Combined-Modality Therapy for Locoregionally Advanced Head and Neck Cancer

By Anthony J. Cmelak, MD, Barbara A. Murphy, MD, and Terry Day, MD

Traditionally, treatment for locally advanced resectable head and neck cancer has been surgical resection followed by postoperative radiation. In unresectable patients, primary radiation has been the mainstay of treatment.

Introduction

At presentation, 40% of newly diagnosed head and neck cancer patients have only localized disease, 40% to 50% also have regional disease, and less than 10% have distant metastases.[1] The survival for those with early-stage disease (T1-2, N0, M0) is acceptable, with 5-year survival rates of 70% to 90% with single-modality therapy.[2] In this setting, the decision to use surgical resection or definitive radiation is based on surgical or radiation morbidity, cosmesis, and patient reliability.[3] For patients who present with large primary tumors or regional disease (American Joint Committee on Cancer stages III/IV), historical therapy has been surgery followed by postoperative radiation. Overall 5-year survival in this cohort is only 20% to 60% with this approach. The majority of these patients fail locoregionally. Thus, clinical investigations have centered on methods to decrease locoregional relapse. Such approaches include neoadjuvant or adjuvant chemotherapy, neoadjuvant or adjuvant radiation, and the concomitant use of chemotherapy and radiation. This article will delineate the current data available from clinical trials investigating combined-modality therapy for locally advanced head and neck carcinoma.

Primary Surgery With Adjuvant Treatment

Surgery With Radiation

Locally or regionally advanced (T3-4, N0-3) disease has historically been treated with combined-modality therapy to maximize local control and survival. Radiation has been investigated in both preoperative and postoperative settings. Advocates of preoperative radiation cite a lower risk of positive surgical margins and therefore improved local control and survival. In addition, lower doses of radiation can be used preoperatively because of better tumor oxygenation, and tumor downsizing with radiation can promote surgical resection with a greater chance for function preservation. Advocates of postoperative radiation suggest that surgical morbidity is lowest when operating on nonirradiated tissue; tissue planes may also be easier to identify and intraoperative frozen section analysis is more reliable. In addition, postoperative radiation can be tailored according to pathologic findings, such as nodal status, surgical margins, and extent of tumor spread.[4] The Radiation Therapy Oncology Group (RTOG) conducted a randomized trial (RTOG 73-03) comparing preoperative 50 Gy to postoperative 60 Gy in 277 patients with locally advanced carcinoma of the supraglottis and hypopharynx. With a median follow-up of 10 years, postoperative radiation demonstrated superior locoregional control (70% postoperative vs 58% preoperative, P = .04).[5] No survival differences were seen (P = .15) (Table 1).

In an attempt to determine the optimal dose of postoperative radiation for both low-risk and high-risk patients, the University of Texas M. D. Anderson Cancer Center (Houston) conducted a randomized trial in the 1980s.[6] A total of 302 patients were assigned to either low-risk or high-risk groups according to histopathologic features, such as margin status, T stage, N stage, direct invasion of tumor into adjacent structures, perineural spread, or extracapsular nodal extension. Utilizing daily fraction sizes of 1.8 Gy postoperatively, the study demonstrated that low-risk patients receiving less than 54 Gy had a significantly higher failure rate than those receiving at least 57.6 Gy (P = .02); 63 Gy is required for patients with extracapsular spread. Higher doses than 63 Gy increased toxicity but did not improve locoregional control.
Surgery With Chemotherapy

During the late 1970s and 1980s, investigators attempted to add induction chemotherapy to surgery and postoperative radiation. Theoretically, chemotherapy could convert inoperable tumors to operable tumors by decreasing tumor bulk, allowing for organ function preservation and the eradication of micrometastases, thereby improving survival.

A number of randomized trials have been conducted comparing surgery (with or without postoperative radiation) vs induction chemotherapy and surgery. To date, no overall survival benefit has been demonstrated, despite relatively high response rates to induction chemotherapy.[7-18] Two trials have demonstrated improved overall survival in select subsets only (Table 2). However, confirmatory prospective randomized data have not been obtained.

