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Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck

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ABSTRACT

BACKGROUND

Despite the use of resection and postoperative radiotherapy, high-risk squamous-cell carcinoma of the head and neck frequently recurs in the original tumor bed. We tested the hypothesis that concurrent postoperative administration of cisplatin and radiotherapy would improve the rate of local and regional control.

METHODS

Between September 9, 1995, and April 28, 2000, 459 patients were enrolled. After undergoing total resection of all visible and palpable disease, 231 patients were randomly assigned to receive radiotherapy alone (60 to 66 Gy in 30 to 33 fractions over a period of 6 to 6.6 weeks) and 228 patients to receive the identical treatment plus concurrent cisplatin (100 mg per square meter of body-surface area intravenously on days 1, 22, and 43).

RESULTS

After a median follow-up of 45.9 months, the rate of local and regional control was significantly higher in the combined-therapy group than in the group given radiotherapy alone (hazard ratio for local or regional recurrence, 0.61; 95 percent confidence interval, 0.41 to 0.91; P=0.01). The estimated two-year rate of local and regional control was 82 percent in the combined-therapy group, as compared with 72 percent in the radiotherapy group. Disease-free survival was significantly longer in the combined-therapy group than in the radiotherapy group (hazard ratio for disease or death, 0.78; 95 percent confidence interval, 0.61 to 0.99; P=0.04), but overall survival was not (hazard ratio for death, 0.84; 95 percent confidence interval, 0.65 to 1.09; P=0.19). The incidence of acute adverse effects of grade 3 or greater was 34 percent in the radiotherapy group and 77 percent in the combined-therapy group (P<0.001). Four patients who received combined therapy died as a direct result of the treatment.

CONCLUSIONS

Among high-risk patients with resected head and neck cancer, concurrent postoperative chemotherapy and radiotherapy significantly improve the rates of local and regional control and disease-free survival. However, the combined treatment is associated with a substantial increase in adverse effects.

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Despite regimens that permit organ preservation in selected patients with advanced carcinomas of the head and neck,[1-3] ablative surgical resection and postoperative radiotherapy are required in many patients. Typically, local or regional disease recurs in 30 percent of patients, and distant metastases appear in 25 percent; the five-year survival rate is 40 percent.[4] Patients who have two or more regional lymph nodes involved, extracapsular spread of disease, or microscopically involved mucosal margins of resection have particularly high rates of local recurrence (27 to 61 percent) and distant metastases (18 to 21 percent) and a high risk of death (five-year survival rate, 27 to 34 percent).[5]

Advanced tumors at some sites respond better to concurrent chemotherapy and radiotherapy than to radiotherapy alone.[6-11] However, there are insufficient data to permit evaluation of this combination for resected cancers of the head and neck. This trial was based on our previous analysis[5] and was designed to determine whether concurrent cisplatin therapy and postoperative radiotherapy improve the rates of local and regional control among patients who have high-risk operable head and neck cancer.

METHODS

The Radiation Therapy Oncology Group (RTOG), supported by the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG), conducted this intergroup phase 3 trial (RTOG 9501, ECOG R9501, and SWOG 9515). Eligible patients had squamous-cell carcinoma arising in the oral cavity, oropharynx, larynx, or hypopharynx; had undergone macroscopically complete resection of disease; had high-risk characteristics (any or all of the following: histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, and microscopically involved mucosal margins of resection); and could tolerate chemotherapy, as defined by a Karnofsky performance score of at least 60, a white-cell count of at least 3500 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, and a creatinine clearance of more than 50 ml per minute. All patients gave written informed consent in accordance with institutional guidelines. The study was approved by the institutional review board of each center.

