Only Pathologic Complete Response to Neoadjuvant Chemotherapy Improves Significantly the Long Term Survival of Patients with Resectable Esophageal Squamous Cell Carcinoma

Final Report of a Randomized, Controlled Trial of Preoperative Chemotherapy versus Surgery Alone

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BACKGROUND. Surgery is the standard treatment for patients with resectable esophageal carcinoma, but the long term prognosis of these patients is unsatisfactory. Some randomized trials of preoperative chemotherapy suggest that the prognosis of patients who respond may be improved.

METHODS. This randomized, controlled trial compared patients with clinically resectable esophageal epidermoid carcinoma who underwent surgery alone (Arm A) with those who received preoperative chemotherapy (Arm B). Overall survival and the prognostic impact of major response to chemotherapy were analyzed. Forty-eight patients were enrolled in each arm. Chemotherapy consisted of two or three cycles of cisplatin (100 mg/m^2 on Day 1) and 5-fluorouracil (1000 mg/m^2 per day continuous infusion on Days 1–5). In both study arms, transthoracic esophagectomy plus two-field lymphadenectomy was performed. The two groups were comparable in terms of patient characteristics.

RESULTS. Forty-seven patients were evaluable in each arm. The curative resection rate was 74.4% (35 of 47 patients) in Arm A and 78.7% (37 of 47 patients) in Arm B. Treatment-related mortality was 4.2% in both arms. The response rate to preoperative chemotherapy was 40% (19 of 47 patients), including 6 patients (12.8%) who achieved a pathologic complete responses. Overall survival was not improved significantly. The 19 patients in Arm B who responded to chemotherapy and underwent curative resection had significantly better 3-year and 5-year survival rates (74% and 60%, respectively) compared with both nonresponders (24% and 12%, respectively; $P = 0.0002$) and patients in Arm A who underwent complete resection (46% and 26%, respectively; $P = 0.01$): Patients who achieved a pathologic complete response ($P = 0.01$), but not those who achieved a partial response ($P = 0.2$), had significantly improved survival.

CONCLUSIONS. Patients with resectable esophageal carcinoma who underwent preoperative chemotherapy and obtained a pathologic complete response had a significantly improved long term survival. Major efforts should be undertaken to identify patients before neoadjuvant treatments who are likely to respond. ***Cancer* 2001;91:2165–74.** © *2001 American Cancer Society.*

KEYWORDS: esophagus, squamous cell carcinoma, neoadjuvant chemotherapy, surgery, randomized controlled trial.

Esophagectomy represents the standard of care for patients with clinically resectable esophageal carcinoma who are medically fit for surgery.[1,2] However, the overall long term results of surgery alone are still unsatisfactory, because < 25% of patients survive 5 years after esophagectomy.[3] Therefore, trials that have combined surgery with preoperative or postoperative chemotherapy and/or radiotherapy have been developed. The available Phase II and Phase III randomized trials of preoperative chemotherapy[1,2,4,5] or chemoradiotherapy versus surgery alone[1,2,6–10] have shown encouraging results but need further confirmation.

By 1991, when this trial was designed, clinical and research data were sufficient to warrant a study comparing surgery alone with preoperative chemotherapy followed by surgery in patients with clinically resectable squamous cell carcinoma of the esophagus.[5,11–14] The primary objective of this single-center, randomized controlled trial was to analyze the overall prognostic impact of preoperative chemotherapy compared with surgery alone. The secondary endpoints were to analyze the influence of major response to preoperative chemotherapy on long term survival and to study the patterns of failure.

MATERIALS AND METHODS

Eligibility criteria included the presence of a clinically resectable squamous cell carcinoma of the esophagus (Stage IIA, IIB, and III; i.e., T2–T3 N0 M0 and T1–T3 N1 M0); the presence of distant lymph node metastasis (i.e., M1 Lym, Stage IV) excluded patient eligibility. All patients satisfied the other eligibility criteria: They were ages 18–70 years; had adequate cardiac, hepatic, renal, and bone marrow reserve; and could tolerate both the planned chemotherapy regimen and the surgical procedure. Patients were ineligible if they had previously undergone treatment for the esophageal carcinoma or had other previous or concomitant primary malignancies.

