

HYPERFRACTIONATED IRRADIATION WITH OR WITHOUT CONCURRENT CHEMOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK CANCER

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ABSTRACT

Background Radiotherapy is often the primary treatment for advanced head and neck cancer, but the rates of locoregional recurrence are high and survival is poor. We investigated whether hyperfractionated irradiation plus concurrent chemotherapy (combined treatment) is superior to hyperfractionated irradiation alone.

Methods Patients with advanced head and neck cancer who were treated only with hyperfractionated irradiation received 125 cGy twice daily, for a total of 7500 cGy. Patients in the combined-treatment group received 125 cGy twice daily, for a total of 7000 cGy, and five days of treatment with 12 mg of cisplatin per square meter of body-surface area per day and 600 mg of fluorouracil per square meter per day during weeks 1 and 6 of irradiation. Two cycles of cisplatin and fluorouracil were given to most patients after the completion of radiotherapy.

Results Of 122 patients who underwent randomization, 116 were included in the analysis. Most patients in both treatment groups had unresectable disease. The median follow-up was 41 months (range, 19 to 86). At three years the rate of overall survival was 55 percent in the combined-therapy group and 34 percent in the hyperfractionation group ($P=0.07$). The relapse-free survival rate was higher in the combined-treatment group (61 percent vs. 41 percent, $P=0.08$). The rate of locoregional control of disease at three years was 70 percent in the combined-treatment group and 44 percent in the hyperfractionation group ($P=0.01$). Confluent mucositis developed in 77 percent and 75 percent of the two groups, respectively. Severe complications occurred in three patients in the hyperfractionation group and five patients in the combined-treatment group.

Conclusions Combined treatment for advanced head and neck cancer is more efficacious and not more toxic than hyperfractionated irradiation alone. (N Engl J Med 1998;338:1798-804.)

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CURE of locally advanced squamous-cell carcinoma of the head and neck is uncommon whether a single treatment, including high-dose external-beam irradiation, or a combination of treatments is used. The rate of relapse-free survival is approximately 25 percent, and most patients die from complications of progressive local disease. Repopulation of tumor cells during treatment, tumor hypoxia, and resistance to radio-

therapy have all been implicated as causes of treatment failure after primary radiotherapy.¹⁻³

Accelerated fractionation irradiation, which shortens the total time of treatment, has been employed to increase the probability of locoregional control by reducing the risk of tumor repopulation. With hyperfractionated irradiation, multiple small fractions of radiation are given each day to increase the total dose but not the risk of long-term toxicity.⁴ Retrospective studies of patients treated with accelerated fractionation and hyperfractionation have demonstrated an improvement in disease control of about 20 percentage points, as compared with historical controls treated with conventional daily radiation, without an increase in long-term toxicity.⁵⁻⁷ A prospective, randomized trial by the European Organization for the Research and Treatment of Cancer (EORTC) showed an increase of 20 percentage points in the rate of locoregional control of oropharyngeal carcinoma at five years and an improvement of 14 percentage points in survival after treatment with 8050 cGy of radiation in hyperfractionated doses as compared with the rates achieved with once-daily radiotherapy (total dose, 7000 cGy), without any increase in acute or chronic toxic effects.⁸

Combination radiotherapy and chemotherapy is another promising approach to locally advanced head and neck cancer. Most studies have used sequential chemotherapy followed by radiotherapy. However, as compared with the use of radiotherapy alone, this strategy has generally failed to improve overall survival or disease-free survival.^{9,10}

We initiated a phase 3 trial in 1990 to test the hypothesis that accelerated hyperfractionation irradiation plus concurrent chemotherapy followed by adjuvant chemotherapy (combined therapy) leads to better locoregional control, relapse-free survival, and overall survival than accelerated hyperfractionation alone. We have demonstrated the feasibility of this program in a phase 1-2 study.¹¹ Accelerated hyperfractionation alone was selected as the control treatment because it represented the most intensive ap-

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proach to primary radiotherapy, even though it had not been proved at the time to be superior to once-daily treatment.

