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TOPIC HIGHLIGHT

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Chemotherapy advances in locally advanced head and neck cancer

Peter Georges, Kumar Rajagopalan, Chady Leon, Priya Singh, Nadir Ahmad, Kamyar Nader, Gregory J Kubicek

Peter Georges, Kumar Rajagopalan, Chady Leon, Priya Singh, Kamyar Nader, Department of Medical Oncology, Cooper University Hospital, Camden, NJ 08103, United States
Nadir Ahmad, Department of Otolaryngology, Cooper University Hospital, Camden, NJ 08103, United States
Gregory J Kubicek, Department of Radiation Oncology, Cooper University Hospital, Camden, NJ 08103, United States
Author contributions: Georges P and Kubicek GJ wrote the paper; Rajagopalan K, Leon C, Singh P, Ahmad N and Kubicek GJ edited the article; all the authors contributed to this paper.
Correspondence to: Gregory J Kubicek, MD, Department of Radiation Oncology, Cooper University Hospital, One Cooper Plaza, Camden, NJ 08103,
United States. greg.kubicek@gmail.com
Telephone: +1-856-3422300 Fax: +1-856-3658504
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Abstract

The management of locally advanced unresectable head and neck squamous cell cancer (HNSCC) continues to improve. One of the major advances in the treatment of HNSCC was the addition of chemotherapy to radiation in the treatment of non-surgical patients. The majority of the data regarding chemotherapy in HNSCC involve cisplatin chemotherapy with concurrent radiation. However, several new approaches have included targeted therapy against epidermal growth factor receptor and several recent studies have explored the role of induction chemotherapy in the treatment of HNSCC. The purpose of this article is to provide an overview of the role of chemotherapy in the treatment of locally advanced HNSCC.

Key words: Head and neck cancer; Chemotherapy; Induction

Core tip: For select patient subsets the addition of chemotherapy to radiation in head and neck squamous cell cancer improves outcome. Most data is for concurrent cisplatin although other agents are also being explored. There has recently been interest in induction chemotherapy, the induction studies although heterogeneous have failed to show an improvement in overall survival. In this article we discuss the data regarding concurrent chemotherapy and also the data regarding induction therapy and which patient subsets we feel are best suited for induction chemotherapy (patients with N3 disease and those expected to have a delay in starting concurrent concurrent chemoradiotherapy).

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SOURCES AND SELECTION CRITERIA

We performed a Pubmed search for manuscripts published between 1995 and November 2013 using the following search keywords: "head and neck cancer and chemotherapy", "head and neck cancer and radiation", "head and neck cancer and chemoradiation", "head and neck cancer and induction chemotherapy", and "head and neck cancer and epidermal growth factor receptor (EGFR) targeted therapy". The search was limited to the English language to and humans. In addition, we reviewed the references from the National Comprehensive Cancer Network (NCCN) guidelines and those from the selected publications to include landmark articles. Manuscripts were selected for inclusion based on the author's assessment of the paper's relevance to the topics included

in this review.

CONCURRENT CHEMORADIOTHERAPY

Head and neck squamous cell carcinoma (HNSCC) is a challenging cancer to treat and cure. Surgical management continues to be the standard of care for many HNSCC including most cancers in the oral cavity. For patients with locally advanced disease not amenable to surgical resection, concurrent chemoradiotherapy (CRT) is now recognized worldwide as a standard treatment option[1]. Evidence has largely supported the use of radiation treatment concurrent with three cycles of bolus cisplatin[2], although several other agents have also been studied[3-5]. Despite improved outcomes with CRT, disease recurrence and treatment toxicity continue to be challenges with this treatment paradigm[6]. To obtain improved outcomes and mitigate disease recurrence and treatment toxicity, new agents such as cetuximab[7] and induction chemotherapy[8] have been explored.

Prior to 2000, radiation alone was the predominant non-surgical treatment modality offered to patients with HNSCC. The introduction of CRT was based on several phase Ⅲ trials showing a survival benefit of adding chemotherapy to radiation *vs* radiation alone in locally advanced HNSCC[1,3-5].