The clinical tumor stage formed the basis for patient eligibility. Preoperative tumor staging and evaluation of the patient's operative risk included a complete medical history and physical examination, complete blood count, biochemical screening (including evaluation of hepatic and renal function), electrocardiography, pulmonary function tests with blood gas analysis, chest X-ray, barium-contrast radiography of the upper gastrointestinal (GI) tract, esophagogastroduodenoscopy, ear-nose-throat evaluation and tracheobronchoscopy, computed tomography (CT) scans of the chest and upper abdomen, and ultrasound of the neck. Endoscopic ultrasonography was not performed routinely. Laparoscopy plus abdominal ultrasonography was performed only when indicated.

TABLE 1
Patient and Tumor Characteristics According to Treatment Group

Characteristic	Surgery	Chemotherapy plus surgery	*P* value
Registered (no.)	48	48	—
Evaluable	47	47	—
Gender (M/F)	38/9	38/9	ns
Mean age (yrs)	58 ± 9.3	58 ± 9.7	ns
Tumor location			
Cervical	4	3	ns
Upper thoracic	19	20	—
Midthoracic	15	11	—
Lower thoracic	10	14	—
Clinical tumor stage			
IIA (T2–T3, N0, M0)	31	32	ns
IIB (T1–T2, N1, M0)	6	4	—
III (T3, N1, M0)	11	12	—

ns: Not significant.

The 1987 International Union Against Cancer TNM classification of esophageal malignancies was used both to define the anatomic subsites of the esophagus and to define the TNM classification and Stage groupings.[15] Informed consent was obtained from all patients in this study before randomization. Ninety-six eligible patients were randomized to compare those who underwent surgery alone (Arm A; 48 patients) with those who received two or three cycles of preoperative chemotherapy plus surgery (Arm B; 48 patients). The method of randomization used a "random permuted blocks" allocation scheme, with blocks of six patients, using the Moses–Oakford algorithm.[16] The primary endpoint was overall survival. The secondary endpoints were to analyze the prognostic impact of a major response to preoperative chemotherapy and to study the patterns of tumor recurrence.

Patient and tumor characteristics according to treatment group are summarized in Table 1. The two study arms were well balanced with respect to major prognostic factors, such as patient gender and age and tumor location, T and N classification, and clinical stage before treatment.

Surgery

Patients assigned to Arm A underwent surgery immediately after randomization. The same operation was performed 3–4 weeks after chemotherapy in patients in Arm B. The following surgical procedure was used in all patients: Esophagectomy was performed through a right thoracotomy, laparotomy, and a left cervical incision when indicated; at least 6–8 cm of healthy esophagus were resected above the proximal edge of the tumor to avoid neoplastic involvement of

the section margin; en bloc lymph node dissection included the periesophageal, infracarinal, posterior mediastinal, and paracardial lymph nodes and those located along the lesser gastric curvature and at the origin of the left gastric artery, celiac trunk, common hepatic artery, and splenic artery; the azygos vein and thoracic duct were not included in the en bloc dissection. Alimentary tract reconstruction was performed immediately, preferably using the gastric pull-up technique.

Complete tumor resection was defined as R0, and incomplete resections with microscopic or macroscopic residual disease were defined as R1 and R2, respectively. Only patients who had an incomplete surgical resection were also treated with additive postoperative radiotherapy and/or chemotherapy whenever possible.

