Concurrent Chemotherapy and Radiotherapy for Head and Neck Cancer

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Abstract and Introduction

Abstract

Head and neck cancer is best managed in a multidisciplinary setting. Surgery, radiation therapy, chemotherapy and, more recently, biologic therapy are often employed in various combinations in an attempt to eradicate both clinically apparent and occult disease. The goals of treatment include maximizing tumor control while maintaining function and quality of life. Most patients present with locally advanced disease, and multimodality organ-conserving therapy is often employed for these patients based on the results of multiple Phase III clinical trials. This article focuses on the rationale and evidence supporting the use of concurrent chemotherapy and radiation therapy in the management of locally advanced head and neck cancers.

Introduction

Approximately 47,000 new cases of head and neck cancer were diagnosed in the USA in 2008, representing roughly 5% of all new cancer diagnoses.[1] Worldwide, more than 500,000 cases are diagnosed each year.[2] Long-term survival is improving with advances in therapy, but outcomes remain suboptimal. This is largely because the majority of patients present with locoregionally advanced disease. Surgery was once the mainstay of treatment for all resectable cases of head and neck cancer but led to significant morbidity. Radiotherapy had been reserved for unresectable or palliative cases, but this treatment modality has overtaken surgery as the primary local treatment option for most head and neck cancers, largely in the setting of organ-conservation approaches to treatment. In addition, for those patients whose head and neck cancers are managed with primary surgical resection, patients at high risk of locoregional recurrence are often treated with either adjuvant radiotherapy alone or adjuvant concurrent chemoradiotherapy, for enhancement of locoregional control. As locoregional control has improved with the implementation of altered fractionation schedules and concurrent chemoradiotherapy, distant metastasis as the site of first failure has become an increasing concern. In addition, while advances in radiotherapeutic techniques, such as intensity-modulated radiation therapy (IMRT), have not directly been shown to improve local control over older techniques, an improved therapeutic ratio as a result of this technology may lead to enhanced locoregional control. This has led to a renewed interest in the use of induction chemotherapy as a strategy for reducing the incidence of distant metastases and for potentially improving survival. Finally, in a novel approach to management, radiotherapy combined with concomitant biologically targeted

therapy for patients with locally advanced head and neck cancer has been shown to improve overall survival compared with radiotherapy alone.[3] The ultimate goal in moving forward will be to enhance the therapeutic ratio in the treatment of head and neck cancers through a collaborative, multidisciplinary effort, leading to improved cure rates while decreasing long-term morbidity and optimizing patients' quality of life.

Rationale for Chemoradiotherapy and Concurrent Targeted Therapy and Radiotherapy in Head and Neck Cancers

A rationale for combining chemotherapy and radiotherapy concomitantly in the treatment of locally advanced head and neck cancers exists. Chemotherapy can sensitize tumors to radiotherapy by inhibiting tumor repopulation, preferentially killing hypoxic cells, inhibiting the repair of sublethal radiation damage, sterilizing micrometastatic disease outside of the radiation fields and decreasing the tumor mass, which leads to improved blood supply and reoxygenation.[4] Fractionated radiotherapy, in turn, may sensitize tumors to chemotherapy by inhibiting the repair of drug-induced damage and by decreasing the size of the tumor mass, leading to improved blood supply and enhanced drug delivery.[4] With respect to targeted therapy, the EGF receptor (EGFR) is overexpressed in many head and neck cancers, and its overexpression is associated with a poor prognosis.[5] EGFR inhibition through anti-EGFR antibody therapy or small-molecule inhibitors of EGFR may act in a synergistic fashion with radiotherapy through inhibition of cellular proliferation, tumor angiogenesis and DNA repair.[4]

Does Local Control Impact Survival in Head and Neck Cancer?

Improvement in the rates of local control, through higher radiation dose, sophisticated delivery techniques or the use of radiosensitizing chemotherapy, is one of the central objectives in head and neck radiation oncology. Whether the attainment of this goal ultimately leads to enhanced overall survival is an important question. To address this issue, Wadsley and Bentzen published an analysis of 19 randomized trials of radiotherapy in head and neck cancer to explore the relationship between local control and overall survival.[6] They concluded that a 10% absolute improvement in the 2-year local control rate in head and neck cancer translated into a 6.7% absolute improvement in overall survival.

