Maximizing Local Control and Organ Preservation in Stage IV Squamous Cell Head and Neck Cancer With Hyperfractionated Radiation and Concurrent Chemotherapy


Purpose: Results are reported from an aggressive chemoradiotherapy protocol for advanced squamous cell head and neck cancer.

Patients and Methods: Patients with advanced squamous cell head and neck cancer were treated with hyperfractionated radiation therapy (72 Gy at 1.2 Gy twice per day) and two courses of concurrent chemotherapy with fluorouracil (1,000 mg/m²/d) and cisplatin (20 mg/m²/d), both given as 96-hour continuous intravenous infusions during weeks 1 and 4 of radiation therapy. Primary-site resection was reserved for residual or recurrent primary-site disease after chemoradiotherapy. Neck dissection was considered for N2 or greater disease, irrespective of clinical response, and for residual or recurrent neck disease after nonoperative treatment.

Results: Forty-one patients with stage IV disease were treated. Toxicity was significant, with grade 3 to 4 mucositis in 98%, dysphagia in 88%, and skin reaction in 85%. Neutropenic fever requiring hospitalization occurred in 51%. Despite feeding tube placement in 35 patients (85%), the mean weight loss during chemoradiotherapy was 13.3% of initial body weight. One patient died during treatment as a result of a pulmonary embolus. At a median follow-up period of 30 months, the 3-year Kaplan-Meier projected overall survival was 59%, disease-specific survival 69%, likelihood of local control without surgical resection 91%, and local control with surgical resection 97%. The likelihood of distant disease control at 3 years was 74%, and distant metastases were present in eight of 13 patients who died.

Conclusion: This chemoradiotherapy schedule produces considerable but manageable toxicity. Survival and organ preservation are excellent for this poor-prognosis patient cohort. Distant metastases are the most common cause of treatment failure.


The prognosis for patients with stage IV squamous cell head and neck cancer remains poor despite recent advances in multimodality management. Although patients may die as a result of distant metastatic disease, as a result of comorbid illness, or as a result of the development of a second primary neoplasm, the high frequency of local or regional recurrence poses the greatest threat. These locoregional failures highlight the inadequacy of the most aggressive multimodality treatments.

During the past 20 years, systemic chemotherapy has been extensively tested in the management of this disease, and many chemotherapeutic agents have been found to have antineoplastic activity. The combination of fluorouracil and cisplatin remains the best-studied and most active drug regimen. One advantage of this drug combination is that both agents are radiosensitizers, and attempts to exploit this property have been successful. Several recent randomized phase III studies have convincingly demonstrated both a survival and locoregional control benefit for concurrent radiation and chemotherapy regimens with fluorouracil, cisplatin, or both when compared with radiation therapy alone.

Altered fractionation radiation therapy is another approach that has been studied in recent years in an effort to improve locoregional control. Several schedules have been examined with evidence of increased efficacy when compared with conventional daily fractionation. Recent data from a large randomized Radiation Therapy Oncology Group trial suggest that there is an improvement in both locoregional control and disease-free survival from several such altered fractionation schedules.

These recent treatment innovations would be expected to most benefit patients with the most advanced locoregional disease. At the Cleveland Clinic Foundation, we explored an aggressive treatment protocol that used hyperfractionated radiation therapy with concurrent fluorouracil and cisplatin chemotherapy as definitive treatment for patients with advanced squamous cell carcinoma of the head and neck.

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We report our results in the subset of patients with the worst prognosis, those with stage IV disease, and assess end points, including survival, locoregional control, and distant metastatic disease control, in an effort to evaluate the effect of these aggressive interventions.

PATIENTS AND METHODS

Eligibility for this clinical trial required a diagnosis of stage III or IV squamous cell carcinoma of the head and neck. Patients with primary sites in the nasopharynx, paranasal sinus, and salivary glands were excluded, as were patients with metastatic disease involving neck but an unknown primary site. Tumor and lymph node classifications were assigned according to the 1992 staging system of the American Joint Committee on Cancer,\(^6\) and patients with hematogenous metastases (M1) disease were excluded. All patients were previously untreated and had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Pretreatment evaluation in all patients included a medical history, an examination while the patient was anesthetized via panendoscopy, and a chest radiograph. Computed tomographic or magnetic resonance imaging scans of the involved head and neck region or other staging procedures for distant metastases were obtained if clinically indicated. Pretreatment laboratory evaluation included a complete blood cell count and serum chemistry tests, including urea nitrogen, creatinine, calcium, phosphorous, alkaline phosphatase, AST, albumin, total protein, bilirubin, and uric acid. Adequate hematologic renal and hepatic function was required for the patient to enter the study. Patients with uncontrolled angina, active infection, or other uncontrolled malignancy were ineligible.