Postoperative chemotherapy has theoretical advantages over a neoadjuvant approach because (1) the definitive surgical procedure is not delayed; (2) the number of tumor clonogens is reduced so resistance is less likely to develop; (3) tumor margins are best seen by the surgeon de novo, before chemotherapy is administered; and (4) a substantial number of patients refuse surgery after symptoms subside with tumor response to induction chemotherapy.

Adjuvant chemotherapy has been evaluated in a number of large prospective randomized trials. An overall survival advantage has not been demonstrated, although a number have reported a decrease in distant metastases. However, many of these trials have statistical or design flaws. Two recent well-conducted trials confirm the lack of efficacy of adjuvant chemotherapy. In Japan, 424 patients with locally advanced head and neck carcinomas were randomized to 1 year of adjuvant uracil and tegafur (in a molar ratio of 4:1 [UFT]) or resection alone.[19] Despite a high compliance rate with chemotherapy, no survival advantage was observed. The RTOG sponsored an intergroup trial of 442 stage III and IV patients comparing immediate postoperative radiation to three cycles of cisplatin (Platinol) and fluorouracil followed by postoperative radiation. No overall difference was observed in actuarial 4-year survival (44% vs 48%), disease-free survival (38% vs 46%), or locoregional failure (29% vs 26%).[20] However, chemotherapy-treated patients developed fewer distant metastases (15% vs 23%, P = .03).

Surgery With Adjuvant Concomitant Chemoradiation

The addition of chemotherapy to postoperative radiation has the theoretical advantage of utilizing radiosensitization to improve the efficacy of radiation. Several conflicting randomized trials have been reported.

Bauchaud et al randomized 88 postoperative patients with extracapsular nodal disease to receive postoperative radiation alone or in combination with cisplatin 50 mg weekly.[21] Median and 5-year survival were significantly improved with the addition of cisplatin (median survival, 40 vs 22 months; 5-year survival, 36% vs 13%, P < .01). In addition, a trend toward improved locoregional control was observed (77% vs 59%, P = .08). Overall, 15% of patients who received radiation alone (RTOG grade > 2) and 20% of chemoradiation-treated patients experienced severe complications.

Haffty et al reported improvement in 5-year local recurrence-free survival (87% vs 67%, P < .015) and disease-free survival (67% vs 44%, P < .03) with the addition of mitomycin C.[22] No overall survival advantage was seen (56% vs 41%, P = ns).

In a study by Domenge et al, 287 patients with high-risk, extracapsular nodal extension received postoperative radiation with or without cisplatin, bleomycin (Blenoxane), and methotrexate.[23] Patients on the adjuvant chemotherapy arm had significantly worse overall survival despite an improvement in locoregional control.

In order to clarify the role of chemotherapy given concomitantly with postoperative radiation, the RTOG is randomizing high-risk postoperative patients (extracapsular spread, multiple involved nodes, positive surgical margins) to 60 Gy alone in 30 fractions or the same radiation with cisplatin 100 mg/m² given on days 1, 22, and 43. Accrual is anticipated to be completed in early 2000.

Primary Radiation With Adjuvant Treatment Induction Chemotherapy

A large number of phase II trials have shown the feasibility of administering single-agent or combination chemotherapy prior to definitive radiation. The most widely used induction combination has been cisplatin and fluorouracil, as initially reported by Wayne State University (Detroit, Mich) in 1982.[24] In 26 evaluable patients, the most common toxicity was nausea and vomiting, and 26% of patients developed grade 3 or grade 4 leukopenia. A 19% complete response rate and a 70% partial response rate (overall response rate, 89%) was reported using two induction cycles. Similar results have been demonstrated by other investigators using this combination.

