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Head and Neck Cancers

Induction Chemotherapy for Locoregionally Advanced Head and Neck Cancer: Past, Present, Future?

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

The treatment of patients with locoregionally advanced squamous cell cancer of the head and neck is still evolving. Induction chemotherapy (IC) is widely used in this patient population and it is unclear how to best incorporate IC into multimodality treatment. Recently, the results of two randomized clinical trials were presented (the PARADIGM and Docetaxel Based Chemotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer trials), which showed no demonstrable benefit of IC followed by concurrent chemoradiation over concurrent chemoradiotherapy alone. However, a lower rate of distant metastatic disease was noted, suggesting that patients who are at high risk for metastatic disease may benefit from IC. This review summarizes how IC has evolved over the years, provides an update of recent developments, and discusses how IC may develop in the future. ***The Oncologist*** 2013;18:288–293

Implications for Practice: Chemotherapy remains an integral part of management of the patient with locoregionally advanced squamous cell cancer of the head and neck. Data from recent trials do not show a survival advantage from induction chemotherapy (IC) over concurrent chemoradiation, but there are significant limitations to these studies as detailed in this review. IC remains an option for treating locoregionally advanced disease and could be considered for patients who are at high risk for distant failure.

PERSPECTIVE

Malignancies of the head and neck account for an estimated 52,160 newly diagnosed cancers in the U.S. each year, and nearly 12,000 deaths [1]. Squamous cell carcinoma of the head and neck (SCCHN) accounts for 90% of such malignancies. Despite treatment advances and early multimodality therapy, 5-year survival rates have remained dismal for patients with locoregionally advanced disease [2–4].

Treatment strategies for patients with locoregionally advanced SCCHN have moved away from poorly effective single-modality therapy and now encompass a multimodality approach (surgery, chemotherapy, radiation [RT], and targeted molecular therapeutics). In 2009, a large meta-analysis of the use of chemotherapy in head and neck cancer was updated, incorporating data from 87 trials and 17,346 patients, confirming the benefit of chemotherapy (given as concurrent chemoradiotherapy [CRT], induction chemotherapy [IC], or adjuvant treatment) in patients with locoregionally advanced SCCHN at all tumor sites (Table 1) [5, 6]. The observed benefit of chemotherapy was an absolute 4.5% higher 5-year survival rate. Subgroup analysis revealed that there was a 2.4% overall survival (OS) benefit in favor of IC (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.90–1.02; $p = .18$) compared with locoregional treatment with concomitant CRT, with 26 of the 31 induction trials combining 5-fluorouracil (5-FU) and platinum therapy. Although the risk for death was lower in patients who were treated with concomitant CRT (HR, 0.81; 95% CI, 0.78–0.86) in the indirect comparison, there was a more pronounced effect on distant metastasis in the IC group (HR, 0.73; 95% CI, 0.61–0.88 vs. HR, 0.88; 95% CI, 0.77–1).

Historically, the rationale behind the concept of induction-based therapies relates to a number of advantages: tumor shrinkage, reducing metastatic disease, assessment of tumor responsiveness, and organ preservation in patients with laryngeal cancer [7]. Following initial studies with earlier regimens in the 1980s, cisplatin plus 5-FU (PF) became known as the Wayne State regimen and had been the standard for IC for many years based on the observation of high response rates and the elimination of the need for surgery in some patients [8–11]. One of the main questions debated was whether or not the advantages of induction treatment by achieving tumor control locally and at distant sites could offset the potential harm resulting from the delay of definitive treatment—surgery or RT with or without chemotherapy in patients with locoregionally advanced curable stage III and stage IV SCCHN [12].

