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Long-Term Results of Concomitant Boost Radiation plus Concurrent Cisplatin for Advanced Head and Neck Carcinomas: a Phase II Trial of the Radiation Therapy Oncology Group (RTOG 99-14)

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Abstract

Purpose—The feasibility of combining concomitant boost accelerated radiation regimen (AFX-C) with cisplatin was previously demonstrated in this phase II trial. This manuscript reports the long-term toxicity, relapse patterns, and survival in patients with advanced head and neck carcinoma (HNC).

Patients and Methods—Between April and November 2000, 84 patients with stage III–IV HNC were enrolled, and 76 patients were analyzable. Radiation consisted of 72 Gy over 6 weeks. Cisplatin dose was 100 mg/m^2 on days 1 and 22. Tumor and clinical status were assessed and acute-late toxicities were graded.

Results—The median follow-up for surviving patients is 4.3 years. The 2- and 4-year local-regional failure rates are 33% and 36%, respectively, and the 2- and 4-year survival rates are 70% and 54%, respectively. The worst overall late grade 3 or 4 toxicity rate was 42%. The prevalence rates of a

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gastrostomy at any time during follow-up, at 12 months, and at 48 months were 83%, 41%, and 17%, respectively. Five of 36 patients (14%) alive and without disease at last follow-up were gastrostomy tube dependent..

Conclusion—These data of long-term follow-up of patients treated with AFX-C with cisplatin show encouraging results with regard to locoregional disease control and survival, with few recurrences after 2 years. The late toxicity rates are relatively high. However, while prolonged dysphagia was noted in our preliminary report, its prevalence does decrease over time. A phase III trial comparing AFX-C plus cisplatin against standard radiation plus cisplatin has completed accrual.

Keywords

Radiation; chemoradiation; accelerated radiotherapy; late toxicity

INTRODUCTION

Over the past several decades, clinical trials have been conducted aimed at either improving disease control rates in patients with advanced head and neck carcinomas (HNC) or determining the feasibility of organ preservation. Two separate strategies have been investigated. One strategy has been to combine radiation with chemotherapy. Over this time, the systemic agents added to radiation have varied over the time based on emergence of newer agents. Numerous randomized trials have validated the superiority of chemoradiation compared to radiation alone, but as highlighted by the MACH-NC metaanalysis[1], approaches to chemoradiation have been very heterogeneous. One successful approach tested was the addition of high-dose cisplatin every 3 weeks during a course of conventionally fractionated radiation. One study in particular, that changed the standard of care was Intergroup trial 0099[2], which showed dramatic improvement in survival and disease control in patients with nasopharynx cancer treated with radiation (70 Gy in 7 weeks) and concurrent high-dose (100 mg/m^2) cisplatin followed by adjuvant cisplatin and fluorouracil compared to patients treated with radiation alone. Subsequently, multiple other trials in different settings of HNC (larynx preservation, unresectable disease, and adjuvant postoperative radiation) have demonstrated superiority of the addition of high-dose cisplatin to conventionally fractionated radiation compared to the same course of radiation alone.[3–6]

A second approach tested in multiple randomized trials has been to alter the radiation fractionation schedule. Based on sound biological principles, both accelerated fractionation and hyperfractionation have been compared to the standard once daily radiation delivered 5 days per week. A phase III trial of the Radiation Therapy Oncology Group (RTOG 90-03) enrolling 1,113 patients revealed that both the hyperfractionation regimen and accelerated fractionation by concomitant boost regimen (AFX-C) yielded significantly better local-regional (LR) control than did standard fractionation in patients with advanced HNC.[7] Results of multiple large randomized trials addressing the optimization of radiation fractionation collectively show that a number of biological-based modifications of fractionation schedules have improved the LR control rate in the order of 10–15%, and in a recent metaanalysis, there has also been an impact, albeit modest, on the overall survival rate.[8] Although altered fractionation regimens consistently induce more severe acute mucositis than standard fractionation, the general observation is that the late toxicity is not appreciably increased.