PRETREATMENT PROCEDURES

Before surgery, a medical history was obtained for each patient; each patient underwent a physical examination, complete blood count, serum chemical profile, urinalysis, chest radiography, and dental evaluation; and a diagram of the primary tumor and neck nodes was made. The protocol required radiotherapy to begin as soon after surgery as adequate healing had occurred. Normally, this occurs four to six weeks after the surgical procedure; the protocol required radiotherapy to begin no later than 8 weeks (56 calendar days) after surgery. Patients were stratified according to age (younger than 70 years vs. 70 years or more) and the presence or absence of microscopic tumor at the mucosal surgical margins, and then randomly assigned at RTOG headquarters to receive radiotherapy alone (60 Gy in 30 fractions over a six-week period, with or without a boost of 6 Gy in 3 fractions over a period of three days to high-risk sites) or concurrently with cisplatin (100 mg per square meter of body-surface area intravenously on days 1, 22, and 43). In the cisplatin group, hydration was prescribed before and after treatment; the use and choice of antiemetics were left to the physician's discretion. In both groups, the use and timing of feeding tubes were optional. The permuted-block allocation scheme described by Zelen was used, in which the treatment assignments were balanced initially within the institution and then according to patient factors.[12]

TREATMENT MODIFICATION

A continuous course of radiotherapy was maintained if at all possible; any interruptions resulting from treatment-related adverse effects had to be kept to a minimum and reported. Cisplatin therapy was postponed if, on the day of scheduled treatment, the absolute neutrophil count was below 1000 per cubic millimeter or the platelet count was below 75,000 per cubic millimeter. The dose of cisplatin was reduced by 40 percent if neurotoxicity occurred, decreased to 75 mg per square meter if the creatinine clearance dropped to 40 to 50 ml per minute, and discontinued in the event of lower values.

FOLLOW-UP

During treatment, patients were examined at least weekly. Once treatment ended, an evaluation was required at nine weeks, then every three months for the first year, twice annually in years 2 and 3, and

annually thereafter. The tumor status, the patient's status, and treatment-related adverse effects were recorded.

STUDY END POINTS

The primary end point was local and regional tumor control; failure was defined as the reappearance of tumor in the original tumor bed or the development of cervical-node metastases after treatment. Secondary end points were disease-free survival, overall survival, and adverse effects. Disease-free survival was measured from the time of randomization to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. Overall survival was measured from the date of randomization to the date of death from any cause. Treatment-related adverse effects were scored according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0, for chemotherapy and according to RTOG criteria for radiotherapy.[13] Treatment-related adverse effects were categorized as acute (occurring within 90 days after the start of radiotherapy) or late (continuing or occurring after 90 days).

STATISTICAL ANALYSIS

On the basis of the previous trials of the RTOG, patients treated with postoperative radiation were expected to have a two-year rate of local or regional recurrence of 38 percent. The study required the randomization of 398 eligible patients to have the statistical power to detect an absolute improvement of 15 percent in this rate with the use of a two-sided test with 0.80 statistical power and a significance level of 0.05. To compensate for an expected rate of ineligibility and loss to follow-up of up to 10 percent, 438 patients were scheduled to be enrolled. The study was overseen by an independent data-monitoring committee. The analytic plan called for early significance testing at an α value of 0.001 when 50 percent and then 100 percent of the targeted number of patients had been enrolled and for the definitive analysis to be performed after each patient had potentially been followed for two years. The reported P values are unadjusted.

Rates of local and regional control were estimated according to the method of cumulative incidence,[14] and differences were assessed by means of Gray's test.[15] Rates of overall and disease-free survival were estimated according to the Kaplan–Meier method,[16] and differences between groups were assessed by means of the log-rank statistic.[17] The hazard ratios are reported with 95 percent confidence intervals.

RESULTS

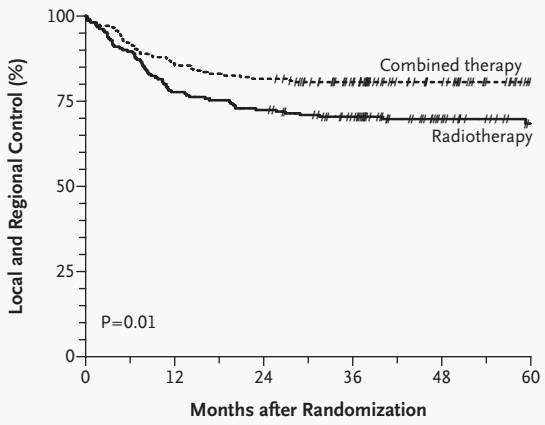
PATIENTS

Between September 9, 1995, and April 28, 2000, 459 patients were enrolled: 231 were randomly assigned to receive radiotherapy alone, and 228 to receive concurrent combined therapy. All information received at RTOG headquarters by June 20, 2003, is included in this report. After a case-by-case non-

Table 1. Pretreatment Characteristics of the Patients.

