Published in final edited form as:

J Clin Oncol. 2006 July 20; 24(21): 3438–3444. doi:10.1200/JCO.2006.05.8529.

High Survival and Organ Function Rates After Primary Chemoradiotherapy for Intermediate-Stage Squamous Cell Carcinoma of the Head and Neck Treated in a Multicenter Phase II Trial

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Abstract

Purpose—Patients with intermediate-stage squamous cell carcinoma of the head and neck traditionally have been treated with initial surgical resection followed by radiotherapy (RT) alone or chemoradiotherapy. A previous study in this patient population reported a 91% locoregional control rate and 65% overall survival (OS) rate at 5 years, with chemoradiotherapy used as primary treatment. This study was undertaken to assess whether shortening treatment duration with hyperfractionated RT would be feasible and improve locoregional control, organ preservation, and progression-free survival.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Methods—Eligible patients with stage II or III disease received fluorouracil, hydroxyurea, and RT given twice daily on a week-on/week-off schedule. Quality-of-life scores were measured using three validated indexes.

Results—All 53 patients enrolled are included in the analysis, with a median follow-up of 42 months (range, 5 to 98 months). Grade 3 or 4 in-field mucositis was observed in 77% and 9%, respectively. No patients required surgical salvage at the primary tumor site (pathological complete response rate, 100%). The 3-year progression-free and OS rates are 67% and 78%, respectively. The 3-year disease-specific mortality rate is 7%. At the time of analysis, 87% of surviving patients do not require enteral feeding support. Quality-of-life and performance assessment indicated that, although acute treatment toxicities were severe, most patients returned to pretreatment function by 12 months.

Conclusion—Concurrent chemoradiotherapy with hyperfractionated RT is feasible in this patient population and yields high local control and cure rates. Compared with our historical control using once-daily fractionation, hyperfractionation is accompanied by increased acute in-field toxicity.

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) will affect 40,000 individuals in the United States in 2005, with approximately 30% of these patients diagnosed with stage II or III disease.¹ These intermediate-stage patients traditionally have been treated with initial resection for curative intent and many require adjuvant radiotherapy (RT) to augment local control.² Recently, chemoradiotherapy (CRT) in intermediate-stage patients has been validated postoperatively for those with high-risk pathologic features^{3,4} and as an organ-preservation strategy for those with primary tumors of the larynx.⁵

In 1999, we reported results of a phase II trial in a similar cohort of patients using CRT as initial treatment with surgery as salvage treatment.⁶ That regimen consisted of split-course, once-daily fractionated CRT and yielded locoregional control (LC) and 5-year disease-specific survival rates of 86% and 82%, respectively. With surgical salvage, which was necessary in eight of 60 patients, the LC rate increased to 91%. Thus it appeared efficacious to treat intermediate-stage SCCHN patients with up-front fluorouracil (FU), hydroxyurea, and RT (FHX). However, this regimen exposed patients to a relatively long duration of therapy, especially compared with postoperative RT (13 v 6 weeks).

Accelerated fractionation RT schedules proved superior with respect to LC in a randomized trial performed by the Radiation Therapy Oncology Group.⁷ The utility of split-course, hyperfractionated, FHX-based CRT regimens in patients with stage IV disease has been reported in sequential phase I and II trials enrolling more than 400 patients.⁸ Thus it appeared feasible and efficacious to develop the FHX regimen administering twice-daily RT in intermediate-stage disease with the goal of improving LC, reducing the need for salvage surgery, and positively influencing survival. In addition, three quality-of-life (QOL) instruments were administered to all patients. These validated questionnaires were designed to determine the degree to which the regimen influenced performance, function, and emotional and social adjustment.

METHODS

Patient Eligibility and Enrollment

Patients were enrolled after signing informed consent documents approved by the institutional review board at each participating site. All participants are included in the analysis. Eligibility included stage II or III SCCHN (American Joint Committee on Cancer, fifth edition), no prior treatment, Eastern Cooperative Oncology Group performance status 0 to 2, leukocyte count $\geq 3,500/\mu\text{L}$, and platelet count $\geq 100,000/\mu\text{L}$.

