Induction Chemotherapy followed by Concomitant TFHX Chemoradiotherapy with Reduced Dose Radiation in Advanced Head and Neck Cancer

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ABSTRACT

Purpose: Induction chemotherapy with carboplatin and paclitaxel followed by concomitant TFHX (paclitaxel, infusional 5-fluorouracil, hydroxyurea, and twice-daily radiation therapy administered every other week) has resulted in 70% 3-year survival in stage IV patients. Locoregional and distant control rates were 94 and 93%, respectively. In an attempt to decrease toxicity without compromising local control, a second cohort of patients was treated with a lower dose of radiation to sites of potential microscopic disease.

Experimental Design: Sixty-four patients were entered on study. Patients received six weekly doses of carboplatin (area under the curve 2) and paclitaxel (135 mg/m²) followed by five cycles of TFHX. The radiation dose to gross disease was 75 Gy as in the previous trial. The radiation dose to high-risk microscopic disease was reduced from 60 to 54 Gy, and the dose to low-risk microscopic disease was reduced from 45 to 39 Gy.

Results: Ninety-seven percent of patients had stage IV disease. The response rate to induction chemotherapy was 82% with a complete response rate of 42%. At the completion of therapy the clinical complete response rate rose to 100% with a median follow-up of 29 months. The actuarial 2 and 3-year survival was 77 and 70%, respectively. Five patients developed progressive disease for an overall 3-year progression-free survival of 90%. Two patients failed in locoregional sites alone, resulting in a 3-year locoregional control of 97%. The 3-year systemic control was 95%. Four patients were completely feeding tube dependent at the time of analysis. Only 1 of these patients had normal swallowing function before treatment.

Conclusions: In this second trial, induction chemotherapy with carboplatin and paclitaxel followed by TFHX chemoradiotherapy results in high survival and progression-free survival. The reduction in radiation dose did not compromise survival or disease control compared with our prior study using higher radiation doses. Data continues to support definitive evaluation of this approach.

INTRODUCTION

Chemotherapy in the treatment of locoregionally advanced head and neck cancer is in a state of evolution (1, 2). Improved disease-free and/or overall survival has been demonstrated in randomized trials and meta-analyses, and concomitant chemoradiotherapy has been accepted as a standard treatment for patients with locoregionally advanced unresectable disease (3–11). An improvement in locoregional control appears to be primarily responsible for the positive effects seen in disease-free survival and overall survival when patients receive concomitant chemoradiotherapy. Thus, concomitant treatment addresses the traditional site of failure.

The role of induction chemotherapy is less well defined (12–15). Although few trials of induction chemotherapy have conclusively shown an improvement in survival, they have demonstrated a decrease in the incidence of distant metastases, indicating activity against systemic micrometastatic disease. Also, it has been shown to have a role as first-line therapy in patients with laryngeal cancer or hypopharyngeal cancer as an alternative to surgery and postoperative radiation (16, 17). In these patients induction chemotherapy has not affected survival but provides patients with a treatment option that allows for organ preservation.

Studies at the University of Chicago, Northwestern University, and the University of Illinois have reported the results of regimens using intensive concomitant chemoradiotherapy (18–23). In patients with stage IV disease, a treatment regimen of TFHX and twice-daily radiotherapy administered on 5 con-
secutive days of every other week resulted in locoregional control over 84% and 3-year survival of ~60% with surgery reserved for salvage (21, 22). In these studies, we observed a reversal in the historical patterns of failure as the distant failure rates exceeded the local failure rates. Our observation is not isolated because other authors have reported higher systemic failure rates after treating patients with effective locoregional therapy (24, 25). These finding suggest that the dose intensity of chemotherapy achieved in concurrent regimens may not be sufficient to control systemic micrometastatic disease.

Recently, we tested the hypothesis that administration of induction chemotherapy before intensive concomitant chemoradiotherapy can eradicate systemic micrometastases (23). In that study (University of Chicago protocol 9502), we investigated the weekly administration of carboplatin and paclitaxel for a brief, intensive 6-week course of induction chemotherapy. This was followed by concomitant chemoradiotherapy with concomitant TFHX and twice-daily radiation therapy administered on an every other week schedule in patients with locally advanced disease. The regimen demonstrated a high level of activity with an 87% response rate to induction and an 87% response rate overall at the completion of therapy. More importantly, the reported 2-year survival was 77% with a 2-year progression-free survival of 80%. The 2-year control of local and distant disease was 94 and 93%, respectively.