Building on the results of these two approaches, the RTOG developed a phase II study combining AFX-C and cisplatin to determine the feasibility and efficacy of this combination strategy. Single-agent cisplatin was chosen because it’s benefit in combination with conventionally fractionated radiotherapy was shown in 5 phase III cooperative group trials.

[2–6] whereas AFX-C was selected based on the results of the preceding RTOG trial (90-03).[7]

The preliminary results of this trial, specifically the acute toxicity and feasibility of drug delivery, have been reported.[9] The goal of this current report is to focus on long-term results with regards to disease outcomes and late toxicity.

METHODS

Study Objectives and Patient Eligibility

The details of patient eligibility have previously been reported.[9] Patients with previously untreated locally advanced (stage III or IV) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, Zubrod performance status of 0–1, adequate organ system function, and consented to receive non-surgical primary therapy were enrolled. The disease was staged according to the 1998 classification of the American Joint Committee on Cancer Staging. Both physical examination and imaging were used to determine clinical stage.

Treatment

Radiotherapy was delivered in 1.8 Gy per fraction, 5 fractions a week to 54 Gy in 30 fractions over 6 weeks to the initial target volume encompassing gross tumor and clinically/radiologically involved nodes along with regions of potential contiguous and lymphatic spread. At 32.4 Gy/18 fractions (i.e., latter part of week 4), a second daily dose of 1.5 Gy per fraction (with at least 6 h interval) was given to the boost volume covering gross tumor and involved nodes for a total of 18 Gy in 12 treatment days. The primary tumor and clinically/radiologically involved nodes received 72 Gy in 42 fractions over 6 weeks and uninvolved nodes received 54 Gy in 6 weeks. Clinically/radiologically negative posterior and lower neck nodes received a minimum dose of 50.4 Gy at 3 cm. A combination of lateral-opposed portals, anterior and lateral wedged fields, or other field arrangements was used to treat the primary tumor and the lymph nodes in the upper neck. A single anterior field was used to treat the neck below the fields for the primary tumor. All fields were treated on each treatment day.

Cisplatin was administered in a dose of 100 mg/m^2 intravenously on days 1 and 22 with granisetron or ondansetron premedication and vigorous hydration and diuresis. Guidelines for dose modification due to cytopenia, neurotoxicity, or nephrotoxicity were specified in the protocol. A planned neck dissection was optional for patients with N2 and N3 disease at initial staging and clinical complete response after chemoradiation. Neck dissection was required for patients with a palpable or suspicious radiographic abnormality persisting 6 weeks beyond completion of radiation and chemotherapy.

Follow Up and Data Analysis

Patients underwent weekly examination during treatment. First follow up evaluation occurred around 4 weeks after completion of therapy. Subsequently, patients were assessed every 3 months for the first 2 years, every 6 months in years 3–5, and annually thereafter. In addition to tumor and clinical status, acute and late normal tissue effects were graded. Systemic and acute radiation effects were scored using the NCI Common Toxicity Criteria version 2.0, while late radiation effects (>90 days from start of radiation therapy) were scored according to the RTOG/EORTC criteria. [10]

The primary endpoint of the study was the local-regional failure rate at one year. Failure was defined as the failure to obtain a complete response following definitive chemo-radiation, or the re-appearance of local and/or regional head and neck cancer after a complete response was obtained. Patients that failed to obtain a complete response were considered a failure at day 1.

Death without failure was considered a competing risk. Additional endpoints included toxicity rates, as well as overall and disease-free survival rates, and the incidence of distant metastases. Due to the intensity of the chemoradiation regimen and the associated length of time required for healing of acute mucositis, the acute toxicity period was extended to 180 days for purposes of analysis and reporting. All time-to-failure endpoints were calculated from the date of registration to the study. Survival and disease-free survival rates were estimated using the Kaplan-Meier method[11], while the rates of local-regional failure and distant metastases were calculated using the method of cumulative incidence[12], as this accounts for competing risk (i.e. death without disease relapse).