Characteristic	Radiotherapy (N=210)	Combined Therapy (N=206)
Age		
18–69 yr — no. (%)	196 (93)	195 (95)
≥70 yr — no. (%)	14 (7)	11 (5)
Median — yr	55	56
Range — yr	28–79	24–80
High-risk characteristic — no. (%)		
Positive margins	39 (19)	34 (17)
≥2 Involved nodes or extracapsular spread	171 (81)	172 (83)
Sex — no. (%)		
Male	181 (86)	177 (86)
Female	29 (14)	29 (14)
Racial or ethnic group — no. (%)*		
White	154 (73)	156 (76)
Hispanic	12 (6)	5 (2)
Black	38 (18)	43 (21)
Asian	3 (1)	1 (<1)
Native American	2 (1)	0
Other	1 (<1)	1 (<1)
Karnofsky performance score — no. (%)		
60	6 (3)	1 (<1)
70	19 (9)	33 (16)
80	62 (30)	56 (27)
90	95 (45)	93 (45)
100	28 (13)	23 (11)
Differentiation of tumor — no. (%)		
Low	15 (7)	15 (7)
Intermediate	118 (56)	113 (55)
High	72 (34)	69 (33)
Not stated	5 (2)	9 (4)
Site of tumor — no. (%)		
Oral cavity	62 (30)	50 (24)
Oropharynx	78 (37)	99 (48)
Hypopharynx	26 (12)	15 (7)
Supraglottic	32 (15)	29 (14)
Glottic	11 (5)	11 (5)
Subglottic	1 (<1)	2 (1)

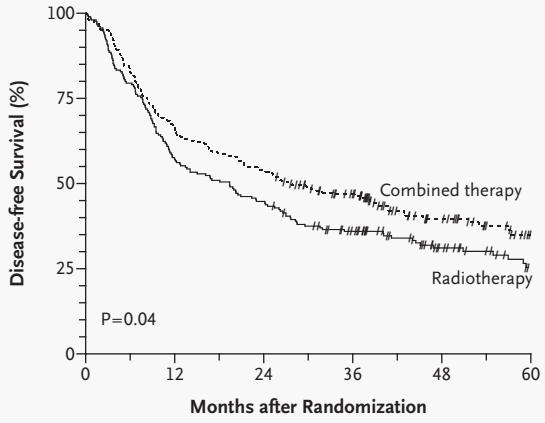
* Racial or ethnic group was self-reported.



No. at Risk			
Combined therapy	206	123	26
Radiotherapy	210	108	24

Figure 1. Rates of Local and Regional Control.

Patients assigned to receive radiotherapy and concurrent chemotherapy had a higher rate of local and regional control than patients assigned to receive radiotherapy alone (P=0.01 by Gray's test). Tick marks indicate censored data.



No. at Risk			
Combined therapy	206	111	21
Radiotherapy	210	94	19

Figure 2. Kaplan–Meier Estimates of Disease-free Survival.

Patients assigned to receive radiotherapy and concurrent chemotherapy had a higher rate of disease-free survival than patients assigned to receive radiotherapy alone (P=0.04 by the log-rank test). Tick marks indicate censored data.

blinded review by the study chairs, 43 patients (21 assigned to radiotherapy and 22 to concurrent combined therapy) were deemed ineligible. Of these 43 patients, 23 (11 in the radiotherapy group and 12 in the combined-therapy group) did not have one of the specified high-risk characteristics; 10 (5 in each group) did not have tumors that clearly arose in one of the specified sites; 7 (4 in the radiotherapy group and 3 in the combined-therapy group) did not undergo macroscopically complete resection of disease, 2 (1 in each group) had metastatic disease at study entry, and 1 (in the combined-therapy group) had an inadequate creatinine clearance. Thus, we report the outcome among 416 patients (210 in the radiotherapy group and 206 in the combined-therapy group). All surviving eligible patients were followed for a minimum of 24 months; as of June 20, 2003, 45 percent of the patients were alive. Table 1 lists the baseline characteristics of the patients. There were no significant differences in these characteristics between the groups.