However, there are limitations to the local control rates that can be achieved with radiotherapy dose escalation alone in head and neck cancer owing to the proximity of several critical normal structures, including the parotid glands, brainstem, spinal cord, and optic chiasm and optic nerves. This observation has led to the investigation of radiosensitizing concurrent chemotherapy as an attempt to enhance local control in locally advanced head and neck cancers.

A recently updated meta-analysis of trials of chemotherapy in head and neck cancer concluded that the addition of chemotherapy to radiotherapy results in a

4.4% absolute improvement in overall survival compared with radiotherapy alone at 5 years.[7] Concurrent chemotherapy was associated with an absolute survival benefit of 6.5% at 5 years. Induction chemotherapy was not associated with a significant survival benefit compared with radiotherapy alone. The addition of chemotherapy to radiotherapy in patients over the age of 70 years did not translate into a survival benefit. Finally, multiagent chemotherapy did not provide a significant benefit over single-agent cisplatin in the concurrent setting.

The following sections review the data supporting the use of concurrent chemotherapy and radiation therapy in the setting of locally advanced head and neck cancers.

Surgery Versus Chemoradiotherapy

One trial has directly compared primary surgical management with definitive concurrent chemoradiotherapy in patients with locally advanced head and neck cancers. In this randomized trial of 119 patients with stage III or IV nonmetastatic squamous cell carcinoma of the larynx, hypopharynx, oropharynx, maxillary sinus and oral cavity, investigators in Singapore randomized participants to either surgical resection followed by radiotherapy or definitive concurrent chemoradiotherapy.[8] Adjuvant radiotherapy was delivered to a dose of 60-70 Gy depending on the margin status. The dose of radiotherapy for concurrent chemoradiotherapy was 66 Gy. Chemotherapy comprised cisplatin 20 mg/m^2/day and fluorouracil 1000 mg/m^2/day for 5 consecutive days as a continuous infusion for two cycles. With a median follow-up of 6 years, there was no difference in disease-free or overall survival. The overall organ preservation rate was 45%, and the larynx and hypopharynx organ preservation rates were higher than those of other primary sites. A major criticism of this study is its lack of power to detect a small difference in either disease-free or overall survival between the treatment arms; therefore, the possibility of a type II error exists.

Randomized Trials in Squamous Cell Carcinoma of the Head and Neck

Adelstein et al. reported the results of an intergroup trial that randomized 295 patients with unresectable head and neck cancer to one of three arms: radiotherapy alone (70 Gy); concurrent cisplatin (100 mg/m^2 days 1, 22 and 43) and radiotherapy (70 Gy); or concurrent cisplatin and 5-fluorouracil (every 4 weeks) with split-course radiotherapy (radiotherapy to 30 Gy, evaluation for surgical respectability, then 30-40 Gy additional radiotherapy if unresectable or complete response).[9] With a median follow-up of 41 months, concurrent cisplatin and radiotherapy without a planned treatment break resulted in superior 3-year overall survival (37 vs 23 and 27% for radiation alone and split-course radiation, respectively; $p = 0.014$). Toxicity was increased with concurrent chemotherapy and radiation. The rates of distant metastases were similar among the three groups.