RESULTS

Study Population

Between April and November 2000, 84 patients were registered. Six patients were determined to be ineligible on review, and two additional patients were excluded, one who did not receive any protocol therapy and one for delinquent on-study data. Of the 76 analyzable patients, 67 (88.2%) had stage IV disease; 49 (64.5%) had T3 or T4 disease. Other patient characteristics were detailed in the prior publication. [9]

Disease Control and Survival

The present analysis was performed at a median follow-up of 2.9 years (range 0.1 – 4.9) for all patients and 4.3 years (1.4 – 4.9) for surviving patients. Twenty-seven patients (35.5%) had either persistent or recurrent disease at the primary site or regional lymphatics. The estimated 2- and 4-year local-regional failure rates (and their respective 95% confidence intervals) are 32.9% (22.2, 43.6) and 35.6% (24.7, 46.5). Only 2 LR recurrences were reported after 2 years from registration.

Sixteen patients (21.1%) developed distant metastases, of whom 8 had no evidence of local-regional failure. The estimated 2- and 4-year distant metastasis rates (and their respective 95% confidence intervals) are 17.2% (8.6, 25.8) and 21.6% (12.1, 31.0). Figure 1 shows the estimated cumulative incidence of local-regional failure and distant metastasis.

In total, 40 patients had disease persistence or recurrence or died without documented disease progression. No second primary tumors have been reported. The estimated 2- and 4-year disease-free survival rates (and their respective 95% confidence intervals) are 53.9% (42.7, 65.2) and 48.5% (37.2, 59.8). Only 5 events were reported after 2 years.

At the time of analysis, 40 patients were alive, of whom 36 had no evidence of disease Thirty-six patients have died; 27 due to their index cancer, 3 due to complications of treatment, 3 due to causes unrelated to cancer or treatment, and 3 from unknown causes. The estimated 2- and 4-year overall survival rates (and their respective 95% confidence intervals) are 69.6% (59.3, 80.0) and 53.8% (42.2, 65.3). Figure 2 shows the estimated overall and disease-free survival.

Late Toxicity

Three (3.9%) patients died of treatment-related toxicities: sepsis, pneumonia with acute respiratory distress syndrome, and/or renal failure. Late toxicities were recorded in 71 patients who survived >180 days from start of radiation therapy. Table 1 summarizes the type and frequency of severe (Grade 3–4) late side effects. Grade 3 and 4 late side effects were recorded in 19 (26.8%) and 11 (15.5%) patients, respectively. There were 42 grade 3 events reported. The most common grade 4 late complication was mucosal ulceration (4). Thirteen patients (18.3%) had late grade 3 esophageal toxicity. Only 2 patients experienced a first late event more than 2 years from start of radiation therapy.

Eighteen patients (23.7%) had a gastrostomy tube placed prior to registration, and 63 patients (82.9%) had a gastrostomy tube at any time during follow-up. Five of the 36 patients (13.9%) alive and without disease at last follow-up were gastrostomy tube dependent. There was no relationship between the placement of gastrostomy tube prior to registration and the need for a gastrostomy tube documented at last follow-up. The prevalence of gastrostomy tubes at years 1, 2, 3, and 4 were 40.9%, 21.8%, 18.1%, and 16.7% of patients, respectively

DISCUSSION

Numerous phase II and III trials have validated the general concept that the addition of chemotherapy delivered concurrently with radiation improves disease-related outcomes compared to radiation alone. Despite general agreement that concurrent chemoradiation is the standard therapy for patients with advanced HNC requiring radiation, the ideal radiation schedule and cytotoxic regimen remain controversial. While there is clear evidence that cisplatin-based regimens are effective[13] there is not universal agreement on the specific regimen. Based on the successful Intergroup trial[2], and at the time of development of this current phase II trial, 4 additional phase III trials studying high-dose cisplatin concurrent with radiation[3–6], it was elected to build on the experience of the RTOG fractionation study 9003[7] and combine AFX-C with high-dose cisplatin.

