Management of Locally Advanced or Unresectable Head and Neck Cancer

September 01, 2008

About 500,000 head and neck carcinomas are diagnosed worldwide annually. This accounts for approximately 8% of all newly diagnosed cases of cancer, ranking head and neck carcinoma the sixth most common.[1] In the United States, 47,560 new head and neck carcinomas are expected to be diagnosed in 2008,[2] and this disease accounts for 5% of all newly diagnosed cases of cancer. Approximately 90% to 95% are squamous cell carcinomas of the head and neck (SCCHNs).

About 500,000 head and neck carcinomas are diagnosed worldwide annually. This accounts for approximately 8% of all newly diagnosed cases of cancer, ranking head and neck carcinoma the sixth most common.[1] In the United States, 47,560 new head and neck carcinomas are expected to be diagnosed in 2008,[2] and this disease accounts for 5% of all newly diagnosed cases of cancer. Approximately 90% to 95% are squamous cell carcinomas of the head and neck (SCCHNs). The majority (60%) of patients present with stage III/IV poor-prognosis disease.[3] Historically, 50% to 60% of patients with locoregionally advanced head and neck cancer treated with radiation therapy (RT), surgery, or both have developed a locoregional recurrence in 2 years. In addition, 20% to 30% of those patients have developed distant metastases. For unresectable head and neck cancer, the 5-year survival rate with RT alone is less than 25%.

Significant advances have been made in the multimodality treatment of patients with locoregionally advanced or unresectable SCCHN over the past 2 decades, which will be the focus of this review. These advances have included the integration of chemotherapy with radiation therapy, the use of targeted agents, and surgery as salvage or completion neck dissection. Despite this progress, many challenges and questions remain. In the following sections, we will first review the radiotherapy techniques that have been investigated. We will then review the progressive advances achieved with the addition of chemotherapeutic strategies to RT in an attempt to achieve better outcomes.

Definition of Locoregional Advanced and Unresectable

The definition of locoregional advanced is generally related to an advanced T or N stage. Defining the term unresectable is difficult, as resectability has evolved over time due to advances in surgical and reconstruction techniques. Criteria for unresectability of the primary site or adenopathy include fixation to the spine or prevertebral muscles or involvement of skin, dura, base of skull, or brachial plexus. Some patients are also categorized as unresectable due to the expectation of poor functional outcomes following surgery. Also, patients may be considered unresectable due to significant medical comorbidities, rendering them unable to tolerate the extensive resections required for locally advanced disease.

RT and Recent Advances in Management of Unresectable Head and Neck Cancer

Radiation therapy is the primary treatment modality for unresectable head and neck cancer, administered alone or concurrent with chemotherapy. Treatments are traditionally delivered at daily fractions of 1.8 to 2 Gy, to approximately 70 Gy over 6 to 7 weeks, with local control rates of 50% to 70% for locoregionally advanced disease. In an attempt to improve outcomes, altered-fractionation schemes have been investigated.[4-9] Among the altered-fractionation schema investigated were hyperfractionation regimens and accelerated regimens. Hyperfractionation regimens deliver lower doses of radiation, twice daily, with the intent of minimizing acute toxicity. In order to account for the smaller dose per fraction, higher total doses are delivered. Accelerated-fractionation schemes deliver a course of radiation using conventional doses of radiation delivered more than five times weekly, with the intent of shortening overall treatment time at the expense of higher acute toxicity. Accelerated fractionation has been achieved in various ways, such as treating six fractions per week[10] or using a delayed concomitant boost scheme, during which the patient is treated in 6 weeks, with twice-daily treatments delivered.
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Published on Diagnostic Imaging (http://www.diagnosticimaging.com)

during the final 12 days of treatment.[11]

RTOG 90-03

The Radiation Therapy Oncology Group (RTOG) conducted a landmark trial (RTOG 90-03) comparing the leading US altered fractionated regimens for multiple head and neck cancer sites, including oropharyngeal cancers (60%).[12] Patients, the majority of whom had stage III/IV locally advanced SCHN, were randomized to one of four fractionation schemes. TABLE 1

| Randomized Trials of Single-Agent Concurrent Chemoradiotherapy and Radiation Therapy Alone in Locoregionally Advanced Squamous Cell Head and Neck Cancer |
| In a preliminary analysis after a median of 23 months of follow-up, 2-year locoregional control was significantly better for patients treated via either a delayed concomitant boost or a hyperfractionation regimen compared with conventional fractionation (Table 1). The investigators noted a trend toward improved disease-free survival in both the delayed concomitant boost and hyperfractionation arms compared with conventional fractionation. However, overall survival was no different. Hyperfractionation and delayed concomitant boost both increased acute grade 3/4 toxicity. Delayed concomitant boost increased chronic grade 3/4 toxicity at 3 months, but by 6 to 24 months, there was no difference in grade 3/4 toxicity. There was no difference in chronic grade 3/4 toxicity in the hyperfractionation arm.

