Evolving Strategies for Combined-Modality Therapy for Locally Advanced Head and Neck Cancer

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Key Words. Head and neck cancer • Induction therapy • Sequential therapy • Combined modality • Treatment • SCCHN

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the newest options for curative therapy of locally advanced head and neck cancer.
2. List the pros and cons of the different approaches to treating locally advanced head and neck cancer.
3. Describe sequential therapy for head and neck cancer.

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ABSTRACT

Despite continual advances in the treatment of head and neck cancer, disease-free survival, functional outcome, toxicity of therapy, and overall survival remain less than optimal. While traditional treatment has focused on surgical resection with or without radiation and chemoradiotherapy, newer combined-modality regimens may offer patients a better prognosis, organ preservation, and less morbidity. In this paper, single agents and doublet therapy are reviewed, as are emerging data on the utility of induction therapy, chemoradiotherapy, and surgery as a sequential treatment regimen. The Oncologist 2007;12:967–974

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Head and neck cancers account for 3%–5% of all cancer cases in the U.S., annually [1]. The American Cancer Society estimated that 34,360 new cases of oral cavity and pharynx cancers will be diagnosed in the U.S. in 2007, and approximately 7,550 deaths will be attributed to these diseases [2]. While therapeutic options for head and neck cancers have evolved over the past 30 years, the prognosis and disease-free survival interval for patients with locally advanced head and neck cancers, those patients presenting with stage III or stage IV disease, have remained less than optimal [3].

Treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) is complicated by disease site and volume, prognosis, functional deficits associated with therapeutic choices, therapy-associated toxicities, and the needs and condition of individual patients. Initially, standard therapy focused on surgical resec-
tion with or without radiation or radiation therapy alone for technically unresectable cancers. However, in an effort to increase the probability of organ preservation, locoregional control, and survival, advanced clinical studies were directed toward refining the use of chemotherapy and radiotherapy in a combined-modality setting. Emerging data on the benefits of induction, concurrent, and sequential therapy regimens now suggest the possibility of better prognosis and organ preservation, with less morbidity [4–14]. These data offer new insights into optimal treatment regimens for SCCHN.

**COMBINED-MODALITY REGIMENS**

While SCCHN is potentially curable in its early stages, >60% of patients present with advanced locoregional disease [15]. The 5-year relative survival rate is 81% for patients with localized disease and 59% for all stages combined [16]. Standard therapy does not sufficiently address local recurrence or metastatic spread. From 50% to 60% of patients with advanced locoregional disease treated with the standard therapy of surgery, radiotherapy, or both develop locoregional recurrence within 2 years of treatment, and 20%–30% of patients develop distant metastases [17].

Combined-modality regimens, including the use of induction chemotherapy and chemoradiotherapy (CRT), have demonstrated equivalency in survival outcomes between nonsurgical and surgical treatment of resectable, locally advanced head and neck cancers, as well as better locoregional control in inoperable patients, less distant failure, and better organ preservation [4–8, 18, 19]. However, the optimal components, timing, and administration of combined-modality therapy remain to be defined. Current research focuses on the utility of three combined-modality regimens: (a) primary induction chemotherapy or neoadjuvant therapy before definitive surgery and/or radiotherapy; (b) CRT; and (c) sequential therapy consisting of induction chemotherapy, CRT, and surgery.

**INDUCTION THERAPY**

While single-modality treatment with either radiation or surgery is successful in patients with early-stage disease, results are disappointing in patients with stage III or stage IV disease [17]. The Veterans Affairs’ laryngeal cancer trial, which demonstrated functional organ preservation in up to 64% of patients at 2 years, was the first in a series of studies to demonstrate the utility of induction chemotherapy for controlling distant failure in locally advanced disease, improving survival rates, and allowing for organ preservation [4, 8].