Chemotherapy

Patients assigned to Arm B received two cycles of chemotherapy with a combination of cisplatin and 5-fluorouracil before surgery. Cisplatin, at a dose of 100 mg/m^2, was administered intravenously after prehydration on Day 1 of each cycle. 5-Fluorouracil, at a dose of 1000 mg/m^2 per day, was administered in continuous intravenous infusion on Days 1–5 of each cycle. Appropriate antiemetic medications were prescribed. The second cycle was repeated beginning on Day 21. After the second cycle of chemotherapy, the tumor was restaged with barium-contrast swallow, esophagoscopy, and CT scans of the chest and upper abdomen. A third cycle of chemotherapy was begun on Day 42 in those patients who responded to the first two cycles of chemotherapy. Patients with stable or progressive disease after the first two cycles of chemotherapy underwent surgery without further delay. In all patients, surgery was performed 3–4 weeks after the last cycle of chemotherapy.

Response to chemotherapy was graded as follows[17]: A *complete response* was defined as the disappearance of any tumor evidence; a *partial response* was defined as tumor regression $\geq$ 50% without the appearance of any new lesions; *progressive disease* was defined as an increase $\geq$ 25% in the size of the primary tumor or the appearance of new lymph node or distant metastasis; *stable disease* or *no change* was defined as a decrease $<$ 50% or an increase $<$ 25% in tumor size. We defined those patients who had a partial or complete response as major responders and those with stable or progressive disease as nonresponders.

TABLE 2
Surgical Outcome, Morbidity, and Mortality According to Treatment Group

Variable	No. of patients (%)		*P* value
	Surgery	Chemotherapy plus surgery	
Eligible patients	47	47	—
Total resections	41 (87)	40 (85)	ns
Type of resection			
R0	35 (74)	37 (79)	ns
R1–R2	6 (13)	3 (6)	—
Postoperative deaths	2 (4.2)	1 (2.5)	ns
Total morbidity[a]	16 (39)	15 (37)	ns
Anastomotic leakage	1	2	ns
Pulmonary complications	8	8	ns
Cardiovascular complications	2	1	ns
Sepsis	3	3	ns
Miscellaneous complications	2	1	ns

ns: not significant.

[a] Values in parentheses are percentages of the patients who underwent resection.

Treatment-Related Morbidity and Mortality

Treatment-related mortality was defined as any death that occurred before a patient was discharged or even after discharge if there was any possible correlation with the treatment itself. Chemotherapy-related toxicity was graded according to World Health Organization (WHO) guidelines.[17] Any type of complications occurring after surgery was considered postoperative morbidity, including clinically symptomatic anastomotic leakage and pulmonary, cardiovascular, infectious, and miscellaneous complications. Surgical outcome and morbidity and mortality rates according to treatment group are listed in Table 2.

Follow-Up

After surgery, all patients were monitored extensively to obtain the most accurate information regarding the patterns of failure. Tumor progression or recurrence was classified as locoregional or distant. The follow-up program was every 2–4 months during the first year, every 4–6 months during the next 2 years, and every year thereafter. Every follow-up evaluation included a complete physical examination, complete blood count, and biochemical screening, including evaluation of hepatic function. The 4-month follow-up evaluation also included upper GI endoscopy. Subsequently, chest X-ray, barium-contrast upper GI radiography alternating with upper GI endoscopy, ear-nose-throat evaluation and tracheobronchoscopy, and ultrasonography of the neck and upper abdomen were performed every 6 months. CT scans of the chest

and upper abdomen were performed from every 6 months to 1 year or more frequently if clinically indicated.

Statistical Analysis

Based on the results of previous studies, we expected to obtain a 20% difference in survival at 2 years between the two study arms. This required the accrual of 240 patients over 6 years (α, 0.05; power, 0.8).