METHODS

Patient Population and Eligibility Criteria

In this multicenter study, all patients were initially evaluated by a multidisciplinary team consisting of otolaryngologists, radiation oncologists, and medical oncologists. The tumors were classified according to the criteria of the American Joint Committee on Cancer Staging.¹² The stage of the tumor was determined on the basis of each patient's history and physical examination (including examination with the patient under anesthesia), chest X-ray films, and computed tomographic or magnetic resonance imaging studies (or both) of the head and neck. Computed tomography or magnetic resonance imaging was usually repeated four to six weeks after treatment was completed to help assess the response to treatment.

To be eligible for the study, patients had to have previously untreated, histologically proven squamous-cell carcinoma; a tumor that was more than 4 cm in diameter (stage T3), or a tumor that was more than 4 cm in diameter and invaded deep tissues or bone or extended into an adjacent anatomical area (stage T4), with or without massive cervical lymphadenopathy (metastasis to a lymph node measuring more than 6 cm; stage N3); and no evidence of distant metastases. Patients with tumors of the base of the tongue that were between 2 and 4 cm in diameter without palpable cervical lymph nodes (stage T2N0) were also eligible. Primary tumors were classified as resectable or unresectable. Unresectable lesions were defined as those in which a resection plane could not be created without a high probability of gross residual disease.¹³ Resectable primary tumors were defined as those with a low probability of residual disease after surgery. Most patients with resectable primary tumors were enrolled in the protocol for the purpose of preserving the function of the affected organ. Patients had to be at least 18 years of age and no older than 75 years with a Karnofsky performance score of at least 60, a serum creatinine concentration of 2.0 mg per deciliter (177 μ mol per liter) or less, a white-cell count of at least 3000 per cubic millimeter, and a platelet count of at least 100,000 per cubic millimeter.

Patients who had had invasive cancer within the preceding five years, synchronous primary lesions, or squamous-cell carcinoma of the skin of the head and neck were excluded from the study, as were those who were pregnant. The protocol was approved by the protocol-review committee of the Duke Cancer Center and the institutional review board of Duke University Medical Center. Written informed consent was obtained from all patients.

Accelerated Hyperfractionated Irradiation

The primary tumor and draining lymphatic system were treated isocentrically with 4-MV or 6-MV photons and parallel opposed lateral portals with a source-to-isocenter distance of 80 to 100 cm. Supraclavicular nodes and nodes in the lower part of the neck were treated with the use of a single anterior field, with midline blocking to prevent spinal cord overlap. The spinal cord was blocked in the inferior aspect of both lateral fields for laryngeal primary tumors. The inferior border of the lateral fields and the superior border of the supraclavicular fields coincided on the skin.

Lateral-field doses were prescribed at midplane, whereas a depth of 3 cm was used for the supraclavicular field. Initial fields received a total of 4000 cGy, given in dosages of 125 cGy twice a day with a six-hour interval between doses. The use of the supraclavicular field was discontinued after 4000 cGy had been administered if there were no palpable lymph nodes in the lower part of the neck. In order to shield the spinal cord, the size of the lateral fields was reduced after 4000 cGy had been administered. Electron-beam irradiation was used to boost the dose to the posterior cervical lymph-node chains. The size of the field was again

reduced after 5500 to 6000 cGy had been administered. The total dose delivered to the primary tumor was 7500 cGy in a six-week period. Treatment was delivered continuously without any planned interruptions.

Accelerated Hyperfractionated Irradiation and Concurrent Chemotherapy

The dosage and techniques of irradiation were the same as in the group that received accelerated hyperfractionated irradiation alone. A seven-day interruption of radiotherapy was planned after 4000 cGy had been administered, since our phase 1-2 trial had shown that this was necessary to manage treatment-induced mucositis. The total dose intended for the primary tumor was 7000 cGy in a seven-week period.