The Department of Veterans Affairs Laryngeal Cancer Study, a large, randomized multi-institutional trial, compared IC with PF followed by RT with laryngectomy followed by RT alone and found similar survival outcomes in both arms but an

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Table 1. Summary of the meta-analysis of the Meta-Analysis of Chemotherapy in Head and Neck Cancer collaborative group [4]: Effects of chemotherapy on survival rate (SR) at 5 years

Trial category	*n* of trials (patients)	Hazard ratio (95% confidence interval)	*p*-value	5-yr SR
All trials	108 (17,493)[a]			
Adjuvant	12 (1,244)	1.06 (0.95–1.18)	.31	
Induction	34 (5,311)	0.96 (0.90–1.02)	.18	+2.4%
Concomitant	62 (9,615)	0.81 (0.78–0.86)	<.0001	+6.5%

[a]Some trials had strata that corresponded to different locoregional treatments or chemotherapies, and some trials had three arms or a 2 × 2 design, which led to some arms being used twice in the analysis such that the number of comparisons in the meta-analysis was 108.

encouraging 64% organ preservation rate in patients with advanced laryngeal cancer who received IC [13]. Thereafter, the French Groupe d'Etude des Tumeurs de la Tête et du Cou study by Domenge et al. [14] compared PF followed by locoregional treatment (surgery plus RT vs. RT alone) with the same locoregional treatment alone in patients with resectable and unresectable oropharyngeal carcinoma and demonstrated a significantly longer survival time among patients who had received IC with PF (median survival time, 5.1 years compared with 3.3 years; $p = .03$). That study also confirmed results from a previous Italian study by Paccagnella and colleagues that had shown a superior survival outcome in patients with unresectable disease who underwent IC [15].

The Radiation Therapy Oncology Group (RTOG) 91–11 trial compared IC with PF followed by RT, concurrent CRT using bolus cisplatin, and RT alone for organ preservation in patients with stage III and stage IV laryngeal cancer [2]. The results from 547 patients showed that the proportion of patients with an intact larynx at 2 years was higher in the IC and concurrent CRT groups than in the RT alone group. Survival rates were similar in all groups. A 5-year follow-up of that trial demonstrated that concurrent CRT and IC were equivalent in terms of the laryngectomy-free survival interval and, again, were better than RT alone ($p = .011$). The laryngeal preservation rate was greater with concurrent CRT than with PF followed by RT ($p = .029$) and with RT alone ($p = .00017$), but the survival outcome was surprisingly better with PF than with either concurrent CRT or RT alone, although the difference did not reach statistical significance (IC, 59.2%; CRT, 54.6%; RT, 53.5%: HR for IC vs. CRT, 1.244; 95% CI, 0.938–1.649; $p = .13$; HR for IC vs. RT, 1.2; 95% CI, 0.9–1.608; $p = .21$; HR for RT vs. CRT, 1.04; 95% CI, 0.789–1.372; $p = .78$) [16].

As mentioned earlier, the data from the updated Meta-Analysis of Chemotherapy in Head and Neck Cancer meta-analysis suggested only a modest benefit in terms of the OS rate (2.4%) with IC, which led some clinicians to question the benefit of IC treatment [6]. However, one should note that IC had a more pronounced effect on distant metastasis, with an absolute difference of 4.3% ($p = .001$) at 5 years, suggesting a possible benefit to adding neoadjuvant therapy to concomitant CRT. Furthermore, trials investigating taxane-based induction therapy added to the PF regimen were not included in the meta-analysis, thus potentially muting a more pronounced effect.

The European Organization for Research and Treatment of Cancer evaluated PF IC with definitive RT versus standard surgery and RT in a phase III trial in patients with operable, locoregionally advanced piriform sinus cancer [17]. When compared with surgical resection, organ preservation was achieved in 42% of cases, with lower distant failure rates and without compromising the OS outcome. Recently, the 10-year follow-up data were published, which also demonstrated similar long-term OS rates in the two arms (13.8% vs. 13.1%) but perhaps a slightly better progression-free survival (PFS) rate without achieving statistical significance in patients who had received IC (8.5% vs. 10.8%; HR, 0.81; 95% CI, 0.60–1.09) [18]. A more recent phase III trial in 2009 evaluated PF IC and RT (sequential arm) compared with alternating PF-based CRT (alternating arm) in patients with operable, advanced laryngeal and hypopharyngeal cancer [19]. That study found similar median OS and PFS rates, as well as similar survival times with a functional larynx at a median follow-up duration of 6.5 years. Consistent with results from previous trials, IC appeared equivalent to concurrent CRT in terms of the survival outcome and organ preservation rate.