All patients were deemed appropriate for initial nonoperative management. Patients with gross bone involvement that was considered potentially resectable were not approached in this fashion; instead, they underwent definitive surgical resection. Similarly, patients with oral cavity lesions for whom there was a significant risk of radiation damage to the mandible were also in general not offered this treatment approach.

The study was approved and reviewed yearly by the Cleveland Clinic Foundation’s institutional review board. Written informed consent was obtained from all patients before the initiation of treatment. Patient care was provided by a multidisciplinary management team, which included head and neck surgeons and medical, radiation, and nurse oncologists. All patients underwent a pretreatment dental evaluation with appropriate care, and all received a pretreatment audiogram.

The treatment schema is provided in Fig 1. All patients were treated with a full course of hyperfractionated radiation therapy, 1.2 Gy twice daily to a total dose of 72 Gy in 6 weeks. Concurrently, two courses of chemotherapy with 4-day continuous infusions of fluorouracil (1,000 mg/m\(^2\)/d) and cisplatin (20 mg/m\(^2\)/d) were given during weeks 1 and 4 of radiation therapy.

At the Cleveland Clinic Foundation, patients receiving this chemotherapy regimen are hospitalized for hydration and antiemetic therapy. No chemotherapy dose modifications were made, irrespective of nadir blood counts or the blood count at the time of treatment, although the second course of chemotherapy was delayed until recovery if a neutropenic fever had developed. Peripheral intravenous catheters were used for drug administration. Megavoltage radiotherapy was generated by a 6-MV linear accelerator. Opposed lateral fields generally were used with an electron beam boost given to selected lymph node regions as indicated. There were no planned or toxicity-mandated breaks scheduled during the administration of the radiation therapy, nor were there any toxicity-mandated delays in the administration of the second course of chemotherapy.

Patients were monitored at least weekly during their therapy in an effort to manage treatment-induced side effects, particularly mucositis and myelosuppression. Neutropenia with fever resulted in mandatory hospitalization and appropriate antibiotic therapy. Hospitalization was also required when mucosal injury precluded an adequate oral intake. Percutaneous endoscopic gastrostomy feeding tubes were placed as needed. Tracheostomies were performed in patients with significantly compromised airways, either at presentation or during the course of their treatment.

Between 6 and 12 weeks after completion of definitive chemoradiotherapy, a formal response analysis was undertaken. This analysis included an examination made while the patient was anesthetized (when clinically appropriate) and biopsy of any abnormalities suggestive of disease. A complete response required the disappearance of all clinical, radiographic, and, if applicable, pathologic evidence of disease. Any response less than complete was considered to be a treatment failure, and the patient underwent appropriate surgical resection if possible.

Primary-site resection was reserved for patients with histologically verified residual primary-site disease after completing chemoradiotherapy. Neck dissection was performed if clinical evidence of residual neck node disease was present after completion of nonoperative management. It was also recommended for patients with N2 or greater disease at presentation, irrespective of clinical response, and for patients undergoing primary-site resection. Salvage surgery was recommended for all patients if appropriate for local or regional disease recurrence.

After the completion of therapy, patients were observed by all members of the multidisciplinary team. Careful clinical examination was performed at 2- to 3-month intervals, and any suspected locoregional or distant recurrence underwent biopsy. Radiographic studies were performed as clinically indicated. Survival times and times to specific events were calculated from the date radiation therapy was initiated, and the results were analyzed as of March 1, 2001. No patient was lost to follow-up study. The Kaplan-Meier method was used to estimate the events of interest, including overall survival, disease-specific survival, distant control, local control without surgery, and local control with surgery.\(^20\) Except for the overall survival calculations, a patient was considered censored at death if the event in question had not occurred. The patterns of failure analyses (local and distant control calculations) excluded the single patient who died during treatment and who therefore could not be assessed for this parameter.
RESULTS

Between January 1996 and September 2000, 44 patients with advanced squamous cell head and neck cancer were enrolled onto this clinical trial. Forty-one of these patients had stage IV disease at diagnosis and constitute the subject of this report. All patients were eligible, and all patients were assessable for toxicity and survival. The clinical characteristics of these 41 patients and their tumors are detailed in Table 1. Tumor and lymph node distribution is presented in Table 2. It should be noted that 35 (85%) of 41 patients had either T3 or T4 primary tumors and that 32 patients (78%) were either T4 or N3 at presentation, confirming the advanced locoregional disease present in this cohort.