**Platinum, 5-Fluorouracil**

Cisplatin plus 5-fluorouracil (PF), now widely accepted as the standard in induction chemotherapy, was developed in the late 1970s based on the observation that PF induction chemotherapy could eliminate the necessity for surgery in some patients, while maintaining survival rates [20, 21]. Standard PF combines cisplatin at a dose of 100 mg/m² on day 1 and continuous infusion (CI) 5-fluorouracil (5-FU) at 1,000 mg/m² per day over 5 days. Known as the Wayne State regimen, PF has remained the single, evidence-based standard in advanced head and neck cancers [15, 21].

In a phase III study of induction chemotherapy, Paccagnella and colleagues randomized 237 patients to standard treatment with or without PF neoadjuvant therapy. Patients were stratified into resectable and unresectable disease, and treated in one of four treatment arms (Fig. 1) [8]. Postchemotherapy surgery did not lead to longer survival times in operable patients, and may have resulted in a higher risk for locoregional recurrence and precluded primary site preservation. However, PF did lead to a lower occurrence of distant metastases in resectable patients (arms A and C). Unresectable patients (arms B and D) showed a significantly longer overall survival duration with PF treatment, as well as better local control, a lower occurrence of distant metastases, and a higher rate of complete remission. However, it should be noted that the primary endpoint of this study was overall survival in all subjects combined. A 10-year follow-up confirmed a longer survival time in the larger subset of patients with unresectable disease treated with PF [9].

A French study by Domenge et al. [7] compared PF followed by locoregional treatment (surgery plus radiotherapy or radiotherapy alone) with the same locoregional treatment alone in patients with oropharyngeal carcinoma. The overall survival duration was significantly longer among patients who received PF ($p = .03$), with a median survival time of 5.1 years, versus 3.3 years for patients who did not receive PF. The effect on event-free survival was of borderline significance ($p = .11$). These results confirm the findings from Paccagnella and colleagues, that induction chemotherapy is effective in populations with advanced, unresectable disease, and extend the observation to resectable patients.

A 2002 meta-analysis reported a significant 5% absolute higher 5-year survival rate for PF compared with control treatment ($p = .01$), although this improvement was not observed with other platinum-containing regimens [15]. However, the continued high risk for locoregional failure in resectable patients and the lack of good, randomized comparisons of PF with CRT have hindered the adoption of PF as an alternative “standard of care” by medical or radiation
oncologists, except for patients with late-stage cancers, and as a means of organ preservation.

A Taxane, Cisplatin, and 5-FU
Recent studies suggest that three-drug induction chemotherapy with a taxane, cisplatin, and 5-FU (TPF) is significantly more effective than PF in head and neck cancers because the triplet combination provides better outcomes without greater toxicity [10–12].

In the phase III TAX 323 study, 358 patients with unresectable stage III or IV SCCHN were randomized to receive either PF or TPF every 3 weeks for four cycles, unless there was progression, unacceptable toxicity, or refusal (Fig. 2) [10]. Patients without progressive disease received radiotherapy. Surgery was permitted either before radiotherapy or 3 months after. Progression-free survival (PFS) (8.2 months for PF versus 11.0 months for TPF; hazard ratio [HR], 0.72; \( p = .0071 \)) and overall survival (14.2 months for PF versus 18.6 months for TPF; HR, 0.71; \( p = .0052 \)) were both significantly longer with the addition of docetaxel. The estimated 3-year survival rate (36.5% versus 23.9%) and response rate (67.8% versus 53.6%; \( p = .006 \)) were also greater with TPF. Overall, TPF followed by radiotherapy demonstrated superior PFS, overall survival, and response rates compared with PF followed by radiotherapy. TPF was also associated with less toxicity and treatment-related mortality. Furthermore, quality of life (QoL) measures remained stable with TPF treatment, while head and neck-specific functional QoL scores fell following radiotherapy and PF [11].