Chemotherapy

Chemotherapy was administered during weeks 1 and 6 of the course of treatment. Patients received prophylactic hydration and antiemetics. Chemotherapy consisted of fluorouracil and cisplatin (Platinol, Bristol-Myers Squibb, Princeton, N.J.). Fluorouracil was administered as a continuous infusion at a dose of 600 mg per square meter of body-surface area per day for five days. Cisplatin was given as a daily bolus of 12 mg per square meter per day for five days, for a total dose of 60 mg per square meter. Two additional cycles of cisplatin and fluorouracil were planned after the completion of all local therapy, with the cisplatin again divided into five daily boluses, and the dose increased to 80 mg per square meter in cycle 3 and to 100 mg per square meter in cycle 4. There were no provisions for reductions in the doses of chemotherapy.

Management of the Neck

Patients with no regional lymph-node metastases of the neck (stage N0) or metastasis to a single ipsilateral lymph node measuring 3 cm or less in diameter (stage N1) were treated only with radiotherapy, or radiotherapy and chemotherapy. Patients who presented with neck disease of stage N2 (metastasis to a single ipsilateral lymph node that was more than 3 cm in diameter but not more than 6 cm) or higher were reevaluated four to six weeks after irradiation. Elective neck dissection was planned in patients who had a complete response at the primary site even if they also had a complete response in the neck.¹⁴

Experimental Design

The primary outcome measures were the rate of complete response at the primary site and the rate of locoregional control. We estimated that 126 patients (63 in each group) were needed in order to achieve an approximate power of 0.80 to detect a difference in complete-response rates of 0.20 (0.60 in the hyperfractionation group and 0.80 in the combined-treatment group at an alpha level of 0.05 with a one-sided test). The achievement of the response rates stipulated by the experimental design would in turn lead to a power of 0.80 to detect a difference in the rate of locoregional control of 0.25.

Randomization Procedures

The randomization strategy was designed by the biostatistics unit of the Duke Cancer Center and executed independently by the cancer-center protocol office. The principal investigator telephoned the protocol office to receive a patient's treatment assignment, with subsequent written confirmation provided by the protocol registrar.

The randomization scheme was a permuted block design with an equal probability of assignment to either treatment and stratification according to the resectability of the tumor (resectable or unresectable) and the hemoglobin concentration at randomization (<12 g per deciliter vs. \geq 12 g per deciliter). The hemoglobin concentration was selected because of the adverse prognostic

effect of anemia in patients undergoing radiotherapy.^{15,16} The block size was six.

Statistical Analysis

Exact tests for contingency tables, Kaplan–Meier estimates of survival,¹⁷ and stratified log-rank tests were used to test for differences in response rates, estimated times to events, and differences in the distributions of these events. All P values are two-sided. Competing risk factors are a fundamental problem in the design of studies that use local control as an end point, since relapses at distant sites or deaths may occur before the end point is reached.^{18,19} This problem ordinarily requires one to assume that the risk factors are independent, an untestable and potentially implausible assumption. Therefore, in addition to analyzing locoregional control, we analyzed both relapse-free survival — that is, survival free of relapse at a local or a distant site — and overall survival, which included death from any cause.

RESULTS

Characteristics of the Patients

From June 1990 to December 1995, 142 eligible patients were identified. Twenty patients declined to enroll in the study. Of the 122 who underwent randomization, 6 were excluded from the analysis for the following reasons: synchronous primary tumors (2 patients), distant metastases at diagnosis (2), loss to follow-up before the start of treatment (1), and refusal of all treatment (1). Thus, only 116 patients were included in the analysis.