Analysis of protocol 9502 revealed: (a) 95% pathological complete response in those patients with N2 or N3 disease undergoing a neck dissection at the end of treatment; (b) the failures that were observed were in sites of prior gross disease; and (c) most of the significant acute toxicity occurred during the concomitant portion of treatment (23). Because none of the locoregional failures were in sites of potential microscopic disease, we thought it might be possible to reduce the dose of radiation to grossly uninvolved areas without compromising control or survival. A secondary goal would be to reduce the toxicity of treatment because the toxicities observed during and after radiation are dependent upon the total dose of radiation, overall treatment time, fraction size, and overall volume of tissue in the radiation field (26–29). We therefore initiated a second trial (9502b). The trial was identical to 9502 with the exception of lower doses of radiation to grossly uninvolved sites.

MATERIALS AND METHODS

The study was opened in January 2000 and closed to accrual in January 2001. For this study, patients were followed through January 2003. Eligible patients had squamous cell carcinoma, poorly differentiated carcinoma, lymphoepithelioma, or unknown primary carcinoma of the head and neck. Patients were required to have stage IVa or IVb disease. Those with stage III disease were eligible if the primary site was located in the base of tongue or hypopharynx. Each patient was evaluated at a joint conference with representatives from surgical, radiation, and medical oncology before study entry. A performance status of 0–2 was required, as well as no prior radiation or chemotherapy. Surgical therapy before induction chemotherapy was allowed if it consisted of organ-sparing procedures such as simple excision of the primary, debulking of airway compromising tumors, or a neck dissection. Initial staging procedures consisted of a history and physical, panedoscopy with tumor measurements, biopsy, dental evaluation, head and neck chest CT scan, bone scan, oropharyngeal motility study, and quality of life assessments. Placement of a feeding tube was recommended for those patients presenting with impaired swallowing on the initial oropharyngeal motility study. All patients signed informed consent before the beginning of therapy.

Chemotherapy. Induction chemotherapy consisted of carboplatin and paclitaxel administered weekly for 6 consecutive weeks as described previously (23). Paclitaxel was administered at 135 mg/m² in 500 ml of D5W over 3 h. Carboplatin at a calculated area under the curve of 2 was administered in 100 ml of normal saline over 30 min after the completion of the paclitaxel infusion. A 24-h urine creatinine clearance was measured before the first week of chemotherapy. The carboplatin dose remained unchanged over the course of six doses unless the serum creatinine increased by >25%; in that case, a calculated creatinine clearance was used for up to 1 week until a new measured creatinine clearance was obtained. The calculated creatinine clearance was determined as follows: \((140\ - \text{age}) \times \text{weight in kg} \times (0.85 \text{ in females}) \div 72 \times \text{creatinine (mg/dl)}\). Antiemetics consisted of ondansetron (24 mg p.o.) before paclitaxel, with dexamethasone (20 mg i.v.) and diphenhydramine hydrochloride (25 mg i.v.) push.

Concomitant chemoradiotherapy with TFHX has been described previously (21, 22, 30, 31). Chemotherapy consisted of hydroxyurea at 500 mg p.o. every 12 h for 6 days (11 doses) with the first daily dose of hydroxyurea on days 1–5 given 2 h before the first fraction of daily radiotherapy. A continuous infusion of FU at 600 mg/m²/day was given on days 1 through 5. Paclitaxel (100 g/m²) was given as a 1-h infusion on day 1 of each cycle after the first dose of radiation. Radiation therapy was administered twice daily at 1.5 Gy/fraction with a minimum 6-h interval between fractions on days 1 through 5. No chemotherapy or radiotherapy was given on days 6 through 14 of each cycle. Chemoradiotherapy cycles were repeated every 14 days until the completion of radiotherapy. For grade 3 neutropenia on the previous cycle or neutropenia ≥ grade 2 on day 1 of the next cycle, GCSF support (5 µg/kg s.c.) was given on days 6 through 12 of any remaining cycles, beginning ≥12 h after the completion of FU. Dose modifications during induction chemotherapy and TFHX have been described previously (21, 23).