In the last 10 years, taxane therapy has inspired a resurgence of interest in IC for treating patients with locoregionally advanced SCCHN. In 1998, a trial from the Eastern Cooperative Oncology Group enrolled 30 patients with recurrent, metastatic, or locoregionally advanced, incurable SCCHN to receive high-dose paclitaxel, noting a response in 40% of patients (four complete and eight partial responses) [20]. These results led the way for investigating the active role of taxane therapy in the treatment of patients with SCCHN. Several groups aimed to investigate the clinical benefit, if any, of adding taxane therapy to the IC regimen. A series of phase I and phase II trials used a high- and intermediate-dose docetaxel, cisplatin, and 5-FU (TPF)-based IC regimen for patients with advanced SCCHN [21–24].

Following phase II trials involving the addition of taxane therapy, three randomized phase III trials emerged to explore the benefit of induction TPF versus PF alone in terms of clinical outcomes (Table 2). In the European TAX-323 study, 358 patients with stage III or stage IV unresectable disease and no evidence of distant metastasis (80% of patients included had T3 or T4 lesions and 71% had N2 or N3 nodal disease) were randomized to TPF (docetaxel, 75 mg/m^2 on day 1; cisplatin, 75 mg/m^2 on day 1; 5-FU, 750 mg/m^2 by continuous infusion for 5 days) or PF therapy (cisplatin, 100 mg/m^2; 5-FU, 1,000 mg/m^2 by continuous infusion on days 1–5) for up to four cycles followed by RT in both treatment arms [4]. Dosing in the experimental arm was selected based on previous studies, which had demonstrated a reasonable safety profile while maintaining efficacy [24]. At a median follow-up of 32.5 months, the PFS interval was longer in the TPF arm (11 months vs. 8.2 months; HR, 0.72; 95% CI, 0.57–0.91; $p = .007$). Treatment with TPF resulted in a lower risk for death of 27% ($p = .02$), with an OS time of 18.8 months, compared with 14.5 months

Table 2. Experience with docetaxel-based induction therapy in the treatment of patients with locally advanced squamous cell carcinoma of the head and neck

Study	*n* (criteria)	Primary endpoints	Regimen	Summary of results
Vermorken et al. (2007) [4] (TAX-323)	358 (unresectable)	PFS	PF → RT vs. TPF → RT	TPF had longer PFS time (11 mos vs. 8.2 mos) and OS time ($p < 0.05$)
Posner et al. (2007) [3] (TAX-324)	501 (advanced)	OS	PF → CRT vs. TPF → CRT	TPF had higher OS rate (62% vs. 48%; $p < .01$)
Pointreau et al. (2009) [30] (GORTEC)	213 (resectable)	Larynx preservation	PF vs. TPF → RT or CRT	Larynx preservation rate higher with TPF (70% vs. 58%), higher CR rate

Modified from Lorch J, Posner MR, Wirth LJ et al. Induction chemotherapy in locally advanced head and neck cancer: A new standard of care? Hematol Oncol Clin N Am 2008 22:1155–1163.