In the Radiation Therapy Oncology Group (RTOG) 91-11 trial, 547 patients with resectable stage III and IV laryngeal squamous cell carcinoma were randomized to either definitive radiotherapy alone, induction chemotherapy followed by radiotherapy, or concurrent chemoradiotherapy.[10] Radiotherapy was prescribed to a dose of 70 Gy in 35 daily 2-Gy fractions in all arms. Induction chemotherapy was cisplatin 100 mg/m^2 and 5-fluorouracil 1000 mg/m^2/day over 120 h every 3 weeks for two cycles. After two cycles, patients with a complete or partial response went on to receive a third cycle of induction chemotherapy followed by radiotherapy as described. Patients with disease progression or less than a partial response after two cycles of induction chemotherapy went on to laryngectomy. Concurrent chemotherapy was cisplatin 100 mg/m^2 on days 1, 22 and 43 of radiotherapy. With a median follow-up of 3.8 years, the 2-year rate of larynx preservation was better with concurrent chemotherapy than with either radiotherapy alone or with induction chemotherapy followed by radiotherapy (88 vs 75% [p = 0.005]and 70% [p < 0.001]). Overall, 2-year laryngectomy-free survival was significantly better with concurrent chemotherapy compared with radiotherapy alone (66 vs 53%; p = 0.01), while there was no significant difference at 2 years in terms of laryngectomy-free survival between the induction group (59%) and the radiotherapy-alone group.

In an update with a median of 6.9 years of follow-up for survivors, 5-year locoregional control was 68.8% for concurrent chemoradiotherapy, 54.9% for induction chemotherapy and 51% for the radiotherapy-alone arm (p = 0.0018 and 0.0005, respectively).[11] The 5-year rate of larynx preservation continued to suggest the superiority of concurrent chemotherapy over either radiotherapy alone or induction chemotherapy followed by radiotherapy (83.6 vs 70.5% [p = 0.005] and 65.7% [p < 0.001], respectively). However, at 5 years, laryngectomy-free survival was similar for both the induction chemotherapy (44.6%) and concurrent chemotherapy arms (46.6%), and both sequential and concurrent chemotherapy had superior laryngectomy-free survival compared with radiotherapy alone (33.9%; p = 0.011 for both comparisons). The 5-year disease-free survival was significantly better with either induction therapy (38.6%; p = 0.016) or concurrent chemotherapy (39%; p = 0.0058) compared with radiation alone (27.3%). Overall survival at 5 years was similar across all three groups, at approximately 55%. Induction and concurrent chemotherapy increased acute toxicity, while late side effects were similar among the three groups.

While some controversy surrounded the publication of this trial with respect to the primary outcome (i.e., laryngectomy-free survival versus larynx preservation rate), local control is clearly better with concurrent chemoradiotherapy compared with either induction chemotherapy or radiotherapy alone; thus, concurrent chemoradiotherapy continues to represent the standard of care in locally advanced squamous cell carcinoma of the larynx.

The French Head and Neck Oncology and Radiotherapy Group (GORTEC) trial 94-01 randomized 226 patients with stage III and IV oropharyngeal cancer to

either definitive radiotherapy alone (70 Gy) or radiotherapy (same radiation) plus concurrent chemotherapy with three cycles of carboplatin and fluorouracil (every 3 weeks during radiotherapy).[12] Chemotherapy comprised carboplatin as a daily bolus of 70 mg/m^2/day for 4 days and fluorouracil continuous infusion at 600 mg/m^2/day for 4 days. With a median follow-up of 5.5 years, 5-year overall survival favored chemoradiotherapy over radiotherapy alone (22.4 vs 15.8%; p = 0.05). The 5-year disease-free survival was significantly improved with the addition of concurrent chemotherapy (26.6 vs 14.6%; p = 0.001). Locoregional control at 5 years was better in the group randomized to chemoradiation compared with the group treated with radiation alone (47.6 vs 24.7%; p = 0.002). Chemoradiotherapy was associated with increased acute toxicity but late grade 3-4 toxicity was similar.

Concern over the tolerability of high-dose cisplatin chemotherapy administered every 3 weeks has led investigators to explore weekly low-dose concurrent chemotherapy as an alternative. Preliminary results suggest that weekly low-dose platinum chemotherapy is efficacious and well tolerated in the setting of concurrent radiotherapy,[13] and prospective trials are underway exploring this approach.

In summary, these seminal Phase III trials form the basis for the recommendation of concurrent chemoradiotherapy as the standard of care in locally advanced head and neck cancer.