Reduced Dose Radiation Therapy. All patients were required to undergo CT-based treatment planning. Target volumes were defined based on tumor maps drawn at the time of panendoscopy, physical exam, and prechemotherapy CT scan. When possible, patients underwent CT-based simulation before induction chemotherapy for later image correlation and treatment planning. The gross target volume was defined as all gross disease detected on physical exam or radiographic examination and outlined on the postchemotherapy planning CT. Efforts were made to accurately reconstruct the original primary tumor on the postchemotherapy scan in patients responding to induction chemotherapy. The gross target volume was expanded by 1 cm to create the primary planning target volume (PTV1). A second planning target volume (PTV2) was defined as PTV1 plus the first echelon of uninvolved lymph nodes. The third
planning target volume (PTV3) was defined as PTV2 plus the second echelon of uninvolved lymph nodes. All volumes were drawn on individual CT slices by the attending radiation oncologists. Because of anatomical constraints, PTV volumes were modified to avoid overlap with the spinal cord or extension of the PTV beyond the skin. Treatment plans were individualized. Individualized treatment plans were developed for each patient. All patients were treated with three-dimensional conformal or IMRT.

In the initial trial (9502), the radiation doses prescribed to PTV1, PTV2, and PTV3 were 75, 60, and 45 Gy, respectively. In an attempt to decrease toxicity while maintaining control of disease, the dose of radiation to clinically uninvolved sites at risk for harboring microscopic disease was reduced by 6 Gy. Thus, the total dose delivered to PTV2 and PTV3 was 54 and 39 Gy, respectively. Attempts were made to limit the spinal cord dose to 39 Gy when conventional treatment techniques were used for treatment. In IMRT cases, the spinal cord dose was limited to a 45-Gy dose to the lower dose/fraction to the spinal cord with IMRT treatment. Typical three-dimensional conformal treatment used an exact match with opposed lateral fields to treat the upper neck and an anterior posterior field to treat the lower neck. Electrons were used to boost the posterior neck with three-dimensional conformal radiotherapy to avoid exceeding spinal cord tolerance. IMRT used 6-MV photons exclusively.

**Surgery.** Limited surgery was permitted with the goal of organ preservation. Most patients underwent a biopsy only before induction chemotherapy and TFHX. Initial simple excision of the primary lesion was allowed and ranged from excisional biopsy to resection of an oral cavity or tonsillar primary tumor. In no case was a total glossectomy or laryngectomy allowed. Modified neck dissection could also be performed. Salvage surgery was recommended for residual disease at the primary site or neck after the completion of chemoradiotherapy. A selective neck dissection was recommended for patients presenting with N2 or N3 disease at the completion of TFHX, even in the absence of overt residual tumor. Surgery at the primary site was omitted in patients who achieved a complete remission confirmed by physical examination, radiographic imaging, and/or a negative biopsy.

**Quality of Life.** We prospectively evaluated quality of life using the same standard battery of validated instruments as in previous trials (32): Function Assessment of Cancer Therapy (version 4) (33); Performance Status Scale for Head and Neck Cancer (34, 35); selected items from the McMaster Radiotherapy Questionnaire (36); and the Center for Epidemiological Studies Depression Scale (37). Patients were assessed preinduction, postinduction, immediately before and during chemoradiotherapy, at 3-month intervals through 12 months posttreatment, and annually thereafter.

**Treatment Evaluation and Statistical Considerations.** Response evaluation was performed after induction chemotherapy and TFHX chemoradiotherapy. Response criteria were based on bidimensional tumor measurements and defined complete response, partial response, stable disease, and progressive disease as described previously (20, 21).

Time to progression was measured as the time from the first day of treatment until first disease progression; patients dying of toxicity and those with residual disease at the primary site 30 days after treatment were counted as treatment failures. Location of progressive disease within or outside the irradiated area was documented. Survival was measured from the first day of treatment until the date of last follow-up or death. Time to progression, survival, local control and distant control were calculated using Kaplan-Meier curves.

**RESULTS**

A total of 64 patients was registered on study. The median follow-up was 27 months for all patients and 30 months for surviving patients. Patient characteristics at the time of diagnosis are listed in Table 1. The median age was 57 years (range, 31–79 years). The most common primary site was oropharynx with 15 patients having base of tongue primary tumors. Ninety-seven percent of patients presented with stage IV disease as shown in Table 2. The two patients with stage III disease had base of tongue primary tumors. Sixty-one percent of patients required a feeding tube for nutritional support at some time during treatment. A feeding tube was place in 22 patients (34%) before the start of treatment and an additional 17 patients (27%) required placement of a feeding tube during TFHX. The surgical procedures performed and timing of the surgery are listed in Table 3.

