Chemoradiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck for Organ Preservation and Palliation

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Objectives: To measure the efficacy and toxic effects of our chemoradiotherapy regimen by means of response and survival in patients with advanced squamous cell carcinoma of the head and neck (HNSCC) for organ preservation in resectable disease or palliation in unresectable disease.

Design: All patients underwent evaluation by the multidisciplinary head and neck cancer team, with pathological diagnosis and staging. All patients underwent assessment for response to therapy using results of physical examination and radiologic imaging. Patients were followed up at 3-month intervals for a planned period of 5 years.

Setting: Academic center.

Patients: Thirty-eight previously untreated patients with newly diagnosed HNSCC were treated from June 1, 1996, through December 31, 1998, of whom 20 had resectable and 18 had unresectable tumors.

Intervention: Patients received intravenous cisplatin, 100 mg/m² for 1 hour on days 1 and 29; a 24-hour continuous infusion of fluorouracil, 1000 mg/m² on days 1 through 4 and 29 through 32; and radiation therapy, 150 rad twice daily for 12 days. The patients were given a 7- to 10-day break, and radiation therapy was restarted on day 29 for 12 additional days (total dose, 7200 rad).

Main Outcome Measures: Complete, partial, and total response rates; disease-free survival; overall survival; and toxic effects.

Results: Toxic effects of treatment were moderately severe, including grades III to IV mucositis (89%), neutropenia (71%), and renal toxic effects (8%). In the 18 patients in the unresectable group, complete response in the 17 primary tumors and 15 cervical nodal metastases was achieved in 12 (71%) and 9 (60%), respectively; in the 20 patients undergoing organ preservation, complete response rates were 100% in the 23 primary tumors and 15 cervical nodal metastases. Complete response for all 38 patients was achieved in 31 (82%). In the unresectable group, the Kaplan-Meier relapse-free survival estimate is 56%, with follow-up from 29 to 45 months. In the organ preservation group, 75% of patients are alive without disease, and 8 have been followed up for 36 to 48 months. Of the 5 patients who have died, only 2 died of disease, with recurrences at 13.0 and 16.5 months.

Conclusions: Chemoradiotherapy consisting of cisplatin, fluorouracil, and twice-daily external beam radiation is highly effective in achieving durable complete responses in patients with resectable HNSCC undergoing organ preservation and patients with unresectable HNSCC undergoing palliation. Toxic effects of this regimen were moderate to severe.


Head and neck squamous cell carcinoma (HNSCC) constitutes 5% of all cancers in the United States, with approximately 45,000 new cases and 13,000 deaths per year. Most of these cancers originate in the oral cavity, but the larynx is the most common specific anatomical site. Two to three new cases present with advanced local disease and/or regional lymph node involvement, and 10% to 20% present with distant metastasis. Locoregional recurrence after therapy is noted in 60% of patients with advanced disease. Standard therapy for locally advanced HNSCC has been surgery and radiation. However, these treatment modalities are associated with significant morbidity. Chemotherapy has been reserved for palliation of unresectable, recurrent, or metastatic disease. The combination of cisplatin and fluorouracil routinely provides a response rate of approximately 85%, with a complete response (CR) rate of 35%. In recent years, chemotherapy has been used in the neoadjuvant or induction setting in an attempt to increase overall survival by increasing locoregional control or by eradicating micrometastases. Concomitant che-
PATIENTS AND METHODS

Patients with locally advanced and/or metastatic, newly diagnosed, previously untreated HNSCC underwent evaluation by specialists in otolaryngology—head and neck surgery, radiation oncology, and medical oncology and were presented at a multidisciplinary conference. All patients underwent panendoscopy, computed tomographic scanning and/or magnetic resonance imaging, and dental evaluation and were classified according to the system of the American Joint Committee on Cancer Staging. All computed tomographic and magnetic resonance imaging scans were read by a single radiologist who is a specialist in head and neck radiology. Criteria for treatment included being older than 18 years and having an Eastern Cooperative Oncology Group performance status of 0 (fully active) to 2 (ambulatory and capable of all self-care, but unable to carry out any work activities), no previous chemotherapy or radiation therapy to the head and neck, white blood cell count of greater than 4,000 cells/µL, platelet count of greater than 100,000 cells/µL, and serum creatinine level of less than 2.0 mg/dL (177 µmol/L).

The group with resectable disease, treated for organ preservation, consisted mainly of patients with primary tumors in the base of the tongue or hypopharynx, but other primary sites were also treated for patients who were considered to be at poor surgical risk or who refused surgery as primary therapy. Tumors were considered to be unresectable if they involved the base of the skull, carotid artery, vertebral bone, or prevertebral musculature.