Table 1 outlines the characteristics of the patients. Fifty-five percent of the 60 patients in the hyperfractionation group and 52 percent of the 56 patients in the combined-treatment group had unresectable disease. Eighty-seven percent of the patients in the hyperfractionation group and 90 percent of those in the combined-treatment group had stage T3 or T4 primary tumors. The mean diameter of the primary tumor exceeded 5 cm in both groups. Nodal metastases were present in 73 percent of the patients in the hyperfractionation group and 70 percent of those in the combined-treatment group. Sixty-three percent of the patients in the hyperfractionation group had advanced nodal disease (stage N2 or N3), as compared with 44 percent of those in the combined-treatment group ($P=0.31$). Most patients (89 percent) were enrolled at Duke University Medical Center or the Durham Veterans Affairs Hospital.

Treatment

Radiotherapy in the hyperfractionation regimen was designed to be more intensive than in the combined-treatment regimen, in terms of both total dose and the time of delivery. The mean (\pm SD) dose delivered to the primary tumor was 7400 ± 273 cGy in the hyperfractionation regimen and 7050 ± 160 cGy in the combined-treatment regimen ($P<0.001$ by the two-tailed t-test). The average numbers of days of administration were 42 ± 6 and 47 ± 5 , respectively ($P<0.001$ by the two-tailed t-test). There were no unplanned treatment breaks.

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT RANDOMIZATION.*

CHARACTERISTIC	HYPERFRACTIONATION GROUP (N=60)	COMBINED-TREATMENT GROUP (N=56)	TOTAL (N=116)
Sex — M/F	52/8	44/12	
Age — yr	60 \pm 9	58 \pm 9	
Mean Karnofsky performance score	80	80	
Resectability of tumor — no. (%)			
Resectable	27 (45)	27 (48)	54 (47)
Unresectable	33 (55)	29 (52)	62 (53)
Hemoglobin concentration — no. (%)			
≥ 12 g/dl	52 (87)	46 (82)	98 (84)
< 12 g/dl	8 (13)	10 (18)	18 (16)
Site of primary tumor — no. (%)			
Base of tongue	13 (22)	8 (14)	21 (18)
Tonsil	16 (27)	15 (27)	31 (27)
Larynx	8 (13)	10 (18)	18 (16)
Hypopharynx	10 (17)	13 (23)	23 (20)
Paranasal sinus	5 (8)	1 (2)	6 (5)
Nasopharynx	2 (3)	5 (9)	7 (6)
Oral cavity	3 (5)	3 (5)	6 (5)
Other	3 (5)	1 (2)	4 (3)
Tumor stage — no. (%)†			
T2	7 (12)	6 (11)	13 (11)
T3	29 (48)	25 (45)	54 (47)
T4	23 (38)	25 (45)	48 (41)
TX	1 (2)	0	1 (1)
Tumor size — cm	5.3 \pm 2.0	5.6 \pm 1.7	
Nodal stage — no. (%)†			
N0	16 (27)	17 (30)	33 (28)
N1	7 (12)	14 (25)	21 (18)
N2	29 (48)	18 (32)	47 (41)
N3	8 (13)	7 (12)	15 (13)
Size of node — cm	3.7 \pm 2.9	3.4 \pm 2.8	

*Plus-minus values are means \pm SD. Because of rounding, not all percentages total 100.

†The tumor and nodal stages were defined according to the American Joint Committee on Cancer Staging for head and neck cancer.¹² T2 denotes a tumor measuring > 2 cm, but ≤ 4 cm; T3 a tumor measuring > 4 cm; T4 a tumor that has invaded adjacent structures (e.g., cortical bone, deep muscle of tongue, maxillary sinus, skin); and TX a primary tumor that cannot be assessed. N0 denotes the absence of regional lymph-node metastases; N1 metastasis to a single ipsilateral lymph node (≤ 3 cm); N2 metastasis to a single ipsilateral lymph node (> 3 cm, but ≤ 6 cm), to multiple ipsilateral lymph nodes (none > 6 cm), or to bilateral or contralateral lymph nodes (none > 6 cm); and N3 metastasis to a lymph node measuring > 6 cm.

