JCO.2004.08.021
41. Bourhis J, Sire C, Graff P, Grégoire V, Maingon P, Calais G, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol*. (2012) 13:145–53. doi: 10.1016/S1470-2045(11)70346-1
42. Bourhis J, Tao YG, Blanchard P, Sire C, Aupérin A. Absent benefit of accelerated concomitant chemoradiotherapy - authors' reply. *Lancet Oncol*. (2012) 13:e136–7. doi: 10.1016/S1470-2045(12)70089-X
43. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. (2006) 354:567–78. doi: 10.1056/NEJMoa053422
44. Petrelli F, Coinu A, Riboldi V, Borgonovo K, Ghilardi M, Cabiddu M, et al. Concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced head and neck cancer: a systematic review and meta-analysis of published studies. *Oral Oncol*. (2014) 50:1041–8. doi: 10.1016/j.oraloncology.2014.08.005
45. Magrini SM, Buglione M, Corvò R, Pirtoli L, Paiar F, Ponticelli P, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J Clin Oncol*. (2016) 34:427–35. doi: 10.1200/JCO.2015.63.1671
46. Bauml J, Vinnakota RR, Park YHA, Bates SE, Fojo AT, Aggarwal C, et al. Cisplatin (CIS) versus cetuximab (CET) with definitive concurrent radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC): an analysis of veteran's health data. *J Clin Oncol*. (2018) 36:6073. doi: 10.1200/JCO.2018.36.15_suppl.6073
47. Tao Y, Auperin A, Sire C, Martin L, Khoury C, Maingon P, et al. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. *J Clin Oncol*. 2018:JCO2017762518. doi: 10.1200/JCO.2017.76.2518
48. Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiother Oncol*. (1997) 43:29–37. doi: 10.1016/S0167-8140(97)00048-0
49. Fountzilas G, Ciuleanu E, Dafni U, Plataniotis G, Kalogera-Fountzila A, Samantas E, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. *Med Oncol*. (2004) 21:95–107. doi: 10.1385/MO:21:2:095
50. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet*. (2006) 368:843–54. doi: 10.1016/S0140-6736(06)69121-6
51. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol*. (2017) 18:1221–37. doi: 10.1016/S1470-2045(17)30458-8
52. Sanguineti G, Richetti A, Bignardi M, Corvo' R, Gabriele P, Sormani MP, et al. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. *Int J Radiat Oncol Biol Phys*. (2005)61:762–71. doi: 10.1016/j.ijrobp.2004.07.682
53. Bachaud JM, David JM, Boussin G, Daly N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced squamous cell carcinoma of the head and neck: preliminary report of a randomized trial. *Int J Radiat Oncol Biol Phys*. (1991) 20:243–6. doi: 10.1016/0360-3016(91)90098-O
54. Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, Daly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys*. (1996) 36:999–1004. doi: 10.1016/S0360-3016(96)00430-0
55. Fletcher GH, Evers WT. Radiotherapeutic management of surgical recurrences and postoperative residuals in tumors of the head and neck. *Radiology*. (1970) 95:185–8. doi: 10.1148/95.1.185
56. Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol*. (2014) 32:2486–95. doi: 10.1200/JCO.2013.53.9163
57. Chen AM, Felix C, Wang PC, Hsu S, Basehart V, Garst J, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. *Lancet Oncol*. (2017) 18:803–11. doi: 10.1016/S1470-2045(17)30246-2
58. Fietkau R, Iro H, Hecht M, Hofner B, Gefeller O, Balermpas P, et al. Randomised phase-III-trial of concurrent chemoradiation (CRT) for locally advanced head and neck cancer (stage III-IVB): comparing dose reduced radiotherapy (63,6 Gy) with paclitaxel/cisplatinum to standard radiotherapy (70,6 Gy) with fluorouracil/cisplatinum. *J Clin Oncol*. (2017) 35:6016. doi: 10.1200/JCO.2017.35.15_suppl.6016

59. Araki D, Redman MW, Martins R, Eaton K, Baik C, Chow L, et al. Concurrent cetuximab and postoperative radiation in resected high-risk squamous cell carcinomas of the head and neck: a single-institution experience. *Head Neck*. (2016) 38:1318–23. doi: 10.1002/hed.24437
60. Argiris A, Karamouzis MV, Johnson JT, Heron DE, Myers E, Eibling D, et al. Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer. *Laryngoscope*. (2008) 118:444–9. doi: 10.1097/MLG.0b013e31815b48f4
61. Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol*. (2018) 36:1275–83. doi: 10.1200/JCO.2017.77.0941
62. Tsan DL, Lin CY, Kang CJ, Huang SF, Fan KH, Liao CT, et al. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. *Radiat Oncol*. (2012) 7:215. doi: 10.1186/1748-717X-7-215
63. Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol*. (2018) 36:1064–72. doi: 10.1200/JCO.2017.74.9457

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