Randomized Trials in Nasopharyngeal Carcinoma

In the intergroup 0099 trial, investigators randomized 147 patients with stage III-IV nasopharyngeal carcinoma to either definitive radiotherapy alone or to radiotherapy with concurrent chemotherapy followed by adjuvant chemotherapy.[14] Radiation therapy was delivered using 2D planning techniques to a dose of 70 Gy in 35 daily fractions. Concurrent chemotherapy was given at a dose of 100 mg/m^2 on days 1, 22 and 43 of radiotherapy. Adjuvant chemotherapy comprised cisplatin 80 mg/m^2 on days 71, 99 and 127 and fluorouracil 1000 mg/m^2/day continuous infusion for 96 h on days 71-74, 99-102 and 127-130. In total, 63% of patients were able to complete all planned concurrent chemotherapy, while only 55% of patients completed all planned adjuvant chemotherapy. Grade 3-4 toxicity was increased with concurrent chemoradiation therapy compared with radiation therapy alone. With a minimum follow-up of 5 years, 5-year progression-free survival was 58 versus 29% (p < 0.001), overall survival was 67 versus 37% (p < 0.001) and disease-free survival was 74 versus 46% (p < 0.001), all favoring concurrent chemotherapy over radiotherapy alone.[15] Local control was improved with the addition of chemotherapy.

In Singapore, Wee et al. randomized 221 patients with stage III and IV nasopharyngeal carcinoma to either radiotherapy alone or to chemoradiation

therapy as in the intergroup 0099 trial.[16] The 3-year overall survival was improved with the addition of chemotherapy (80 vs 65%; p= 0.0061). As in the intergroup trial, grade 3-4 toxicity was more common in the chemoradiotherapy group. Distant failure was much more common than locoregional failure. The use of chemotherapy in combination with radiotherapy was associated with a decrease in the development of distant metastases at 2 years compared with radiotherapy alone (13 vs 30%; p = 0.0029).

In Hong Kong, Chan et al. conducted a Phase III randomized trial of chemoradiotherapy versus radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma.[17] Overall, 350 patients were randomized. Radiotherapy was delivered to 66 Gy in 33 daily fractions, with or without a parapharyngeal boost or intracavitary brachytherapy. Chemotherapy comprised cisplatin 40 mg/m^{2}weekly during radiotherapy. With a median follow-up of 5.5 years, 5-year overall survival was better with chemoradiotherapy than with radiotherapy alone (70.3 vs 58.6%; p = 0.049). The benefit was largest for patients with T3 and T4 tumors.

A meta-analysis of ten randomized trials of chemoradiotherapy versus radiation alone in nasopharyngeal carcinoma concluded that there was a 4% absolute survival benefit at 5 years with the addition of chemotherapy to radiotherapy.[18] The largest effect was seen with concomitant chemotherapy, which was associated with a 20% absolute increase in overall survival at 5 years. Three additional meta-analyses of chemotherapy in nasopharyngeal cancer have reported similar findings.[19-21]

It is important to mention that patients in the Eastern studies mentioned previously had different distributions of WHO classes when compared with those in the US study. Overall, however, the amount of data in support of concurrent chemoradiotherapy followed by radiotherapy is significant. In summary, concurrent chemoradiotherapy followed by adjuvant chemotherapy represents the standard of care in nasopharyngeal carcinoma.

Nonrandomized Data Using Modern Radiotherapy Techniques

Lee et al. published the University of California San Francisco (UCSF, CA, USA) experience of 67 patients treated with IMRT for nasopharyngeal cancer.[22] Of these patients, 50 were treated with concurrent and adjuvant chemotherapy as per the intergroup 0099 trial. With a median follow-up of 31 months, 4-year local progression-free survival was 97%, and 4-year overall survival was 88%; 4-year distant-metastasis-free survival was 66%. In this trial, nearly all patients were able to complete the planned chemotherapy, suggesting that IMRT may help to optimize the delivery of concurrent chemotherapy in patients with nasopharyngeal carcinoma.

Wolden et al. published the Memorial Sloan-Kettering Cancer Center (MSKCC, NY, USA) experience of 74 patients treated with IMRT for nasopharyngeal cancer.[23] In total, 69 patients received chemotherapy as per the intergroup 0099 trial. With a median follow-up of 35 months, local control at 3 years was 91%. The 3-year progression-free survival was 67% and 3-year overall survival was 83%.