The initial report of this trial highlighted the feasibility of this regimen.[9] Ninety-three and 95% of patients received their radiation and chemotherapy respectively per protocol or with acceptable variation, and 92% received both cycles of cisplatin. The acute toxicity of the treatment was severe, as expected. Three patients (4%) died of treatment-related complications which is within the range of 2–5% observed in other intergroup trials testing sequential or concurrent cisplatin-based regimens combined with radiation. [3, 7]

Encouraging 2-year local-regional control and overall survival rates were also described in the preliminary report.[9] Now, with a median follow-up of over 4 years, these results have held up, as the 4-year local-regional failure and overall survival rates are 36% and 54% respectively. Very few disease-related events occurred past year 2.

The incidence of worst overall late grade 3 – 4 toxicity in 71 evaluable patients was 42%. The most common sites of grade 3 toxicities were salivary gland and esophagus. This trial, conducted in 2000, was performed prior to most institutions using intensity modulated radiotherapy (IMRT) techniques. The use of IMRT has not been demonstrated to decrease acute mucosal and skin toxicity, but has had an impact on the severity of late xerostomia[14]. Ideally if this or other chemo-radiation intensive regimens become routine after further investigation, xerostomia can be minimized with improvements in radiation techniques such as IMRT.

The late gastrostomy tube dependence rate remains high at 14%, although after longer follow-up the incidence is lower than previously reported (29%). Data regarding dysphagia and chronic feeding tube use in chemoradiation trials is sparse, and makes comparison of dysphagia rates between trials testing different regimens difficult, though the rates in the current trial are still higher than those seen in trials of radiation alone. The results of this trial also indicate that many patients regained swallowing function between years 1 and 2 but very few did so thereafter.

In conclusion, RTOG 99-14 tested the feasibility of a regimen of high-dose cisplatin and accelerated fractionated (concomitant boost) radiation. The regimen was feasible to deliver despite a high rate of acute toxicity. Long-term follow-up results remain encouraging with regards to local-regional control and survival. Late toxicity leading to gastrostomy tube dependence is high, relative to other reports, though this difference may reflect the

thoroughness of recording and reporting of this side effect. The RTOG elected to test this regimen in a phase III setting (RTOG 0129) to directly compare the efficacy and toxicity of AFX-C plus cisplatin against those of standard fractionation plus cisplatin to determine whether AFX-C can yield an additional therapeutic benefit in the concurrent chemo-radiation setting. Until the results of this Phase 3 trial are reported, the regimen of AFX-C plus cisplatin should only be attempted under protocol or in a large center with the multi-disciplinary resources to safely treat patients in this aggressive manner.