European Trials

Horiot et al reported similar results from European Organisation for Research and Treatment of Cancer (EORTC) 22791, a randomized trial comparing hyperfractionation vs conventional fractionation.[13] Hyperfractionation improved 5-year actuarial locoregional control compared with conventional fractionation (59% vs 40%, respectively; P = .02), with a trend toward improved survival.

The Danish Head and Neck Cancer Study (DAHANCA) 6 and 7 trials were multicenter phase III investigations of conventional fractionation vs accelerated fractionation using six weekly fractions of radiation with a hypoxic cell sensitizer (DAHANCA 6 examining glottic tumors, and DAHANCA 7 studying other head and neck sites).[10] The accelerated regimen resulted in improved 5-year local control, locoregional control, and disease-specific survival, but no significant effect on overall survival was seen.

Several other randomized trials examining altered-fractionation schemes have been reported to date, most of which also demonstrate an improvement in local and locoregional control at the expense of increased acute toxicity, but without an impact on overall survival.[14-20] Thus, conventional fractionation and accelerated fractionation yield equivalent survival results, but accelerated fractionation yields higher local and locoregional control, at the expense of increased acute mucosal toxicity.

Meta-analyses of Fractionation Schemes and Concurrent Chemoradiation Regimens

Large randomized trials have been included in meta-analyses to achieve greater statistical significance to determine the efficacy of altered-fractionation RT. Budach et al reported a meta-analysis of hyperfractionation, accelerated fractionation, and chemoradiation regimens used to treat locally advanced SCCHN, which included 32 trials with 10,225 patients.[21] Eligible trials included patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx treated with definitive radiation or chemoradiation, with no surgery to the primary site (although a neck dissection was allowed). Accelerated radiation was defined as a course of treatment time shortened by 10% to 50% (with the total dose decreased by < 5%); or if the total dose was decreased by > 5%, the radiation dose could be decreased by > 50%. Hyperfractionation was defined as twice-daily radiation with < 1.25 Gy per fraction and > 5% increase in total dose.
The addition of simultaneous chemotherapy to all RT fractionations resulted in an overall survival benefit of 12 months (P < .0001), with an absolute survival gain of 13% to 15% at 2 years. In patients who did not receive chemotherapy, there was no significant gain in overall survival for accelerated fractionation compared to conventional fractionation, but hyperfractionation increased median survival by 14.2 months (P < .001). Thus, concurrent chemotherapy with hyperfractionation or accelerated fractionation yielded the greatest benefit.

Another meta-analysis, by Bourhis et al, compared conventional-fractionation, hyperfractionation, and accelerated-fractionation schedules utilized in 15 trials to treat 6,515 patients.[22] Tumor sites were primarily the oropharynx and larynx; 74% of patients were diagnosed with stage III/IV disease. Altered fractionation—both accelerated fractionation and hyperfractionation—led to a significant overall survival benefit of 3.4% at 5 years. The benefit was significantly higher with hyperfractionation (8% at 5 years) than with accelerated fractionation (approximately 2% at 5 years). Moreover, altered-fractionation RT led to a significant decrease in locoregional failure, with a 23% reduction in risk and an absolute benefit of 8.5% at 5 years. These results are comparable to the benefits achieved by chemoradiotherapy reported in the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC).[23] which is discussed later in this article, with a 5-year overall survival benefit of 6.5% in the altered-fractionation meta-analysis vs 8% in the MACH-NC. In summary, based on the convincing data from the pivotal EORTC 22791 and RTOG 90-03 trials, there is a benefit to hyperfractionation therapy for unresectable head and neck cancers. However, radiation therapy alone is utilized only in select cases; the standard of care for unresectable SCCHN is concurrent chemoradiation. The Budach and Bourhis meta-analyses have shown that there is a benefit to accelerated-fractionation RT, which is similar to that observed for concurrent chemoradiation.[21,22]

There may be an added benefit to concurrent chemoradiation with altered-fractionation radiation; however, the role of concomitant chemotherapy in the setting of altered fractionation is unclear. RTOG 0129 may clarify the issue. In RTOG 0129, patients with locally advanced SCCHN treated with concurrent cisplatin were randomized to standard-fractionation RT or accelerated fractionation with concomitant boost (the same fractionation employed in the delayed concomitant boost arm of RTOG 90-03). The trial closed in 2005, and the data are presently maturing.