Based on the impressive outcome data from the UCSF series,[22] the RTOG initiated a Phase II study to test the transportability of using IMRT (i.e., the capability of IMRT to be successfully employed in a multi-institutional setting) with or without concurrent chemotherapy for the management of nasopharyngeal carcinoma. The preliminary results were presented at the 2008 Annual Meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO).[24] In total, 68 patients were enrolled. With a median follow-up of 2 years, the estimated 2-year progression-free survival was 73.2%, and overall survival at 2 years was 79.1%. Xerostomia scores were improved compared with previous RTOG trials.

Since the predominant mode of failure in nasopharyngeal cancer is now distant failure, the RTOG has opened a Phase II trial (RTOG 0615) testing the ability of bevacizumab, a monoclonal anti-VEGF antibody that is an inhibitor of angiogenesis, to decrease the rate of distant metastases in patients with nasopharyngeal cancer. Bevacizumab will be administered during radiotherapy (IMRT) along with concurrent cisplatin 100 mg/m^2 on days 1, 22 and 43, and will be given with adjuvant chemotherapy comprising cisplatin and fluorouracil. While there is some concern regarding the potential toxicity of this regimen, a recent Phase I trial from the University of Chicago (IL, USA) demonstrated the feasibility of adding bevacizumab to a regimen of concurrent chemoradiotherapy with no major additive toxicities observed.[25]

Postoperative Chemoradiotherapy

For patients treated with primary surgical resection, the European Organization for the Research and Treatment of Cancer (EORTC) 22931 trial randomized 334 patients with operable stage III and IV head and neck cancers with high-risk features (pT3 - except pT3 larynx - or pT4; T1 or T2 with N2 or N3; T1 or T2 with N0 or N1 if there was evidence of extranodal disease, positive margins, perineural invasion or vascular tumor emboli; and patients with oral cavity or oropharyngeal tumors with level IV or V involvement) to either postoperative radiotherapy alone to 66 Gy in daily 2-Gy fractions or to the same radiotherapy with concurrent cisplatin chemotherapy.[26] Cisplatin was delivered at a dose of 100 mg/m^2 on days 1, 22 and 43 during radiotherapy. Primary sites included the oral cavity, oropharynx, hypopharynx and larynx. With a median follow-up of 5 years, 5-year overall survival favored combined modality therapy (53 vs 40%; p = 0.02) and 5-year locoregional control was better with concurrent chemotherapy (82 vs 69%; p = 0.007). Acute toxicity was worse with combined modality therapy, while the incidence of late effects was similar between the groups.

In a similar trial (RTOG 9501), Intergroup investigators from the RTOG, Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) randomized 459 patients with operable head and neck cancers with high-risk features (two or more positive lymph nodes, extranodal tumor extension or microscopically involved mucosal margins) at surgical resection either to postoperative radiotherapy alone to 60-66 Gy in daily 2-Gy fractions, or to the same radiotherapy plus concurrent cisplatin chemotherapy.[27] Cisplatin was delivered at a dose of 100 mg/m^2 on days 1, 22 and 43 during radiotherapy. Primary sites included the oral cavity, oropharynx, larynx and hypopharynx. With a median follow-up of 45.9 months, 2-year locoregional control was higher with combined modality therapy (82 vs 72%; p = 0.01). Disease-free survival was improved with combined modality therapy (p = 0.04). Overall survival was not different between the two groups. Acute toxicity was increased in the concurrent chemotherapy arm.

The results were updated at the 2006 ASTRO annual meeting with a minimum of 5 years of follow-up;[28] 5-year overall survival rates were 45.1 and 37.0% in the chemoradiation arm and radiation-alone arm, respectively (p = 0.23). The differences in local control and disease-free survival were not significant.

A pooled analysis of the patients from the EORTC and RTOG postoperative chemoradiation trials was performed in an attempt to identify a subset of patients who might profit the most from the addition of chemotherapy to radiotherapy in the postsurgical setting.[29] The conclusion of this combined analysis was that microscopic positive margins and extracapsular nodal extension were the most predictive factors for a poor outcome. Therefore, patients with either of these features would be expected to benefit from concurrent chemoradiation in the postsurgical setting.