Fifty-five of the patients in the combined-treatment group (98 percent) received two cycles of chemotherapy concurrently with irradiation; a cardiac arrhythmia developed in one patient as a result of fluorouracil therapy, and he received only one cycle of chemotherapy. Thirty-two patients in this group (57 percent) received the third and fourth cycles of post-radiation chemotherapy. Seventeen patients refused to undergo post-radiation chemotherapy, and it was not offered to the seven patients who did not have a complete response at the primary site after combined therapy.

Toxicity of Treatment

Table 2 outlines the adverse effects of treatment. Sepsis, including one case that was fatal, was more frequent in the combined-treatment group, as is expected with the use of myelosuppressive agents. The incidence of confluent mucositis was virtually the same in the two treatment groups, although the mean length of time before mucositis resolved was longer in the combined-treatment group (six vs. four weeks). There were no significant differences regarding weight loss, although a higher proportion of patients in the combined-treatment group required temporary nasogastric or gastrostomy feeding tubes. Severe long-term effects requiring surgery or hyperbaric oxygen — namely, osteonecrosis and soft-tissue necrosis — were rare in both groups.

Outcome

A complete response was defined as the disappearance of all clinical and radiographic evidence of disease at the primary site six weeks after radiotherapy. Of the 60 patients in the hyperfractionation group, 44 (73 percent) had a complete response, whereas 49 of the 56 patients in the combined-treatment group (88 percent) had a complete response ($P=0.52$). The response was pathologically confirmed in patients who subsequently underwent elective neck dissection, since the presence of persistent disease would have necessitated more comprehensive surgery than a neck dissection.

Of the 37 patients in the hyperfractionation group who had stage N2 or N3 cervical lymphadenopathy, 25 had a complete response. Neck dissection was performed in 16 of these patients, and residual cancer was identified in specimens from 6. Among the 25 patients in the combined-treatment group with adenopathy of stage N2 or N3, 19 had a complete response. Neck dissection was performed in 14 patients, and residual cancer was present in 3.

The median follow-up of surviving patients was 41 months (range, 19 to 86); 82 percent of such patients were followed for at least 2 years. All relapses occurred within 18 months after enrollment. Patients in the combined-treatment group had better rates of locoregional control of disease at three years (70 percent vs. 44 percent, $P=0.01$) (Fig. 1), relapse-free survival (61 percent vs. 41 percent, $P=0.08$) (Fig. 2), and overall survival (55 percent vs. 34 percent, $P=0.07$) (Fig. 3) than the patients in the hyperfractionation group. The respective P values for these three end points were 0.01, 0.11, and 0.12 after adjustment for differences in nodal stage at base line between the two treatment groups.

Patterns of Relapse

The tumor recurred in 33 patients who received only hyperfractionation. The primary site was the most common location of a first recurrence (in 21

TABLE 2. SHORT-TERM AND LONG-TERM ADVERSE EFFECTS OF TREATMENT.

ADVERSE EFFECT	HYPERFRACTIONATION GROUP (N=60)	COMBINED-TREATMENT GROUP (N=56)
	percent	
Short-term effects		
Mucous membranes		
Erythema	3	0
Patchy mucositis	20	23
Confluent mucositis	75	77
Necrosis	2	0
Alimentation related		
Mean weight loss*	8	10
Need for feeding tube	29	44
Sepsis	4	14†
Long-term effects		
Osteonecrosis	2	0
Soft-tissue necrosis	7	11

*The mean weight loss was the average loss in relation to pretreatment weight.

†One patient died of sepsis.

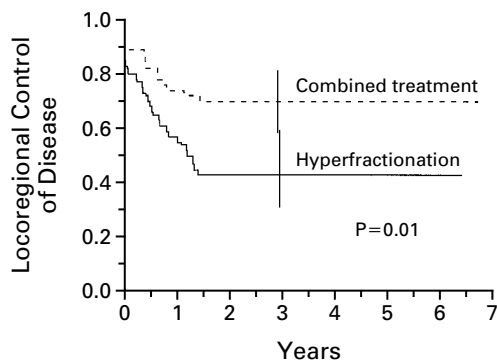
of 33 patients, or 64 percent). Lymph nodes were involved in 15 patients (45 percent), and distant metastases were a component in 6 patients (18 percent). The percentage of recurrences totals more than 100 because some patients had recurrences at multiple sites.