Another phase III study, the Groupe d’Oncologie Radiothérapie Tête Et Cou (GORTEC) 2000–01 trial, evaluated TPF (docetaxel, 75 mg/m² on day 1; cisplatin, 75 mg/m² on day 1; 5-FU, 750 mg/m² CI on days 1–5; for three cycles with a 21-day interval) versus PF (cisplatin, 100 mg/m² on day 1; 5-FU, 1,000 mg/m² per day CI on days 1–5) or paclitaxel, cisplatin, and 5-FU (PCF) (paclitaxel, 175 mg/m² on day 1; cisplatin, 100 mg/m² on day 2; and 5-FU, 500 mg/m² CI on days 2–6). The CR rate was significantly higher in the PCF arm (33% versus 14%; \( p < .001 \)). Patients who received PCF also trended toward a longer overall survival duration (43 months versus 37 months; log-rank test, \( p = .06 \)). Fewer toxicities were observed in the PCF arm than in the PF arm. At this time, there are no head-to-head trials comparing the use of paclitaxel and docetaxel in induction therapy.

CRT
Despite obvious success with induction chemotherapy, there is still room for improvement with locoregional failure [22]. Concurrent CRT allows higher locoregional dose density and has demonstrated superior organ preservation, disease control, and survival in patients with advanced disease [4–6, 19, 23–25]. However, CRT has also been shown to increase toxicity, particularly mucositis, and is not effective in eliminating distant metastases [6, 19].
The French Groupe d’Etude des Tumors de la Tête et du Cou (GETTEC) conducted a phase III trial (94–01) of 226 patients with stage III or IV disease [6]. Patients were randomized to receive either radiotherapy alone or CRT (three cycles of a 4-day regimen of carboplatin, 70 mg/m² per day, and 5-FU, 600 mg/m² per day CI). Patients who received CRT demonstrated a higher 3-year overall actuarial survival rate, disease-free survival rate, and locoregional control rate; however, CRT patients experienced greater toxicity (Table 1).

The 5-year overall survival, specific disease-free survival, and locoregional control rates were 22% and 16% (log-rank, \( p = .05 \)), 27% and 15% (\( p = .01 \)), and 48% and 25% (\( p = .002 \)) in the CRT arm and radiotherapy alone arm, respectively [25]. However, treatment failure resulting from distant metastases appeared equivalent in the two arms. Concomitant CRT produced superior overall survival and locoregional control rates and did not statistically increase severe late morbidity, but the 5-year survival rate was poor.

The Radiation Therapy Oncology Group 91–11 phase III trial focused on larynx preservation [5]. In that trial, 547 patients were randomized to receive PF followed by radiotherapy, CRT, or radiotherapy alone. Initial results indicated that CRT was superior to induction therapy followed by radiotherapy and radiotherapy alone for organ preservation and locoregional control.

The 5-year follow-up results of the 91–11 trial were presented at the 2006 American Society of Clinical Oncology (ASCO) Annual Meeting [26]. Follow-up data were available for 515 eligible patients and demonstrated that CRT and PF induction chemotherapy were equivalent for laryngectomy-free survival and better than radiotherapy alone (\( p = .011 \)). Laryngeal preservation was greater with CRT than with PF followed by radiotherapy (\( p = .0029 \)) and radiotherapy alone (\( p = .00017 \)), but survival was surprisingly better with PF than with either CRT or radiotherapy, although not significantly so. Additionally, disease-free survival was also equivalent between CRT and PF, and was significantly better than with radiotherapy alone. Because laryngectomy-free survival (i.e., being alive with an intact larynx) is the important endpoint, it can be concluded that the 91–11 trial demonstrated that organ preservation strategies were equivalent between PF induction and CRT.

Further studies have suggested that hyperfractionated accelerated CRT is superior to hyperfractionated accelerated radiotherapy in oropharyngeal carcinomas, although hyperfractionated therapy is associated with a significant late incidence of esophageal stenosis with or without chemotherapy [27].