**Intensity-Modulated Radiation Therapy**

Intensity-modulated radiation therapy (IMRT) is becoming routinely adapted by the radiation oncologist in order to treat the target volume(s) with nonuniform amounts of radiation in a given beam. Multiple coplanar beam angles—typically five to nine beam angles—are used. The planning involved with IMRT is labor-intensive for the physician to draw target volumes and normal structures and also for the physicist to generate a plan. However, IMRT creates very tight target volume coverage with rapid radiation dose falloff, allowing for critical normal tissues such as the spinal cord and parotid glands to be spared, and has been routinely adopted by radiation oncologists due to improved salivary function compared to that seen with two- or three-dimensional radiation planning.[24]

Most centers do not employ altered-fractionation schedules of radiation when using IMRT treatment planning, due to the added expense of time and labor required for IMRT. However, the simultaneous integrated boost (SIB) strategy, wherein multiple targets are treated simultaneously with different prescribed doses, has commonly been used with IMRT. For example, the primary tumor and gross nodal disease may be treated to 66 Gy in 30 fractions (2.2 Gy/fraction), while at the same time, high-risk areas receive 60 Gy (2 Gy/fraction) and low-risk areas receive 54 Gy (1.8 Gy/fraction). Due to the higher dose per fraction, however, this scheme may produce increased late morbidity. Alternatively, the gross disease may be treated with standard doses of 1.8 to 2 Gy per fraction, while subclinical disease is treated with a lower-than-standard daily dose. When this approach is employed, particularly in patients with advanced disease, concurrent chemotherapy should be administered. It should be noted that the highest doses per fraction, such as those described by Butler et al,[25] should not be delivered with concurrent chemotherapy, given the risk of severe acute mucositis.

The use of SIB has not been compared with traditional altered-fractionation radiation in a randomized study and, therefore, whether IMRT with a SIB offers the same benefit as the aforementioned altered-fractionation schemes is, at present, unknown.

**The Chemotherapy Variable in Combined-Modality Therapy**
While the advances in radiation therapy described above have been evolving, there have also been numerous clinical trials incorporating chemotherapy in patients with locoregionally advanced or unresectable head and neck cancer. Through the 1980s, surgery and radiation were the mainstays of treatment. These approaches resulted in relatively poor outcomes, with 5-year survival rates of 10% to 40%.[26] In an effort to improve this dismal outcome, investigators became increasingly interested in the incorporation of chemotherapy.

**Induction Chemotherapy**

The initial focus was on the addition of induction (neoadjuvant) chemotherapy. Numerous randomized trials were published in the 1980s and 1990s. Although high response rates were noted and a decrease in distant metastases was often observed, most trials failed to consistently demonstrate a significant benefit for locoregional control or overall survival.[27-28] In contrast to the predominant observations, two trials did yield positive results.

In 1994, Paccagnella et al published a phase III trial involving 237 patients with stage III or IV nonmetastatic resectable and unresectable SCCHN randomized into two groups.[29] One group received induction chemotherapy (cisplatin and fluorouracil [5-FU]) followed by locoregional treatment, which included either resection and RT for resectable patients or RT alone for unresectable disease. The second group received locoregional treatment alone. The primary endpoint was overall survival. The results were analyzed separately for patients with resectable and unresectable disease. For the unresectable patients, induction chemotherapy resulted in an overall survival benefit at 3 years of 24% compared to 10% (P = .04). This was maintained with 10-year follow-up at 16% compared to 6% (P = .04). No survival advantage was seen for the resectable patients.