A meta-analysis of 87 trials conducted by Pignon *et al*[9] from 1965 to 2000, which included 16485 patients, found an absolute survival benefit for chemotherapy of 4.5% at 5 years and an absolute benefit for concurrent CRT of 6.5%. The hazard ratio (HR) of death was 0.81 (0.78-0.86, $P < 0.0001$). In this meta-analysis, there was a statistically insignificant benefit for induction chemotherapy with an absolute benefit of 2.4% at 5 years with a HR of death of 0.96 (0.9-1.02, $P = 0.18$)[9]. Another important finding of this meta-analysis is that adding chemotherapy to radiation was not beneficial in certain patient subsets, an observation that would have been impossible to establish in smaller studies due to limited sample size in individual trials. These subsets included patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 and 3, stage Ⅰ-Ⅱ tumors, and "orphan cancers", which included HNSCC outside the oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx. Additionally, no survival advantage was seen in patients over age 70 when concurrent platinum based chemotherapy was administered concurrently with radiation. Analysis of various chemotherapeutic regimens showed that single agent platin was the most efficacious.

Although chemotherapy in combination with radiation improves survival in patients with locally advanced HNSCC, it does increase toxicity. Adelstein *et al*[1] showed increased treatment related toxicities such as nausea/vomiting, leukopenia, anemia and kidney injury. In the CRT arm 77% of patients exhibited grade 3 or higher toxicity when given CRT using 70 Gray (Gy) five days per week and cisplatin *vs* 52% of patients who received radiation alone[1].

ROLE OF EPIDERMAL GROWTH FACTOR RECEPTOR TARGETED THERAPY

EGFR is overexpressed in almost all HNSCC tumors, and overexpression of EGFR correlates with higher disease stage, lymph node metastasis, and poorer survival[10,11]. An important breakthrough has been molecular targeted therapies to target EGFR[12,13]. Cetuximab, a chimeric humanized monoclonal antibody against EGFR, has lead the way in targeted therapy after first receiving Food and Drug Administration (FDA) approval in 2011 in HNSCC for recurrent and metastatic HNSCC and subsequently in 2006 for locally advanced HNSCC, which we discuss below in the Bonner *et al*[14] study. It has also received FDA approval in the first line setting for metastatic colorectal cancer in 2012. Other monoclonal antibodies and oral tyrosine kinase inhibitors, specifically erlotinib and gefitinib, have shown modest activity without a survival advantage[13].

Prior to CRT being established as standard of care, Bonner *et al*[14] completed a phase Ⅲ study looking at the addition of cetuximab to radiation therapy in patients with locally advanced HNSCC. In this trial, 213 patients were randomized to receive either radiation therapy alone and 211 were randomized to radiation therapy given concurrently with cetuximab. Cetuximab was administered as a onetime dose of 400 mg/m^2 prior to starting radiation therapy, followed by 250 mg/m^2 weekly for the duration of radiotherapy therapy for six or seven weeks. As compared to the radiation therapy alone arm, patients who received concurrent cetuximab and radiation had a statistically significant increase in median locoregional control (LRC) of 9.5 mo (14.9 mo *vs* 24.4 mo, $P = 0.005$), progression free survival (PFS) of 17.1 mo *vs* 12.4 mo ($P = 0.006$) and overall survival (OS) of 49 mo *vs* 29.3 mo ($P = 0.03$). Toxicity was minimally increased in the cetuximab arm, with adverse events related to infusion reactions, fevers, chills, pruritus, acneiform rash, nausea, weight loss, and anemia[14]. This trial was designed prior to adoption of CRT as standard of care for locally advanced HNSCC, and thus, the standard arm of the study was the standard treatment at that time (radiation alone).

Panitumumab, a fully monoclonal antibody, targeting EGFR was also evaluated in the treatment of HNSCC in an attempt to decrease toxicity. Concert-1, a phase Ⅱ trial, randomized patients with previously untreated HNSCC in a 2:3 fashion to receive concurrent therapy using cisplatin for three doses with or without panitumumab. The primary endpoint of the study was LRC rate at 2 years. There was no statistically significant difference in LRC between the cisplatin plus radiotherapy arm (CisRT 68%) and the panitumumab plus CisRT (PCisRT 61%). Progression free survival was 35% in the CisRT arm *vs* 40% in the PCisRT group ($P = 0.61$). There was increased grade 3+ toxicity noted in the group treated with panitumumab, and this included mucositis, skin injury in the radiation field, and dysphagia[15].