**Induction Chemotherapy.** After 6 weeks of induction chemotherapy, 52 patients were evaluable for response. Twelve
patients could not be evaluated for the following reasons. Ten patients had no measurable disease after initial organ-preserving surgery. Two additional patients did not complete the planned course of induction chemotherapy (1 patient refused additional chemotherapy after cycle 2). Overall, 22 of 52 patients with measurable disease (42%; 95% CI 28–56%) had a clinical complete response and 21 patients (40%; 95% CI 27–54%) had a partial response to induction chemotherapy. Eight patients had stable disease and 1 patient progressed distantly. Thus, the overall response rate was 82% (95% CI 72–93%).

Toxicities to induction chemotherapy are listed in Table 4. Grade 3 or 4 neutropenia was noted in 18 and 13% of patients, respectively. GCSF was administered to 10 patients. Grade 2 or 3 neuropathy was noted in 8 and 2% of patients, respectively. Fifty-seven patients (89%) completed all six cycles of chemotherapy. More than 80% of the intended carboplatin and paclitaxel dose was given to 69 and 64% of patients, respectively.

Concomitant Chemoradiotherapy. After completing induction chemotherapy, patients underwent locoregional therapy with TFHX. Patients were evaluated for a final response to therapy ~4–6 weeks after the completion of all treatment. The 10 patients without measurable disease were not evaluable along with the patient who died in cycle 2 of induction chemotherapy. The remaining 53 patients achieved a complete response for an ultimate response rate of 100%.

Toxicities of TFHX are listed in Table 6. The chemoradiation treatment was delivered in an inpatient setting for virtually all patients. Twenty-five percent of patients developed grade 3 or 4 infection and 20% of patients required additional hospitalization for treatment. The remaining 53 patients achieved a complete response for an ultimate response rate of 100%.

The toxicities of TFHX are listed in Table 6. The chemoradiation treatment was delivered in an inpatient setting for virtually all patients. Twenty-five percent of patients developed grade 3 or 4 infection and 20% of patients required additional hospitalization for treatment. Grade 3 or 4 neutropenia occurred in 34% of patients and GCSF was administered to 27 patients. Mucositis was grade 3 or 4 in 75% of patients, whereas 45% of patients experience grade 3 or 4 in field dermatitis. Eighty-three percent of patients completed TFHX without any treatment delays and an additional 11% completed treatment with only a 1-week delay in the planned course of therapy. The dose intensity achieved during TFHX is listed in Table 5.

Survival and Patterns of Failure. The median follow-up time for surviving patients is 31 months with a minimum follow-up of 24 months. The median follow-up for all patients is 29 months. The actuarial 2- and 3-year overall survivals were 77% (95% CI 64–85%) and 70% (95% CI 57–80%) (Fig.1). Progression-free survival is shown in Fig. 2. The 3-year actu-
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Fig. 1 Overall survival.

Fig. 2 Progression-free survival.

Overall, 45 patients are alive and well, and 1 patient is alive with lung metastases. Eighteen patients have died. Four patients died as a result of head and neck cancer. One patient died of sepsis related to treatment (sepsis after treatment). Four patients died of second cancers (1 patient each; pancreatic cancer, non-small cell lung cancer, melanoma, and acute myelogenous leukemia). Nine patients died of intercurrent disease.

At a minimum follow-up of 24 months, only 5 patients have had documented progression of their disease. Locoregional failure (within the irradiated volume) was observed in 2 patients. An additional 3 patients progressed in distant sites. The 2- and 3-year actuarial locoregional control was 97% (95% CI 88–99%). The 2- and 3-year actuarial distant control was 95% (95% CI 85–98%).