Treatment

Patients were treated as previously described⁶ consisting of CRT administered on a 2-week cycle of continuous-infusion FU $800 \text{ mg}/\text{m}^2/\text{d}$ for 5 consecutive days and hydroxyurea 1 g orally every 12 hours for 13 doses starting the evening before the start of RT, which was given as 1.5-Gy fractions bid for 5 consecutive days with chemotherapy. Each 5 days of treatment was followed by a 9-day break during which no additional treatment was given. Treatment cycles were repeated until the completion of planned RT. Insertion of a feeding tube for nutritional support during therapy was not required. RT was delivered with 4- to 6-MV photons from a linear accelerator. A shrinking-field technique was used to deliver 45 to 60 Gy to areas at risk for microscopic disease and 66 to 75 Gy to areas of gross disease. Supraclavicular fossae were irradiated to 39 to 51 Gy. Spinal cord dose was limited to 45 Gy. Electrons were used to boost the posterior neck nodes when necessary. Custom blocking was used for all patients to spare normal tissue.

Dose Modifications

The National Cancer Institute Common Toxicity Criteria version 2.0 was used to grade toxicities. Grade 4 mucositis, dermatitis, or diarrhea on a prior cycle required a reduction of FU to $600 \text{ mg}/\text{m}^2/\text{d}$ on subsequent cycles. Grade 3 leukopenia or thrombocytopenia required reductions in hydroxyurea dose. Persistent or unresolved grade 4 toxicity required postponement of CRT by 1 week.

QOL Instruments

QOL questionnaires were administered before treatment (baseline), during treatment, and then at 3, 6, 12, 18, 24, 36, 48, and 60 months after treatment completion. The instruments included the Performance Status Scale for Head and Neck Cancer Patients,^{9,10} selected questions from the Head and Neck Radiotherapy Questionnaire,¹¹ and the Functional Assessment of Cancer Therapy (FACT) –Head and Neck.^{12,13}

Statistical Analysis

Patients were evaluated for response at least 4 weeks after the completion of CRT.⁶ Evaluation included a physical examination and computed tomography scans of the head, neck, and chest. A biopsy of the primary site was recommended. Overall survival (OS) and progression-free survival (PFS) were calculated using the method of Kaplan and Meier. Time to progression was defined from the time the patient was enrolled onto the study until progression or death. Differences in survival between groups were analyzed using the log-

rank test. Disease-related deaths were classified as being due to disease or treatment, and their cumulative incidence was estimated. Cox proportional hazards regression was used for multivariate survival time analysis. Baseline demographic characteristics were compared between those with QOL scores available at baseline and 12 months versus those with at least one score missing. In addition, baseline QOL scores were compared between patients with baseline and 12-month scores versus those with only baseline QOL. Fisher's exact tests were used to compare categorical variables between groups, and Wilcoxon rank sum test was used to compare continuous measures. Paired *t* tests or signed-rank tests were used, as appropriate based on the normality assumptions, to determine whether there were significant changes in QOL scores relative to baseline. Changes of 20 points or more on the diet scale were considered to be of clinical significance, and the McNemar test was used to compare the numbers of patients whose scores declined or improved relative to baseline. QOL changes from baseline to 12 months were of primary interest, but changes from pretreatment to other time points were assessed using similar methods.

RESULTS

Patient Characteristics

From October 1996 to February 2003, 53 patients were enrolled with a median age of 56 years (range, 29 to 81 years). Patient demographics and disease characteristics are presented in Tables 1 and 2, respectively. The median follow-up for all patients is 42 months (range, 5 to 98 months). Eight patients were enrolled after initial surgery to remove gross disease that allowed for maintenance of organ function (Table 1).

Dose-Intensity

The majority of patients received therapy as prescribed and 38 (73%) did not require any treatment delay. With respect to chemotherapy delivery, 81% and 74% of patients received 80% of the intended dose-intensity of FU and hydroxyurea, respectively. Neutropenia (16 patients), mucositis (seven patients), and dermatitis (three patients) were the most common reasons necessitating dose reductions. The median RT dose administered to gross disease was 71 Gy.