Both cisplatin and cetuximab have demonstrated survival advantages when used as single agents in combination with radiation therapy in the management of locally advanced HNSCC. RTOG 1055 was designed to evaluate whether multi-agent therapy in combination with radiation would provide added benefit. This is a phase Ⅲ clinical trial in which 940 patient were randomized to receive either chemoradiation therapy with cisplatin on day 1 and 22 or the same regimen with the addition of weekly cetuximab. After a median follow-up of 2.4 years, there was no difference in progression free survival between the two arms. However, there was an increase in acute toxicity, including mucositis and skin reactions within the radiation field. Long term toxicity was similar in the two groups[16]. While the addition of single agent cisplatin or cetuximab to radiation therapy can improve outcomes in locally advanced HNSCC, combination therapy with cisplatin and cetuximab does not improve outcomes.

While the abundance of data in HNSCC support chemotherapy using cisplatin administered at a bolus of 100 mg/m^2 every 3 wk during radiation, data supporting the use of cetuximab is confined to one phase Ⅲ study. Additional studies are needed to directly compare concurrent chemoradiation with cetuximab *vs* cisplatin. RTOG 1016 is such a trial in progress which is comparing radiation with cetuximab to radiation with cisplatin in patients with human papillomavirus (HPV) positive HNSCC of the oropharynx. It will be several years before survival data becomes available[17].

CHEMOTHERAPY AND RADIATION SCHEDULES

In addition to advancements in chemotherapy, there have been significant improvements in radiation treatment and delivery. RTOG 9003 showed that accelerated radiation, given over six weeks rather than seven weeks, was associated with better locoregional disease control at five years than standard radiation, although more toxic[18]. Despite improvements in disease control, several studies have shown that accelerated radiation schedules are not a substitute for chemotherapy[3,4]. When patients receiving concurrent chemotherapy were randomized to standard *vs* accelerated radiation, there was no benefit in the accelerated radiation arm[5]. Therefore, conventional radiation is preferable to accelerated radiation when administered concurrently with chemotherapy.

SEQUENTIAL THERAPY: THE ROLE OF INDUCTION THERAPY

In an attempt to improve distant disease control and overall survival in unresectable locally advanced HNSCC, induction chemotherapy has emerged over the last decade as an alternative treatment modality. In the meta-analysis by Pignon *et al*[9], 31 induction chemotherapy trials that included 5311 patients showed that induction chemotherapy did not have a statistically significant improvement in survival with a [HR of 0.96 (0.9-1.02), $P = 0.18$]. On the other hand, induction chemotherapy did show a greater benefit in regard to distant disease control at 3.5% [HR = 0.73 (0.61-0.88), $P = 0.001$] *vs* 2.9% for concurrent platin and 5FU studies [HR = 0.88 (0.77-1.00), $P = 0.04$]. The comparison of the two hazard ratios was insignificant ($P = 0.12$ for all trials, $P = 0.56$ for 5-FU-platin trials)[9].

Two large subsequent clinical trials evaluated the addition of Taxotere© (docetaxel) to an induction regimen using cisplatin and fluorouracil in locoregionally advanced HNSCC. The TAX 324 study compared induction therapy with docetaxel, cisplatin, and fluorouracil (TPF) to cisplatin and fluorouracil (PF), followed by chemoradiotherapy. In this trial, 501 patients were randomly assigned to receive induction chemotherapy with either TPF or PF administered every 3 wk for 3 cycles. Both groups were subsequently treated with concurrent chemoradiotherapy using weekly carboplatin at an area under the curve (AUC) of 1.5. Radiation was administered to a total of 70 to 74 Gy. After a minimum follow up of 2 years, the survival benefit was significant in the TPF group with a hazard ratio for death of 0.7 ($P = 0.006$). The median overall survival was 71 mo for the TPF group *vs* 30 mo in the PF group ($P = 0.006$). There was also better LRC for the TPF group ($P = 0.04$)[19].

Additionally, the TAX 323 study compared induction therapy with TPF to PF followed by radiotherapy alone. In this European trial, 358 patients were randomized to receive induction chemotherapy with TPF *vs* PF every 3 wk for four cycles followed by radiotherapy alone administered on different schedules (conventional, accelerated, hyperfractionated) to 66-74 Gy. After a median follow-up of 32.5 mo, there was a 2.8 mo progression free survival benefit in the TPF group. The HR for disease progression or death in the TPF group was 0.72 with a p value of 0.007. The main toxicity associated with the TPF regimen in both the TAX 323 and the Tax 324 was leukopenia and neutropenia[20].