Abbreviations: 5-FU, 5-fluorouracil; CR, complete response; CRT, chemoradiation; GORTEC, Groupe Oncologie Radiotherapie Tête et Cou; OS, overall survival; PF, cisplatin plus 5-FU; PFS, progression-free survival; RT, radiation therapy; TPF, docetaxel, cisplatin, and 5-FU.

in the PF group (HR, 0.73; 95% CI, 0.56–0.94; $p = .02$). TPF was better tolerated, with fewer adverse events (including nausea, mucositis, vomiting, grade 3 hearing loss). However, there were higher incidences of neutropenia (76.9% vs. 52.5%) and febrile neutropenia (5.2% vs. 2.8%) in patients receiving TPF, although the rates of death from toxicity were lower (2.3% vs. 5.5%). Thirty-eight patients in the TPF arm and 60 patients in the PF arm discontinued chemotherapy, with the most frequent reasons being disease progression, adverse events, and death. Distant relapses were slightly more frequent in the PF group but the difference was not statistically significant (12.3% vs. 10.3%). Short-term health-related quality of life (HRQoL) data suggest that, 6 months following the completion of RT, the global HRQoL was higher in the TPF arm, and it even has demonstrated cost-effectiveness [25, 26]. Long-term follow-up was recently presented from 308 (86%) of the randomized patients from the original TAX-323 cohort [27]. The 5-year PFS rate remained greater in the TPF group than in the PF treatment group (22.9% vs. 13.5%). The median OS duration was also significantly greater in the TPF arm (18.8 months vs. 14.5 months), as was the 5-year OS rate (27.5% vs. 18.6%).

The second phase III trial, TAX-324, randomized 501 patients with both resectable and unresectable stage III or stage IV disease without distant metastasis (>70% of patients in both arms had T3 or T4 disease; >60% had N2 or N3 disease) and those who were candidates for organ preservation to either TPF (docetaxel, 75 mg/m^2 on day 1; cisplatin, 100 mg/m^2 on day 1; 5-FU, 1,000 mg/m^2 by continuous infusion for 5 days) or PF (cisplatin, 100 mg/m^2; 5-FU, 1,000 mg/m^2 by continuous infusion on days 1–5) for three cycles followed by concurrent CRT with weekly carboplatin and daily RT [3]. At a minimum of 2 years of follow-up (≥3 years for 69% of patients), the median OS time was significantly longer in the TPF arm than in the PF arm (71 months vs. 30 months). There was better locoregional control in the TPF arm than in the PF arm ($p = .04$), but the incidences of distant metastasis in the two groups did not differ significantly ($p = .14$). Those rates were quite low in both arms at 5% and 9%, respectively. Similar to the TAX-323 study, the rates of neutropenia and neutropenic fever were higher in the TPF group (83% vs. 56% and 12% vs. 7%, respectively). Most patients went on to complete definitive concurrent CRT, but 68 patients (27%) in the TPF group and 79 patients (32%) in the PF group discontinued treatment, primarily as a result of disease progression. Recently, a 5-year update of the TAX-324 study was published [28]. Follow-up data from 425 of the 501 patients was collected with a median follow-up of 71 months and a minimum follow-up of 5 years. The median OS time in the TPF treatment arm remained significantly longer (71 months vs. 35 months; $p = .013$). At 5 years, 52% and 42% of the TPF and PF patients were alive, respectively. As stated, in both the TAX-323 and TAX-324 studies, TPF was associated with a higher rate of febrile neutropenia. Prophylactic use of antibiotics was required, but the use of growth factors was optional, perhaps accounting for the difference in infectious complications from the three-drug combination. However, deaths related to toxic events were less frequent in the TPF groups in both trials. To achieve good outcomes, administration of TPF requires meticulous supportive care, including aggressive i.v. hydration, mouth care, and the use of prophylactic antibiotics, and a low threshold for the use of growth factors. With these measures, only a small percentage of patients should be unable to complete RT or concurrent CRT as shown in the TAX-323 and TAX-324 studies.

In recent years, the importance of the human papillomavirus (HPV) as a prognostic marker in head and neck cancer has been recognized. The association between HPV status and OS time was examined in the TAX-324 study population [29]. Tissues from untreated oropharyngeal (OPC) tumors were studied using polymerase chain reaction for HPV subtype 16. Of 264 patients with OPC tumors, 111 (42%) had evaluable biopsies, of which 56 (50%) were HPV$^+$. OS and PFS rates at 1–5 years were significantly better for HPV$^+$ patients (OS rate at 5 years, 82% vs. 35%).

