

CHEMORADIOTHERAPY FOLLOWED BY SURGERY COMPARED WITH SURGERY ALONE IN SQUAMOUS-CELL CANCER OF THE ESOPHAGUS

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ABSTRACT

Background We conducted a multicenter, randomized trial to compare preoperative chemoradiotherapy followed by surgery with surgery alone in patients with stage I and II squamous-cell cancer of the esophagus.

Methods The preoperative combined therapy consisted of two one-week courses; each involved radiotherapy, in a dose of 18.5 Gy delivered in five fractions of 3.7 Gy each, and 80 mg of cisplatin per square meter of body-surface area, administered 0 to 2 days before the first day of radiotherapy. The surgical plan included one-stage en bloc esophagectomy and proximal gastrectomy by the abdominal and right thoracic routes, to be performed immediately after randomization in the group assigned to surgery alone and two to four weeks after the completion of preoperative chemoradiotherapy in the group assigned to combined therapy.

Results A total of 297 patients entered the study; 11 were found to be ineligible, and 4 were lost to follow-up. Of the remaining 282, 139 were assigned to surgery alone and 143 to combined therapy. After a median follow-up of 55.2 months, no significant difference in overall survival was observed; the median survival was 18.6 months for both groups. As compared with the group treated with surgery alone, the group treated preoperatively had longer disease-free survival ($P=0.003$), a longer interval free of local disease ($P=0.01$), a lower rate of cancer-related deaths ($P=0.002$), and a higher frequency of curative resection ($P=0.017$). However, there were more postoperative deaths ($P=0.012$) in the group treated preoperatively with chemoradiotherapy. Three prognostic factors were found to influence survival in a multivariate analysis: the disease stage, based on computed tomography; the location of the tumor; and whether the surgical resection was curative.

Conclusions In patients with squamous-cell esophageal cancer, preoperative chemoradiotherapy did not improve overall survival, but it did prolong disease-free survival and survival free of local disease. (N Engl J Med 1997;337:161-7.)

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ESOPHAGEAL cancer is a highly malignant disease. Data from French tumor registries indicate that five-year overall survival ranges from 2 percent to 8 percent for all stages.¹⁻³ The squamous-cell type predominates, but the incidence of adenocarcinoma of the esophagus is increasing rapidly.⁴

Surgical resection is the standard treatment for early esophageal cancer.⁵ During the past decade, outcomes with surgery have improved, as indicated by an increased rate of curative resection, a decreased rate of postoperative death, and better five-year survival.^{6,7} However, the proportion of patients who survive for five years remains low, ranging from 30 to 50 percent for those with stage I disease, 15 to 30 percent for those with stage IIA disease, and 5 to 15 percent for those with disease in stage IIB.^{5,8} Patterns of treatment failure point to the need for better control of local and distant recurrences.⁹⁻¹³

Several phase 2 studies have indicated that preoperative treatment with a combination of chemotherapy and irradiation (chemoradiotherapy), followed by surgery, produces a complete response, as determined pathologically, in 20 to 40 percent of patients; such combination treatment thus offers the prospect of improved survival.¹⁴ From 1985 to 1988, we conducted a phase 2 study of preoperative treatment with radiotherapy and cisplatin in 119 patients with squamous-cell carcinoma of the thoracic esophagus.¹⁵ In 101 of the 111 surgically treated patients, the resection was curative. There were eight postoperative deaths. Pathological specimens from 24 patients contained no visible cancer cells. The median survival was 18 months.¹⁵ These promising results led the Fondation Française de Cancérologie Digestive and the European Organization for Research

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and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Cooperative Group to initiate a prospective, multicenter, randomized trial comparing preoperative chemoradiotherapy followed by surgery with surgery alone. The main end point was overall survival. Secondary end points were disease-free survival and survival free of local disease or distant metastases.

METHODS

Eligibility Criteria

Patients were included in the study if they had all of the following: invasive squamous-cell carcinoma of the thoracic esophagus; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; an age of less than 70 years; medical fitness for surgery; and a tumor judged to be resectable, according to the policy of each center. Other criteria included a leukocyte count above 3500 per cubic millimeter, a serum creatinine level of at least 1.4 mg per deciliter (120 μ mol per liter), and a platelet count above 120,000 per cubic millimeter. Written informed consent was required. Patients were excluded if they had lost more than 15 percent of their body weight or if they had previously undergone treatment for this disease or any other cancer except basal-cell carcinoma of the skin.