In 2010, Paccagnella *et al*[8] reported a phase Ⅱ study comparing concurrent therapy to sequential therapy using TPF as induction. One hundred and one patients were randomized to receive concurrent chemoradiotherapy *vs* induction chemotherapy (TPF) followed by concurrent treatment. The primary end point of the trial was radiologic complete response (CR) rate, evaluated 6-8 wk after the completion of concurrent therapy. This study showed superiority of sequential chemotherapy with CR of 50% compared to 21.2% ($P = 0.004$). Although the study was not powered for assessing PFS and OS, there was a 13.6 mo and 9.2 mo PFS and OS advantage respectively when induction chemotherapy was used, without an increase in toxicity[8].

Additional data regarding the use of induction therapy is provided by two recently completed phase Ⅲ studies. The PARADIGM trial randomized patients to concurrent chemoradiotherapy *vs* sequential therapy. The study was halted early due to slow accrual with only

Table 1 DeCIDE and PARADIGM Protocols

	DeCIDE	PARADIGM
Stages	Ⅳ	Ⅲ, Ⅳ
Arm 1 (standard)	CRT CRT: five 14 d cycles of docetaxel (day 1), fluorouracil (day 0-4) and hydroxyurea (day 0-4) with twice daily radiation (day 1-5)	CRT cisplatin (100 mg/m^2) Q 3 wk, 12 cycles Radiation: accelerated concomitant boost over 6 wk (72 Gy)
Arm 2 (experimental, induction)	TPF (2) → CRT TPF two cycles: docetaxel 75 mg/m^2 day 1, cisplatin 100 mg /m^2 day 1, fluorouracil 1000 mg/m per day continuous for 5 d CRT: five 14 d cycles of docetaxel (day 1), fluorouracil (day 0-4) and hydroxyurea (day 0-4) with twice daily radiation (day 1-5)	TPF (3) → CRT TPF three cycles: docetaxel 75 mg/m^{21}, cisplatin 100 mg/m^2 day^1, fluorouracil 1000 mg/m^2 continuous for 4 d Responders to induction: CRT (carboplatin AUC 1.5, weekly) Poor responders to induction CRT (docetaxel 20 mg/m^2 weekly) Radiation: accelerated concomitant boost over 6 wk (72 Gy) for poor responders. Induction chemotherapy responders 70 Gy over 7 wk

[1]Statistically significant. CRT: Chemoradiation.

Table 2 DeCIDE and PARADIGM results

Study	Patients	Randomization (induction regimens)	PFS (3 yr)	OS (3 yr)	DM
PARADIGM	145	CRT	69%	78%	11%
		TPF (3) → CRT	67%	73%	7%
DeCIDE	280	CRT	59%	73%	19%[1]
		TPF (2) → CRT	67%	75%	10%[1]

[1]Statistically significant. CRT: Chemoradiation; DM: Distant metastasis.

145 out of the originally planned 330 patients accrued. Patients were randomized in a 1:1 fashion to induction therapy using TPF × 3 followed by concurrent therapy using either weekly carboplatin and conventional radiation or weekly docetaxel and accelerated boost radiotherapy (Arm A) or accelerated boost concurrent therapy using bolus cisplatin × 2 (Arm B). This study allowed for post-induction chemotherapy to be based on response to induction chemotherapy. Patients with poor response including progression of disease, not completing all cycles of TPF, gross disease left at primary site after induction, lymph nodes > 2 cm after induction, or partial response with biopsy proven residual at primary were subsequently treated with weekly docetaxel (20 mg/m^2) and accelerated radiation whereas induction chemotherapy responders had weekly carboplatin (AUC 1.5) and conventional radiation as illustrated in Table 1. The primary endpoint was overall survival. After a median follow-up of 49 mo, three-year survival was excellent in both arms, 78% in the concurrent therapy arm *vs* 73% in the sequential therapy arm (P = 0.77) as shown in Table 2. The secondary end point of the study, progression free survival was not statistically significant at 69% in the concurrent therapy arm *vs* 67% in the induction therapy arm, P = 0.82[21]. There was no significant different in acute toxicity and evaluation for late toxicity is ongoing.

The DeCIDE protocol by Cohen *et al*[22] randomized patients to concurrent CRT using 5 d of docetaxel, 5-FU, and hydroxyurea and radiation given twice daily at 1.5 Gy per fraction followed by a 9 d break *vs* two cycles of TPF followed by the same CRT regimen as demonstrated in Table 1. Of note, radiation in this study was delivered *via* a split course, considered the standard at University of Chicago Medical Center, though this is not often used outside that institution. The study was able to recruit 280 out of 400 patients originally planned. The primary end point of the study was overall survival. After a three years of follow-up, the overall survival was 73% for the CRT arm *vs* 75% for the induction chemotherapy arm (P = 0.70). In terms of secondary end points, progression free survival was 59% for the CRT arm *vs* 67% for the induction therapy arm, not statistically significant with a P value of 0.18. Cumulative incidence of distant failure was 19% in the CRT *vs* 10% in the induction therapy arm, and this was statistically significant in favor of induction chemotherapy with a P value of 0.025 as noted in Table 2[22].