The GORTEC (Groupe Oncologie Radiotherapie Tête et Cou) 2000–2001 trial sought to determine whether or not adding docetaxel to the PF regimen increased larynx preservation rates [30]. Two hundred thirteen patients with resectable laryngeal or hypopharyngeal cancer were randomized to three cycles of TPF or PF. Patients who demonstrated a clinical response to IC (tumor regression >50% and recovery of normal laryngeal mobility) received RT with or without additional chemotherapy, whereas those who failed to respond underwent total laryngectomy followed by RT with or without adjuvant chemotherapy. With a median follow-up of 36 months, the laryngeal preservation rate was significantly higher in the TPF treatment arm (70.3% vs. 57.5%). The overall response rate was 80% in the TPF group, versus 59.2% in the PF group ($p = .002$). As in other IC trials, the TPF treatment arm had higher rates of grade 4 neutropenia and febrile neutropenia, whereas the PF treatment arm had more cases of grade 3 and

4 stomatitis, thrombocytopenia, and grade 4 creatinine elevation. Despite the better larynx preservation rate in the TPF arm, the OS times were similar, as one would expect in a laryngeal cancer study given the viable surgical salvage option for this disease.

Another study, the French Targeted Therapy With An Induction Chemotherapy Platform study, was initially presented in 2009 with an update in 2011 and has further documented the efficacy of TPF in the upfront setting. In that trial, 153 previously untreated patients with stage III—IV larynx or hypopharynx SCC and candidates for total laryngectomy were treated with three cycles of TPF (docetaxel and cisplatin, both at 75 mg/m^2 on day 1; 5-FU, 750 mg/m^2 per day on days 1–5). Patients with a $<$50% response underwent surgery. Responders who had a $>$50% reduction in tumor size were randomized to either concurrent CRT with bolus cisplatin (70 Gy plus cisplatin at 100 mg/m^2 on days 1, 22, and 43 of RT, resulting in a very high cumulative cisplatin dose of 525 mg/m^2) or concurrent CRT with cetuximab (70 Gy with a 400-mg/m^2 cetuximab loading dose before RT and 250 mg/m^2 on the first day of the 7 weeks of RT). Among the 116 patients (75.8%) who achieved a significant response and continued on concurrent CRT, the larynx preservation rates and larynx function preservation rates were similar in the two arms, with a better adherence to treatment and less toxicity in the cetuximab arm. Although the study arm showed good compliance with the regimen, there was more in-field grade 3 and 4 skin toxicity (57% vs. 26%) and a higher rate of locoregional failure. Surgical control could be achieved in a majority of these cases (seven of 12), accounting for the similar OS outcome as in the standard treatment arm, in which seven relapses occurred, none of which could be salvaged surgically.

With TPF established as a standard for IC, a number of randomized trials have attempted to define the role of IC (as part of sequential treatment) versus the current standard of care, concurrent CRT. A European phase II randomized trial recently investigated the efficacy of adding a TPF-based IC regimen to traditional concurrent CRT [31]. In total, 101 patients with stage III or stage IV disease without distant metastasis were randomized to concurrent CRT alone (two cycles of cisplatin, 20 mg/m^2 on days 1–4, plus 5-FU, 800 mg/m^2 by continuous infusion for 96 hours during week 1 and week 6 of RT) or three cycles of TPF (docetaxel, 75 mg/m^2 on day 1; cisplatin, 80 mg/m^2 on day 1; 5-FU, 800 mg/m^2 by continuous infusion for 96 hours every 3 weeks) followed by the above concurrent CRT regimen. The primary endpoint was the rate of radiologic complete response (CR) at 6–8 weeks. The CR rate was significantly higher in the TPF IC arm followed by concurrent CRT than in the concurrent CRT only arm (50% vs. 21.2%). Remarkably, the median PFS and OS times were longer in the TPF IC treatment group (33.3 months vs. 19.7 months and 39.6 months vs. 30.4 months, respectively) in this relatively small study. Hematologic and nonhematologic toxic effects during concurrent CRT were similar in the two study groups. These findings led to the currently ongoing Italian phase III study with the same regimen.