In 2000, Domengé et al published the results of a phase III trial in patients with resectable and unresectable, stage III or IV, nonmetastatic oropharyngeal carcinoma randomized to receive either cisplatin plus 5-FU followed by locoregional treatment (resection with RT or RT alone), or locoregional treatment alone.[30] The investigators found a significant overall survival benefit of induction chemotherapy, which resulted in a median survival of 5.1 vs 3.3 years in the group receiving locoregional treatment alone (P = .03). No difference in locoregional control rate was noted. Also important at this time were the results from the MACH-NC meta-analysis, published by Pignon et al in 2000,[23] which did not demonstrate an overall survival benefit with induction chemotherapy. The MACH-NC meta-analysis showed a benefit in trials of a platinum agent plus 5-FU (P = .05), and is described in greater detail in the next section. Based on the bulk of available data at that time, induction chemotherapy did not become widely accepted as standard practice in the management of this group of patients. Nevertheless, two trials reported during this time did demonstrate a benefit with induction chemotherapy in the context of organ preservation in patients with advanced squamous cell cancers of the larynx and hypopharynx.[31,32]

**Concurrent Chemoradiotherapy**

Historically, what followed was the concept of concurrent chemoradiotherapy. This strategy appeared attractive based on the potential radiosensitizing properties of selected chemotherapeutic agents with an expectation of improving locoregional control. Beginning in the 1990s, several published trials that will be discussed later reported improved outcomes using chemoradiotherapy compared to radiation alone. Chemoradiotherapy gained a wider acceptance with the publication of the pivotal MACH-NC.[23] This meta-analysis of data from 63 published and unpublished trials, evaluated 10,741 patients with resectable and unresectable cancer of the oropharynx, oral cavity, larynx, and hypopharynx. The study compared induction, concurrent, and adjuvant chemotherapy to locoregional therapy alone. The chemotherapy differed greatly. Overall survival was the primary endpoint. The study revealed that chemotherapy delivered neoadjuvantly, concurrently, or adjuvantly carried an absolute survival benefit of 4% at 5 years (P < .0001). Concurrent chemotherapy was found to produce the greatest benefit, with an absolute overall survival benefit of 8% at 5 years (27% vs 35%, P < .0001). In contrast, induction chemotherapy was found to have a statistically insignificant overall survival benefit of 2% at 5 years. No significant benefit was observed with the addition of adjuvant chemotherapy.

An update of the MACH-NC meta-analysis reported in 2004 by Bourhis et al included an additional 24 trials (and increased the total number of patients to 16,000).[33] This subsequent analysis confirmed the 5% overall survival benefit for patients receiving chemotherapy and an 8% absolute overall survival benefit with chemoradiotherapy, with a 19% reduction in the risk of death (hazard ratio = 0.81, P < .001).[33]
Randomized Trials of Multiagent Chemotherapy Agents in Concurrent Chemoradiation and RT Alone in Locoregionally Advanced Squamous Cell Cancer of the Head and Neck

**Single-Agent vs Combination Chemotherapy**—The benefit of chemoradiotherapy has also been established by several published randomized trials. These trials have used a variety of chemotherapeutic agents as well as varying radiation techniques. Several agents have been investigated in the setting of concurrent chemoradiation including bleomycin, mitomycin, methotrexate, 5-FU, and cisplatin. Table 2 lists selected randomized trials that have studied single-agent regimens vs RT alone. These trials have demonstrated improvements in locoregional control and, most often, an improvement in overall survival in the chemotherapy-containing arm. Several randomized trials incorporating combination chemotherapy regimens given concurrently with radiation also reported improved outcomes compared to RT alone. Table 2 lists some of these trials with varying chemotherapeutic regimens as well as differing radiation schedules. Despite these apparent differences, results have shown a fairly consistent demonstration of benefit in terms of locoregional control and overall survival.

Only one of these trials directly compared two differing chemotherapy regimens. As outlined in Table 2, a phase III Intergroup trial undertaken between 1992 and 1999 randomized 295 patients with unresectable head and neck cancer into three treatment arms.[34] Arm A (the control group) received conventional fractionated RT at 2 Gy/d for a total of 70 Gy. Arm B received identical radiation therapy with concurrent high-dose cisplatin at 100 mg/m$^2$ given on days 1, 22, and 43. Patients in arm C received a split course of single daily fractionated radiation with three cycles of concurrent infusional 5-FU and bolus cisplatin chemotherapy, 30 Gy given with the first cycle and 30 to 40 Gy given with the third cycle. Surgery was encouraged if disease was rendered resectable after the second chemotherapy cycle in arm C patients. The 3-year projected overall survival for arm A (RT alone) was 23%, compared to 37% (P = .014) for arm B (chemoradiotherapy). No survival benefit was noted in arm C, which incorporated 5-FU and cisplatin. It should be noted that the split-course radiation schedule used in arm C is not considered an optimal schedule and makes any direct comparison difficult.