These studies provide insight into the population of patients that may benefit from postoperative chemoradiotherapy. An important, unanswered question is whether concurrent cetuximab and chemoradiotherapy in the postoperative setting will provide added benefit over concurrent chemoradiotherapy without targeted therapy. A randomized Phase II trial from RTOG 0234 has completed accrual, and the outcome data are maturing.

Altered Fractionation and Concurrent Chemoradiation Therapy

The rationale for altered fractionation schedules in radiotherapy is based on a difference in tumor and normal tissue cellular repair and repopulation kinetics. In RTOG 90-03, investigators randomized 1113 patients with locally advanced head and neck cancer to one of four radiation fractionation arms:

- Standard fractionation at a dose of 2 Gy per day to a total of 70 Gy in 35 fractions;
- Hyperfractionation at a dose of 1.2 Gy twice daily, 6 h apart, to a total of 81.6

Gy in 68 fractions;
- Accelerated fractionation with a split at 1.6 Gy twice daily, 6 h apart, for a total of 67.2 Gy in 42 fractions with a 2-week break planned after 38.4 Gy to allow for resolution of expected acute toxicity;
- Accelerated fractionation with concomitant boost at 1.8 Gy per day to a large field, with a 1.5-Gy boost dose to a smaller field in the afternoon, 6 h after treatment of the larger field, during the last 12 treatment days for a total dose of 72 Gy in 42 fractions.[30]

All treatments were delivered 5 days per week. No chemotherapy was administered. Local control was improved with both concomitant boost and hyperfractionation, and there was a trend toward improved disease-free survival with these arms. Overall survival did not differ between the groups.

A meta-analysis of 15 trials examining the role of altered fractionation radiotherapy in head and neck cancer was published in 2006 and reported that altered fractionation improves 5-year local control by 6.7% and 5-year overall survival by 3.4% compared with standard fractionation radiotherapy.[31] The effect was more pronounced with hyperfractionation than with accelerated concomitant boost radiotherapy.

This finding, in concert with the positive results from the concurrent chemoradiotherapy trials, led investigators to pursue the combination of altered fractionation and concurrent chemotherapy in patients with locally advanced head and neck cancers in an attempt to further improve both local control and overall survival.

In one of the first trials to examine this approach, Brizel et al. randomized 116 patients with locally advanced head and neck cancers to either radiotherapy alone (75 Gy in 1.25-Gy twice-daily fractions) or the same radiotherapy plus concurrent cisplatin and 5-fluorouracil for two cycles.[32] Both arms received two cycles of adjuvant cisplatin and 5-fluorouracil following radiotherapy. Primary sites included the oropharynx, hypopharynx, oral cavity, nasopharynx and paranasal sinuses. With a median follow-up of 41 months, the 3-year overall survival was better with concurrent chemoradiotherapy than with the radiation alone treatment (55 vs 34%; $p = 0.07$); 3-year local control was higher with concurrent chemotherapy (70 vs 44%; $p = 0.01$). There was no difference in the rate of distant metastases or toxicity between the two groups.

This trial was updated at the 2007 ASTRO annual meeting with long-term follow-up.[33] With a median follow-up of 113 months in survivors, 10-year local control was superior in the concurrent chemotherapy arm, and there was a strong trend favoring improved cause-specific survival in the chemoradiotherapy group.

Budach et al. randomized 384 patients with stage III or IV oropharyngeal, oral cavity or hypopharyngeal cancers to either altered fractionation radiotherapy with concurrent chemotherapy (30 Gy in 2-Gy daily fractions then 1.4 Gy twice daily to

70.6 Gy with 5-fluorouracil and mitomycin C) or altered fractionation radiotherapy alone (14 Gy in 2-Gy daily fractions followed by 1.4 Gy twice daily to 77.6 Gy).[34] Locoregional control at 5 years was 49.9 versus 37.4%, favoring combined modality therapy ($p = 0.001$); 5-year overall survival was 28.6 versus 23.7%, favoring the chemotherapy arm ($p = 0.023$). Progression-free survival was better with combined modality therapy (29.3 vs 26.6%; $p = 0.009$). Toxicities and the rate of distant metastases were similar in the two groups.