Surgery. Of the 64 patients, 54 had no surgery before treatment, 6 patients had a lymph node dissection, and 4 patients had a lymph node dissection with removal of the presumed primary tumor (Table 3). A neck dissection was recommended for patients presenting with ≥N2 disease ~4–6 weeks after the completion of TFHX. Forty-six patients had ≥N2 disease at the time of diagnosis and 31 underwent a neck dissection. Nine patients had the surgery performed before the start of treatment. Twenty-two patients had the neck dissection performed after the completion of TFHX (15 unilateral and 7 bilateral neck dissections). Only 3 of the pathological specimens contained any residual cancer. No patient underwent salvage surgery.

Quality of Life. Forty-nine patients were alive at 2 years and 8 (16%) still had a feeding tube in place. At the time of this analysis, 45 patients are alive and free of disease. Thirty-nine (87%) of these patients are able to eat and do not require a G-tube for nutritional support. Four patients (9%) are completely dependent upon a G-tube for nourishment, and 2 patients (4%) use the tube to supplement oral feedings. One patient who is still using a G-tube had a normal swallowing study before the start of therapy. One patient had mildly impaired swallowing on the pretreatment oropharyngeal motility study. The remaining 4 patients had either moderate or severe swallowing dysfunction before any treatment was initiated.

DISCUSSION

Previous trials at our institutions have demonstrated high locoregional control, distant control, and overall survival rates in the setting of organ preservation for patients with advanced head and neck cancer. Our most recent trial reported an actuarial 3-year overall survival and progression-free survival of 70 and 80%, respectively (23). The actuarial 2-year locoregional and distant control in this study was 94 and 93%, respectively. These results were obtained with an induction chemoradiotherapy regimen of carboplatin and paclitaxel followed by intense concomitant chemoradiotherapy with TFHX. However, the intensity of the concomitant regimen resulted in significant acute toxicity. In that study, we reported 23% grade 3–4 neutropenia, 76% grade 3–4 mucositis, and 61% grade 3–4 dermatitis. We also noted that 25% (14 of 57) of patients alive at 12 months still had feeding tubes.

On the basis of these results, we concluded the regimen was highly effective in eradicating the cancer and that there was little room for improvement in disease control. We were also aware of the significant toxicity seen during treatment and the potential for long-term swallowing difficulty after the completion of treatment. Therefore, we decided to focus on how to modify the treatment regimen in a way that would not compromise cancer control but would reduce the acute and long term toxicity.

Additional analysis of our data indicated the most severe acute toxicity occurred during the concomitant portion of treatment. It was our impression that the majority of the toxicity observed during concomitant therapy was the direct result of the radiation therapy. The radiation therapy regimen used in our previous study was aggressive using hyperfractionated radiation at 1.5 Gy twice daily to a total dose of 75 Gy to gross disease and lower doses to sites of potential microscopic disease using a shrinking field technique. The typical initial fields for patients with advanced head and neck cancer are large and treat all nodal groups in the neck from the base of skull down to the supraclavicular fossae. Thus, a large amount of grossly uninvolved normal tissue is subjected to moderately high radiation doses in an effort to eradicate potentially microscopic disease.

Radiation complications are directly related to the total radiation dose, fraction size, overall treatment time, and volume...
of tissue in the irradiated field (26–29). A change in any one of these parameters could result in a greater or lesser observed toxicity. We therefore postulated that it might be possible to change the radiation schema to decrease the observed toxicity without compromising the overall outcome. Analysis of our data in 9502 revealed all locoregional failures were in sites of previously known gross disease. Thus, we felt any reduction in dose to gross disease ran a moderate risk of reducing the locoregional control rates. Because no failures developed in regional sites of potential microscopic disease, we thought it might be possible to decrease the radiation dose to these areas. The following reasoning was used to support this hypothesis.

(a) Few distant failures were observed in 9502 and may be the result of induction chemotherapy. If induction chemotherapy were effective in addressing potential microscopic distant disease, it would be effective in addressing regional microscopic disease permitting the dose of radiation to be reduced.

(b) The concomitant portion of treatment uses agents with known radiation-sensitizing properties. The delivery of traditional doses of radiation with continuous sensitizing chemotherapy may be over treating areas that are not grossly involved with cancer. Thus, it might be possible to reduce the radiation dose to uninvolved sites without compromising the effectiveness of treatment.

(c) An analysis of prior studies revealed that the neck dissection specimens obtained after treatment in patients with ≥N2 disease contained residual carcinoma in 35% of patients (38). This is in contrast to 9502 where only 5% of the specimens contained residual disease (23).