Results from a Spanish trial were presented as an abstract in 2009 [32]. Four hundred thirty-nine patients with stage III and stage IV locally advanced HNC were randomized to either concurrent CRT (cisplatin and RT), IC with PF, or IC with TPF (as part of sequential treatment). In patients who had received at least one cycle of IC, the median time to treatment failure was 12.5 months with sequential treatment, versus 4.9 months with concurrent CRT alone ($p < .001$; HR, 0.57; 95% CI, 0.44–0.74). The locoregional control rate was 60.9% for IC and CRT, versus 44.5% for CRT ($p = .003$; odds ratio, 0.52; 95% CI, 0.3–0.81). Grade 3 or 4 adverse events (sequential treatment vs. concurrent CRT) occurred in 83% versus 69% of patients and included febrile neutropenia (10% vs. 1%) and stomatitis (43.7% vs. 37%). The analysis of that trial is compromised because of the lack of an intent-to-treat analysis and the absence of survival data as well as detailed failure data. A full updated analysis has not been published to date.

Recently, the results of the PARADIGM study, an international multicenter phase III clinical trial comparing TPF IC followed by concurrent CRT (sequential treatment) and cisplatin-based concurrent CRT in 145 patients with stage III or stage IV locally advanced SCCHN were reported [33]. The trial was stopped early before reaching its full accrual of 300 patients because of slow enrollment. Patients were randomized to induction TPF for three cycles followed by stratification according to treatment response versus concurrent CRT alone. Good responders to IC continued with the concurrent CRT regimen as in the experimental arm of the TAX-324 study with weekly carboplatin. Poor responders received weekly docetaxel with accelerated RT along the lines of the experimental arm in the RTOG 0129 trial, which since has been shown to be as effective as three doses of cisplatin and standard daily RT. This was compared with concurrent CRT, which consisted of two doses of cisplatin at 100 mg/m^2 every 3 weeks on day 1 and day 22 of standard RT. At a median follow-up duration of 49 months, 41 patients had expired (20 in the standard therapy arm and 21 in the concurrent CRT arm). The 3-year survival rates were remarkably similar at 73% in the ST arm and 78% in the concurrent CRT arm (HR, 1.09; 95% CI, 0.59–2.03; $p = .77$). The 3-year PFS rates were 67% in the ST arm and 73% in the concurrent CRT arm (HR, 1.2; 95% CI, 0.65–2.22; $p = .55$). As expected, the ST arm had a greater number of patients with grade 3 or 4 febrile neutropenia. There was no significant difference in the distant failure rates but the number of events was small.

Results of the Docetaxel Based Chemotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer (DeCIDE) trial, a randomized, open-label phase III clinical trial, were also reported at the annual American Society of Clinical Oncology convention [34]. Two hundred eighty patients with locoregionally advanced SCCHN and N2 or N3 disease were randomized to receive concurrent CRT alone (5 days of docetaxel, 25 mg/m^2, 5-FU, 600 mg/m^2, hydroxyurea, 500 mg twice daily, and RT, 150 cGy twice daily, followed by a 9-day break) or two cycles of IC (docetaxel, 75 mg/m^2; cisplatin, 75 mg/m^2; 5-FU, 750 mg/m^2 on days 1–5) followed by the same concurrent CRT regimen. That trial also accrued slowly and the originally planned accrual goal of 400 was not achieved. The primary endpoint was the OS time with a minimum follow-up duration of 24 months. Of the 142 patients randomized to the IC arm, 87% continued to concurrent CRT. However, $<$75% of patients received the target dose of 5-FU in both arms. Overall, high survival rates were noted in both treatment arms and no difference in the OS time, the study's

primary endpoint, was observed. Interestingly, however, there was a lower number of distant failures with IC, providing more evidence to support the concept that IC is able to eliminate micrometastatic distant disease. The most common added grade 3 or 4 toxicities in the IC arm included—as expected—febrile neutropenia (9%) and mucositis (8%).