The tumor recurred in 22 patients after combined therapy, with the most common location being the primary site (in 16 of 22 patients, or 73 percent). In the remaining 6 patients (27 percent) the recurrences consisted of distant metastases; 5 of these patients were among the 17 who refused to undergo post-radiation chemotherapy. There were no recurrences in the neck in the patients who underwent elective neck dissection in either treatment group.

DISCUSSION

In most patients with advanced head and neck cancer, conventional radiotherapy does not result in long-term locoregional control of the tumor, and it is this failure that ultimately proves fatal. Investigators have sought to improve this situation through the use of several strategies.

Accelerated fractionation and hyperfractionation both use multiple daily dosages of irradiation. The purpose of accelerated fractionation is to reduce tumor proliferation during therapy by shortening the overall treatment time. With hyperfractionated irradiation, the treatment time is kept constant relative to once-daily treatment. Hyperfractionation is an attempt to improve the therapeutic ratio by increasing the total dose of radiation, but not the risk of long-term toxicity. The size of each fraction is less than

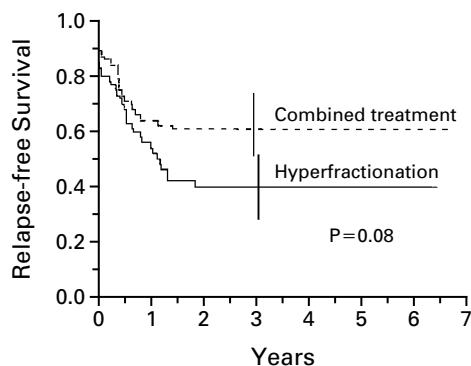


NO. AT RISK

Hyperfractionation	60	31	17	13	8	6	3	0
Combined treatment	56	39	27	21	14	11	4	1

Figure 1. Kaplan-Meier Estimates of the Duration of Locoregional Control of Disease.

Combined treatment was better than hyperfractionation alone ($P=0.01$). The I bars indicate the 95 percent confidence intervals for the hyperfractionation group (0.32 to 0.58) and the combined-treatment group (0.56 to 0.82). Data on patients with distant metastases as a first event were not censored, and such patients were still considered to be at risk for local failure.

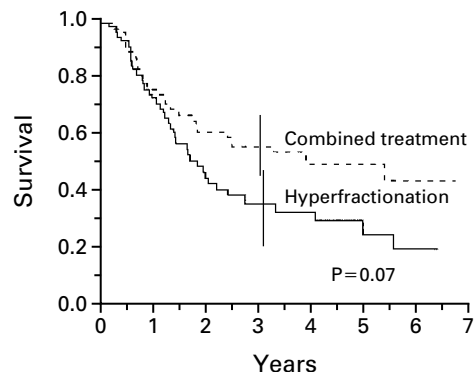


NO. AT RISK

Hyperfractionation	60	29	16	10	8	6	3	0
Combined treatment	56	35	26	21	14	11	4	1

Figure 2. Kaplan-Meier Estimates of Relapse-free Survival.

Combined treatment was better than hyperfractionation alone ($P=0.08$). The I bars indicate the 95 percent confidence intervals for the hyperfractionation group (0.27 to 0.53) and the combined-treatment group (0.48 to 0.74). Data on patients who died of other causes were censored at the time of death.



NO. AT RISK

Hyperfractionation	60	43	23	12	9	6	1	0
Combined treatment	56	42	28	22	14	11	4	1

Figure 3. Kaplan-Meier Estimates of Overall Survival.