Currently, novel chemotherapy combinations are being evaluated in the induction setting with the
goal of increasing complete response rates and decreasing toxicity. The most promising new agents at this time are paclitaxel (Taxol) and docetaxel (Taxotere). Both have demonstrated single-agent overall response rates of 30% to 50% in patients with metastatic or locally recurrent head and neck carcinoma.[25,26] In the induction setting, taxane-based regimens have demonstrated excellent overall and complete response rates. Investigators at Dana Farber Cancer Institute (Boston, Mass) conducted a phase I/II trial evaluating three cycles of induction docetaxel, cisplatin, fluorouracil, and leucovorin in 23 patients with locally advanced squamous carcinoma of the head and neck.[27] The maximum tolerated dose with granulocyte colony-stimulating factor support was docetaxel 60 mg/m² with cisplatin 25 mg/m² administered by continuous intravenous infusion (CI) for 5 days, leucovorin 500 mg/m² (CI x 5 days), and fluorouracil 700 mg/m² (CI x 4 days). Toxicity was substantial. At the maximum tolerated dose, the incidence of grade 3 or 4 mucositis was 46%, of grade 3 or 4 febrile neutropenia was 10%, and toxicity-related hospitalization was 35%. The complete response rate was 61% (14/23), and the partial response rate was 39% (9/23), for an overall response rate of 100%. The Vanderbilt Cancer Center (Nashville, Tenn) has reported its experience with induction therapy using carboplatin (area under the concentration-time curve [AUC in mg/mL • min] 6.0 to 7.5) and paclitaxel (135 to 175 mg/m²).[28] The complete response rate with two to four cycles (median, three) was 53% (10/19), and the partial response rate was 42% (8/19). The toxicity profile was favorable: Three patients experienced grade 3 or 4 leukopenia, and one patient experienced grade 3 thrombocytopenia. One grade 5 toxicity occurred in a noncompliant patient. The cause of death was presumably nadir sepsis.

Induction chemotherapy has been used prior to definitive radiation in three distinct settings: In resectable patients for organ preservation, in patients with unresectable squamous carcinoma, and in patients with stage III/IV cancer of the nasopharynx. Induction chemotherapy followed by radiation has become an accepted treatment option in patients who would otherwise have substantial loss of organ function with definitive surgical resection. This approach has been used most commonly in patients with laryngeal, hypopharyngeal, and base-of-tongue tumors. Phase II data indicate that induction chemotherapy followed by radiation has acceptable toxicity, comparable survival outcome to historical surgical controls, and reasonable rates of organ preservation.

Two sentinel phase III studies have compared induction chemotherapy with radiation to primary surgery with postoperative radiation. The Veterans Affairs Laryngeal Cancer Study Group randomized 332 patients with stage III/IV laryngeal cancer to total laryngectomy with postoperative radiation or induction chemotherapy with three cycles of cisplatin and fluorouracil followed by definitive radiation (66 to 76 Gy). Local recurrences were increased in the induction chemotherapy/radiation arm (P = .0005), although distant metastases were fewer (P = .016). Nonetheless, the 2-year survival was 68% for both treatment arms. The larynx preservation rate was 64% with induction chemotherapy and radiation.[29] An analogous result was shown by the European Organization for Research and Treatment of Cancer. Patients went on to 70 Gy irradiation only after a clinical complete response to induction cisplatin and fluorouracil. The median survival observed with induction chemotherapy and radiation was 44 months vs 25 months for immediate surgery (P = NS). At 3 years, 42% of patients receiving induction chemotherapy and radiation retained a functional larynx. Treatment failures at local, regional, and second primary sites occurred at the same frequency (12%, 19%, and 16%, respectively, for surgery, and 17%, 23%, and 13%, respectively, for induction chemotherapy/radiation).

These trials have been criticized because they lack a third treatment arm with radiation alone. For this reason, an intergroup phase III trial is ongoing to determine if induction chemotherapy is an essential component of organ preservation.[31] Treatment arms include radiation alone (70 Gy), induction cisplatin and fluorouracil followed by radiation, and concomitant cisplatin with radiation. Accrual is scheduled to be completed in the next few months.

In the unresectable patient population, the role of induction chemotherapy is less clear. Paccagnella et al reported the results of a phase III trial of initial chemotherapy in stage III/IV head and neck cancer patients.[18] Patients were segregated into two groups: Those who could undergo primary surgical resection, and those who were to receive primary radiation. Within each cohort, patients were randomized to receive induction chemotherapy with four cycles of cisplatin and fluorouracil or no induction therapy. Results indicate no survival advantage with induction chemotherapy in patients undergoing primary surgery. The overall 3-year survival in patients receiving primary radiation, however, was statistically improved with induction chemotherapy (24% vs 10%, P = .04). Similarly, a prospective randomized study comparing radiation preceded by continuous intra-arterial
methotrexate (3 mg/day to 5 mg/day; total dose, 90 mg to 120 mg) to radiation alone showed improvement in overall 5-year survival with the addition of methotrexate (43% vs 25%, P < .05).[32] In contrast, other trials investigating induction regimens have failed to consistently demonstrate an improvement in survival over radiation alone (Table 3).[33-35]