Both induction therapy and CRT have demonstrated advantages and disadvantages in patients with advanced SCCHN. Induction therapy offers systemic treatment, treats distant disease, improves survival rates, and allows for response assessment prior to subsequent therapy. However, locoregional failure rates continue to be high [7, 8, 15]. CRT improves locoregional control, but it is associated with greater toxicity and may not reduce the rate of distant metastases; locoregional failure rates still remain high, although they are better [5, 6, 25].

**Sequential Therapy**

Sequential therapy consists of induction chemotherapy followed by CRT and subsequent surgery. The use of sequential therapy may allow for optimized timing of treatment components, thereby enhancing benefits and limiting drawbacks.

The benefits of sequential therapy may include a combination of benefits from induction chemotherapy (high response rates, organ preservation, longer survival, systemic treatment, reduced tumor volume, better function, and intermediate assessment of response [4, 7, 8, 12, 15]); CRT (better locoregional control and treatment adjustments based on response to induction therapy, potential toxicity, prognostic factors, and planned surgery [5, 6]); and surgery (removal of areas of initial bulk disease and preservation of the primary site [13]). Sequential therapy provides two distinct advantages for the patient and the radiation oncologist. Preradiotherapy tumor shrinkage improves planning and delivery of intensity-modulated radiation therapy; patient response to induction chemotherapy allows better selection for more or less aggressive CRT and can reduce acute and late toxicity and potentially improve functional outcomes.

The phase III study by Hitt et al. [13], which was discussed earlier as an example of paclitaxel use in an induction setting, randomized patients to induction therapy followed by one of three sequential therapies (Table 2). The primary endpoint of this study was to compare CR rates of patients treated with PF (arm A) versus PCF (arm B) as induction therapy. At the end of induction therapy, PCF significantly surpassed PF in achieving CR (33% versus 14%; \( p < .01 \)).

Of the 190 patients who went on to receive protocol-established CRT, 78% in arm A achieved a CR and 10% achieved a PR, for an ORR of 88%; in arm B, 88% of patients achieved a CR and 10% achieved a PR, for an ORR of 98% [13]. Among patients with resectable disease at study entry, 7% in arm A and 12% in arm B underwent radical surgery on the primary tumor (\( p < .05 \)). Thus, TPF improved locoregional control, although the effect on survival...
in this population was less robust because of the allowance by trial design for nonresponders to receive an intervention of lesser efficacy (i.e., salvage surgery, and the larger percentage of use of salvage surgery in arm B than in arm A). Unresectable patients had a significantly longer survival time on the TPF arm, compared with patients treated with PF. The median follow-up for the study was 23.2 months, with a 2-year overall survival rate of 61.5%. Overall survival for all patients by arm is shown in Figure 3. Overall survival for patients with resectable disease is shown in Figure 4.

The results of the studies by Hitt et al. [13] and Paccaggnella et al. [8] suggest that the sequence of chemotherapy followed by CRT should be brisk and uninterrupted. Delaying regional therapy with surgery may allow growth at the primary site and partial resistance, accelerate tumor repopulation with potential doubling times, and enable expanded populations with partial resistance. Furthermore, regional sensitization may be improved with weekly administration of CRT.

TAX 324, a phase III study, evaluated induction PF (cisplatin, 100 mg/m² i.v. on day 1; 5-FU, 1,000 mg/m² per day CI on days 1–5; every 3 weeks for three cycles) versus induction TPF (docetaxel, 75 mg/m² i.v. on day 1; cisplatin, 100 mg/m² i.v. on day 1; 5-FU, 1,000 mg/m² per day CI on days 1–4; every 3 weeks for three cycles) followed by CRT (carboplatin, area under the concentration–time curve 1.5, i.v. weekly plus daily radiotherapy, 5 days per week) and surgical resection, as needed, in 501 patients with stage III or IV locally advanced SCCCHN (Table 3) [14]. The primary endpoint was overall survival. As with earlier studies, the ORR after induction chemotherapy trended toward an improvement with the addition of docetaxel (72% versus 64%; p = .07). The median overall survival time following induction therapy (HR, 0.70; 95% confidence interval [CI], 0.54–0.90; p = .0058) and PFS (HR, 0.71; p = .004) also favored the TPF arm. The 3-year survival rate was 62% with TPF and 48% with PF. TAX 324 demonstrated that TPF significantly improves survival over that seen with PF [14]. Data suggest that the optimal regimen with TPF includes three cycles of induction chemotherapy followed by immediate CRT and post-CRT surgery. Other studies are under way to further explore components of sequential therapy.