Toxicity

The most common acute toxicities are presented in Table 3. In addition to these toxicities, four patients developed pneumonia during therapy and one patient developed an infection of the indwelling venous catheter. Two patients died during therapy as a result of pneumonia and myocardial infarction, respectively. One patient suffered a fatal stroke 3 weeks after completing therapy. Among patients surviving and available for analysis at 6, 24, and 36 months, 13% (six of 47), 10% (four of 40), and 16% (six of 38), respectively, continued to require gastrostomy tubes. Long-term toxicity observed after therapy is presented in Table 4. There were no deaths attributable to long-term treatment-related complications.

QOL

Forty-three patients were captured in the QOL component of the study. Of the 43 patients, 39 were alive at 12 months and data are available on 32; 26 patients had QOL data at both

baseline and 12 months. There were no differences in patient demographic or disease characteristics between those patients with QOL data at baseline and 12 months ($n=26$) and all patients ($n=53$). With one exception (dry mouth; $P=.05$), there were no differences on baseline QOL scores between the group with both baseline and 12-month data and the group with only baseline QOL data.

Figure 1 presents mean scores and SE bars over time for selected variables. Statistical analyses (t tests comparing baseline and 12-month scores) of these data were limited to the cohort of patients with data at both baseline and 12 months. Before treatment, 75% of patients were eating relatively normal diets and were comfortable eating in public, whereas 13% to 22% had problems with pain, swallowing, dry mouth, sticky saliva, or taste. One patient of 36 with baseline data was unable to take anything by mouth (ie, scored 0 on the diet scale). There was a significant decline ($P<.01$) during treatment on all performance (diet, eating in public, understandability of speech; $n=26$) and adverse effect (dry mouth, mouth and throat pain, sticky saliva, tasting, and hoarseness; $n=22$) items as well as FACT physical, functional, head and neck subscales, and overall FACT–General global QOL ($n=26$). Acute treatment morbidity can also be described by the high number of patients with severely restricted diets (87% with diet ≤ 50), and those reporting moderate to severe problems with swallowing, sticky saliva, and mouth or throat pain (60% to 70%). As illustrated in Figure 1, there was a gradual improvement over time, with the majority of scores returning to baseline levels by 12 months. The exceptions were mouth pain, which showed a significant improvement ($P=.04$), and sticky saliva ($P=.02$) and dry mouth ($P=.08$), which showed worsening at 12 months compared with pretreatment. Similar patterns were seen when McNemar's statistics were used to compare dichotomized scores.

Normalcy of diet scores changed on average by 13.08 (SE = 8.26) points ($P=.12$). Four patients showed an improvement (increase in score ≥ 20 points) at 12 months compared with baseline, 13 patients showed no difference, and nine patients had declined by ≥ 20 points or more, and thus had more restricted diets at 12 months. Five of those whose scores declined could not take anything by mouth (ie, scored 0 on the diet scale). These five patients represented three supraglottic larynx, one glottic larynx, and one pyriform sinus primary tumor; their pretreatment diet scores were 100 (two patients), 60 (two patients), and 30 (one patient).

Response

A total of 42 patients were assessable for response. Seven patients underwent resection of measurable disease before therapy, three patients died, and one patient was lost to follow-up before response evaluation. The clinical complete response rate was 95% (40 with complete response, two with partial response). Twenty-eight patients underwent pathologic assessment of disease after completing CRT, including one patient who received radical neck dissection and two patients who received selective neck dissections. No surgical complications were encountered. There was no evidence of disease in any of the pathologic specimens, including the patients assessed as partial response, yielding an overall combined clinicopathologic response rate of 100%.

Survival

Nine patients have experienced disease progression (four locoregionally and five distantly), with an overall median PFS of 76 months and a 3- and 5-year PFS rate of 67% and 61%, respectively (Fig 2A). Two patients with late locoregional failure were offered resection or reirradiation and achieved complete disease remission. One patient remains alive and free of disease after locoregional recurrence. One patient with distant progression is still alive after resection of lung metastases. Among those who had disease progression, the median time to disease recurrence was 10 months (range, 6 to 44 months) and was not different based on site of failure.

A total of 34 patients are alive, with a median survival time of 87 months, and 3- and 5-year OS rates of 78% and 64%, respectively (Fig 2B). Cause-specific death rates were estimated using cumulative incidence curves (Fig 2C). The 3- and 5-year disease-related death rates were 6% and 17%, respectively. The most common etiology of mortality not related to disease or treatment was a second primary tumor (SPT). Eight patients have developed SPT, including five aerodigestive tract malignancies resulting in four deaths (Table 5). In univariate analysis, survival was positively associated with white race ($P = .049$) and had a negative trend with disease stage ($P = .07$). The difference in survival by race was also significant in multivariate analysis incorporating stage, performance status, and age ($P = .02$). Other factors examined, including performance status, sex, tobacco and alcohol use, treating institution, T stage, N stage, primary tumor site, chemotherapy dose-intensity, and prior surgical resection were not predictive of survival in univariate analysis.

DISCUSSION

This study presents the first report of hyperfractionated RT administered concurrently with chemotherapy in intermediate-stage SCCHN patients. The trial was designed to achieve higher locoregional control rates and survival in this group of patients compared with identical chemotherapy administered with once-daily fractionated RT.⁶ A comparison between sequential phase II trials must always be viewed with caution because inherent and unavoidable biases can influence the results. Theoretically, a shorter overall treatment course with hyperfractionated RT would be beneficial with respect to tumor cell repopulation and subsequent locoregional control, but improvements in supportive care, stage migration, and differences in patient population could also affect outcome. After a median follow-up of 4.5 years, the efficacy of the present regimen is reflected in the universal achievement of CR and the low locoregional failure rate of 7.5%. Interestingly, the 5-year survival rate of 64% is identical to that achieved in the prior study. Thus, although the hyperfractionated regimen was able to control local disease, this did not translate into improved survival mostly secondary to death from distant failure, second primary tumors, and comorbid illnesses.

Patients with intermediate-stage SCCHN traditionally have been treated with surgery followed by adjuvant RT in those believed to be at high risk of relapse. However, even for T2-3 tumors, significant dysfunction can result, and although organ-preserving surgical techniques have been described, their application is limited by operator expertise and the need for appropriate patient selection. Furthermore, RT without primary surgery in

resectable intermediate-stage patients has yielded local control rates comparable to those from surgery followed by RT,¹⁴⁻¹⁷ especially if hyperfractionated RT is administered.¹⁸ In fact, a retrospective review of North American trials suggested an advantage to RT as primary therapy followed by neck dissection with respect to treatment complications and functional outcome.¹⁹ Disease control and survival rates with RT alone are encouraging but locoregional failure still occurs in 30% to 40% of patients depending on primary tumor site and lymph node involvement.

Recently an improvement in local control and survival was observed with the addition of cetuximab (a monoclonal antibody directed against the epidermal growth factor receptor) to RT compared with RT alone.²⁰ Approximately 25% of the study population presented with stage III disease and subset analysis revealed hazard ratios in favor of the experimental arm with respect to locoregional control (0.69) and OS (0.77) paralleling the overall study results. Furthermore, the benefit of adding cetuximab appeared to be greatest for patients receiving twice-daily or concomitant boost RT. Beyond being well tolerated, these results suggest that cetuximab plus hyperfractionated RT is an efficacious regimen for patients with intermediate-stage SCCHN. Additional trials are warranted to define the precise role of cetuximab and other epidermal growth factor receptor inhibitors in the treatment of high-risk stage II and stage III SCCHN.

The reversal of failure pattern seen in the current study with equal numbers of patients experiencing locoregional treatment failure as those experiencing distant treatment failure has been noted in CRT trials in patients with more advanced disease.^{21,22} Presumably as local control is maximized, distant disease begins to manifest even in a population of patients thought to be at greatest risk for local tumor recurrence. One must note that the chemotherapy used in this trial was designed to achieve radiosensitization and not systemic control. Strategies to reduce distant failure are being examined in stage IV SCCHN but similar attempts in intermediate-stage patients may also be warranted.

In this study, 15% of the cohort developed SPT and mostly in the upper aerodigestive tract, emphasizing the hypothesis of field cancerization.²³ Clearly, primary and secondary prophylactic measures remain of paramount importance in this population. In fact, the group of intermediate-stage SCCHN patients represents an ideal group to study in future chemoprevention trials coupling relatively high long-term survival and incidence of SPT.

There was a notable cost for the high local control rate achieved. Moderate or severe neutropenia was observed in one third of patients, whereas the incidence of acute grade 3 and 4 mucositis and dermatitis was 86% and 41%, respectively. This was reflected in the proportion of patients requiring treatment delays (27% compared with 8% in the prior study). Similarly, patient-reported adverse effects, QOL, and performance measures indicated that the majority of patients experienced moderate to severe acute dysfunction across a spectrum of functional and symptom areas.

As evidenced by the QOL instruments and the relatively few patients requiring a feeding tube (10% at 2 years), long-term toxicity appeared acceptable. Comparable data regarding gastrostomy tube dependence rates are limited because the number of prospective trials in

this patient population is few with many do not report this measure.^{3,4,20} Nevertheless, from retrospective reviews, it appears that the long-term rate of feeding tube requirement is similar,^{17,19} with the notable exception of the study by Fein et al,¹⁴ who reported on 490 patients treated with radiotherapy alone for oropharyngeal primary tumors and noted permanent gastrostomy tubes in only two patients. In our cohort, similar to reports by other groups,^{24–26} patients with hypopharyngeal and laryngeal primary tumors were at greatest risk for swallowing dysfunction after CRT. These patients may benefit from intensive swallowing and physical therapy before, during, and after treatment.

The only symptom indices that did not return to baseline were manifestations of xerostomia. This trial was performed before the availability of intensity-modulated radiation therapy, which offers a technically achievable method of excluding the salivary glands in the treatment volumes of many SCCHN plans. It will be intriguing to observe whether these QOL parameters improve with the widespread use of intensity-modulated radiation therapy.

Arguably, without an improvement in OS, it is difficult to justify the use of hyperfractionated RT in the FHX regimen in intermediate stage disease. Survival in these patients is influenced by factors other than the primary cancer, whereas local recurrence can often be salvaged by surgery or reirradiation. Future efforts should concentrate on integration of agents that can improve disease control without exacerbating radiation stomatitis; reduction of treatment-related acute toxicity and xerostomia; and chemoprevention of SPT.

Acknowledgments

Supported by the Valda and Robert Svendsen Foundation and University of Chicago Cancer Research Center (National Cancer Institute Grant No. 5P30CA14599-31).

We thank Alfred Rademaker, Cathy Eng, Athanassios Argiris, Maureen Crowley, Laura Sulzen, Mary Jesse, and Allison Dekker for help in the conduct of this trial.

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Fig 1.

Mean quality-of-life scores with SE bars from baseline (BL) to 36 months for selected variables. Higher scores represent better functioning. The y-axis represents raw scores obtained on each respective instrument. (A) Diet; (B) pain in mouth; (C) stick saliva; (D) dry mouth; and (E) FACT-G. N, number of patients with available data at each time point; FACT-G, Functional Assessment of Cancer Therapy–General.

Fig 2.
 (A) Kaplan-Meier curve of progression-free survival. (B) Kaplan-Meier curve of overall survival. (C) Cumulative incidence of disease-related mortality.

Table 1

Patient Characteristics

Characteristic	No. of Patients	%
Sex		
Male	33	62
Female	20	37
Race/ethnicity		
White	33	62
Black	15	28
Hispanic	3	6
Asian	2	4
PS		
0	35	66
1	16	30
2	2	4
Treating institution		
UC	31	58
NWU	9	17
UIC	7	13
ENH	4	8
Weiss	2	4
Percent weight loss prior to therapy		
0	35	66
< 5	7	13
5–10	4	8
> 10	5	9
NA	2	4
Tobacco use		
Never	13	24
Pipe/cigar	1	2
Cigarettes < 20 pack-years	11	21
Cigarettes 20–40 pack-years	13	25
Cigarettes > 40 pack-years	15	28
Alcohol use *		
None	10	19
< 1/wk	18	34
1/d	8	15
> 1/d	17	32

Characteristic	No. of Patients	%
Pretreatment surgery [†]		
Partial glossectomy	5	—
Tonsillectomy	1	—
Neck dissection	4	—

Abbreviations: UC, University of Chicago; NWU, Northwestern University; UIC, University of Illinois at Chicago; ENH, Evanston Northwestern Healthcare; Weiss, Weiss Memorial Hospital; NA, not available.

* Defined by the average reported number of alcoholic beverages consumed.

[†] Eight patients underwent surgical resection prior to trial enrollment; one patient underwent partial glossectomy and neck dissection.

Table 2

Disease Characteristics

Characteristic	No. of Patients	%
Primary site		
OC	14	26
OP	11	21
HP	3	6
SGL	13	25
L	9	17
Unknown*	3	6
T stage [†]		
0*	3	6
1	3	6
2	17	34
3	30	60
N stage [†]		
0	32	60
1	21	40
Overall stage		
II	13	25
III	40	75
Histologic differentiation of the primary tumor*		
Well	9	18
Moderately well	6	12
Moderate	20	40
Poor	10	20
Unknown	5	10

Abbreviations: OC, oral cavity; OP, oropharynx; HP, hypopharynx; SGL, supraglottic larynx; L, larynx.

* Three patients were enrolled with unknown primary sites.

[†] Tumor and nodal staging was scored according to the American Joint Committee on Cancer, 5th edition.

Table 3**Toxicity During Treatment**

	Grade							
	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
Toxicity (n = 53)								
Anemia	28	53	21	40	3	6	1	2
Leukopenia	4	8	19	36	21	40	4	8
Neutropenia	11	21	15	28	15	28	3	6
Thrombocytopenia	16	30	0	0	0	0	0	0
Nausea	27	51	5	9	4	8	0	0
Vomiting	16	30	3	6	2	4	1	2
Mucositis	3	6	3	6	41	77	4	9
Dermatitis	11	21	16	30	17	32	5	9
Palmar-plantar erythrodysesthesia	6	11	7	13	3	6	4	2
Diarrhea	9	17	2	4	0	0	0	0
Fatigue	21	40	19	36	6	11	0	0
Anorexia	20	38	14	26	4	8	1	2
Pain	7	13	22	42	19	36	1	2

NOTE. National Cancer Institute Common Toxicity Criteria version 2.0 was used to grade toxicity.

Table 4

Long-Term Toxicity Observed

Toxicity	No. of Patients Experiencing Toxicity	Treatment Required
Esophageal stricture	1	Dilatation
Soft tissue necrosis, neck	1	Reconstructive surgery
Cervical spinal stenosis	1	C3-7 laminectomy
Laryngeal edema	1	Laryngeal reconstruction
Tracheal stricture	1	Tracheostomy

NOTE. Results are from the 47 patients available for analysis longer than 6 months after completion of therapy.

Table 5

Second Primary Tumors Detected

Second Primary Tumor Anatomic Site	Histology	Interval Between Primary and Secondary Tumors (months)
Nasal	SCC	84
Lung	SCC*	10
Lung	Adenocarcinoma	4
Lung	SCLC	19
Lung	Adenocarcinoma	27
Breast	Ductal adenocarcinoma	12
Gastric	Adenocarcinoma	2
Skin	SCC	54

Abbreviations: SCC, squamous cell carcinoma; SCLC, small-cell lung cancer.

* This patient was treated on study for an oral tongue carcinoma. Pathology of the lung tumor was consistent with poorly differentiated SCC arising from a moderate-sized bronchus. The histologic appearance was not similar to the initial tongue cancer.