DISCUSSION

Concurrent CRT is superior to radiation alone for a selected group of patients with unresectable HNSCC, including patients with stage Ⅲ and Ⅳ disease, younger than 70 years of age, and who have an ECOG performance status of 0-1. The chemotherapy regimen with the most evidence is three cycles of single agent cisplatin, although other agents have also been studied and have demonstrated efficacy, such as cetuximab. In order to further improve on these results several studies have examined induction chemotherapy.

The TAX 324 and TAX 323 trials clearly demonstrated superiority of the TPF induction regimen over PF

Table 3 Tax 323 and 324 results

Study	Patients	Randomization (induction regimens)	PFS (mo)	OS (mo)	DM (%)
Tax 323	358	PF	8.2[1]	14.5[1]	10.3
		TPF	11[1]	18.8[1]	12.9
Tax 324	501	PF	13[1]	30[1]	9
		TPF	36[1]	71[1]	5

[1]Statistically significant. PFS: Progression free survival; OS: Overall survival; DM: Distant metastasis.

in the management of locoregionally advanced HNSCC. However, neither study addressed or included a control arm of concurrent chemoradiation therapy, which is the current standard of care[20] (Table 3). Though these studies resulted in FDA approval of docetaxel as part of induction chemotherapy, they were criticized for comparing two experimental regimens, rather than comparing them to the accepted standard of care[23,24]. It remains unknown if induction chemotherapy is more effective than concurrent CRT in the treatment of local advanced, unresectable HNSCC.

The notion that induction chemotherapy reduces distant metastasis and thus improves overall survival seems compelling; however, the induction studies to date do not support this. There was no difference between the groups in rates of distant metastasis in the PARADIGM study. In the DeCIDE study, there was a decrease in distant metastasis from 19% to 10%; however, the study failed to show an improvement in OS or distant failure free survival (DFFS) for the induction arm. Both PARADIGM and DeCIDE trials were limited by several factors. Both studies had accrual difficulties, which caused each to close prior to planned accrual. The difficulty with accrual was due to competing trials in the United States at that time, patient preference, and strong physician preferences within the community. A strong pre-existing preference in regards to induction chemotherapy for more advanced disease might have created a selection bias against the risk of randomization to chemoradiotherapy alone[21]. Additionally, the importance of HPV was not known when these studies were initiated. An increasing number of new HNSCC cases are HPV positive which has an improved prognosis. As a result of growing number of HPV related oropharyngeal cancers, the overall outcome was better than expected for both studies. This limited the study's power to detect differences in the treatment arms, and would have meant that even larger numbers would have been required in what was already a poorly accrued study. All current HNSCC studies stratify by HPV status because of the significantly improved outcome for HPV positive patients[25].

Even with the limitations of these studies, it is clear that there is no improvement in PFS or OS to using induction chemotherapy, as opposed to CRT for all patients. It remains unclear from the current data if there is a subset of patients who may benefit from induction chemotherapy. One of the advantages of induction therapy is the theoretical ability to eliminate systemic micrometastatic disease and thus prevent distant failure[26]. The TAX 324 study noted a trend towards improved distant metastasis rates with TPF *vs* PF induction therapy (5% DM with TPF *vs* 9% with PF, $P = 0.14$). TAX 323 did not confirm this trend. The PARADIGM study showed DM rates of 7% and 11% using induction and concurrent therapies, respectively, and this did not reach statistical significance. The DeCIDE study did show a reduction in DM using induction (10%) as compared to concurrent treatment (19%).There were subtle differences in study design that could have accounted for the discrepancy in reduction in rates of distant metastasis between the two studies. The PARADIGM study allowed stage Ⅲ patients to enroll whereas DeCIDE was limited to stage Ⅳ. The inclusion of lower stage patients may have accounted for patients with less distant metastases in the PARADIGM study. Additionally, the CRT regimens were different in the two studies. It is possible that induction chemotherapy is more useful in split course radiation and is not beneficial in conventional RT.