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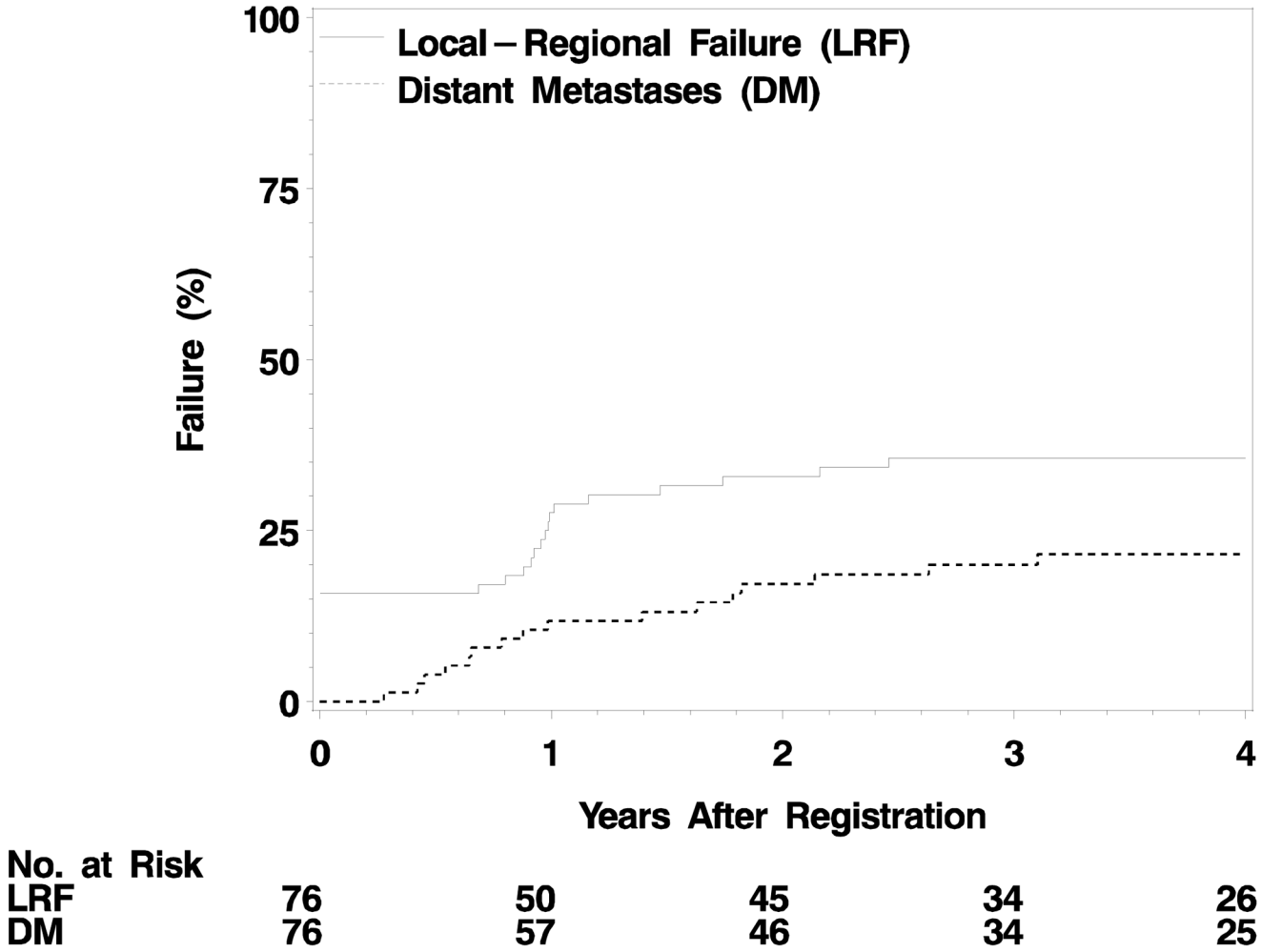

Figure 1.
Relapse pattern of patients with advanced head and neck cancer treated with accelerated fractionation by concomitant boost regimen plus concurrent cisplatin.