All data received and processed through May 31, 2000, were included in the analyses. Statistical analyses were performed using the SAS statistical package (SAS Institute, Cary, NC). Differences between groups were assessed with the Pearson chi-square test, Fisher exact test, Mann–Whitney test, or Student *t* test, as indicated. All statistical comparisons were made with two-tailed tests, and *P* values < 0.05 were reported as significant. Survival was measured from the date of randomization to the date of death or last follow-up. Survival rates and standard errors were calculated with the Kaplan–Meier method, including deaths from all causes. All patients had a minimum follow-up of 30 months. Chemotherapy-related toxic deaths and postoperative deaths were included in the survival analysis. The statistical significance of differences in survival was analyzed with the log rank test, with $P < 0.05$ considered as significant.

RESULTS

Patient Characteristics

From 1992 until 1997, 434 patients with squamous cell carcinoma of the esophagus were observed at our surgical unit, which is a high-volume referral center for patients with esophageal diseases (Chief, A.P. before 1993 and E.A. since 1993). Two hundred fifty-one patients (58%) had a Stage IIA, IIB or III (i.e., T2–T3 N0 M0 or T1–T3 N1 M0), clinically resectable esophageal tumor, whereas 30 patients (7%) had less advanced tumors, and 153 patients (35%) had tumors of a more advanced stage. One hundred fifty-three of 251 patients who were potentially eligible for the study according to clinical tumor stage did not meet the other eligibility criteria: Seven patients had already undergone some form of treatment of the esophageal tumor; 31 patients were age > 70 years; 44 patients had previous or concomitant malignancies in other organs; 9 patients were age > 70 years and also had previous or concomitant malignancies; 45 patients had concurrent diseases or poor general condition contraindicating chemotherapy, surgery, or both; 14 patients had a clinical T3–T4 tumor, suggesting that complete surgical resection was unlikely; and 5 patients refused to enter the study.

During the study period, 96 patients satisfied all the eligibility criteria and entered this single-center, randomized, controlled study: There were 47 evaluable patients in each study arm. One patient in Arm A was excluded because of an inoperable pancreatic tumor diagnosed at surgery. One patient in Arm B was excluded because of major violation of the therapy protocol. The study was closed after the accrual of 96 patients because of the lengthy recruitment phase and the lack of overall survival advantage of Arm B patients over Arm A patients, as shown by the interim analysis.

Tumor Resectability

Arm A

Forty-one of 47 patients (87%) who underwent surgery alone had an esophagectomy, and 6 patients had an unresectable tumor disclosed at thoracotomy: In all, 35 (74.4%) complete resections and 6 (12.7%) incomplete resections were performed. Two of 6 patients with unresectable tumors (tracheobronchial infiltration) found at thoracotomy underwent chemoradiotherapy (three cycles of cisplatinum-etoposide plus 45 grays of external irradiation) and subsequent complete R0 resection surgery.

Arm B

Forty of 47 patients (85%) underwent resection surgery after chemotherapy, because 1 patient died during chemotherapy, 3 patients showed progressive disease (T4) under chemotherapy, 2 patients had an increased anesthesiologic risk (ASA 4) after chemotherapy contraindicating surgery, and 1 nonresponding patient refused surgery. Thirty-seven (78.7%) complete resections and 3 (6.3%) incomplete resections were performed. All 19 patients who showed a major response to first-line chemotherapy underwent complete (R0) resection surgery.

Treatment-Related Morbidity and Mortality

Of the 47 evaluable patients assigned to preoperative chemotherapy, 32 patients (68%) received three cycles, 13 patients (27.7%) received two cycles, and 2 patients (4.3%) received only one cycle. The major adverse effects of chemotherapy were neutropenia and mucositis. WHO Grade 3 or 4 toxicity was recorded in 10 patients (21.3%); Grade 4 toxicity was hematologic in two patients, neurologic in one patient, and GI in one patient.

The overall postoperative morbidity rate was 39% (16 of 41 patients) in Arm A and 37.5% (15 of 40 patients) in Arm B ($P = 1$) (Fig. 2). The overall treatment-related mortality rate was 4.2% (2 of 47 patients) in Arm A and 4.2% (2 of 47 patients; one chemotherapy-related cardiac toxicity and one postoperative) in Arm B.