Induction chemotherapy has theoretical advantages in terms of reducing distant metastasis and may be useful in patient subsets at increase risk for distant metastasis such as those with bulky, or lower cervical lymph node involvement. Induction chemotherapy may also be useful for patients who would have a delay in starting concurrent CRT. For example, it is common practice to have dental extractions of diseased teeth prior to starting radiation in order to help prevent osteoradionecrosis. After the dental extraction, it takes 2 wk for the extraction site to heal enough to begin radiation. Thus, if patients are expected to have long delays in starting CRT secondary to getting dental consult, extractions, and post-extraction healing, it may be beneficial to start induction chemotherapy while the dental issues and radiation planning is under way. At the current time, further clinical trials will be helpful in refining the role of induction chemotherapy in those subsets of patient with HNSCC most likely benefit from this treatment. Several studies have found that pre-treatment PET scans may also help guide therapy. Independent studies have shown that HNSCC lymph node SUV greater than 10 is predictive for higher rates of distant metastasis[27]. This or other predictive tests may help determine risk for distant metastasis and potentially select patients to benefit from induction chemotherapy.

The optimal induction regimen is unclear from the limited studies performed. As seen in Tables 1 and 4, there are many differences in both induction and post-

Table 4 Tax 323 and 324 Protocols

	Tax 323 study	Tax 324 Study
Stages	Ⅲ, Ⅳ	Ⅲ, Ⅳ
Induction therapy regimens	TPF: docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, fluorouracil infusion 750 mg/m^2 per day continuous infusion day 1 to 5 PF: cisplatin 100 mg/m^2 day 1, fluorouracil 1000 mg/m^2 continuous infusion days 1 to 5	TPF: docetaxel 75 mg/m^2 day 1, cisplatin 100 mg/m^2 day 1, fluorouracil 1000 mg/m^2 per day, continuous 24 h IV infusion for 4 d PF: cisplatin 100 mg/m^2 day 1, fluorouracil 1000 mg/m^2 per 24 h continuous infusion for 5 d
Concurrent therapy regimens	Start 4-7 wk after completing induction therapy: Radiation administered over 7 wk, either conventional (66 to 70 Gy), accelerated (70 Gy) or hyperfractionated (74 Gy)	Start 3-8 wk after completing induction therapy: Radiation 2 Gy per day, 5 d a week for a total of 70-74 Gy plus weekly carboplatin AUC 1.5

Gy: Gray; TPF: Docetaxel, cisplatin, and fluorouracil; PF: Cisplatin and fluorouracil.

Table 5 Concurrent regimens after induction

Study	Concurrent chemotherapy	Radiation	Notes
Tax 323	None	Conventional (66 to 70 Gy), accelerated (70 Gy) or hyperfractionated (74 Gy)	Only study not to use concurrent chemotherapy
Tax 324	Carboplatin AUC 1.5, weekly	Radiation 2 Gy per day, 5 d a week for a total of 70-74 Gy	
PARADIGM: responders	Carboplatin AUC 1.5, weekly	70 Gy over 7 wk	Regimen varied by response to induction
PARADIGM: non-responders	Docetaxel 20 mg/m^2 weekly	Accelerated concomitant boost over 6 wk (72 Gy)	Regimen varied by response to induction
DeCIDE	CRT: five 14 d cycles of docetaxel (day 1), fluorouracil (day 0-4) and hydroxyurea (day 0-4)	Twice daily radiation (day 1-5)	Split course radiation

induction treatment regiments. As summarized in Table 5 there is evidence to support a wide range of post-induction chemoradiation regimens including docetaxel, carboplatin, radiation alone and the more complex split-course poly-chemotherapy University of Chicago regimen.

CONCLUSION

Chemotherapy is an important component in the treatment of local advanced HNSCC in selected patients. Most published chemotherapy data supports the use of bolus cisplatin given concurrently with radiation. Newer data supports targeted therapy with cetuximab as well. The role of alternative chemotherapy regimens is less clear. Studies looking at induction chemotherapy did not reveal a survival benefit to induction chemotherapy although it is possible that patients at increased risk for distant metastatic disease may benefit from induction chemotherapy, future studies will need to be performed to further clarify which patients are best suited to an induction chemotherapy approach.

While waiting for further data to help pick ideal patients for induction chemotherapy, at our institution we currently recommend induction chemotherapy for patients with N3 disease and patients who are expected to have a delay in starting concurrent CRT. We feel that this patient subset is most likely to benefit from induction therapy.

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