The extent of the tumor was evaluated by clinical examination, esophagography, esophagoscopy, bronchoscopy, computed tomography (CT) of the lower neck, chest, and upper abdomen, and ultrasonography of the liver. Since endoscopic ultrasonography was not available for this study, we used a staging system based on the results of the CT scan.¹⁶ The T stage was defined by the maximal transverse diameter of the esophageal tumor: less than 1 cm (T1), between 1 and 3 cm (T2), and larger than 3 cm (T3). Tumors with invasion of any neighboring structure were classified as T4. The mediastinal and celiac lymph nodes were classified as N1 (invaded) if the maximal transverse diameter of these nodes was larger than 1 cm; otherwise, they were classified as N0.

We included patients with stage T1N0, T1N1, T2N0, T2N1, or T3N0 disease. We excluded patients with one or more of the following: a tumor located within the first 4 cm of the esophagus, metastases in cervical lymph nodes, evidence of invasion of the bronchus on bronchoscopy, and tumor classified T3N1, T4N0, or T4N1. These three stages were thought by the surgeons' panel to be usually not curable by surgical resection.

Treatment

Surgery

For tumors in the middle and lower parts of the mediastinum, the recommended resection procedure was a one-stage en bloc esophagectomy and proximal gastrectomy via the abdominal and right thoracic routes. For tumors in the upper mediastinum, an additional cervical route was recommended. In either case, a two-field lymph-node resection was recommended. In the combined-treatment group, surgery was planned two to four weeks after the last preoperative treatment and after the leukocyte and platelet counts returned to normal. Curative resection was defined by the surgeon as a macroscopically complete excision of the tumor.

Radiotherapy

The target of radiotherapy was the macroscopic tumor and enlarged lymph nodes, if any, surrounded by 5-cm proximal and distal margins and a 2-cm radial margin. The target was extended to the inferior cervical area in the case of tumors located above the carina. No attempt was made to treat systematically the anatomical mediastinum or the celiac area. The use of multiple-field techniques and daily treatment of all fields were mandatory. Irradiation was delivered in two one-week courses, separated by two weeks. During

each course, five daily fractions of 3.7 Gy each were delivered. The specified dose was delivered at the intersection of the central axis of the beams, according to international guidelines.¹⁷ The delivered dose was 18.5 Gy per course, for a total of 37 Gy. The maximal recommended dose to the spinal cord was 25 Gy.

Chemotherapy

Cisplatin, at a dose of 80 mg per square meter of body-surface area, was given on an outpatient basis to patients assigned to preoperative treatment 0 to 2 days before each course of radiotherapy; standard techniques were used for hydration and alkalization. The second dose of cisplatin was reduced by 50 percent if there was a grade 1 increase in the serum creatinine level or grade 2 neutropenia, thrombocytopenia, or both, according to the classification system of the World Health Organization (WHO). Treatment with the drug was discontinued if more severe acute toxic effects developed.

Pathological Analysis

Analysis of the surgical specimen included a determination of the histologic type of the tumor, the degree of extension of the tumor through the esophageal wall, whether there was nodal involvement, and the status of proximal and distal margins. For patients treated preoperatively, the response was defined according to the Tumor Regression Grade, which ranges from 1 (indicating complete regression) to 5 (no change), as described by Mandard et al.¹⁸

Follow-up

Follow-up evaluation was performed every four months after surgery until death or the end of the study period. Each evaluation included a clinical examination, esophagography, chest radiography, and ultrasonography of the liver. Treatment failure was defined as indicated by any morphologic evidence of tumor; only the first failure in a patient, which could be local, distant, or both, was reported. Subsequent sites of involvement by tumor were not recorded. After recurrence, the patients could be treated by any method considered useful.