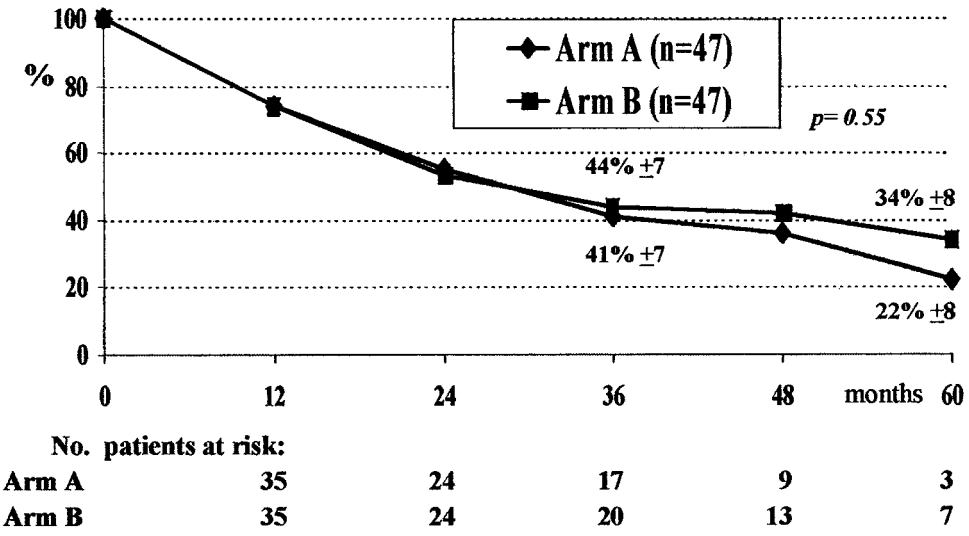


FIGURE 1. Overall survival of all evaluable patients based on the intention-to-treat analysis comparing survival in the 47 patients in Arm A who underwent surgery alone with survival in the 47 patients in Arm B who underwent preoperative chemotherapy and surgery.

Response to Preoperative Chemotherapy

The final tumor stage (i.e., the pathologic stage for patients undergoing surgery and the final clinical stage for those who did not undergo surgery for any reasons) in Arm A was Stage IIA or less in 13 of 47 patients (27.6%) and Stage IIB or more in 34 patients (72.4%) compared with 22 of 47 patients (46.8%) and 25 patients (53.2%), respectively, for patients in Arm B ($P = 0.05$).

After chemotherapy, the overall response rate (complete and major responses), as assessed by pathologic examination of the operative specimen, was 40% (19 of 47 patients). Complete responses (pT0 N0 M0) were obtained in 12.8% (6 of 47 patients). The preoperative staging of these patients was Stage IIA (T3 N0 M0) in two patients, Stage IIB (T2 N1 M0) in two patients, and Stage III (T3 N1 M0) in two patients. Two more patients had a residual in situ carcinoma (pTis N0 M0), and two other patients had a complete response of the primary tumor (pT0), but they had lymph node metastasis.