This trial was updated at the 2007 ASTRO annual meeting with long-term follow-up.[35] With a median follow-up of 120 months in survivors, 10-year local control, progression-free survival and overall survival were superior in the concurrent chemotherapy arm. There continued to be no difference in the rate of distant metastases between the two arms.

A meta-analysis of 32 trials of altered fractionation radiotherapy with or without chemotherapy reported that the use of chemotherapy resulted in a significant improvement in overall survival, regardless of the radiation fractionation employed.[36]

Toxicities may be significant when combining chemotherapy and altered fractionation radiotherapy.[37] Recently, Garden et al. reported a 42% late grade 3-4 toxicity rate in patients treated on a multicenter Phase II trial of concomitant chemotherapy and accelerated fractionation with concomitant boost radiotherapy.[38]

The RTOG 0129 trial recently randomized 743 patients with stage III or IV cancer of the oral cavity, oropharynx, hypopharynx or larynx to either standard fractionation radiotherapy with concurrent cisplatin or altered fractionation radiotherapy using an accelerated concomitant boost with concurrent cisplatin. In an abstract presented at the 2007 ASTRO annual meeting with 2-year median follow-up, no toxicity differences have been observed between the two arms.[39] Outcome data are pending.

Bourhis et al. presented the preliminary results of a large randomized trial of altered fractionation radiotherapy and chemotherapy in head and neck cancer at the 2008 annual meeting of ASTRO.[40] Investigators randomized 840 patients with locally advanced head and neck cancer to one of three treatment arms: 70 Gy in 7 weeks with concurrent carboplatin and 5-fluorouracil (standard fractionation with concurrent chemotherapy), 70 Gy in 6 weeks via accelerated concomitant boost with concurrent carboplatin and 5-fluorouracil (altered fractionation with concurrent chemotherapy) and 64.8 Gy in 3.5 weeks with twice daily fractionation without chemotherapy (altered fractionation alone). With a median follow-up of 3.5 years, progression-free survival was significantly better in the standard fractionation with concurrent chemotherapy arm compared with the altered fractionation-alone arm. There was no significant improvement in progression-free survival with the use of altered fractionation versus standard

fractionation in the setting of concurrent chemotherapy.

Overall, altered fractionation schedules represent an important advance in the delivery of radiotherapy in head and neck cancer. Whether the addition of altered fractionation to concurrent chemoradiotherapy will result in significantly improved outcomes without adding undue toxicity remains an unanswered question that is the topic of current trials.

Biologically Targeted Therapy and Concomitant Radiotherapy

Bonner et al. reported the results of the first major randomized trial in head and neck cancer that directly compared radiotherapy alone with radiotherapy and concurrent biologic-targeted therapy in the definitive treatment of patients with locally advanced or unresectable head and neck cancers.[3] In this trial, 424 patients with stage III or IV oropharynx, larynx or hypopharynx cancer were randomized to either radiotherapy alone (either 2 Gy daily to 70 Gy, 1.2 Gy twice daily to 72-76.8 Gy, or accelerated fractionation with concomitant boost to 72 Gy as per RTOG 90-03) or to the same radiotherapy plus cetuximab, an anti-EGFR antibody. Cetuximab was given as an intravenous infusion with a loading dose administered 1 week prior to the initiation of radiotherapy and then weekly during radiotherapy. Local control at 3 years favored combined modality therapy (47 vs 34%; $p < 0.01$); 3-year overall survival was superior with cetuximab and radiotherapy (55 vs 45%; $p = 0.05$). The rate of distant metastases was similar in both groups. Toxicities were similar in both groups except that acneiform rash and infusion reactions were more common in the combined modality group.