A third setting in which the role of induction chemotheraphy has been investigated is locally advanced nasopharyngeal cancer. The International Nasopharyngeal Cancer Study Group recently reported the results of a phase III trial in 339 patients randomized to radiation (70 Gy) alone vs three cycles of induction bleomycin 15 mg intravenous bolus (day 1), plus 12 mg/m²/day CI (days 1 to 5), epirubicin (Ellence) 70 mg/m² IV (day 1), and cisplatin 100 mg/m² (day 1), followed by radiation.[36] Disease-free survival was improved in patients receiving induction chemotherapy (41% vs 30%, P < .002). However, no survival advantage was noted (median, 52 months for induction chemotherapy vs 39 months for radiation alone, P = NS).

**Concomitant Chemoradiation**

Concomitant chemoradiation has been investigated predominantly in two patient populations: Those with advanced unresectable disease and those with nasopharyngeal carcinoma. More recently, the role of concomitant chemoradiation has been explored in patients with resectable disease for organ preservation.

There are several postulated mechanisms for radiosensitization: (1) alteration in repair of sublethal cell damage; (2) alteration of cell-cycle kinetics favoring G2/M arrest; and (3) elimination of clonogens responsible for accelerated repopulation. Preclinical data indicate that a number of commonly used chemotherapy agents can enhance radiation efficacy. These include cisplatin, fluorouracil, mitomycin, hydroxyurea (Hydrea), bleomycin, actinomycin D, and doxorubicin (Adriamycin). Phase I/II data demonstrate that these agents can be administered concomitantly with radiation at the expense of increased toxicity. Several studies have reported encouraging results and merit discussion.

The University of Chicago reported a phase II trial in 76 patients with locally advanced disease who received cisplatin 100 mg/m² (day 1), fluorouracil 800 mg/m² (CI × 5 days), and hydroxyurea 1 g orally (every 12 hours × 11 doses, days 0 to 5) given concomitantly with split-course hyperfractionated radiation (1.5 Gy twice daily) for 5 days.[37] Cycles were repeated every 2 weeks × 5 (75 Gy over 10 weeks). Three-year progression-free survival was 69%, locoregional control was 95%, distant control 80%, and 3-year survival was 55%. Toxicity was severe. However, attempts are currently under way to identify less toxic regimens.

The University of Tennessee at Memphis reported the results of a phase II trial of supradose intra-arterial targeted cisplatin (SIT-P) at 150 mg/m² weekly (× 4 weeks) concomitantly with conventional 70-Gy radiation.[38] The majority of the 60 patients had either T4 or N2-3 disease. The complete response rate was 91% at the primary site and 67% at sites of nodal disease. Four-year actuarial locoregional control was 84%, disease-specific survival was 46%, and the overall survival was 29%. In these and other phase II trials, the response rates, local control, and survival for concomitant chemoradiation in the unresectable patient population appear superior compared to historical results with radiation alone.

A number of reported phase III trials also support the addition of chemotherapy to radiation over radiation alone in terms of progression-free, disease-free, relapse-free, and overall survival (Table 4).[39-54] Calais et al reported initial data from a randomized trial in stage III/IV oropharyngeal carcinoma.[51] Patients were randomized to radiation alone (70 Gy over 7 weeks) vs carboplatin (Paraplatin) 70 mg/m² IV (day 1), and cisplatin 100 mg/m² (day 1), followed by radiation.[36] Three-year progression-free survival was 69%, locoregional control was 95%, distant control 80%, and 3-year survival was 55%. Toxicity was severe. However, attempts are currently under way to identify less toxic regimens.

