ORIGINAL ARTICLE

ACCELERATION OF HYPERFRACTIONATED CHEMORADIATION REGIMEN FOR ADVANCED HEAD AND NECK CANCER

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Abstract: *Background.* Our aim was to evaluate the acceleration of a hyperfractionated, concurrent chemoradiation regimen (HxCRT) for advanced head and neck squamous cell carcinoma (HNSCC).

Methods. Patients with unresectable HNSCC were treated based on a previously published HxCRT regimen: 1.25 Gy twice daily to 70 Gy concurrent with cisplatin 12 mg/m^2/day and 5-fluorouracil 600 mg/m^2/day for 5 days, weeks 1, 5. This regimen was accelerated in this series by shortening the treatment from 7 to 6 weeks by omitting the planned mid-treatment 1-week break.

Results. Forty-six patients with T3-4/N3 disease were treated. The main acute toxicity was pharyngeal. Median weight change during therapy in patients with and without enteral feeding tubes was −3.8% and −7.9%, respectively ($p = .08$). Fifteen percent had late grade III pharyngeal toxicity. Local/regional and distant failure rates were 28% and 17%, respectively; 52% are alive without evidence of disease.

Conclusions. In nonresectable HNSCC, acceleration of the HxCRT regimen is feasible, requiring enteral feeding tubes during therapy in most patients. *Head Neck* **29:** 137–142, 2007

Keywords: head and neck cancer; radiotherapy; chemotherapy; altered fractionation; dysphagia

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Locally advanced squamous cell carcinoma of the head and neck (HNSCC) remains a challenging disease to treat, with overall survival with current therapy of 50%.[1] Recent approaches to improve standard treatment have included: adding concurrent chemotherapy to radiation,[2,3] altered fractionated irradiation,[4] and combinations of altered fractionation and concurrent chemotherapy.[1,5,6] In 1998, Brizel et al,[1] from Duke University, published a randomized study comparing hyperfractionated chemoradiation (HxCRT) to hyperfractionated radiotherapy (RT) alone in locally advanced HNSCC. They demonstrated that the addition of concurrent chemotherapy to hyperfractionated RT resulted in a significant advantage in local tumor control and a borderline significant benefit in overall survival, compared with hyperfractionated RT alone.

An important limitation of the intensification of the treatment regimens is their accompanying toxicity. Frequent grade III-IV mucositis and significant weight loss have become expected toxicities of aggressive regimens.[1,5–7] To manage these toxicities, the Duke University HxCRT protocol required a 1-week planned treatment break in mid-therapy. Another strategy that has been used to reduce treatment-related weight loss and to prevent hospitalizations and treatment breaks is prophylactic enteral feeding tubes.[8–10]

We report in this paper our experience in accelerating the HxCRT regimen (AccHxCRT) for patients with locally advanced HNSCC. The patients selected for this series had unresectable local/regional disease that precluded them from other institutional protocols of organ preservation that were open at the time (in those protocols, resectable disease was an eligibility criterion and induction chemotherapy was used to select patients for surgery vs. chemoradiation). Acceleration was achieved by the elimination of the planned 1-week treatment break in the original HxCRT regimen, resulting in reduced overall treatment time from 7 to 6 weeks, and prophylactic enteral feeding tubes were used in an effort to reduce weight loss during therapy. We expected this regimen modification to be beneficial, in view of local/regional tumor control advantages gained by reduced overall treatment time to a similar extent in randomized studies of accelerated radiation alone.[4,11]