Taking into account all of these results, concurrent chemoradiotherapy became a standard of care in treating patients with locoregionally advanced or unresectable SCCHN. Except for the Intergroup trial, no subsequent randomized trials have directly compared cisplatin in varying dosing schedules or against other combination regimens.

Several phase II trials have also investigated the incorporation of taxane-based regimens given concurrently with radiation. Although these regimens are feasible, no phase III data are available to allow a direct comparison to single-agent cisplatin. Cisplatin administered at 100 mg/m$^2$ on days 1, 22, and 43 of radiation therapy is viewed by many as the standard of care in the treatment of this cohort of patients. The addition of chemotherapy to radiation clearly increases both acute and late toxicities of therapy, and this is an important factor in selecting the most appropriate treatment regimen for any given patient. Several studies of this cisplatin schedule in organ preservation,[35] in the postoperative adjuvant setting,[36] and in numerous phase II chemoradiotherapy regimens have further supported the effectiveness of this treatment strategy.

**Targeted Therapy With Cetuximab**—The epidermal growth factor receptor (EGFR) is abnormally activated and overexpressed in cancers of epithelial origin, which includes SCCHN.[37-38] Cetuximab (Erbitux), a monoclonal antibody against EGFR has been associated with clinically significant rates of tumor regression in patients with platinum-refractory head and neck cancer.[39-40] Bonner et al reported the results of a phase III trial that compared radiation therapy alone to concurrent cetuximab and RT.[41]. In this study, 424 patients with locoregionally advanced SCCHN were randomized to receive treatment with either definitive RT or RT plus weekly cetuximab.
Cetuximab was administered at an initial dose of 400 mg/m², followed by 250 mg/m² weekly for the duration of therapy. The median duration of locoregional control was improved from 14.9 months in the RT-alone arm to 24.4 months in the cetuximab-plus-RT arm (P = .005). In addition, a benefit in overall survival was seen in the cetuximab-plus-RT arm after a median follow-up of 54 months. The overall survival was 49 months among patients who received the combined therapy and 29.3 months in the RT-alone group (P = .03). There was no difference in the incidence of distant metastases between the two groups. Importantly, with the exception of cetuximab-related acneiform rash and infusion reactions, the incidence of toxic effects did not differ significantly between the two groups. Although this study clearly revealed a benefit in locoregional control and survival when cetuximab was added to RT, it is unclear how this regimen compares to cisplatin-based chemoradiotherapy. However, in light of no significant added toxicity with cetuximab, it emerges as a valuable therapeutic option in patients with coexisting medical conditions and decreased performance status, for whom the risks of chemotherapy may outweigh its benefits.

RTOG 0522 is an ongoing phase III randomized trial that is further exploring the activity of cetuximab in combination with radiation for locoregionally advanced SCCHN. In this trial, patients are randomized to receive either RT and cisplatin or RT, cisplatin, and cetuximab.[42]

Revisiting Induction Chemotherapy

With the improvement in locoregional control and overall survival achieved with chemoradiotherapy, distant metastases emerged as a leading problem. As discussed previously, the vast majority of the earlier induction trials did not support this approach as the optimal treatment strategy, in part because of the inability to improve locoregional control. Induction chemotherapy followed by concurrent chemoradiotherapy is an alternative strategy being evaluated. There are compelling theoretical advantages to induction chemotherapy, including high response rates and clear benefit with regard to organ preservation. It has also been shown that a response to induction chemotherapy predicts response to definitive therapy by RT or chemoradiation.[43] Sequencing induction chemotherapy followed by chemoradiotherapy, addresses many of the issues arguing against induction chemotherapy. Over the past decade, the addition of newer agents to known active regimens has been actively investigated. Much of the interest has focused on the incorporation of a taxane in various treatment settings. In the induction setting, several phase II trials have investigated the incorporation of a taxane to a variety of induction regimens, most commonly a cisplatin/5-FU (PF) backbone in the treatment of patients with locoregionally advanced SCCHN. Response rates greater than 90% have been reported with impressive survival rates.[27,44,45]

In an attempt to build on these encouraging results, the logical next step has been to incorporate induction chemotherapy into the chemoradiotherapy approach. The high response rates as well as an expected decrease in the development of distant metastases added to the previously noted gains in locoregional control and overall survival demonstrated with chemoradiotherapy could potentially lead to further improvements in outcomes. Although several phase II trials have investigated this approach, we will focus on three recent phase III trials (Table 3).