However, the toxicity of concurrent cetuximab and radiotherapy may be more significant than previously thought. Two recently published reports provide some insight into this question, and the interested reader is referred to them for further information.[41,42]

The RTOG is currently coordinating a large multi-institutional Phase III trial (RTOG 0522) to assess the impact of the addition of biologically targeted therapy to concurrent chemoradiation therapy in the setting of altered fractionation radiation for patients with locally advanced head and neck cancer. The early results from several recent Phase I and II trials that combined targeted therapy, chemotherapy and radiotherapy in the definitive treatment of head and neck cancer are encouraging.[43-49]

Impact of Concurrent Chemoradiation Therapy on Distant Metastases

While concurrent chemoradiotherapy is associated with improved local control and overall survival compared with radiotherapy alone,[7] there is debate regarding the relative efficacy of concurrent chemotherapy to decrease the rate of distant metastatic disease given the conflicting results of randomized trials (see Table 1 [section on distant metastases] for a summary of randomized trials comparing concurrent chemoradiotherapy with radiation alone).

Induction Chemotherapy Followed by Radiation with or without Concurrent Chemotherapy

Two recently published trials have renewed enthusiasm for pursuing induction chemotherapy as a way to decrease the likelihood of distant metastatic disease and to potentially improve overall survival.

The TAX 323 trial randomized 358 patients with unresectable stage III and IV head and neck cancer to either docetaxel, cisplatin and fluorouracil (TPF) or cisplatin and fluorouracil (PF) every 3 weeks for four cycles, followed by radiotherapy without concurrent chemotherapy if there was no evidence of disease progression.[50] Most patients were treated with standard fractionated radiotherapy. With a median follow-up of 32.5 months, the median progression-free survival was significantly improved with the addition of docetaxel. Most failures were locoregional and there was no difference in the rate of distant metastases with the addition of docetaxel.

The TAX 324 trial randomized 501 patients with resectable and unresectable stage III and IV head and neck cancer to either TPF or PF followed by concurrent chemoradiotherapy.[51] Concurrent chemotherapy in this trial was weekly carboplatin with an AUC of 1.5. Radiotherapy was delivered in standard fractionation. With a minimum follow-up of 2 years, 3-year overall survival was 62% in the TPF group versus 48% in the PF group ($p = 0.006$). Locoregional control was better in the TPF group ($p = 0.04$) but the rate of distant metastasis was not affected by the addition of docetaxel.

It is worth mentioning that these trials compared different induction regimens directly and did not compare induction chemotherapy versus concurrent chemoradiotherapy without induction chemotherapy. Two major multicenter, prospective, randomized trials (Paradigm and DeCIDE) that are examining the latter are currently accruing patients.

Expert Commentary

Concurrent chemoradiotherapy improves both local control and overall survival in locally advanced head and neck cancer. When patients cannot be treated with concurrent chemoradiotherapy, a reasonable alternative would be concurrent cetuximab and radiotherapy. If patients are not candidates for combined modality therapy, consideration of an altered fractionation radiation schedule should be made. The combination of altered fractionation radiotherapy and concurrent chemotherapy did not result in improved outcomes compared with standard fractionation with concurrent chemotherapy in a recent French trial, and outcomes data are pending in a US trial with a similar design. The role of induction chemotherapy remains to be defined in patients with locally advanced head and neck cancers. For patients with resected disease and positive margins

or extracapsular nodal extension, postoperative chemoradiotherapy improves outcome over adjuvant radiotherapy alone.

Five-year View

Concurrent chemotherapy with altered fractionation radiotherapy is being tested in a randomized fashion in RTOG 0129, and the outcomes data are currently pending. The addition of biologically targeted therapy to concurrent chemoradiation therapy in the setting of altered fractionation is the topic of another Phase III trial that is currently open to accrual through the RTOG (RTOG 0522). In addition, the value of concurrent cetuximab and chemoradiotherapy in the postoperative setting is being studied in the context of RTOG 0234. The integration of induction chemotherapy into regimens that combine altered fractionation, concurrent chemotherapy, biologic therapy and IMRT will be the subject of future trials. Moving forward, it is important to continue attempting to enhance the therapeutic ratio through these interventions, as improvements in local control and survival may come at the cost of increased treatment-related morbidity.