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**Table 1.** GORTEC 94–01 oropharynx trial results [6]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CRT</th>
<th>Radiotherapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Year overall actuarial survival rate</td>
<td>51% (95% CI, 39%–68%)</td>
<td>31% (95% CI, 18%–49%)</td>
<td>.02</td>
</tr>
<tr>
<td>Disease-free survival rate</td>
<td>42% (95% CI, 30%–57%)</td>
<td>20% (95% CI, 10%–33%)</td>
<td>.04</td>
</tr>
<tr>
<td>Locoregional control rate</td>
<td>66% (95% CI, 51%–78%)</td>
<td>42% (95% CI, 31%–56%)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; GORTEC, Groupe d’Oncologie Radiothérapie Tête Et Cou.

**Table 2.** Hitt et al. [13] phase III study design

<table>
<thead>
<tr>
<th>Arm</th>
<th>Cisplatin, 100 mg/m², day 1; 5-FU, 1,000 mg/m² per day CI over 5 days Followed by one of the following</th>
<th>If CR or PR &gt;80% in the primary tumor and no progression in the neck and lymph nodes: CRT (cisplatin, 100 mg/m² on days 1, 22, and 43, plus conventional radiotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B</td>
<td>Paclitaxel, 175 mg/m², day 1; cisplatin, 100 mg/m², day 2; 5-FU, 500 mg/m² CI days 2–6</td>
<td>If no response in the primary tumor or progressive disease, either in the primary tumor or in neck lymph nodes: remove from study and treat according to the guidelines of the participating institution If PR &lt;80% or stable disease in lymph nodes (especially if N2 or N3 disease): surgery followed by CRT (cisplatin, 100 mg/m² on days 1, 22, and 43, plus conventional radiotherapy)</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; CI, continuous infusion; CR, complete response; CRT, chemoradiotherapy; PR, partial response.
SAFETY

As treatment options expand and survival rates increase, addressing issues of toxicity, QoL, and long-term morbidity become increasingly important. Induction chemotherapy with PF has been associated with grade 3 or 4 toxicities that include nausea and vomiting, leukopenia, thrombocytopenia, mucositis, cutaneous changes, fatigue, renal complications, and infection [7]. One study of induction therapy found that PF did not increase the rate of treatment-related deaths or long-term side effects [8]. TAX 323 found that TPF was associated with a higher rate of severe leukopenia (41.6% versus 22.9%) and neutropenia (76.9% versus 52.5%) than PF regimens [10]. However, the same study found that PF was associated with a higher rate of severe thrombocytopenia (17.9% versus 5.2%), hearing loss (2.8% versus 0%), and toxic death (7.8% versus 3.7%). Similarly, updates to the GORTEC 2000–01 study presented at the 2006 ASCO Annual Meeting reported a greater rate of grade 3 or 4 mucositis with CRT (71%; 95% CI, 54%–85%) compared with radiotherapy (39%; 95% CI, 29%–56%). Hematologic toxicity, as measured by neutrophil count and hemoglobin level, were also greater. At the 5-year follow-up, 56% of patients treated with CRT had experienced a grade 3 or 4 complication, compared with 30% of patients treated with radiotherapy alone (p = .12) [25]. However, there were no statistical differences between treatment arms with regard to grade 3 or 4 late effects or grade 4 toxicities alone. A study that compared PF, CRT, and radiotherapy alone found that the rate of high-grade toxic effects was greater with the chemotherapy-based regimens (81% with PF followed by radiotherapy, 82% with concurrent PF and radiotherapy, and 61% with radiotherapy alone) [5]. Furthermore, the rate of mucosal toxicity with CRT was nearly twice that observed for the other two regimens.