Randomization and Statistical Analysis

Patients were randomly assigned to a treatment group by a central office after their eligibility was established. Randomization was balanced by institution, without any other type of stratification. The two treatment groups were compared with respect to base-line characteristics with use of the t-test for continuous variables and the chi-square test for categorical variables. When necessary, Fisher's exact test was used. To detect an improvement in five-year survival from 15 percent in the surgery-alone group to 25 percent in the combined-treatment group, with a one-sided type I error of 0.05 and a power of 80 percent, a total of 256 deaths would have to occur.¹⁹ Assuming an average follow-up of five years, the intended number of randomized patients was 320. Recruitment was stopped earlier than anticipated because of a slightly higher than anticipated rate of postoperative mortality in the combined-treatment group. For each end point, the probability of successful treatment or of adverse events was estimated as a function of time by the Kaplan-Meier method,²⁰ and all the comparisons were made with the log-rank test.²¹ Data on patients were analyzed according to intention-to-treat principles. Survival was calculated from the date of randomization to the most recent follow-up contact or to the date of recurrence or death and included all patients in the study. For the analyses of disease-free survival and time without local or distant recurrence, treatment was considered to have failed at the time of surgery in patients who did not undergo curative resection. All P values are two-sided.

Analysis of Prognostic Factors

The following variables were studied as potential prognostic factors with respect to overall survival: age, sex, WHO perform-

ance status, weight loss, location of the tumor, tumor stage as determined by CT, whether the resection was curative or palliative, and the status of histologic margins. A Cox-model analysis was performed that included the variables that were significant in the univariate analysis.²² The positive predictive value of the tumor-stage classification based on the CT scan was investigated in patients with curative resections in the surgery-alone group.

RESULTS

Patients

From January 1989 to June 1995, 297 patients were enrolled. Eleven patients (five in the group assigned to surgery alone and six in the combined-treatment group) were found to be ineligible; the reasons for ineligibility were the presence of another primary cancer (in five patients), excessive weight loss (three), distant metastasis (one), previous treatment for esophageal cancer (one), and refusal on the part of the patient (one). An additional four patients were lost to follow-up after randomization. Thus, a total of 282 patients (139 assigned to surgery alone and 143 assigned to combined treatment) remained in the analysis. The two treatment groups were similar except for a slightly higher proportion of patients with WHO performance status 1 in the combined-treatment group (Table 1).

Compliance with Treatment

Among the 139 patients assigned to surgery alone, 2 received preoperative chemoradiotherapy; 1 of these 2 patients and 1 other did not undergo resection because of progression of the disease outside the mediastinum. Among the 143 patients assigned to combined treatment, 1 had surgery before receiving preoperative chemoradiotherapy; 2 patients did not undergo the second course of irradiation (1 died of toxic effects and 1 had disease progression); 3 patients did not undergo the second course of chemotherapy because of toxic effects. Five patients in this group did not undergo surgery for the following reasons: disease progression (three), refusal by the patient (one), and preoperative death (one). The mean (\pm SD) total delivered dose of radiation was 37 ± 3 Gy; the mean delivered dose of cisplatin per course was 77 ± 11 mg per square meter. Cisplatin induced vomiting in 37 patients and WHO grade 3 neutropenia in 3. The median time from the end of the preoperative treatment to surgery was 21 days (range, 6 to 126).

Surgery

Overall, 275 patients underwent surgery. There was no difference in surgical procedures between the two groups; more than 80 percent of all patients had a transthoracic resection, but resection was curative in more patients in the combined-treatment group (112 of 138 vs. 94 of 137, $P=0.017$). During the postoperative period, 36 (26.3 percent) of the pa-

TABLE 1. CHARACTERISTICS OF THE 282 PATIENTS, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	SURGERY ALONE (N=139)	COMBINED TREATMENT (N=143)
Sex — no. (%)		
Male	134 (96.4)	129 (90.2)
Female	5 (3.6)	14 (9.8)
Mean age \pm 2 SD — yr	56.6 \pm 7.6	56.7 \pm 8.0
Mean weight loss \pm 2 SD — kg	5.0 \pm 2.8	4.9 \pm 2.6
ECOG performance status — no. (%) [†]		
0	80 (57.6)	74 (51.7)
1	25 (18.0)	48 (33.6)
2	3 (2.2)	4 (2.8)
Unknown	31 (22.3)	17 (11.9)
Location of tumor — no. (%)		
Upper esophagus	26 (18.7)	22 (15.4)
Middle esophagus	72 (51.8)	74 (51.7)
Lower esophagus	41 (29.5)	47 (32.9)
Histologic classification — no. (%)		
Well or moderately differentiated	90 (64.7)	97 (67.8)
Poorly differentiated	44 (31.7)	42 (29.4)
Undifferentiated	5 (3.6)	4 (2.8)
Disease stage — no. (%) [‡]		
T1N0	25 (18.0)	24 (16.8)
T2N0	44 (31.7)	48 (33.6)
T3N0	38 (27.3)	38 (26.6)
T1N1 or T2N1	32 (23.0)	33 (23.1)

*Patients found to be ineligible or lost to follow-up have been excluded. Because of rounding, percentages do not always total 100.