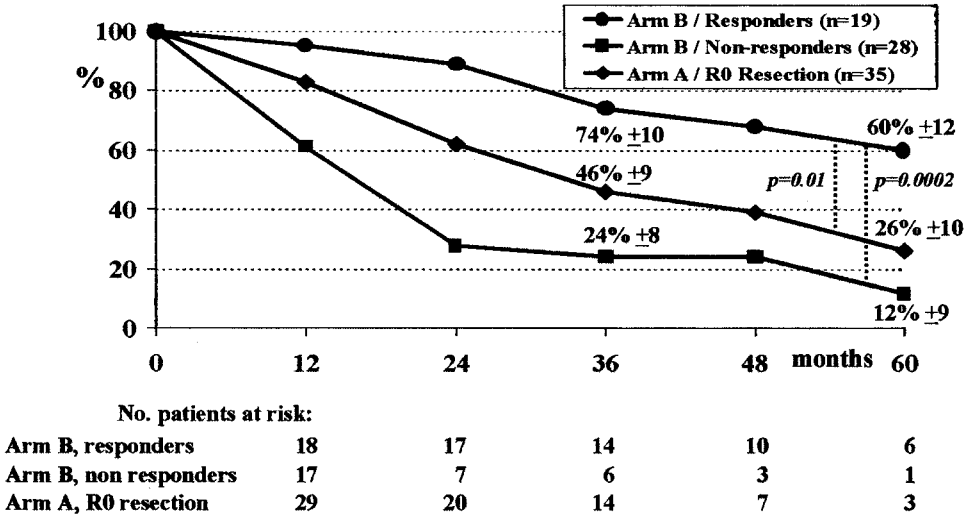
Long Term Survival

Adequate follow-up information was obtained in all patients, and an intention-to-treat survival analysis was performed. The median duration of survival was 24 months for patients who underwent surgery alone and 25 months for patients who had chemotherapy and surgery. The 3-year and 5-year survival rates ± standard error were 41% ± 7% and 22% ± 8%, respectively, for patients in Arm A and 44% ± 7% and 34% ± 8%, respectively, for patients in Arm B ($P = 0.55$) (Fig. 1). Of the two patients in Arm A who, after explorative thoracotomy disclosing an unresectable tumor, underwent chemoradiotherapy and subsequent R0 resection surgery, one patient died from local and distant recurrences 55 months after randomization, and the other patient is alive and disease free after 60 months. Also, excluding these two patients from the survival analysis, the survival of patients in Arm A (median, 22 months; 3-year and 5-year survival rates: 38% ± 7% and 22% ± 8%, respectively) was comparable to the survival of patients in Arm B ($P = 0.45$).

When the survival analysis was limited to patients who underwent a complete R0 resection, the long term prognosis was comparable in the two study arms. However, a trend toward an improved survival was observed for those patients who underwent preoperative chemotherapy. The median duration of survival was 28 months for patients who underwent surgery alone and 36 months for patients who had chemotherapy and surgery. The 3-year and 5-year survival rates were 46% ± 9% and 26% ± 10%, respectively, for patients in Arm A and 56% ± 8% and 43% ± 10%, respectively, for patients in Arm B ($P = 0.25$).

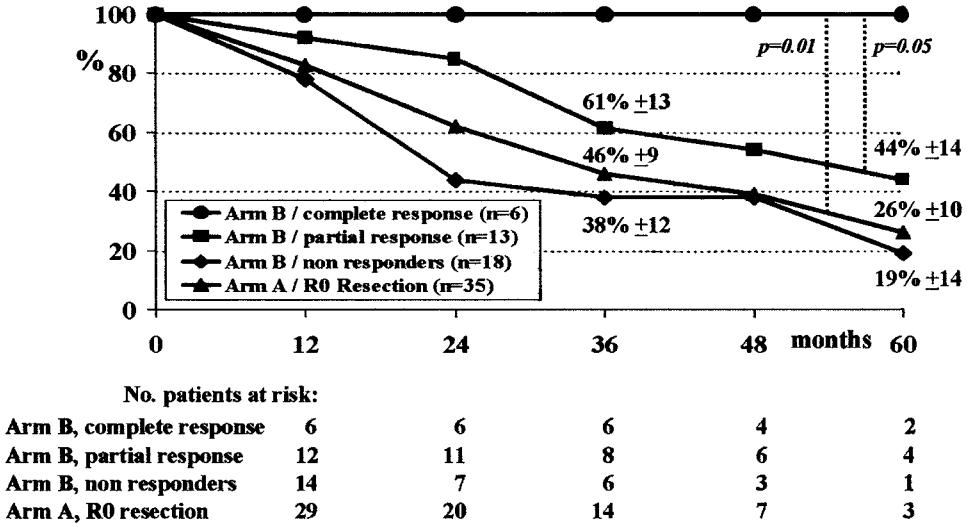
The 19 patients in Arm B who had a major response to preoperative chemotherapy and subsequently underwent complete R0 resection had a significantly better prognosis in terms of both median duration of survival (53 months) and 3-year (74% ± 10%) and 5-year (60% ± 12%) survival rates compared with nonresponders (15 months; 24% ± 8% and 12% ± 9%, respectively; $P = 0.0002$), nonresponders who underwent a complete R0 resection (19 months; 38% ± 12% and 19% ± 14%, respectively; $P = 0.01$), and patients in Arm A who underwent complete R0 resection without prior chemotherapy (28 months; 46% ± 9% and 26% ± 10%, respectively; $P = 0.01$) (Fig. 2).