The toxicity from this treatment was significant and is detailed in Table 3. Grade 3 or 4 mucositis, dysphagia, and skin reaction occurred in almost all patients but were reversible. Sixty-eight percent of patients experienced at least one episode of neutropenia (<1,000/mm³), and 21 (51%) of the 41 patients required an unplanned hospitalization for management of neutropenic fever. Despite feeding tube placement in 35 (85%) of the 41 patients, the mean weight loss during treatment was 10.9 kg (range, 0 to 24.7 kg), or 13.3% of initial body weight. Long-term feeding tube maintenance was required by only one patient. Renal insufficiency was infrequent and entirely reversible. A single toxic death as a result of a pulmonary embolus occurred during treatment.

The median follow-up period for patients at risk was 30 months (range, 6 to 62 months). The Kaplan-Meier projected overall survival at 2 years is 80% and at 3 years is 59% (Fig 2). The projected disease-specific survival is 83% at 2 years and 69% at 3 years (Fig 3), and this curve seems to plateau after 3 years.

Among the 40 patients assessable for pattern of disease failure, 39 experienced a complete response at the primary site after chemoradiotherapy. The single patient with residual primary-site disease after chemoradiotherapy underwent successful salvage surgery, resulting in all 40 assessable patients achieving an initial local complete response. Two delayed local recurrences developed. In one, successful salvage resection was possible. Thus, among the 40 patients assessable for pattern of failure, local control was achieved without surgical resection in 37 and with surgical resection in 39. Two of the three patients who experienced local persistence or recurrence received successful surgical sal-
vage treatment. Figure 4 presents the Kaplan-Meier projection of local control without the need for surgery. This curve plateaus at 91%. The local control rate is 97% if surgical resection is also included (Fig 5).

A clinical complete response was achieved in the neck in 24 of the 36 assessable patients with neck nodes identified at presentation. Neck dissection was performed in 21 of the 34 patients with N2, N3 disease at diagnosis, including all 12 patients with residual palpable neck disease after chemoradiotherapy and nine of the 24 patients who achieved a complete response in the neck. The results of neck node management are detailed in Table 4. Thirteen of the 21 patients undergoing neck dissection had no residual evidence of disease in the neck. This included seven (58%) of the 12 patients with clinical evidence of residual adenopathy. It should also be pointed out that among the nine N2, N3 patients who underwent neck dissection despite being clinically free of neck disease, three (33%) proved to have residual pathologic evidence of cancer in the neck at the time of surgery. Among the entire patient cohort, only one patient experienced regional disease recurrence. This was a patient who initially presented with N3 disease and subsequently underwent a neck dissection for palpable and pathologically demonstrated disease persistence after chemoradiotherapy, who nonetheless experienced recurrence on the dissected side.

Contrary to the usual pattern of failure, distant metastases were relatively common, occurring in eight of the 40 assessable patients. All eight died, including two who subsequently developed hematogenous dissemination to the brain. Thirteen of the 41 patients described herein have died, including the eight who developed distant metastases, one patient who died during treatment, two patients who died as a result of second primary aerodigestive tract malignancies, and two who died as a result of comorbid illnesses. The patient with unresectable local disease recur-

**Table 4. Neck Node Management (n = 40)**

<table>
<thead>
<tr>
<th>Node</th>
<th>No. of Patients</th>
<th>Neck Dissection</th>
<th>Pathologic CR</th>
<th>Neck Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0-N1</td>
<td>6</td>
<td>——</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>N2A</td>
<td>1</td>
<td>——</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>N2B</td>
<td>11</td>
<td>6</td>
<td>4</td>
<td>——</td>
</tr>
<tr>
<td>N2C</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td>——</td>
</tr>
<tr>
<td>N3</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total N2-N3</td>
<td>34</td>
<td>21 (62%)</td>
<td>13 (62%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Abbreviation: CR, complete response.
rence and the patient with regional disease recurrence both died with distant metastases. This striking reversal in the usual pattern of failure is illustrated in Fig 6. The projected likelihood of local control without surgery at 3 years is 91% compared with the projected 3-year likelihood of distant control of only 74%.