[†] $P=0.04$ for the comparison between treatment groups by the maximum-likelihood chi-square test.

[‡]Disease stage was determined on the basis of the results of CT scanning.

tients in the surgery-alone group and 45 (32.6 percent) in the combined-treatment group had one or more severe complications ($P=0.249$), mostly pneumonia, infections, and anastomotic leakage. The postoperative mortality was significantly higher in the combined-treatment group (17 of 138, as compared with 5 of 137 in the surgery-alone group; $P=0.012$), mainly because of the higher number of patients with respiratory insufficiency (6 vs. 0) and mediastinal infection or sepsis (7 vs. 2). The average duration of hospitalization was 24 ± 20 days in both groups. There was no significant difference in morbidity or mortality among the participating centers; five centers enrolled 80 percent of the patients.

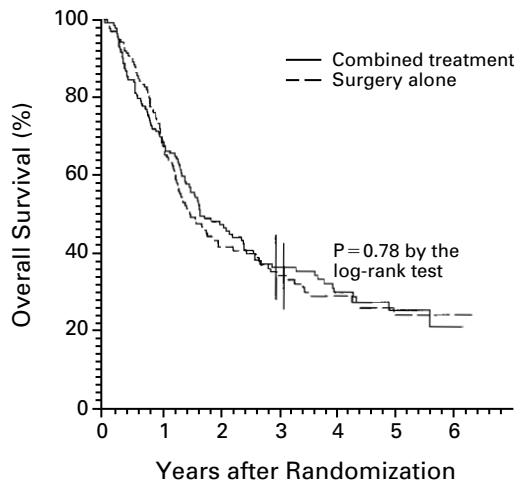
Pathological Responses

After curative resection in the combined-treatment group, a complete pathological response was noted in 29 of 112 patients (26 percent), and 20 patients (18 percent) were scored as having a major pathological response (Table 2). Comparison of the two groups indicated a significantly lower stage of disease after preoperative treatment; this was true

TABLE 2. PATHOLOGICALLY DETERMINED DISEASE STAGE AFTER CURATIVE RESECTION, ACCORDING TO TREATMENT GROUP.

STAGE	SURGERY ALONE (N=94)	COMBINED TREATMENT (N=112)
	no. of patients	
T0 (sterilization)	0	29*
T1	26	27
T2	17	23
T3	47	31
TX	4	2
N0	41	66
N1	52	42
NX	1	4

*Two additional sterilized tumors were observed in patients who had noncurative resections.



Combined treatment						
Patients at risk	143	96	59	38	26	10
No. of deaths	0	45	75	87	93	96
Surgery alone						
Patients at risk	139	92	48	35	24	12
No. of deaths	0	46	79	87	92	95

Figure 1. Overall Survival among Patients with Esophageal Cancer Treated with Surgery Alone or with Preoperative Chemoradiotherapy Followed by Surgery (Combined Treatment).

The vertical bars indicate 95 percent confidence intervals at three years. The numbers of deaths shown below the figure are cumulative.

both for the tumor (T) stage ($P=0.001$) and the nodal (N) stage ($P=0.03$) determined pathologically. The number of patients with mediastinal lymph-node metastases was significantly lower in the combined-treatment group (26 of 105 who had exploratory lymph-node dissection vs. 66 of 115, $P=0.001$), whereas the proportion with celiac lymph-node invasion did not differ significantly between the groups (44 of 115 vs. 48 of 117).

Survival

After a median follow-up of 55.2 months, 203 patients had died. For both groups, the median survival was 18.6 months. The overall survival curves of the two groups did not differ significantly (relative risk of death in the combined-treatment group as compared with the surgery-alone group = 1.0; 95 percent confidence interval, 0.7 to 1.5; $P=0.78$) (Fig. 1); the difference between the groups was still nonsignificant after adjustment for the difference in the WHO performance status and inclusion of all randomized patients in the analysis ($P=0.65$ and $P=0.75$, respectively). There was a significant difference in the proportion of deaths that were due to esophageal cancer in the two groups (87 of 101 patients who had surgery alone vs. 69 of 102 patients who received combined treatment, $P=0.002$) (Table 3).