• **EORTC 24971/TAX 323**—The most recent results of the EORTC 24971 (TAX 323) trial comparing docetaxel (Taxotere), cisplatin, and 5-FU (TPF) and PF induction chemotherapy followed by RT in patients with locoregionally advanced, unresectable SCCHN were recently reported.[46] In this phase III trial, 358 patients were randomized to receive either PF or TPF every 3 weeks for four cycles. This was followed by RT within 4 to 7 weeks. The primary endpoint of median progression-free survival (with a median follow-up of 32.5 months) was 11.0 months in the TPF group and 8.2 months in the PF group (P = .007). Median overall survival
was 18.8 months and 14.5 months for the TPF and PF groups, respectively (P = .02). The investigators also noted an absolute increase in 3-year survival of 10.9% in the TPF group. TPF induced more leukopenia and neutropenia than PF, but with prophylactic antibiotics, did not lead to more frequent infections. There were fewer treatment delays in the TPF group as well as a lower incidence of grade 3/4 thrombocytopenia, nausea, vomiting, and stomatitis.

• **Spanish Trial**—In 2005, Hitt et al published the results of a Spanish phase III trial[47] in which 382 patients with stage III/IV resectable and unresectable SCCHN were randomized to receive three cycles of induction chemotherapy with either cisplatin and 5-FU (CF) or cisplatin, 5-FU, and paclitaxel (PCF). Following induction chemotherapy, patients were reevaluated and further assigned based on response. Patients who achieved a complete response (CR) or partial response greater than 80% in the primary tumor then received concurrent chemoradiotherapy consisting of cisplatin 100 mg/m² on days 1, 22, and 43 with conventional radiotherapy to a total dose of 70 Gy. The CR rate was 14% in the CF arm and 33% in the PCF arm (P < .001). The researchers found no differences between the two groups in a comparison of overall responses to induction and chemoradiotherapy treatment. A clear survival benefit was seen only in the subgroup of patients with unresectable disease, with a median survival of 36 months in the PCF group vs 26 months in the CF group (P = .04). There was no difference in grade 3/4 neutropenia between the two treatment groups. An increase in mucositis was seen in the CF group.

• **TAX 324**—The results of the TAX 324 trial[48] were published simultaneously with the TAX 323 trial. In this phase III trial, 501 patients with SCCHN who were considered to have unresectable disease or to be a candidate for an organ-preservation approach were randomized to receive three cycles of either TPF or PF induction chemotherapy. This was followed by chemoradiotherapy utilizing weekly carboplatin. The primary endpoint in the study was overall survival. The estimated 3-year survival rate was 62% in the TPF group and 48% in the PF group (P = .002). The median survival was 71 and 30 months for the TPF and PF groups, respectively (P = .006). Locoregional failure was 30% in the TPF group and 38% in the PF group (P = .04). The investigators observed no statistically significant difference in the incidence of distant metastasis. The TPF arm was associated with a significant increase in grade 3/4 neutropenia and febrile neutropenia, compared to the PF group. Despite this finding, there were significantly fewer treatment delays in the TPF group.

• **Further Reflections on Induction Chemotherapy**—Based on the results of these phase III trials, it appears evident that TPF is superior to PF as an induction chemotherapy regimen in patients with locoregionally advanced SCCHN prior to either chemoradiotherapy or radiation alone. However, no completed trials have directly compared induction chemotherapy plus chemoradiotherapy to chemoradiotherapy alone. Until these data become available, the precise role of induction chemotherapy in this group of patients will remain unclear.

It is well understood that that there is a substantial increase in toxicity associated with chemoradiotherapy, compared to radiation alone. With the potential added toxicities of induction chemotherapy as well as a prolongation in the time it takes to complete therapy, an important concern is that a proportion of patients may not complete the chemoradiotherapy portion of treatment as planned. It is also critical not to compromise the previously noted gains achieved with chemoradiotherapy by choosing potentially less effective agents to be delivered during chemoradiotherapy. Another concern is that without further data, the routine incorporation of induction chemotherapy may result in overtreatment for a substantial number of patients. Thus, it is imperative that we are better able to define which subset of patients, if any, should routinely receive this intensive treatment approach.