MATERIALS AND METHODS

Patients and Therapy. This study was approved by the institutional review boards of the University of Michigan and the affiliated Veterans Administration Hospital, and all patients underwent detailed informed consent. Eligible patients included patients without evidence of distant metastatic disease whose tumors were judged to be nonresectable. Nonresectability criteria included neck metastases encircling the carotid artery, tumors involving the prevertebral fascia, and nonnasopharyngeal tumors extending to the base of skull. In addition, patients in whom surgery would have required laryngo-glosso-pharyngectomy and patients with significant nodal involvement of the low neck whose prognosis was judged to be poor and therefore not recommended for extensive surgery were eligible for this treatment protocol. Radiation was given in 1.25-Gy fractions twice a day at least 6 hours apart. A total dose of 70 Gy was delivered to the gross tumor volume over 6 weeks without any planned treatment breaks. Target volumes at risk of subclinical disease received 50 to 60 Gy. Conformal 3-dimensional radiotherapy techniques were used, including beam's-eye views to ensure adequate target coverage. The spinal cord was shielded at 40 Gy. Dose homogeneity was restricted to $\pm 7\%$ prescribed dose. No specific effort was made to spare the salivary glands in most of these patients because of clinic-related constraints on lengthy treatment time in patients receiving twice-daily therapy. Optic nerve doses were limited to maximum of 54 Gy. No reduced dose was required for any substantial part of the gross disease in any of the 8 patients with paranasal sinus cancer. Chemotherapy consisted of 5-fluorouracil (5-FU) given as continuous infusion, 600 mg/m^2/day, and cisplatin, 12 mg/m^2/day, for 5 days in weeks 1 and 5. Hydration and antiemetics during chemotherapy were delivered according to standard clinical care.

All patients received narcotics, mostly starting in the third week and tapered-off on average at 1 month after completing RT. Prophylactic nystatin was provided routinely, and patients developing overt fungal infection received fluconazole. Twice-weekly intravenous fluids were delivered to patients with >10% weight loss (besides cisplatin-related hydration). A dedicated team consisted of a nurse, nutritionist, and physician team during treatment. Patients with dysphagia more than 3 months after therapy were referred to the Speech and Swallowing Therapy service for evaluation.

All patients in whom the pharynx was included in the high-dose treatment volumes (patients with oropharyngeal, hypopharyngeal, and laryngeal primaries, or large neck nodes) were referred for percutaneous endoscopic gastrostomy (PEG) at the start of treatment in order to improve treatment tolerance. Patients were assessed weekly and following treatment every 6 to 8 weeks during the first 2 years and every 3 months thereafter for acute and late toxicity. Progression was defined primarily by clinical exam and contrast-enhanced CT scans performed at 6-month intervals. Toxicity was scored using the Radiation Therapy and Oncology Group (RTOG) Acute and Late Radiation Morbidity Scoring Criteria. In addition, patients had weekly recording of weight while on treatment.

Survival was calculated from the date of treatment initiation to the date of death or last follow-up. Survival curves were calculated by the product-limit (Kaplan-Meier) method. Confidence intervals

for binomial probabilities were calculated by the likelihood ratio method. Two-tailed tests are reported. Local-regional failure was reported by cumulative incidence,[12] which allows estimation of incidence rates in the presence of competing risks from other causes. Statistical calculations were performed using SAS version 9.1.

RESULTS

Forty-six patients with HNSCC were treated with AccHxCRT between November 1999 and December 2003. Patient characteristics are displayed in Table 1. Ninety-one percent of the patients had American Joint Committee on Cancer (AJCC) stage IV disease, with the remainder having stage III disease; all had tumor (T) classification 3-4 except for 1 patient with an unknown primary and advanced neck disease. Fifty-nine percent had oropharyngeal cancers, with base of tongue the most common subsite. Other prominent sites included paranasal sinuses (13%) and oral cavity (9%).

The treatment course was completed in almost all patients within 6 weeks. Three patients had each a treatment break of more than 3 days due to toxicity or poor compliance. Median delivered RT dose was 70 Gy. All but 2 patients received 70 Gy, with the exception of 1 patient who refused the final treatment and received 67.5 Gy and 1 patient who received a small-volume boost to total 78.5 Gy. Full dose chemotherapy was received by 36/46 (78%) patients, with the remaining 10 patients completing only a single cycle or requiring chemotherapy dose reductions in the second cycle, due to severe mucositis/skin desquamation, or due to patient refusal to receive a second cycle.

Table 1. Patient and tumor characteristics.