Disease-free Survival

Overall, 178 patients had persistent or recurrent disease. In 76 patients, local control was never achieved, and among the 206 patients who had curative surgery, 102 had a recurrence (41 local, 26 distant, and 35 both). Disease-free survival was significantly longer in the combined-treatment group (relative risk of recurrence or death from cancer = 0.6; 95 percent confidence interval, 0.4 to 0.9; $P=0.003$) (Fig. 2).

Time without Local or Distant Recurrence

The time free of local disease was significantly longer in the combined-treatment group (relative risk of local recurrence = 0.6; 95 percent confidence interval, 0.4 to 0.9; $P=0.01$), but there was no significant difference in the time to distant metastasis (relative risk = 0.7; 95 percent confidence interval, 0.4 to 1.4; $P=0.24$).

Late Toxic Effects

At two years, the rates of pulmonary insufficiency, cardiac failure, and stenosis of the esophageal anastomosis were 7.2 percent, 1.4 percent, and 12.3 percent, respectively. No statistically significant difference was observed between the treatment groups.

Prognostic Factors

In the univariate analysis, survival was significantly shorter among patients with a loss of more than

5 percent of body weight ($P=0.01$), a tumor whose upper part was located within 25 cm of the mandibular arch ($P=0.04$), and stage N1 disease (based on the results of CT). Curative resection was associated with a significant increase in survival. In the multivariate analysis, only location of the tumor within 25 cm of the mandibular arch (relative risk of death = 1.4; 95 percent confidence interval, 1.0 to 1.9; $P=0.05$), stage N1 disease (relative risk = 1.5; 95 percent confidence interval, 1.1 to 2.2; $P=0.01$), and palliative rather than curative resection (relative risk = 2.3; 95 percent confidence interval, 1.7 to 3.3; $P<0.001$) remained statistically significant.

The positive predictive value of the disease-stage classification based on the CT scan was 76 percent for stage T1 tumors (19 tumors classified as T1 on the basis of the pathological analysis among 25 classified as T1 on the basis of the CT scan) and 84 percent for stage T3 tumors (16 of 19). For T2 lesions, it was only 22 percent (10 of 46); 7 tumors were classified as stage T1 and 29 as stage T3. The values for stages N0 and N1 were 49 percent (36 of 73) and 75 percent (15 of 20), respectively.

DISCUSSION

We found a significant prolongation of disease-free survival among patients with squamous-cell esophageal carcinoma who received chemoradiotherapy before resection. This gain was due mainly to a local effect, as attested by a longer interval free of local disease in the combined-treatment group. Other indicators of efficacy were a higher rate of curative resection, clear-cut evidence of a lower disease stage after preoperative therapy, and a higher rate of major pathological responses. However, overall survival was not significantly different in the two groups, despite a reduced rate of death due to esophageal cancer in the combined-therapy group. The similar mortality rates may reflect excessive postoperative mortality among patients treated preoperatively with chemoradiotherapy.

The value of adjuvant treatment of esophageal cancer has been called into question by the results of several randomized trials. Preoperative irradiation,²³⁻²⁶ postoperative irradiation,^{27,28} and preoperative chemotherapy²⁹⁻³² have not been efficacious. Preoperative combined chemoradiotherapy has been tested in four randomized studies of squamous-cell cancer of the esophagus. A Scandinavian trial³³ assigned 217 patients either to surgery alone or to preoperative treatment (radiotherapy, chemotherapy, or sequential chemoradiotherapy). The postoperative mortality in these groups was not significantly different. Patients who received preoperative irradiation with or without chemotherapy had a significant gain in survival as compared with those treated with surgery with or without chemotherapy. However, the small number of patients in each group and the low rate of curative