COMPLIANCE WITH AND DELIVERY OF TREATMENT

Compliance with the treatment plan was assessed by each of the study chairs. The specified surgery was performed (according to the protocol or with only minor deviations) in 97 percent of patients. Three patients (less than 1 percent) had an unacceptable interval of more than 62 days from surgery to the start of postoperative treatment. The specified radiotherapy was delivered in 80 percent of patients. The treatment portals were inadequate to cover all high-risk disease in 8 percent of patients treated by irradiation and in 10 percent treated by combined therapy; the treatment portals were adequate, but the dose, number of fractions, or total time was unacceptable in 6 percent treated by irradiation and 5 percent treated by combined therapy. The specified chemotherapy was delivered in 83 percent of patients.

TUMOR CONTROL

After a median follow-up among surviving patients of 45.9 months (range, 24.8 to 85.1), 104 local or regional recurrences were observed: 64 in the radiotherapy group (30 percent) and 40 in the combined-treatment group (19 percent) (hazard ratio for local or regional recurrence, 0.61; 95 percent confidence interval, 0.41 to 0.91; P=0.01) (Fig. 1). Including all ineligible randomized patients in the analysis did not change the qualitative result (hazard ratio, 0.58; 95 percent confidence interval, 0.40 to 0.85; P=0.003). The estimated two-year rate of local and regional control was 72 percent for radiotherapy alone and 82 percent for combined therapy. Only eight local and regional recurrences have been ob-

served beyond two years. Of the 189 patients who were alive on June 20, 2003, 177 (94 percent) had not had a local or regional recurrence.

PATTERNS OF FAILURE

Local or regional recurrence as the first site of treatment failure occurred in 61 of 210 patients who received radiotherapy (29 percent) and in 33 of 206 patients given combined therapy (16 percent) (P=0.002). The incidence of distant metastasis as the first evidence of treatment failure was similar in the two groups (23 percent in the radiotherapy group and 20 percent in the combined-therapy group, P=0.46).

SURVIVAL

Disease-free survival was significantly longer after concurrent combined therapy than after radiotherapy alone (hazard ratio for disease or death, 0.78; 95 percent confidence interval, 0.61 to 0.99; P=0.04) (Fig. 2). A total of 148 treatment failures were associated with radiotherapy (70 percent), and 124 (60 percent) with combined therapy. However, overall survival did not differ significantly between groups (hazard ratio for death, 0.84; 95 percent confidence interval, 0.65 to 1.09; P=0.19) (Fig. 3), with 123 deaths associated with radiotherapy and 104 associated with combined therapy.

COMPLIANCE WITH CHEMOTHERAPY

A total of 125 patients (61 percent) received all three planned cycles of cisplatin, 47 (23 percent) received two cycles, 27 (13 percent) received one cycle, and 4 (2 percent) received no chemotherapy. In three other patients documentation of chemotherapy was insufficient. The 171 patients (83 percent) who received chemotherapy exactly as planned in the protocol or with only minor variations had a two-year rate of local and regional control of 82 percent, which is indistinguishable from the 82 percent rate among all patients assigned to concurrent combined therapy.

ADVERSE EFFECTS

The addition of chemotherapy to radiotherapy increased the incidence of severe adverse effects (Table 2). Acute adverse effects of grade 3 or greater occurred in 34 percent of patients who received radiotherapy alone and in 77 percent of patients who received concurrent combined therapy (P<0.001). This increase resulted largely from an increased incidence of hematologic, mucous-membrane, and gastrointestinal adverse effects related to chemotherapy. The incidence of severe late adverse effects did not differ significantly between the groups (17 percent in the radiotherapy group and 21 percent in the combined-therapy group, P=0.29). Combining acute and late adverse effects resulted in a significantly higher likelihood of an adverse effect of grade 3 or greater at any time among patients receiving combined therapy than among those receiving radiotherapy alone (78 percent vs. 46 percent, P<0.001). No patient treated with radiotherapy alone died of a protocol-related adverse effect, whereas four patients (2 percent) who received concurrent combined therapy did so. Four patients died within 30 days after the end of treatment: one in the radiotherapy group (who died of tumor progression) and three in the combined-therapy group (one of whom died of tumor progression).

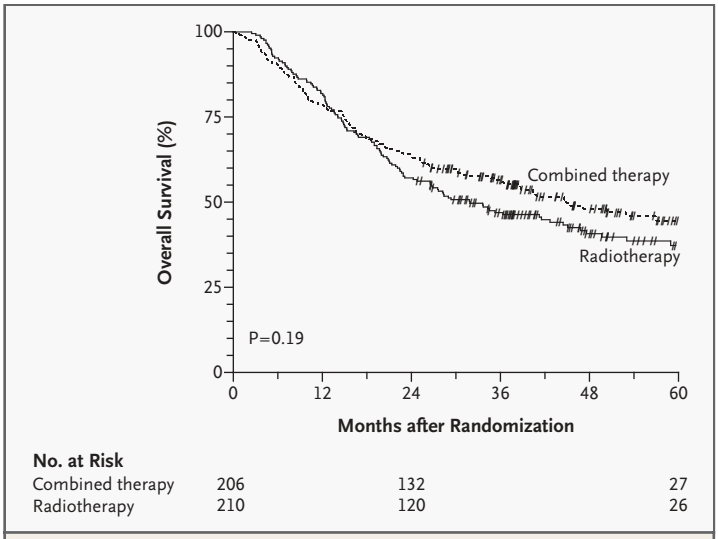


Figure 3. Kaplan–Meier Estimates of Overall Survival.
Overall survival did not differ significantly between groups (P=0.19 by the log-rank test). Tick marks indicate censored data.

DISCUSSION

Postoperative irradiation improves the outcome of advanced squamous-cell carcinoma arising in the head and neck, but the five-year rate of disease-free survival is generally less than 50 percent. Recurrent local and regional disease remains the most common form of treatment failure. One strategy to improve the outcome is to intensify the effects of postoperative radiotherapy by administering concurrent

Table 2. Adverse Effects.*

Adverse Effect	Radiotherapy			Combined Therapy		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	number of patients (percent)					
Acute†						
Hematologic	1	0	0	61	17	0
Mucous membrane	35	2	0	55	7	0
Pharynx and esophagus	32	0	0	49	1	0
Nausea and vomiting	0	0	0	28	12	0
Upper gastrointestinal tract	6	0	0	25	7	0
Skin	20	1	0	14	0	0
Infection	1	0	0	12	0	1
Neurologic	0	0	0	9	1	0
Genitourinary tract	0	0	0	6	0	0
Anemia	0	0	0	6	0	0
Larynx	2	1	0	5	1	0
Renal	0	0	0	3	2	0
Salivary gland	2	0	0	3	1	0
Subcutaneous	0	0	0	2	0	0
Diarrhea	0	0	0	1	1	0
Hepatic	0	0	0	1	1	0
Respiratory tract	0	0	0	1	0	0
Bone	1	0	0	0	1	0
All others	1	3	0	25	6	2
Grade of most severe acute adverse effect	65	7	0	111	44	2
Late‡						
Pharynx and esophagus	12	1	0	15	0	0
Salivary gland	5	0	0	7	0	0
Larynx	3	1	0	5	0	1
Bone	1	1	0	1	5	0
Subcutaneous	6	1	0	3	0	0
Mucous membrane	3	2	0	1	3	0
Upper gastrointestinal tract	1	0	0	3	0	0
Hematologic	1	1	0	3	0	0
Joint	2	0	0	1	0	0
Neurologic	2	0	0	3	0	0
Renal	0	0	0	1	1	0
Skin	2	0	0	2	3	0
All others	5	2	0	4	1	1
Grade of most severe late adverse effect§	28	7	0	29	11	2
Any¶						
Grade of most severe adverse effect§	82 (39)	14 (7)	0	106 (51)	51 (25)	4 (2)