**Phase III Trial Design Considerations**

Clinical trial design is critical in validating the induction chemotherapy hypothesis and should be based on the experience and data available from clinical trials that have addressed this issue. Emphasis should be placed on testing the induction chemotherapy hypothesis in a patient population most likely to benefit from induction chemotherapy. Conceptually, this would parallel “risk adaptive” strategies applied to other cancer sites. For example, patient selection could be limited to patients with oropharynx T4 and N2 or greater nodal involvement. Given the increasing validity of the prognostic implications of human papillomavirus (HPV)-16 positivity, consideration should be given to either stratification for HPV status or exclusion of such patients from induction chemotherapy trials. Locally advanced hypopharyngeal cancer patients are known to be at higher risk of occult metastatic disease and...
distant recurrence after locoregional treatment, and they represent a different subset of patients. Chemoradiotherapy is the “backbone” of treatment and efforts should be made to hold chemoradiotherapy constant in order to provide direct comparison of treatment with and without induction chemotherapy. One of the challenges is to determine which chemoradiotherapy regimen is optimum, particularly in consideration of radiation delivery, variations in chemotherapy, and increasing evidence supporting the contribution of EGFR in chemoradiotherapy regimens. Selection of endpoints is another critical factor in the design of clinical trials. Most would agree that overall survival should be the primary endpoint with adequate power to be able to demonstrate a 10% to 15% advantage. Toxicity endpoints should be designed to capture acute toxicity, especially focusing on delivery of the intended chemoradiotherapy without compromise resulting from the induction chemotherapy. Emphasis needs to be placed on intermediate and long-term toxicities, which are generally thought to be underreported.

**Current Phase III Studies**

As this review is being written, we are aware of three ongoing phase III clinical trials that are testing the induction chemotherapy hypothesis. The Paradigm trial is a randomized phase III trial in patients with stage III/IV SCCHN. Patients randomized to the induction arm will receive three cycles of TPF followed by chemoradiotherapy determined by the response to TPF. Patients with a “less than good response to induction” will receive 4 weeks of accelerated concomitant boost radiotherapy combined with weekly docetaxel. Patients with a “good response to induction chemotherapy” will receive 7 weeks of single-fraction radiation therapy combined with weekly carboplatin. The control arm is chemoradiotherapy of accelerated concomitant boost radiotherapy and cisplatin, 100 mg/m^2^, at 21-day intervals for two cycles.

The second trial is being conducted in Italy with a two-arm randomization of TPF for three cycles with a secondary randomization to chemoradiotherapy with cisplatin/5-FU or radiation therapy with cetuximab. The control arm receives no induction chemotherapy with the same secondary radiation randomization. This design will permit a 2 × 2 factorial design with overall survival as the primary endpoint, comparing induction chemotherapy vs no induction chemotherapy and radiation with either cisplatin/5-FU or cetuximab.

The third trial is an international phase III trial for patients with nodal stage N2 or N3 locally advanced disease. Patients are randomized to receive either two cycles of induction TPF followed by chemoradiation using docetaxel, 5-FU, and hydroxyurea with twice-daily radiation on an alternating-week schedule or the same chemoradiation scheme alone.

**Conclusions**

It is important to keep in mind when evaluating the existing trials that there is considerable heterogeneity with respect to the patient populations included as well as in the chemotherapy regimens and radiation schedules used. Although cisplatin-based chemoradiotherapy can still be considered the standard of care, there remain many unanswered questions, and it is difficult to recommend a “one size fits all” approach. With each new report, although we are able to witness exciting developments, more questions emerge.

In an attempt to achieve the best outcome for our patients, several questions often arise in our daily treatment decisions. Chief among them are the following: Which patients should be considered for induction chemotherapy? Should cisplatin remain the standard agent for patients receiving chemoradiotherapy? What is the optimal radiation schedule when combined with chemotherapy? How can we best integrate the EGFR inhibitors and other targeted agents into our treatment strategies?

At the same time, we must keep in mind the substantial toxicities associated with all of these approaches and give a clear focus to the evaluation of long-term functional outcomes and quality-of-life issues. Only with carefully planned and completed trials will these questions be answered, so that we can best serve this challenging patient population.

This article is reviewed [here](http://www.diagnosticimaging.com).

**Disclosures:** Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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Management of Locally Advanced or Unresectable Head and Neck Cancer
Published on Diagnostic Imaging (http://www.diagnosticimaging.com)


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