All patients were treated using an institutional regimen based on the literature, and data were collected and analyzed after approval by the institutional review board. Chemotherapy consisted of intravenous cisplatin, 100 mg/m² for 1 hour on days 1 and 29, and continuous infusion of fluorouracil, 1000 mg/m² for 24 hours on days 1 through 4 and 29 through 32. All patients received prehydration using intravenous dextrose 5% and 0.45% isotonic sodium chloride, 250 mL/h for 4 hours, with intravenous mannitol, 12.5 g, given before cisplatin therapy. Posthydration was provided during daily fluorouracil administration as a 2-L continuous infusion of dextrose 5% and 0.45% isotonic sodium chloride. Antiemetics consisted of 2 mg of oral granisetron hydrochloride and 20 mg of intravenous dexamethasone sodium phosphate given before cisplatin therapy on day 1, then 10 mg of intravenous prochlorperazine maleate every 6 hours. Intravenous lorazepam, 1 mg every 8 hours, was given as needed for nausea and/or vomiting. Gastrostomy tubes were recommended for all patients with oral cavity, oropharyngeal, hypopharyngeal, and laryngeal primary tumors to provide adequate hydration and nutrition.

Radiation therapy was administered using a 6-MeV linear accelerator. All patients received 130 rad per fraction twice a day on days 1 through 12, with a minimum of 6 hours between fractions. After a dose of 3000 to 3600 rad, the patients received a 10-day treatment break, and radiation therapy was then restarted concomitantly with chemotherapy on day 29, to an average total dose of 7200 rad. Total treatment time for all patients was 6 to 7 weeks.

All patients underwent assessment for response to therapy. Kaplan-Meier curves were used to plot the relapse-free survival and overall survival for the resectable (organ preservation) and unresectable (palliation) groups from the end of therapy. In the relapse-free survival estimates, patients who were lost to follow-up and those who died without disease are censored at that point and are denoted by symbols on the graphs, but are not included in the survival calculations. Treatment of patients not rendered disease-free was considered to have failed at time 0. In the overall survival estimates, deaths due to all causes are included in the calculations, and those who died without disease are denoted by a symbol at that point. Patients who were lost to follow-up are denoted by a symbol at that point, but are not included in the overall survival calculations.

RESULTS

From June 1, 1996, until December 31, 1998, 38 patients with 40 primary tumors were treated with chemoradiotherapy. Eighteen patients with unresectable disease received palliative therapy (unresectable group), and 20 patients with resectable disease received organ preservation therapy (organ preservation group). The male-female ratio was 3:2:1.0; white-black race ratio, 1.1:1.0. Mean age was 55.5 years (range, 30-76 years). The patient and tumor characteristics for each group are shown in Table 1. The sex ratio was essentially equal in each group, but the racial composition was reversed between the 2 groups, with 12 black and 6 white patients in the unresectable group and 6 black and 14 white patients in the organ preservation group. In the unresectable group, 10 (56%) of the 18 patients presented with T4 primary tumors. Three patients in the organ preservation group had synchronous primary tumors, with 11 (48%) of 23 primary tumors staged as T3. Of the 38 patients, 30 (79%) presented with nodal disease. In the unresectable group, 11 (61%) of 18 had N3 disease (>6 cm in greatest dimension). All patients in the unresectable group and 14 (70%) of 20 in the organ preservation group had stage IV disease.

Seven (18%) of the 38 patients were not able to complete the full course of therapy and required an alteration in the treatment. In 4 (11%) of 38 patients, the second course of chemotherapy was omitted because of various toxic effects, including severe mucositis, moderate renal toxic effects, and decreased performance status, but the radiation therapy was completed in all 4 patients. In 3 (8%) of 38 patients, carboplatin (area under the curve, 5) was substituted for cisplatin on day 29 owing to mild renal toxic effects. The response rates for each
group were calculated based on an intent-to-treat basis and are shown in Table 2. Two patients were lost to follow-up, and one of these received only 1 week of therapy. Findings in these 2 patients were considered nonevaluable, and were included in the denominators of the response rates but not in the survival calculations.

Response data are presented in Table 2. In the unresectable group, the CR rates of the primary tumors and the cervical nodal metastases were 71% and 60%, respectively. In the organ preservation group, the CR rates were 100% for the primary tumors and the nodal metastases. When both groups were combined, the CR rate was 35 (88%) of 40 for the primary tumors and 24 (80%) of 30 for the cervical nodal metastases. The total CR rate for all 38 patients was 31 (82%). Among patients who achieved a CR, neck dissections were performed at approximately 8 weeks after completion of therapy for 2 patients in the unresectable group with N3 disease and in 5 patients in the organ preservation group with N2c to N3 disease. Results of pathological examination of all of these dissec-

### Table 1. Patient and Tumor Characteristics

<table>
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<th>Characteristic</th>
<th>Unresectable</th>
<th>Organ Preservation</th>
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<td>Total patients, No. (%)</td>
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**Figure 1, 2, 3, and 4** and Table 3. As of September 30, 2000, 8 of 18 patients in the unresectable group have died with disease at 1, 4, 6, 7, 8, 10, 14, and 19 months since the completion of therapy, for a relapse-free survival estimate of 56%. One patient died without disease at 13 months and 2 patients were lost to follow-up at 5.0 and 7.5 months. Six patients (33%) were alive without disease and have been observed for 29 to 45 months. In the organ preservation group, 2 of 20 patients have died with disease at 19 and 33 months, for a relapse-free survival estimate of 90%. Three patients have died without disease of recurrent vaginal cancer, ischemic heart disease, and lung cancer at 8.5, 27, and 37 months, respectively. Fifteen patients (75%) were alive without disease, with 8 of these having been observed for 36 to 48 months.

Toxic effects were graded according to the National Cancer Institute’s Common Toxicity Criteria, and the combined data of both groups are shown in Table 4. Grades III to IV neutropenia occurred in 27 (71%) of 38 patients, with 15 (39%) requiring hospital admission for fever and treatment with intravenous antibiotics. Thirty-four patients (89%) experienced grades III to IV mucositis, and 22 (58%) had gastrostomy tubes placed before treatment for nutrition and hydration. The average weight loss during therapy was 6.8 kg. Nausea and vomiting were mild to moderate in most patients, with only 1 patient experiencing intractable nausea. Four patients who did not present with dysphagia continued to experience severe dysphagia after therapy. Grades I to II renal toxic effects were seen in 8 (21%) of 38 patients, and grades III to IV effects in 3 patients (8%). There was 1 case of sepsis requiring admission to the intensive care unit and discontinuation of therapy, and 1 case of pulmonary aspergillosis, which was successfully treated.

### Comment

This chemoradiotherapy regimen was associated with significant toxic effects requiring aggressive supportive care, but it also provides a high response rate, even in patients with bulky, unresectable disease. Adelstein published a review of randomized trials of chemoradiotherapy for HNSCC in May 1998, which concluded that chemoradiotherapy improves overall survival and locoregional control through radiosensitization and offers the advantages of decreased duration of treatment and a lower rate of distant metastases. A previous study by Adelstein compared multagent chemotheraphy and radiation therapy with radiation therapy alone. One hundred patients with advanced, resectable disease were randomized to chemoradiotherapy with fluorouracil and cisplatin or to radiation therapy alone. Seventy-six percent of the patients receiving chemoradiotherapy achieved a CR, compared with 50% of the patients who received radiation therapy only. Relapse-free survival at 36 months was 67% and 52%, respectively, and the dis-
tant metastasis rates were 10% and 21%, respectively. In that study,8 overall survival was not significantly different for the 2 groups, but additional follow-up was required for accurate assessment due to the number of patients with recurrent disease remaining alive at the time of publication.

In April 1998, Wendt et al9 published a prospective, randomized, multicenter study to evaluate chemoradiotherapy compared with radiation therapy alone as primary therapy for unresectable disease. In the 270 patients with evaluable results, 130 received chemoradiotherapy con-
Results and Discussion

The study by Brizel et al\(^9\) used a lower total dose of cisplatin (60 mg/m\(^2\)) and fluorouracil (3000 mg/m\(^2\)) for 2 courses and a lower twice-daily fraction of radiation (125 rad) than our regimen. Their percentage of patients with mucositis was similar, but the percentage of patients requiring admission for fever and neutropenia was significantly higher in our report (39% vs 14%). It may be appropriate to consider modifying the therapy by using lower doses of chemotherapy and radiation therapy (per fraction) for patients with resectable tumors undergoing organ preservation to decrease the toxic effects, reserving our current regimen for patients with bulky, unresectable tumors for aggressive palliation.

Chemoradiotherapy consisting of cisplatin, fluorouracil, and twice-daily radiation is extremely effective therapy for locally advanced HNSCC in organ preservation and palliation. Its efficacy is most notable in the high rate of durable CRs in patients with advanced resectable disease. This intensive regimen increases the risk for significant toxic effects, especially fever, neutropenia, and mucositis; therefore, aggressive supportive care is essential. We will continue to follow up these patients for survival and long-term toxic effects.

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References