(d) The initial radiation fields contain the largest amount of uninvolved normal tissue. Because complications are related to total dose and volume, reducing the amount of radiation to these areas could lessen the observed toxicity.

On the basis of the above reasoning, we decided to decrease the radiation dose to sites of potential microscopic disease. Protocol 9502 called for radiation doses of 60 and 45 Gy to grossly uninvolved primary and secondary draining nodes, respectively. Protocol 9502b called for a 6-Gy reduction in these doses. Thus, the first echelon of draining lymph node beyond gross disease received 54 Gy and the second echelon received 39 Gy.

Although the trials were not randomized and contain a relatively small number of patients, an outcome comparison of 9502 and 9502b suggests our hypothesis, that the radiation dose to microscopic disease could be reduced without compromising the outcome, was correct (Table 7). Both trials resulted in identical 2- and 3-year survivals of 77 and 70%, respectively. This is additionally supported by a 3-year progression-free survival of 80% for 9502 and 90% for 9502b. Three deaths were attributed to toxicity in 9502, whereas there was only one death from toxicity in 9502b. Because deaths from toxicity were counted as treatment failures in the analysis of progression-free survival, this helps to explain the observed difference. Thus, the better progression-free survival for 9502b is not statistically different from 9502 and suggests the dose reduction did not increase the number of cancer recurrences. As expected from the progression-free survival, there were no significant differences in the 2-year local control or distant control between the two studies. Although no significant differences were seen in this trial, it does not conclusively show that a difference does not exist. With the small number of patients entered, the trial had an 80% power to detect a 15% difference in outcome.

A comparison of the most common acute toxicities observed during concomitant treatment between the two protocols is shown in Table 7. The change in radiation dose did not result in a significant decrease in the observed grade 3–4 neutropenia (P = 0.154). This is expected because no changes were made to the chemotherapy dosage, which is the major cause of neutropenia. Also there was no difference in the amount of mucositis. This is not unexpected; there was no reduction in radiation dose to the sites of gross disease and little change in the volume of oropharyngeal mucosa irradiated to high dose. In contrast there was a decrease in the incidence of grade 3–4 dermatitis. The reduction in dose to uninvolved lymph node groups would preferentially spare more of the neck and a reduction in the amount of acute dermatitis would be expected. However this was of borderline significance (P = 0.072).

A comparison feeding tube status between the two studies shows little difference (Table 7). A total of 11 patients (19%) had a feeding tube present at the time of analysis compared with 6 patients (13%) in 9502b. Although the percentage of patients with a feeding tube was less in 9502b, the percentage of patients completely dependent on a feeding tube was identical for both studies. The difference was attributable to fewer patients using a feeding tube to supplement oral intake. This suggests that the reduction in radiation dose may not have been sufficient to produce a change in the observed swallowing function. An alternative explanation is that some patients present with poor swallowing function because of damage from an advanced head and neck cancer and that some patients may not be able to recover from this damage. This explanation is supported by the fact that most patients still using a feed tube had abnormal swallowing on a pretreatment oropharyngeal motility study.

In summary, the results of our previous trial and current trial demonstrate the regimen of induction chemotherapy with carboplatin and paclitaxel, followed by TFHX, is a highly effective approach to the treatment of stage IV head and neck cancer in the setting of organ preservation. The regimen has demonstrated high rates of survival, locoregional control, and distant control without the need for initial or salvage surgery in 133 patients. In addition, the current trial has obtained these results with lower radiation doses to areas of potential micro-

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* NS, not significant.
scopic disease. These results suggest that although the regimen uses a split course of radiation, the tight integration of concomitant chemoradiotherapy more than compensates for the planned delays in radiation treatment. On the basis of these encouraging results, we have decided to explore the possibility of additional radiation dose reductions. We have recently completed a trial (9502c) where the radiation dose to gross disease, first echelon uninvolved nodes and second echelon uninvolved nodes has been reduced to 72, 51, and 36 Gy, respectively. The results of this trial are awaiting maturation of the data.

Although concomitant chemoradiotherapy is becoming the standard of care for advanced head and neck cancer, there is little agreement on a standard regimen. Given the strong survival, disease control, and organ preservation rates reported here, we feel this regimen warrants additional investigation. We would welcome a multi-institutional trial to compare this regimen with other regimens that have shown promising results (6, 8, 24).

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