Combined treatment was better than hyperfractionation alone ($P=0.07$). The I bars indicate the 95 percent confidence intervals for the hyperfractionation group (0.22 to 0.48) and the combined-treatment group (0.42 to 0.68). Death from any cause was included in the analysis.

that delivered with standard once-daily treatment. Phase 2 trials have reported that these approaches have considerable benefits. Phase 3 trials of the EORTC have confirmed these findings.^{8,20-22}

Two randomized trials of sequentially administered chemotherapy and radiation, with or without surgery depending on the resectability of the tumor, for advanced laryngeal and hypopharyngeal cancer have demonstrated that this approach can result in a high degree of organ preservation; it can obviate the need for laryngectomy and result in survival rates equivalent to those reported after surgery and post-operative radiation.^{23,24} Despite its widespread use, however, this strategy has not been proved superior to radiation alone.²⁵

Regimens of concurrently administered radiation and chemotherapy have typically employed once-daily irradiation with doses ranging from 65 to 70 Gy. This approach has an apparent advantage as compared with radiation alone.²⁶ Moreover, a randomized study demonstrated the superiority of concurrent combined therapy over sequential combined therapy.²⁷ Recent meta-analyses have also concluded that concurrent administration is superior to sequential treatment.^{9,10}

We combined accelerated hyperfractionated irradiation with concurrent chemotherapy. When our study began in 1990, phase 2 data attested to the superiority of hyperfractionation over conventional radiotherapy.⁵⁻⁷ Other results suggested the superiority of concurrent chemotherapy and radiotherapy for esophageal, anal, and rectal cancer. We therefore de-

cided to compare maximally intensive radiotherapy alone (total dose, 7500 cGy) with a slightly less intense radiotherapy program (total dose, 7000 cGy) plus concurrent chemotherapy.

We found that overall survival, relapse-free survival, and locoregional control were all improved by the addition of concurrent chemotherapy to the hyperfractionation program. Moreover, these results were achieved without a corresponding increase in severe toxicity; long-term complications were the same in both groups, with a slight increase in acute adverse effects in the combined-treatment group.

The outcome of this trial must be interpreted with caution. Despite randomization, there were some imbalances in the two treatment groups. There were more patients with advanced nodal disease (N2 or N3) in the hyperfractionation group than in the combined-treatment group (63 percent vs. 45 percent, $P=0.31$), perhaps making the prognosis worse in the former group. There were other, smaller imbalances regarding the primary site, with more patients with the hypopharynx as a primary site (which is associated with a less favorable result) in the combined-treatment group and more patients with the oropharynx (tonsil and base of tongue) as a primary site (which is associated with a more favorable result) in the hyperfractionation group. The trial was, however, well balanced with respect to resectability, the most important prognostic variable, as well as the stage of the tumor, hemoglobin concentration, and Karnofsky performance status.

Our protocol specified that patients with stage N2 or N3 tumors could undergo elective neck dissection, but the procedure was not always performed. The absence of any relapses in the neck among patients who underwent dissection implies that the overall failure rate in the neck would have been lower had this aspect of the protocol been rigorously followed. A greater proportion of the patients in the combined-treatment group underwent neck dissection than in the hyperfractionation group, another possible contribution to the improved outcome for this group.

This trial was not designed to test the value of adjuvant chemotherapy. Nonetheless, the fact that five of the six recurrences at distant sites occurred among the 17 patients in the combined-treatment group who did not receive post-irradiation chemotherapy suggests that relapse-free survival in this group might have been higher had patients received all planned chemotherapy. The Intergroup Study 0034 demonstrated a reduction in distant metastases with adjuvant chemotherapy with cisplatin and fluorouracil in patients with resectable head and neck cancer, albeit with no improvement in overall survival.²⁸

Despite the improvements in overall survival, relapse-free survival, and locoregional control of disease with the use of hyperfractionated irradiation

and concurrent chemotherapy, approximately half the patients who received this treatment ultimately died of their disease, mostly from sequelae of uncontrolled locoregional disease. Clearly, there is a need for improvement in the treatment of locoregional disease in advanced head and neck cancer.

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