**Table 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chicago</td>
<td>76 patients with locally advanced disease</td>
<td>Complete response rate 91% at primary site and 67% at sites of nodal disease.</td>
</tr>
<tr>
<td>University of Tennessee at Memphis</td>
<td>60 patients with T4 or N2-3 disease</td>
<td>Four-year actuarial locoregional control 84%, disease-specific survival 46%, overall survival 29%.</td>
</tr>
</tbody>
</table>

In contrast, other trials investigating induction regimens have failed to consistently demonstrate an improvement in survival over radiation alone (Table 3).[33-35] An ongoing Eastern Cooperative Oncology Group randomized trial is attempting to corroborate the superiority of chemoradiation. E1392 is a three-arm trial comparing radiation alone vs concomitant...
cisplatin 100 mg/m² (days 1, 22, and 43) with radiation, vs split-course radiation with concomitant cisplatin and fluorouracil × 3 cycles throughout the duration of radiation.

Similar to the unresectable patient population, concomitant chemoradiation has demonstrated a survival advantage in advanced nasopharyngeal carcinoma. The RTOG randomized patients with advanced nasopharyngeal cancer to radiation alone (70 Gy over 7 to 8 weeks) vs radiation with concomitant cisplatin 100 mg/m² (day 1, 22, and 43) followed by three courses of adjuvant fluorouracil and cisplatin. Results demonstrated a marked improvement in all end points with additional chemotherapy, including 3-year progression-free survival (69% vs 24%, P < .001) and overall survival at 3 years (78% vs 47%, P < .005).[52] Concomitant chemoradiation is now considered standard treatment in locally advanced nasopharyngeal cancer patients.

**Meta-Analyses**

Three meta-analyses, two literature-based and one patient-based, evaluating the role of chemotherapy in the primary treatment of squamous cell carcinoma of the head and neck have now been reported.[55-57] El-Sayed and Nelson reported combined results of 25 randomized trials that compared local treatment alone to local treatment with chemotherapy.[55] An overall 11% reduction in mortality was observed with the addition of chemotherapy to primary treatment. Neoadjuvant or adjuvant chemotherapy provided minimal survival advantage. Concomitant chemotherapy, however, was associated with a 22% survival advantage.

Munro et al, in a larger analysis of 54 randomized studies, demonstrated that neoadjuvant chemotherapy increases absolute survival by 3.7% (95% confidence interval [CI], 0.9% to 6.5%) and adjuvant chemotherapy by 6.5% (95% CI, 3.1% to 9.9%). These findings corroborated those of El-Sayed and Nelson, and showed that chemotherapy given synchronously with radiation provided the most significant survival benefit (12.1%, 95% CI, 5% to 19%).[56]

A recently reported patient-based meta-analysis with median follow-up of 6 years confirmed these results in 10,717 patients enrolled in 63 trials between 1965 and 1993.[57] The addition of chemotherapy provided an overall 11% risk reduction, with a 4% absolute survival benefit at 5 years (P = .001). Adjuvant and neoadjuvant chemotherapy provided a risk reduction of 2% and 5%, respectively (absolute 5-year benefit, 1% and 2%, respectively, P = NS). Concomitant chemotherapy provided a risk reduction of 19%, with an absolute survival benefit of 8% at 5 years (P = .0001). It appears, then, that the addition of concomitant chemotherapy confers a modest overall survival advantage to radiation alone; neoadjuvant and adjuvant chemotherapy provides no statistical survival advantage. The cost of concomitant chemotherapy, however, is increased toxicity.

**New Chemotherapeutic Agents**

The above data have generated significant interest in the development of new radiosensitizing agents to enhance locoregional control. Numerous phase I and phase II studies of newer agents with concomitant radiation have been reported, with some agents already being tested in randomized trials (Table 5).[58-66] The most extensively evaluated new agent is paclitaxel.

Paclitaxel has shown efficacy in metastatic head and neck carcinoma with response rates of 40%. Because of its radiosensitization properties, it is an attractive agent to use concurrently with radiation. A number of concomitant schedules have been investigated, including weekly administration, every-3-week administration, and continuous infusion.[58-60]

Hoffman et al reported the results of a phase I trial evaluating weekly paclitaxel with standard-dose radiation.[58] Dose-limiting toxicity was grade 4 mucositis at paclitaxel 40 mg/m². The recommended maximum tolerated dose for further study was 30 mg/m². Similar results have been reported by investigators at Johns Hopkins University (Baltimore, Md).[68] Cisplatin and carboplatin, commonly used as radiation sensitizers in head and neck carcinoma, are being combined with paclitaxel in an attempt to increase efficacy.