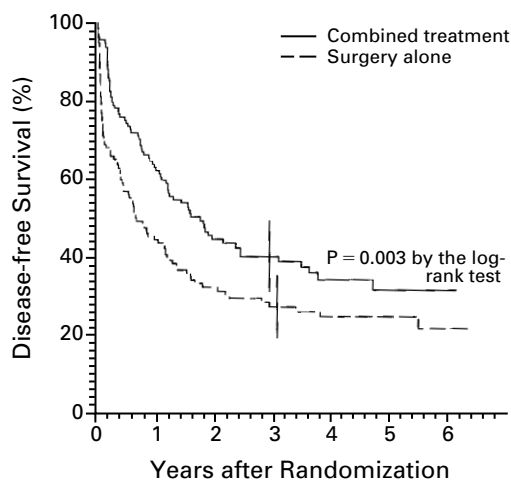
TABLE 3. SURVIVAL AND CAUSES OF DEATH, ACCORDING TO TREATMENT GROUP.*

CATEGORY	SURGERY ALONE (N = 145)	COMBINED TREATMENT (N = 148)
	no. (%)	
Alive at last contact	44 (30.3)	46 (31.1)
Dead	101 (69.7)	102 (68.9)
Died before surgery	0	1 (1.0)
Cause of death after surgery		
Esophageal cancer†	87 (86.1)	69 (67.6)
Postoperative complications‡	5 (5.0)	17 (16.7)
Secondary tumor	2 (2.0)	9 (8.8)
Cardiovascular disease	2 (2.0)	1 (1.0)
Delayed anastomotic leakage	1 (1.0)	1 (1.0)
Other	1 (1.0)	3 (2.9)
Unknown	3 (3.0)	1 (1.0)

*All patients enrolled, with the exception of the four lost to follow-up, were included in this analysis. Because of rounding, percentages do not total 100.

† $P=0.002$ by the chi-square test.

‡ $P=0.012$ by the chi-square test.



Combined treatment	
Patients at risk	143 75 45 30 18 5
No. of treatment failures	0 51 71 76 79 80
Surgery alone	
Patients at risk	139 57 33 24 19 10
No. of treatment failures	0 76 91 95 97 97

Figure 2. Disease-free Survival among Patients with Esophageal Cancer Treated with Surgery Alone or with Preoperative Chemoradiotherapy Followed by Surgery (Combined Treatment).

The vertical bars indicate 95 percent confidence intervals at three years. The numbers of deaths shown below the figure are cumulative.

resection (44 percent) make the results of that study debatable. Le Prise et al.³⁴ randomly assigned 104 patients with squamous-cell cancer to surgery or sequential preoperative chemoradiotherapy, followed by surgery. A curative resection was performed in 84 percent of the patients, and postoperative mortality was 8 percent in both groups. There were no significant differences in survival. Preliminary results of a study by Urba et al.³⁵ in 100 patients, most (75 percent) with esophageal adenocarcinoma, suggest that preoperative concurrent chemoradiotherapy does not increase survival. In another trial,³⁶ 113 patients with adenocarcinoma located mainly in the distal part of the esophagus and the cardia were assigned to surgery or to preoperative concurrent chemoradiotherapy followed by surgery. The overall resection rate was 93 percent, and the postoperative death rates in the two groups were not significantly different. At three years, overall survival was significantly longer in the combined-treatment group ($P=0.01$).

The increased number of postoperative deaths in the combined-treatment group in our study could be due to deleterious effects of the high dose of radiation per fraction or of chemoradiotherapy on lung tissue, to immunosuppression, or to malnutrition. In experimental studies, a deleterious effect of high fractional doses of radiation on lung tissues has been described, but no increase in the toxicity of radiation has been observed when cisplatin has been added.³⁷⁻³⁹ In the randomized trials discussed above, excessive acute toxic effects on the lungs were not reported with doses that varied from 1.8 to 2.67 Gy per fraction. The 3.7-Gy fractional dose used in our study probably had a detrimental effect. Furthermore, the pause between the two courses of treatment is now known to allow repopulation of tumor cells in other anatomical locations.⁴⁰ In future studies, fractional doses in the 2-Gy range and continuous irradiation should be used. Improvements in chemotherapy are also possible; the combination of fluorouracil with cisplatin and radiotherapy has shown promise for the nonsurgical management of localized disease.⁴¹

Our analysis of prognostic factors showed that the determination that the disease is at stage N1 on the basis of the results of the CT scan is a powerful indicator of prognosis. This contrasts with the apparent lack of prognostic value of a determination of the N0 stage, suggesting that the CT scan-based detection of minimal pathological nodal invasion is difficult. The well-established value of the quality of the surgical resection — that is, of whether the resection is curative or not — as a prognostic factor was confirmed in our study.^{5,8}

Preoperative chemoradiotherapy merits consideration as an adjuvant treatment for squamous-cell esophageal cancer. Future efforts should aim to improve the efficacy of the treatment while reducing its toxicity.

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APPENDIX

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