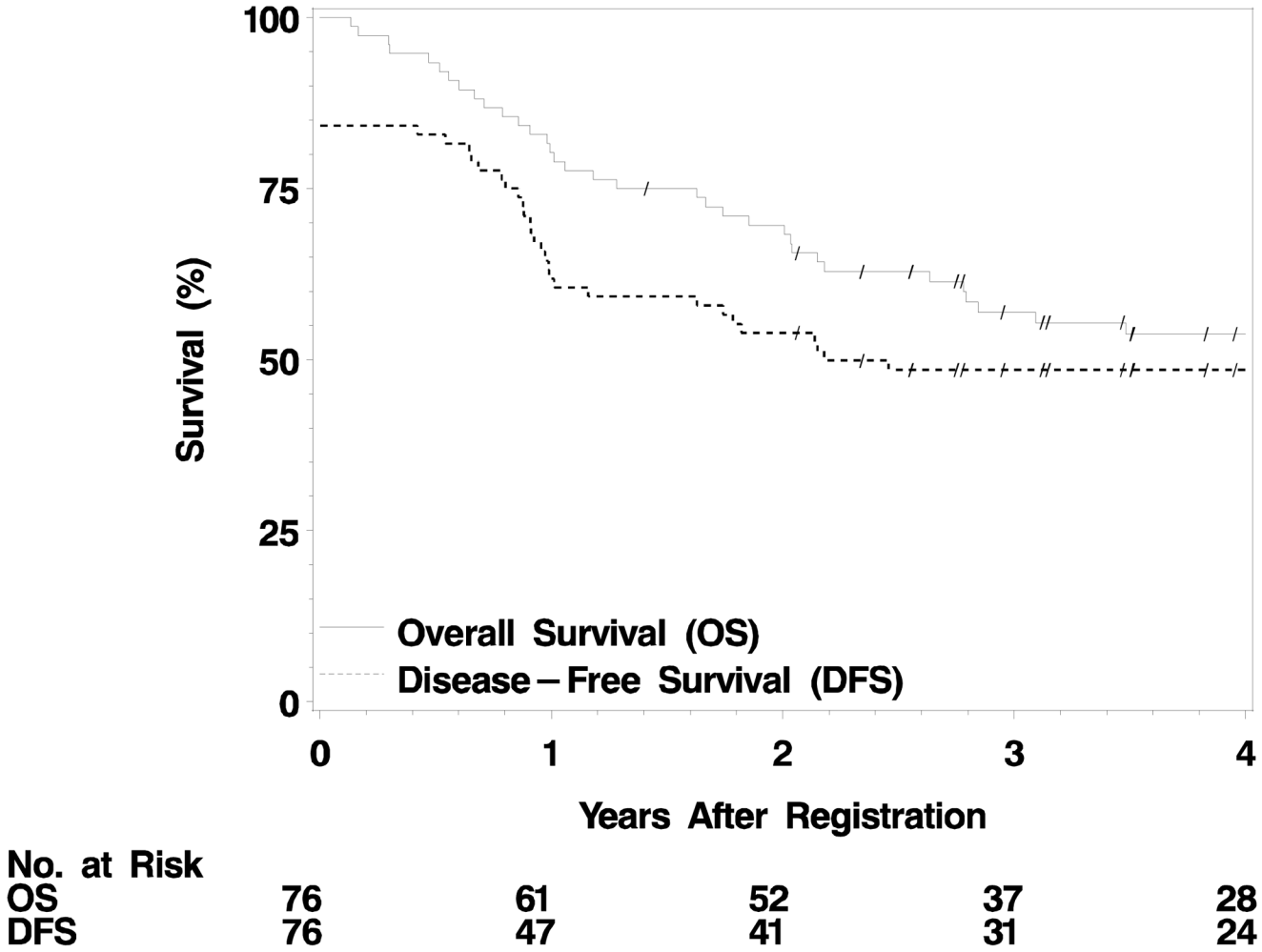

Figure 2.
Overall and disease-free survival of patients with advanced head and neck cancer treated with accelerated fractionation by concomitant boost regimen plus concurrent cisplatin. Forward slashes (/) indicate patients censored alive.

Table 1

Type and Frequency of Late Side Effects Observed in 71 Patients.

Toxicity	Number of Patients	
	Grade 3	Grade 4
RTOG/EORTC: Skin	1	1
RTOG/EORTC: Mucous membrane	2	4
RTOG/EORTC: Subcutaneous tissue	3	1
RTOG/EORTC: Salivary gland	10	0
RTOG/EORTC: Esophagus	13	0
RTOG/EORTC: Layrnx	0	1
RTOG/EORTC: Bone	1	2
RTOG/EORTC: Other	5	1
CTC: Skin-other	1	0
CTC: Weight decreased	2	0
CTC: Fatigue	0	1
CTC: Hearing impaired	2	0
CTC: Hemoglobin decreased	1	0
CTC: Hyperkalemia	1	0
Worst overall	19 (26.8%)	11 (15.5%)