Chougule et al reported the results of a phase II trial using paclitaxel 60 mg/m² and carboplatin (AUC of 1) concurrently with conventional radiation (72 Gy).[69] Thirty-two patients were evaluable for toxicity. Grade 3 or 4 mucositis occurred in 100% of patients. Other grade 3 or 4 toxicities included dermal toxicity (13%), pulmonary toxicity (6%), and neutropenia (9%). Thirty patients were evaluable for response. Seventeen of 30 patients (57%) had a clinical complete response, and 10 (33%) had a partial response. Forty-seven percent of patients had a pathologic complete response at the primary site.

The University of Maryland (Baltimore) reported on 28 patients who received weekly paclitaxel 40 mg/m² to 45 mg/m² (3-hour infusion) with cisplatin 100 mg/m² every 3 weeks concurrently with radiation 1.8 Gy/day.[70] Twenty-seven patients were evaluable for toxicity. Grade 3 or 4 toxicities included mucositis in 13 patients, leukopenia in eight patients, and desquamation in two patients. Of 22 patients evaluable for response, 13 had a partial response and 5 had a complete response.
Combined-Modality Therapy for Locoregionally Advanced Head and Neck Cancer
Published on Physicians Practice (http://www.physicianspractice.com)

(overall response rate, 82%). The RTOG has recently completed a three-arm randomized phase II trial in locally advanced patients to evaluate toxicity and efficacy of three novel concomitant regimens: (1) daily radiation (70 Gy over 7 weeks) with weekly cisplatin and paclitaxel; (2) radiation (70 Gy over 7 weeks) with daily cisplatin and fluorouracil given over the last 10 days of radiation; and (3) radiation (70 Gy over 13 weeks) given concurrently with daily fluorouracil and hydroxyurea. Continued investigation of these and other taxane-based regimens is warranted.

Gemcitabine (Gemzar) is a nucleoside analog that has shown efficacy in locally recurrent and metastatic head and neck cancer, with response rates of 13%. In vitro data demonstrate excellent radiosensitizing qualities at micromolar concentrations. Phase I data show excellent response rates when given weekly with daily radiation (10/12 complete responses). However, substantial early and late soft tissue toxicity has been reported.\(^{[61]}\)

JM-216 is an oral analog of cisplatin that has undergone phase I testing as a radiation sensitizer at the Vanderbilt Cancer Center in patients with squamous carcinoma of the head and neck. Accrual has been completed at the third dose level (20 mg three times weekly concurrently with 70 Gy over 7 weeks).\(^{[71]}\) Identification of oral agents that are active radiation sensitizers is theoretically beneficial in terms of patient compliance, ease of administration, and ability to administer synchronously with delivery of radiation.

**Conclusion**

Attempts to define the role of chemotherapy in the management of head and neck cancer patients continue to challenge medical oncologists. The indications for chemotherapy, though controversial in many clinical scenarios, have expanded since the introduction of methotrexate for palliation of metastatic disease in the 1960s and the development of cisplatin-based treatment regimens in the 1980s. At this time, it is clear that induction chemotherapy followed by radiation is an acceptable alternative to surgical resection in patients with laryngeal, hypopharyngeal, and base-of-tongue carcinomas. The optimal organ preservation approach, however, has yet to be determined. Comparisons of induction therapy vs concomitant therapy vs induction/concomitant therapy are critically needed.

Data continue to build supporting concomitant chemoradiation in the unresectable patient population. Randomized trials and three meta-analyses confirm the efficacy of this approach. Clearly, combined chemoradiation in stage III/IV nasopharyngeal cancer has shown improvement in efficacy and should be considered standard care. New cytotoxic agents continue to be investigated in the hopes of improving patient tolerance and enhancing radiation efficacy. The question of altered radiation fractionation and its role in the setting of combined-modality therapy further increases the complexity of this issue.

**References:**


36. International Nasopharynx Cancer Study Group. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (> or = N2, M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. VUMCA I Trial. Int J Radiat Oncol Biol Phys 35:463-469, 1996.


Source URL:

Links: