Aggressive Concurrent Chemoradiotherapy for Squamous Cell Head and Neck Cancer

An 8-Year Single-Institution Experience

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Background: Since 1989, 105 patients with squamous head and neck cancer have been treated with combined chemoradiotherapy.

Objective: To examine the effectiveness of using combined chemoradiotherapy on patients with squamous head and neck cancer.


Methods: Treatment consisted of fluorouracil, 1000 mg/m² per day, and cisplatin, 20 mg/m² per day, both given as continuous infusions during 4 days beginning on day 1 and 22 of a concurrent radiotherapy course. Radiation was given in single daily fractions of 1.8 to 2 Gy, to a total dose of 66 to 72 Gy. Salvage surgery was performed for any residual or recurrent locoregional disease. Planned neck dissection was recommended for all patients with N2+ neck disease, irrespective of clinical response.

Results: The 105-patient cohort consisted of 79 men and 26 women. The primary site was identified in the oral cavity in 6, oropharynx in 46, larynx in 30, and hypopharynx in 20 patients. Two patients had multiple primaries and 1 patient had an unknown primary. There were 4 patients with stage II, 24 with stage III, and 77 with stage IV disease. Grade 3 and 4 chemoradiotherapy toxic effects included mucositis in 88% of patients, cutaneous reaction in 50%, neutropenia in 49%, thrombocytopenia in 12%, and nausea in 5%. There were no deaths secondary to treatment. The mean weight loss was 12% of initial body weight. To date, primary site persistence or recurrence has occurred in only 14 patients (13%). With a mean follow-up of 39 months, 66 patients (63%) are alive and free of disease. The Kaplan-Meier 4-year projected overall survival is 60% with a disease-specific survival of 74%, a distant metastasis-free survival of 84%, and an overall survival with primary site preserved of 54%.

Conclusions: This chemoradiotherapy regimen, although toxic, is tolerable with appropriate supportive intervention. Locoregional and distant control are likely. Primary site conservation is possible in most patients. Chemoradiotherapy appears to have an emerging role in the primary management of head and neck cancer.

S TANDARD THERAPY for advanced head and neck cancer consists of a combination of surgery and radiation therapy; however, survival for this patient population has not improved during the past 20 years. In general 5-year survival for stage III and IV disease is less than 50%, with most patients dying of their disease.1,2 Chemotherapy, while not a curative modality in the treatment of head and neck cancer, has the potential to improve locoregional control, reduce distant metastases, and improve survival. Many different multimodality treatment schedules have been proposed over the years, using chemotherapy before (neoadjuvant), with (synchronous), or after (adjuvant) conventional therapy.3 Recently, another end point for multimodality treatment has been identified: organ preservation. This potential for organ preservation was suggested by the Veterans Affairs Laryngeal Cancer Study Group, which showed that, without compromising survival, laryngeal preservation was possible in approximately two thirds of patients with advanced laryngeal cancers.4 With all of these benefits, clinicians have attempted to develop treatment regimens that might optimize the chemotherapy and radiation combination and, in the event of a complete response, avoid surgery at the primary site.

This article is also available on our Web site: www.ama-assn.org/oto.
MATERIALS AND METHODS

PATIENTS

Patients with previously untreated stage III and IV squamous cell head and neck cancers or with selected stage II primary tumors that would have required a laryngectomy were eligible to receive concurrent chemoradiation. Patients with primary tumors known to originate from the salivary glands, paranasal sinuses, or the nasopharynx were excluded. Patients with mandibular bony invasion were also excluded. All patients had disease limited to the head and neck (M0). The T and N stage was assigned according to the 1988 staging system of the American Joint Committee on Cancer (AJCC). Patients with unknown and multiple primary tumors were not analyzed according to a single primary tumor site and were given a T4 stage.

Pretreatment evaluation included a medical history, physical examination, panendoscopy with general anesthesia, and a chest x-ray film of all patients. Laboratory evaluation consisted of a complete blood cell count, urinalysis, and serum chemistry values, including urea nitrogen, creatinine, calcium, aspartate aminotransferase, albumin, total protein, bilirubin, and uric acid. Patients with a white blood cell count less than $4 \times 10^9/L$, a platelet count less than $100 \times 10^9/L$, a hemoglobin level less than 100 g/L, a serum creatinine level greater than 150 µmol/L (1.7 mg/dL), a bilirubin level greater than 25.6 µmol/L (1.5 mg/dL), and an aspartate aminotransferase or alkaline phosphatase level greater than twice normal were deemed ineligible to receive this therapy. A computed tomographic or a magnetic resonance imaging scan was performed in most patients and was used as an adjunct to clinical evaluation to further define tumor extent and the presence of nodal metastasis. Staging was modified accordingly. Further evaluation for distant metastasis was only obtained when deemed clinically appropriate. Dental evaluation was obtained in all patients. All treatments were supervised by a multidisciplinary team, consisting of a medical oncologist, a radiation therapist, and a head and neck surgeon.

Chemotherapy administration required hospitalization for appropriate hydration and antiemetic therapy. The chemotherapy regimen consisted of the combination of fluorouracil and cisplatin. Both drugs were given as 4-day continuous intravenous infusions during the first and fourth week of radiation therapy: fluorouracil at 1000 mg/m² per day and cisplatin at 20 mg/m² per day. Chemotherapy courses were administered without dosage modification or delays irrespective of blood cell counts.

Radiotherapy was delivered 5 days a week using single daily fractions of 1.8 to 2.0 Gy. Megavoltage radiation was generated by a 6-MV linear accelerator. Opposed lateral fields were, in general, used with an electron-beam boost given to selected nodal regions as indicated. After approximately 50 to 55 Gy, patients were reevaluated. Patients with an obvious clinical response completed radiation to a total dose of between 66 to 72 Gy. In nonresponders, radiation was discontinued and, after a 3- to 6-week recovery period, surgery was recommended.

In patients completing radiotherapy, a 6- to 8-week period was allowed for recovery before evaluating for final response at the primary site and in the neck. Primary site and neck responses were evaluated separately. For the primary site, a clinical complete response required the disappearance of all clinical evidence of disease. Any response less than complete was considered a treatment failure. Biopsy specimens were obtained as indicated and when positive surgical resection was performed. Patients with clinical evidence of disease but negative biopsy results were not considered complete clinical responders. Patients with complete clinical responses or with negative biopsy results were followed-up clinically with primary site surgery reserved for biopsy-proven tumor recurrence.

The neck response was deemed complete with total disappearance of any palpable adenopathy. Patients with less than a complete neck response and patients whose neck disease was initially stage N2 or greater, irrespective of the clinical response, were considered for a planned neck dissection 6 to 8 weeks after completion of radiation. All patients were followed up regularly and examined for tumor recurrence. Salvage surgery was recommended when appropriate for local and/or regional recurrence.

STATISTICAL METHODS

Descriptive statistics are given as frequency counts and percentages for categorical variables and as the sample size, mean, median, and SD for continuous variables. For all hypothesis testing, statistical significance was set at $\alpha = .05$. Exact $\chi^2$ or $\chi^2$ tests were used to compare groups on categorical variables. Survival was calculated from the date of onset of therapy and the results were analyzed as of October 31, 1997. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. No patient was lost to follow-up.

During the past 8 years, at the Cleveland Clinic Foundation, Cleveland, Ohio, we have treated patients with advanced head and neck cancer with an aggressive combination of chemotherapy and concurrent radiation. Early results of a randomized trial comparing this regimen with radiation alone have been recently published.6 These preliminary results showed that patients treated with chemoradiation experienced an improved relapse-free survival ($P = .03$), fewer distant metastases ($P = .04$), and a better overall survival with the primary site preserved ($P = .02$). The overall survival, however, was not different between the groups, an observation attributed to the use of aggressive surgical salvage for persistent locoregional disease in the patients treated with radiation and an increase in deaths from other causes, including second primary tumors and comorbid illness, in the patients treated with chemotherapy. The purpose of this article is to review our 8-year experience with this treatment approach.

RESULTS

Between November 1, 1989, and June 6, 1997, 105 patients received concurrent chemoradiation as primary therapy for their head and neck cancers. Fifty treated patients were part of a previously reported randomized trial.6 Fifty-five were either ineligible for this study or treated subsequent to study closure. Patient characteristics are
described in Table 1. One hundred two patients had a single primary site. The primary site was not assigned in 3 patients. One patient with N3 (N3 on one side and N2b contralateral) neck disease had an unknown primary. One patient with N2a neck disease had 2 primary sites: a T2 lesion of the oropharynx and a T2 lesion of the oral cavity. One patient with N2b neck disease had 3 primary tumors: a T3 lesion of the supraglottic larynx, a T3 lesion of the oropharynx, and a T2 lesion of the oral cavity. T and N stages are detailed in Table 2. According to the AJCC tumor staging, 4 patients had stage II, 24 stage III, and 77 stage IV tumors. The patients with stage II (T2 N0) disease had either hypopharyngeal (2 patients) or laryngeal (2 patients) primary tumors. They would have required a total laryngectomy and opted for this organ-sparing strategy.

TOXIC EFFECTS

National Cancer Institute grade 3 and 4 toxic effects are listed below.

<table>
<thead>
<tr>
<th>Toxic Reaction</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis/dysphagia</td>
<td>92 (88)</td>
</tr>
<tr>
<td>Cutaneous reaction</td>
<td>53 (50)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51 (49)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Fifty-five patients (52%) required additional unplanned hospitalization for combinations of insufficient oral intake/dehydration (29 patients), febrile neutropenia (42 patients), and/or other causes (11 patients). Despite the aggressive placement of feeding tubes in 72 (69%) of the 105 patients, the mean weight loss was 12.2% of initial body weight for the entire group. There were no deaths caused from toxic reactions to treatment.

There were also few treatment interruptions, with all therapy delivered in a mean of 57 days (range, 40-85 days). Only 6 patients did not receive all intended therapy: 5 not receiving the full curative dosage of radiation and 3 not receiving both cycles of chemotherapy. One patient received 64.8 Gy, refusing his last 3 days of radiation and his second cycle of chemotherapy. In 1 patient, treatment was stopped after 48.6 Gy and 1 cycle of chemotherapy because of tumor progression. Three patients early in the treatment regimen had a suboptimal response at the primary site after 50 Gy and had their treatment interrupted. One patient who had severe infectious complications after the first cycle of chemotherapy went on to receive full dosage of radiation but was not given the second cycle of chemotherapy for medical reasons.

CLINICAL RESPONSE TO CHEMORADIOThERAPY

Clinical response assessment is presented in Table 3. A complete clinical response at the primary site was seen in 97 (93%) of the 104 patients with known primary sites.
The likelihood of a complete clinical response was related to primary site \((P = .002)\) and to T stage \((P < .001)\). Six (86%) of the 7 patients with less than a complete primary site response had a laryngeal primary tumor (5 patients, T4 and 1 patient, T3). Interestingly, 3 (50%) of these 6 patients had a negative laryngeal biopsy result: 1 had a recurrence 6 months later, was saved by having a laryngectomy, and has been alive for 7 years; 1 has not had a recurrence in 7 years; and 1 patient died 8 months later of regional and distant disease before any evidence of recurrence at the primary site. The other 3 patients with laryngeal primary site failure had immediate surgical salvage: 2 died of regional and distant disease at 3 and 5 months and the other has been alive, free of disease for 4.5 years. The last patient with less than a primary site complete response had a T4 lesion of the oral tongue and died at 8 months of local disease despite surgical salvage.

Clinical evidence of residual palpable neck disease after chemoradiation was common and was seen in 23 (29%) of 78 patients with N+ neck disease on presentation. A complete clinical response was more likely with earlier neck stage \((P = .02)\). The neck response showed no relation to the location of the primary tumor \((P = .68)\). Progression of disease was seen in therapy during surgery was noted in only 1 patient, who initially presented with a T4 N2a lesion of the larynx. In this patient, disease progressed both at the primary site and in the neck, and he died at 3 months of regional and distant disease despite surgical salvage.

**INITIAL PLANNED SURGERY**

Forty-six (44%) of 105 patients had planned surgery a median of 54 days (range, 28-186 days) after completing radiation therapy. The surgical procedure in these 46 patients is listed below.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary and bilateral neck</td>
<td>1</td>
</tr>
<tr>
<td>Primary and ipsilateral neck</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral necks</td>
<td>6</td>
</tr>
<tr>
<td>Ipsilateral neck</td>
<td>33</td>
</tr>
<tr>
<td>Contralateral neck</td>
<td>3</td>
</tr>
</tbody>
</table>

Forty-two patients had a planned neck dissection for residual neck disease (21 patients) or following a complete clinical response for advanced N2+ neck disease on presentation (21 patients). Only 4 patients had initial primary site surgery for persistent disease at the primary site. The 3 other patients with less than complete clinical response at the primary site had negative biopsy results and were followed up clinically.

**TUMOR RECURRENCE AND SURGICAL SALVAGE**

A total of 27 (26%) patients had initial tumor recurrence at a mean of 14 months (range, 4-45 months) after the onset of therapy. Tumor recurrence was local in 11 patients, regional in 7, regional and distant in 1, and distant in 8. Eleven (61%) of the 18 patients with local or regional recurrences underwent salvage surgery: 7 for local recurrence and 4 for regional recurrence. One patient had a second recurrence in the contralateral neck for which he underwent a second surgical salvage procedure. Six (33%) of the 18 patients with locoregional recurrences are either alive and disease free (4 patients) or have died of unrelated causes without disease (2 patients) after salvage surgery.

**SECOND PRIMARY**

Fourteen patients (13.3%) developed a second primary malignancy from 2 to 79 months (mean, 30 months) after the onset of therapy. Seven were in the upper aerodigestive tract. Eleven (79%) of these 14 have died. Ten of these patients died of their second primary tumor without recurrent disease: 4 of lung cancer and 6 of nonaerodigestive tract cancers. One patient died of lung cancer but also had recurrent disease at his primary site. The last 3 patients are alive with no evidence of either cancer.

**DISEASE STATUS**

Sixty-six (63%) patients are alive, free of disease, with a mean follow-up of 39 months (range, 5-96 months) after the onset of therapy. Two patients are alive with distant disease. Thirty-seven patients have died: 18 with no evidence of disease and 19 (18%) of disease. Of these 19 patients, 5 died with local disease and 1 also had distant disease. Seven (37%) of 19 died with regional disease; 2 also had distant disease. The last 7 died of distant disease alone.

**ORGAN PRESERVATION**

Of 104 patients with known primary sites, only 14 (13%) had persistent or recurrent disease at the primary site. The other 90 patients (87%) have not required primary site surgery and have not failed at the primary site. Local failure was seen in 2 (33%) of 6 oral cavity lesions, 6 (20%) of 30 laryngeal lesions, 3 (15%) of 20 hypopharyngeal lesions, and 3 (6.5%) of 46 oropharyngeal lesions \((P = .13)\). Local failure was seen in 10 (29%) of 35 T4 lesions, 3 (8%) of 36 T3 lesions, 1 (4%) of 25 T2 lesions, and 0 (0%) of 6 T1 lesions \((P = .01)\). Surgical salvage, either initially or at recurrence, was successful in controlling local disease in 9 (64%) of 14 patients with local failure. Of these 9 patients, 7 are either alive (5 patients) or have died (2 patients) free of disease, and the other 2 have died of regional and distant disease.

**KAPLAN-MEIER SURVIVAL ESTIMATES**

**Overall Survival**

Figure 1 depicts the Kaplan-Meier overall survival estimate. At 4 years, the projected overall survival is 60%. There is no statistical difference in the projected survival according to site \((P = .71)\), T stage \((P = .71)\), N stage \((P = .54)\), and AJCC stage \((P = .64)\). At 4 years, the projected survival was 64% for the complete clinical responders and 50% in the less than complete neck responders \((P = .18)\). Analysis of these data with the Wilcoxon method, which puts more weight on the early period of follow-up, shows a survival advantage in the complete responders \((P = .009)\).
Disease-Specific Survival

Disease-specific survival estimates are displayed in Figure 2. At 4 years, the projected disease-specific survival is 74%. The 4-year projected disease-specific survival according to site is 62% for the oral cavity, 62% for the hypopharynx, 69% for the larynx, and 89% for the oropharynx ($P = .28$). There was a trend for better disease-specific survival in the patients with oropharyngeal primary tumors vs the patients with laryngeal and hypopharyngeal primary tumors ($P = .08$). According to T stage, the projected 4-year disease-specific survival is 100% for T1 lesions, 80% for T2 and T3 lesions, and 63% for T4 lesions ($P = .36$). According to nodal stage, it is 84% for N0 lesions, 76% for N1, 62% for N2, and 90% for N3 ($P = .29$). According to stage, it is 100% for stage II, 83% for stage III, and 69% for stage IV ($P = .23$). Complete clinical response at the primary site, in contrast to the regional nodal response, was an important predictor of disease-specific survival ($P = .001$ vs $P = .08$). Complete clinical responders to chemoradiation have a 78% projected 4-year disease-specific survival vs 62% for the others ($P = .006$).

Distant Metastasis–Free Survival

With only 12 patients with distant metastasis to date, the 4-year projected distant metastasis–free survival is 84%.

According to nodal stage, the same projected figure is 92% for N0, 85% for N1, 73% for N2, and 100% for N3 ($P = .29$).

Overall Survival With Primary Site Preserved

For the entire cohort of 104 patients with known primary sites, the 4-year likelihood of survival with primary site preserved is 54%. The 4-year estimate for primary lesions of the oral cavity, larynx, oropharynx, and hypopharynx are 62.5%, 43.02%, 63.45%, and 50.24%, respectively ($P = .34$). There is no significant difference according to T stage ($P = .42$). There is a significant correlation with the clinical response at the primary site. The complete responders have a 57% likelihood of survival with organ preserved vs 14% for the less than complete responders ($P = .001$).

COMMENT

Despite significant advances in radiation techniques and in surgical resection and reconstruction, the 5-year survival for advanced head and neck cancer patients has remained below 50%. Most patients die of their disease, usually of locoregional recurrence, although distant metastases also occur. Despite promising phase 1 and 2 trials, randomized trials of induction chemotherapy have failed to improve survival. These studies did suggest another potential benefit, however: that of organ preservation. Patients who achieved a significant response to induction chemotherapy and then underwent curative radiotherapy were able to achieve control of their local disease without surgery. Several randomized trials have now confirmed the validity of this approach.

The next therapeutic step after induction chemotherapy was the use of both radiation and chemotherapy concurrently, in an effort to exploit the potential benefit of radiosensitization provided by chemotherapy. Because of concern about the anticipated toxicity of such regimens, however, modifications in the optimal radiation delivery, as well as in the dosage and schedule of chemotherapeutic drugs, were often introduced into the design of these studies. Despite these significant compromises, randomized trials comparing radiotherapy with chemoradiotherapy did not result in diminished survival. More intensive regimens using multiagent chemotherapy have now demonstrated a significant advantage over radiation for relapse-free, disease-free, and/or overall survival. Two recent meta-analysis have confirmed the survival advantage for simultaneous chemotherapy and radiotherapy over induction chemotherapy and/or radiotherapy in the definitive treatment of advanced head and neck cancer.

Our regimen combines standard single daily fraction radiation with conventional doses of cisplatin and fluorouracil. The use of this chemotherapy combination concurrently with radiation thus allows for the additive antineoplastic effects of both modalities and the radiosensitizing effect of the chemotherapy. The regimen was given without interruption and without dosage modification regardless of the severity of the ad-
verse effects, and it resulted in a clinical complete response at the primary site in 93% of patients.

In this article, the response was clinically assessed. This is clearly a suboptimal evaluation, and some patients with a clinical assessment of less than a complete response at the primary site nonetheless had negative biopsy results. One such patient has become a long-term survivor without recurrence. Other patients with complete clinical responses had later recurrences. The actual timing of assessment is also critical, albeit arbitrary. Assessment made too early after treatment often suggests residual tumor. Reassessment later suggests tumor clearance. For our patients, all therapy was delivered and the final assessment of response was made 6 to 8 weeks later.

The evaluation of neck response is even less reliable. We therefore continue to perform neck dissection on all patients with less than a complete clinical response in the neck and in all patients with N2+ neck disease at presentation. Earlier results from our institution have shown persistent viable tumor in the neck in 50% of patients with residual palpable disease after chemoradiotherapy and in 25% of complete clinical responders.13

The possibility of successful surgical salvage either for tumor persistence or for recurrence at the primary site was also apparent in our series. In 9 (64%) of 14 patients undergoing salvage surgery, the disease was subsequently controlled at the primary site. When patients had local and/or regional recurrence, however, the prognosis for overall survival was considerably worse. Among our patients only 4 (22%) of the 18 are currently alive, free of disease.

With a 60% projected 4-year overall survival, our series compares favorably with similar studies in the literature.16-18 With as yet no recurrence seen after 45 months, the projected 4-year disease-specific survival of 74% is also very encouraging. This disease-specific survival was significantly linked to tumor response ($P = .006$). Patients with oropharyngeal primary tumors appeared to have a better survival than those with laryngeal and hypopharyngeal tumors ($P = .08$). The overall low rate of distant metastasis supports the recognized benefit of systemic chemotherapy in controlling subclinical distant disease.14

Many of our primary lesions were T1 and T2 lesions, tumors that might have been controlled with either radiation alone or nonmutilating surgery. Nonetheless, our local control rate without primary site surgery of 87% is impressive. Local control without primary site surgery was 92% for T3 and 71% for T4 lesions. Comparable series report organ preservation rates between 22% and 67%.6,8,18-22 It is of interest, however, that in our cohort 6 (86%) of the 7 patients with less than a complete response at the primary site had advanced laryngeal lesions.

The excellent response rate and disease-specific survival seen with this aggressive concurrent combination of chemotherapy and radiation came at the cost of significant acute morbidity to this patient population. No deaths due to toxic effects resulted from this regimen, however. Second primary cancers developed in 13% of patients. This raised the question whether chemotherapy could have contributed to the incidence of second primary tumors or if it was the result of improved control of the index cancer, allowing time for these patients to develop other cancers. That approximately half our patients die of causes other than the index cancer underlines the importance of comorbid illnesses in this population. It also stresses the hard reality than an improvement in the control of head and neck cancer in this population may not result in a long-term improvement in survival.

Although additional confirmation is necessary, chemotherapy now appears to have a role in the primary management of head and neck cancer. Further investigation is clearly needed, however, to better select these patients most likely to benefit from these multimodality regimens. Even though overall survival may be unaffected, local control with organ preservation and better control of distant metastases seem attainable goals after chemoradiotherapy. Our present indications for this combined modality treatment include (1) patients with advanced T stage lesions where local control combined with organ preservation is important (T3 and T4 oropharynx, T2 to T4 larynx and hypopharynx) and (2) patients with advanced N stage lesions (N2+) in whom the control of regional and, ultimately, distant disease is of concern.

The severity of the toxic effects resulting from this treatment raises concern about the widespread adoption of similar regimens in the community. These concerns were also raised by Taylor et al.,23 who noticed a significant difference between treatment centers in the delivery and results of a similar chemotherapy and radiotherapy regimen. Commitment from all members of the patient-care team to the management, support, and follow-up of these patients is of utmost importance.

**CONCLUSIONS**

This aggressive chemoradiotherapy regimen combined with salvage surgery, when appropriate, has produced impressive locoregional control with a seemingly low rate of distant metastases. It also has impressive organ preservation capabilities. The potential for organ preservation and disease control has resulted in a wider acceptance of this and similar regimens among clinicians routinely involved in the care of this patient population. Careful and continued investigation is necessary before chemoradiotherapy regimens can be adopted as an undisputed part of the standard of care.

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