* Some patients had more than one adverse effect.
† Data were available for 209 patients in the radiotherapy group and 204 patients in the combined-therapy group.
‡ Data were available for 208 patients in the radiotherapy group and 201 patients in the combined-therapy group.
§ Scoring was on a per-patient basis.
¶ Data were available for 209 patients in the radiotherapy group and 206 patients in the combined-therapy group.

chemotherapy after a macroscopically complete resection. RTOG 8824, a nonrandomized, phase 2 trial, suggested that this approach may decrease the risk of local and regional recurrence among high-risk patients.[5]

While our trial was being conducted, the European Organization for Research and Treatment of Cancer (EORTC) was conducting a similar, large-scale trial.[18] (The final results appear elsewhere in this issue of the *Journal*.[19]) The eligibility criteria were similar to ours except with respect to high-risk status. In the EORTC trial, high risk was defined by the presence of any of the following pathological features: involved surgical margins, extranodal spread of disease, nodal tumor at level 4 or 5 in the case of oral-cavity or oropharyngeal primaries, perineural disease, or vascular tumor emboli. The radiotherapy and chemotherapy regimens were identical in the two trials. The EORTC trial was designed to detect a 15 percent increase in the rate of disease-free survival (from 40 percent to 55 percent at three years), whereas our trial was designed to detect a 15 percent increase in the rate of local and regional control.

After a median follow-up of 34 months, the estimated 3-year disease-free survival rates in the EORTC trial were 41 percent in the radiotherapy group and 59 percent in the combined-therapy group ($P=0.009$). The rates of overall survival and of local and regional control were significantly higher and the time to progression was significantly longer in the group given concurrent combined therapy. However, the concurrent administration of cisplatin increased the incidence of grade 3 or 4 functional mucosal reactions (21.3 percent vs. 44.5 percent, $P<0.001$) and caused granulocytopenia and thrombocytopenia of grade 3 or more in 12.8 percent of patients. The authors concluded that postoperative concurrent combined therapy significantly improves the outcome among selected high-risk patients.

Our results also demonstrate a significant improvement in local and regional control with concurrent postoperative chemotherapy and radiotherapy (our primary end point) and disease-free survival (a secondary end point). However, unlike the EORTC trial, overall survival in our trial was not significantly longer in the combined-therapy group than in the radiotherapy group (median, 31.9 vs. 44.9 months). In this regard, it is important to emphasize that the eligibility criteria for the two trials differed. Precisely how much of the difference in overall survival between the two trials is directly attributable to the type of patients selected is unknown. Overall survival among patients with head and neck cancer is a complex issue because of the common occurrence of death from other diseases related to alcohol use, smoking, or both. At the time of the last analysis of this study, the overall survival curves were separating in favor of combined treatment, and if this trend continues, there may eventually be a significant difference in survival between the two groups.

The human cost of intensified treatment with concurrent postoperative chemotherapy and radiotherapy was a significant increase in severe adverse effects. Four patients (2 percent) assigned to concurrent therapy died as a direct result of the treatment (as compared with none of those who were assigned to radiotherapy alone). In addition, 27 percent of patients assigned to concurrent therapy had an adverse effect of grade 4 or 5, as compared with 7 percent of those who received radiotherapy alone.

The frequency of distant metastases in both groups was similar, suggesting that the concurrently administered regimen of chemotherapy that we evaluated did not exert its principal beneficial effect by preventing metastases. Rather, its predominant effect was probably to potentiate both the beneficial and the adverse effects of the radiotherapy. A radiosensitizing regimen that would increase the benefit of radiotherapy without increasing its toxicity would be highly desirable.

In summary, our trial establishes the proof of principle that concurrent postoperative administration of chemotherapy and radiotherapy is a way to intensify treatment for resectable high-risk head and neck tumors. Our results should not be applied to all patients who require postoperative irradiation; in particular, they cannot be applied to patients who would not have qualified for this trial. However, we believe that our data, in combination with the EORTC data, establish a new standard of care for adjuvant therapy of physically fit patients with high-risk head and neck cancer.

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