Future of IC

The DeCIDE and PARADIGM trials were designed to settle the much debated questions around IC. Neither study enrolled the original planned number of patients and this makes the interpretation of the results quite challenging. The negative results came as a disappointment and raise the question of whether or not IC should be administered at all given the added toxicity and expense of treatment.

There are several obvious limitations to these trials. First, both trials were stopped early or the accrual goal was reduced significantly because of slow enrollment. The PARADIGM trial was originally planned to include 300 patients and the DeCIDE trial was originally planned to include 400 patients. It is therefore not surprising that the primary goal to detect a difference in the survival time was not achieved.

Furthermore, the profound impact of HPV on the prognosis of patients with SCCHN was unknown at the time the trials were planned, and tissue for HPV analysis for a post hoc analysis is not available for either study. However, the majority of the patients in both trials had SCC of the oropharynx, which is HPV-associated in the majority of cases and has an excellent prognosis. This certainly contributed to the low rate of events and the negative outcome of these trials by reducing the power of the analysis. Certainly the potential role for IC in treating patients with HPV^+ tumors needs further investigation.

Interestingly, however, the subset analysis in the DeCIDE trial showed a lower number of distant disease metastatic events with IC, suggesting that IC is indeed able to eradicate micrometastatic disease. The strength of this signal was surprising and raises the question of why the effect did not translate into an actual survival benefit. One could speculate that, because both trials included a significant number of patients with stage III (PARADIGM trial) and early stage IV (Paradigm and DeCIDE trials) disease, the number of patients at high risk for distant failure was not sufficient to yield a significant difference in the survival data. Also, the role of surgery in the DeCIDE trial will need to be examined further, because surgery was allowed prior to entering the study. Further subgroup analysis is ongoing and should provide interesting results. The results of an Italian, randomized phase III trial comparing IC with concurrent CRT, which recently finished accrual, will also help to shed light on this complex therapeutic dilemma.

Until further data are available, IC remains an option for treating patients with locoregionally advanced disease and could be considered for patients who are at high risk for distant failure. In the absence of tested and reliable biomarkers for a more sophisticated risk assessment, our practice at Dana Farber Cancer Institute is to include: (a) patients with N2b, N2c, and N3 disease; (b) patients with low neck disease; (c) patients with dermal metastasis; and (d) patients with locally advanced disease and possible distant metastasis on computed tomography scan or positron emission tomography scan imaging that cannot be pathologically confirmed.

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Obviously, these recommendations are subject to debate and further research to reliably identify a patient's risk for distant metastatic disease is critical.

Summary

Chemotherapy remains an integral part of management of the patient with locoregionally advanced SCCHN. TPF has emerged as the new standard of care for cases in which IC is used. Data from recent trials do not show a survival advantage over concurrent CRT, but there are significant limitations to these studies, as detailed in this review. More information from ongoing trials and systematic assessment of biomarkers to assess the risk for distant metastatic spread is urgently needed. Until then, the question of sequential versus concurrent CRT remains open.

Author Contributions

Conception/Design: Jochen H. Lorch
Provision of study material or patients: Jochen H. Lorch
Collection and/or assembly of data: Jochen H. Lorch, Glenn J. Hanna
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Disclosures

Robert I. Haddad: Boehringer Ingelheim, Adler (RF); **Jochen H. Lorch:** Novartis (RF). The other author indicated no financial relationships.
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