**DISCUSSION**

Several important points emerge from this analysis. First, it is apparent that the toxicity of aggressive concurrent chemotherapy and hyperfractionated radiation therapy is significant. Almost all patients experienced severe mucosal and skin toxicity, and more than half required hospitalization for neutropenic fever. More important, however, was the transient nature of this acute toxicity and the effectiveness of current supportive measures. No patient died as a result of these treatment-related side effects. The single toxic death reported resulted from a pulmonary embolus. Aggressive follow-up care, early hospitalization and antibiotic therapy for neutropenic fever, and prompt nutritional intervention with gastrostomy placement was critical in maintaining the dose intensity of this treatment regimen and was in large part responsible for the success achieved. Although the toxicity encountered was formidable, it was manageable and would seem justifiable given these results. Future attention will be directed to the potential long-term toxicities that may develop in this patient cohort.

Second, despite the initial presentation with advanced locoregional tumors, local control of disease was excellent. Organ preservation, or local control without the need for surgical resection, was possible in 91% of these stage IV patients. One can contrast this with the organ preservation rate of ≲ 64% achieved in less advanced larynx/hypopharynx cancer after sequential chemotherapy and radiation, suggesting an additional benefit from the concurrent treatment. The recently reported results from the Intergroup second-generation larynx preservation trial (Radiation Therapy Oncology Group 91-11) confirm this observation.

Regional control proved more problematic. Residual pathologic evidence of neck node disease was found in eight of the patients enrolled onto this trial, some of whom had no clinical evidence of residual cancer in the neck. Although the majority of patients undergoing neck dissection in this series had no residual tumor at the time of surgery, we were unable to accurately identify these patients preoperatively. We therefore continue to recommend neck dissection for all patients with N2 or N3 disease at diagnosis, irrespective of their clinical response after chemoradiotherapy, and in all patients with residual clinical evidence of nodal involvement after nonoperative treatment.

Even when a primary nonoperative treatment approach is chosen, the importance of ongoing surgical involvement in the management of these patients cannot be overstated. The clinical evaluation of the primary site is often difficult after chemoradiotherapy, requiring repeated examinations while the patient is anesthetized as well as multiple biopsies. Similarly, the algorithms for neck management suggest the importance of an ongoing surgical presence and a planned neck dissection in appropriate patients if optimal treatment results are to be achieved. Although the likelihood of organ preservation in this patient cohort is exciting, we cannot lose sight of the fact that the overall treatment goal is cure. Surgical management remains important in the achievement of that end.

These kinds of results, however, suggest that cure is a reasonable and attainable goal, even in patients with advanced locoregional tumors. Aggressive multimodality treatment strategies, with appropriate supportive care, by an experienced management team can produce a significant improvement in results when compared with historical experience. Although these patients may die for many reasons, the overwhelming cause of death in this cohort was distant metastatic disease, not locoregional tumor, comorbidity, or second primary neoplasms. Other investigators who used similar aggressive locoregional treatments have made this same observation, and attention must now be focused on the prevention of these distant metastases. Interventions might include the use of additional multiagent chemotherapy given as either induction or adjuvant treatment, or the use of other, nonchemotherapeutic systemic approaches. The complexity of these treatment regimens and the effect on patient compliance remain a significant concern. Similar attention should also be directed toward possible toxicity modification, if this can be accomplished.

![Fig 6. Kaplan-Meier projections of local control without surgery and distant control in stage IV patients.](image-url)
without a compromise in overall treatment results. Initial efforts with agents such as amifostine\textsuperscript{26} and pilocarpine\textsuperscript{27} have been encouraging.

We conclude that this chemoradiotherapy schedule produces considerable toxicity and requires management by an experienced supportive care team. The survival, local control, and organ preservation were excellent despite the advanced stage of these patients at diagnosis. Distant metastases have now become the most common cause of treatment failure at our institution.

REFERENCES