Characteristic	No. of patients
Sex	
Males	36
Females	10
Race	
Caucasians	43
African-Americans	3
Median age (range), y	56 (31–78)
Tumor site	
Oropharynx	27
Paranasal sinuses/nasal cavity	8
Oral cavity	4
Larynx	3
Hypopharynx	2
Unknown primary/other	2
Tumor stage	
T3-4, N0-1	16
T3-4, N2	24
T3-4, N3	5
TxN3	1

Table 2. Common acute and late severe toxicities.*

Toxicity	No. of patients
Acute toxicity	
Mucositis	
Grade II	21
Grade III	24
Pharyngeal	
Grade II	5
Grade III	37
Skin desquamation	
Grade II	21
Grade III	6
Late toxicity	
Pharyngeal/esophageal	
Grade II	7
Grade III	7
Osteoradionecrosis	1
Skin necrosis requiring surgery	1
Nasal stenosis	1
Hearing loss	1

**Grade V toxicities included 1 each with neutropenic sepsis and aspiration pneumonia, and 1 cerebrovascular event (possibly treatment related).*

Forty-two of 46 (91%) patients had their oral cavity, oropharynx, or hypopharynx in the high-dose RT volumes (excluding 4 patients with paranasal cancer). Twenty-two (52%) of these patients had prophylactic PEG placement. The reasons for nonplacement were patient refusal or need to start therapy before a PEG could be placed. Of the patients without prophylactic PEG, 9 received PEG during treatment and 5 had PEG within 3 weeks after the completion of treatment for progressive dysphagia and weight loss.

Severe toxicity data is summarized in Table 2. Three patients (6.5%) died of treatment-related (neutropenic sepsis and aspiration pneumonia) or possible treatment-related (cerebrovascular event 4 months after therapy) causes. Mucositis and dysphagia were the most prevalent severe acute toxicities. The median weight change relative to pretherapy in all patients was −6.2% (range, −32.9% to +11.2%). The median percentage weight change in patients without prophylactic feeding tube was −7.9% (range, −32.9% to +7.8%), compared with median weight change of −3.8% (range, −19.2% to +11.2%) in patients with prophylactic feeding tube ($p = .08$). Moist skin desquamation was observed in six (13%) patients.

Late grade II-III toxicity excluding xerostomia was observed in 18/46 (39%) patients, and the

most common was dysphagia. Fourteen patients required PEG for >3 months for ongoing nutritional support, and 5 patients required PEG support beyond 6 months, with 1 patient requiring PEG for 2 years. Strictures requiring dilation occurred in 7 patients. All were detected during the workup of dysphagia or aspiration between 2 and 8 months after the completion of therapy. The workup in all these patients included videofluoroscopy and laryngoscopy/esophagoscopy under anesthesia. The primary tumor sites in patients with strictures were posterior pharyngeal wall (3 patients), oropharynx (3 patients), and hypopharynx (1 patient). In 6/7 patients, the strictures were located in the post-cricoid hypopharynx, and in 1 patient in the upper esophagus. The doses delivered to the sites of strictures were 70 Gy (4 patients), 60 Gy (1 patient), and 50 Gy (2 patients). Following dilation of the strictures, 3 patients continued to depend on tube feeding, 2 patients ate most of their food but required supplemental tube feeding, and 2 patients did not require tube feeding.

At a median follow-up of 31 months (range, 6–69 months), 17 patients (37%) have had documented clinical failure, 15 of whom died of disease. Thirteen patients (28%) experienced local/regional failure (see Figure 1), 4 of whom also had distant failure, and 4 patients had distant failure alone. All local failures were in field. Four patients died of other causes; 3 were related to toxicity, or possible toxicity, as detailed above, and 1 patient died of lung cancer. One patient was lost to follow-up. Twenty-four patients (52%) remain alive without evidence of disease (Figures 2 and 3).

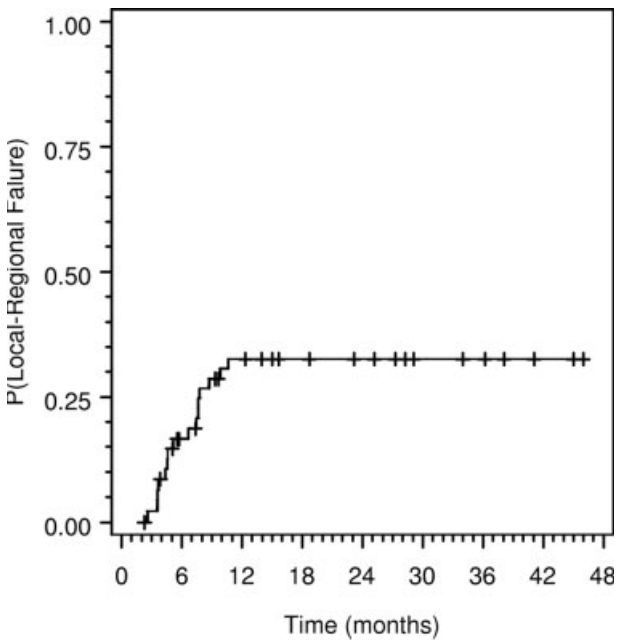

FIGURE 1. Locoregional failures.

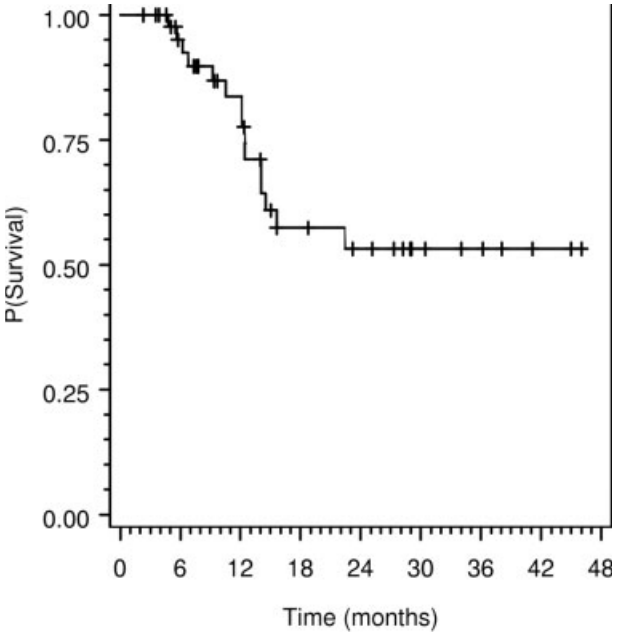

FIGURE 2. Actuarial overall survival.

DISCUSSION

This study demonstrates that an acceleration of the HxCRT regimen, enacted by removing the 1-week treatment break from the original protocol, is feasible when accompanied by temporary enteral feeding in most patients. This conclusion is limited by lack of compliance of many patients with the original recommendation to have feeding tubes inserted prior to therapy.

The importance of weight loss as a predictor of poor outcome has been documented in many cancers, including lung, esophageal, and head and neck cancers.[13–15] Weight loss during chemoradiation of head and neck cancer has also been found to be correlated with cisplatin-related nephrotoxicity.[16] The best approach to maintaining weight and minimizing weight loss during treatment of HNSCC with RT has been shown in multiple studies to be PEG placement.[9,10,17] PEG appears to be superior to jejunal feeding tubes.[18] However, it is possible that PEG may increase the risk of strictures compared with nasogastric feeding tubes.[18] This issue has been controversial.[19]

In the current study we have observed a marginally statistically significant difference in weight

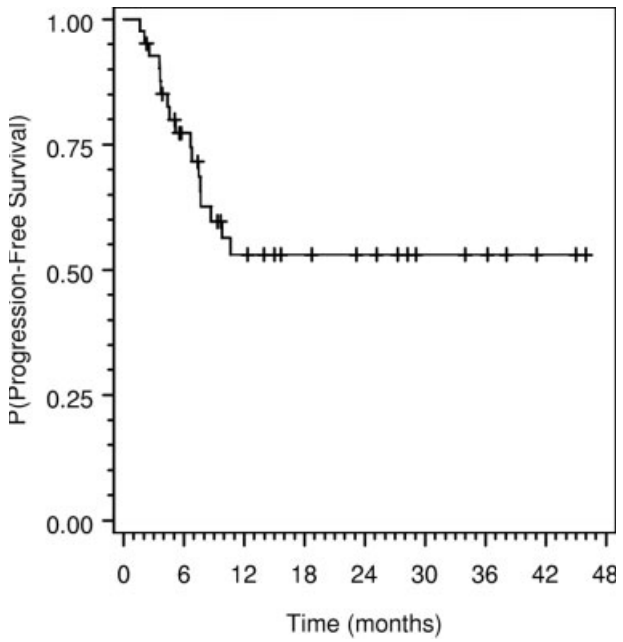

FIGURE 3. Actuarial progression-free survival.

loss during treatment among those patients who had PEG placed compared to those who did not. The weight loss in patients with prophylactic PEG compares favorably to the average 10% weight loss seen in the Duke randomized trial, in which only 44% of patients received PEG, only few of which placed before therapy.[1] Our results mirror the effect of PEG on weight loss reported in a study of patients treated at the University of Pennsylvania with either chemotherapy and standard fractionation RT or hyperfractionated therapy.[8] Two additional studies by Adelstein et al[2,5] also confirm the importance of PEG placement in the maintenance of weight during treatment.

An important factor in predicting outcome of HNSCC is the amount and duration of required treatment breaks. A number of studies have shown that radiation treatment breaks of a week or more are correlated with a poor outcome.[20,21] However, these studies were conducted in patients whose treatment breaks were caused by acute toxicity, who might have had adverse prognostic features. The effect of a planned treatment break, as done in the original Brizel study, is not as clear. While reducing overall treatment time from 7 to 6 weeks has been found to be beneficial in randomized studies of radiation alone,[4,11] it is not yet known whether a similar benefit in accelerating radiotherapy is gained when concurrent chemotherapy is added. This issue is being addressed in current randomized studies such as a study by the RTOG of accelerated versus standard fractionated RT, both delivered concurrent with chemotherapy. The result of this and other similar studies will help resolve this issue in the near future. Furthermore, it should be stated that preventing weight loss to eliminate the need for treatment breaks may not result in the same outcome as in unsupported patients who do not lose weight.

The local/regional tumor control and survival rates in our study are comparable to the data from the original HxCRT study of Brizel et al,[1] with approximately 50% long-term survival and 70% local/regional control rate. However, the patients in our study, selected due to their ineligibility for other organ preservation protocols offered at our institution to those with resectable disease, may have had more advanced local/regional disease. Assessing whether or not the elimination of the planned treatment break has resulted in improved local/regional control rates compared with the original protocol, or compared with other trials, would require a study of this regimen in unselected patients with stage III-IV disease.

The main concern in this accelerated regimen is whether the rate of late complications has been excessive. The primary late complication in our study was hypopharyngeal/esophageal strictures and late dysphagia. Strictures requiring dilation occurred in 15% of the patients. This is equal to the stricture rate of 14% reported in a study of HxCRT regimen identical to the original Duke protocol, containing a planned treatment break of 5 to 11 days, which was conducted in community hospitals.[7] A stricture rate of 21% was reported by investigators from the Cleveland Clinic following RT concurrent with cisplatin and 5-FU, and twice-daily RT resulted in a higher rate compared with once-daily RT.[22] In comparison, lower rates of strictures have been reported following less intensive regimens. Laurell et al[23] reported 22 cases of upper esophageal strictures out of 642 (3.4%) patients with head and neck cancer treated with standard fractionated RT alone. In this study, the lowest dose to the sites of strictures was 60 Gy. In comparison, lower doses to the hypopharynx (50 Gy) associated with strictures were found in the current study and following another regimen of intensive chemo-RT.[23] Thus, concurrent chemo-RT seems to shift the dose–response curve of this complication to the left. However, it does not seem that omitting the mid-treatment break has substantially increased this risk compared with the original, less accelerated regimen. It should be noted that a longer follow-up interval may result in addi-

tional cases of late dysphagia in our series, whose current median follow-up interval is 2.5 years.

Recent studies of potential strategies to reduce late dysphagia following intensive chemoradiation include the use of radiation protectors[24] and of intensity-modulated radiotherapy.[25] The clinical efficacy of these strategies requires validation.

In conclusion, the acceleration of the HxCRT regimen for patients selected due to having advanced nonresectable local/regional disease resulted in tumor control rates similar to those reported for patients who were not selected according to these criteria and had received the original HxCRT regimen. Comparison of the efficacy of the AccHxCRT with other intensive regimens requires its evaluation in nonselected patients with stage III-IV tumors. An aggressive policy of weight management such as prophylactic PEGs is one of the avenues to facilitate the intensification of chemo- RT. Further steps are required in order to reduce late dysphagia in patients treated with similar regimens.

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