Figure 3. Overall survival for all patients in the Hitt et al. [13] study. Arm A, cisplatin and 5-fluorouracil, n = 193; 97 events, 51%; arm B, paclitaxel, cisplatin, and 5-fluorouracil, n = 189; 81 events, 43%; log-rank test, p = .063; Tarone-Ware, p = .031; median overall survival: arm A, 36.8 months (range, 24.5–49.1 months); arm B, 42.9 months (range, 32.9–52.9 months). From Hitt R, Lopez-Pousa A, Martinez-Trufero J et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005;23:8636–8645. Reprinted with permission from the American Society of Clinical Oncology.

The TAX 324 study demonstrated comparable absolute or peak toxicity during chemotherapy and during CRT for both arms (PF followed by CRT versus TPF followed by CRT) [14]. However, patients receiving TPF demonstrated better compliance during induction chemotherapy, which led to a higher relative median dose intensity. Overall, sequential therapy with TPF was found to be safe and tolerable and was associated with fewer treatment delays.

**SUMMARY**

Induction chemotherapy has been established as an effective therapy for SCCHN; it has been shown to reduce tumor volume, allow for organ preservation, and improve survival. Although associated with specific toxicities, induction chemotherapy may be better tolerated if used first in a sequential treatment modality. In sequence, induction chemotherapy also allows for intermediate response assessment and planning for subsequent components, including radiotherapy and intensity-modulated radiation therapy. Data indicate that TPF is the most effective regimen for induction therapy.

Induction chemotherapy, when followed by either definitive surgery or curative-intent radiotherapy alone, has been associated with insufficient locoregional control. CRT allows for a higher dose density, which has been shown to improve locoregional control by increasing local regional dose intensity [4–6, 19, 23–25]. However, the long-term toxicity profile of CRT is considerable, has not been readily appreciated, and contributes to late mortality. New efforts are under way to quantify risk and to intervene earlier to prevent catastrophic events such as infection, aspiration pneumonia, and esophageal stenosis.

Sequential induction chemotherapy, CRT, and surgery, administered with optimized and intentional timing, may allow patients to reap a greater overall benefit while minimizing treatment disadvantages and reducing morbidity. Emerging data indicate that sequential therapy with TPF followed by carboplatin-based CRT and subsequent surgery represents a new, acceptable standard of care for locally advanced SCCHN [13, 14].

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

M.P. has acted as a consultant for Sanofi-Aventis, Bristol-Myers Squibb, GlaxoSmithKline, Amgen, Biovex, Oxi-gene, and Allos.

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| Table 3. Response rates in the TAX 324 trial [14] |
|-----------------|-----------------|
| Response        | PF, % (95% CI) (n = 246) | TPF, % (95% CI) (n = 255) | p-value |
| Overall response |                 |                         |         |
| Postchemotherapy | 64 (57.9–70.2)    | 72 (65.8–77.2)          | .07     |
| Post-CRT        | 72 (65.5–77.1)    | 77 (70.8–81.5)          | .21     |
| Complete response |                 |                         |         |
| Postchemotherapy | 15 (10.8–20.1)    | 17 (12.1–21.6)          | .66     |
| Post-CRT        | 28 (22.5–34.1)    | 35 (29.4–41.5)          | .08     |

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; PF, cisplatin plus 5-fluorouracil; TPF, a taxane, cisplatin, and 5-fluorouracil.


12 Calais G, Pointreau Y, Alfonso M et al. Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000–01. J Clin Oncol 2006;24:281s.