Of the patients who underwent complete R0 re-



No. patients at risk:					
Arm B, responders	18	17	14	10	6
Arm B, non responders	17	7	6	3	1
Arm A, R0 resection	29	20	14	7	3

FIGURE 2. Survival in the 35 patients who underwent complete resection (R0) alone (Arm A) compared with the 19 patients in Arm B who responded and the 28 patients who did not respond to preoperative chemotherapy. All 19 responders to preoperative chemotherapy underwent R0 resection compared with 18 of 28 nonresponders.



No. patients at risk:					
Arm B, complete response	6	6	6	4	2
Arm B, partial response	12	11	8	6	4
Arm B, non responders	14	7	6	3	1
Arm A, R0 resection	29	20	14	7	3

FIGURE 3. Survival after complete resection (R0). Survival in the 35 patients who underwent surgery alone (Arm A) compared with the 6 patients in Arm B who had a pathologic complete response, the 13 patients in Arm B who had a pathologic partial response, and the 18 patients in Arm B who did not respond.

section, those in Arm B who were downstaged to pathologic complete response had a significantly better survival compared with both patients in Arm B who had a pathologic partial response ($P = 0.05$) and patients in Arm A ($P = 0.01$). Conversely, the survival of patients in Arm A was comparable to that of patients in Arm B who had a pathologic partial response ($P = 0.2$) and patients in Arm B who did not respond ($P = 0.5$) (Fig. 3).

Patterns of Failure

No locoregional or distant failures were detected in 15 of 34 patients (44.1%) in Arm A who survived a complete R0 resection compared with 17 of 36 patients (47.2%) in Arm B. The first tumor recurrence after surgery occurred at a median of 12 months ± 11 months (range, 3–47 months) for patients in Arm A and at a median of 16 months ± 12 months (range, 3–48 months) for patients in Arm B ($P = 0.27$). Among patients in Arm B, the first tumor recurrence occurred at a median of 23 months ± 14 months (range, 3–48 months) for responders and at a median of 12 months ± 10 months (range, 3–37 months) for nonresponders ($P = 0.36$). Table 3 summarizes the failure patterns after complete R0 resections according to treatment group. Table 4 summarizes the final outcome of all evaluable patients on an intention-to-treat basis: No significant difference was found between the two treatment groups.

The six patients who were treated with preoperative chemotherapy and surgery who had a pathologic complete response (pT0 N0 M0) are alive with no evidence of disease after 39 months, 43 months, 55 months, 56 months, 64 months, and 79 months. One of these patients developed two metachronous carcinomas: one in the larynx after 24 months and one in

TABLE 3
Patterns of Failure in Patients Who Survived a Complete R0 Resection According to Treatment Group

Outcome	No. of patients (%) Surgery (n = 34)	Chemotherapy plus surgery (n = 36)	*P* value
Failures	19 (56)	19 (53)	ns
Median time to first recurrence (months)	12 ± 11	16 ± 13	ns
Failure pattern[a]			
Locoregional only	6 (32)	5 (26)	ns
Distant only	4 (21)	7 (37)	ns
Local plus distant	9 (47)	7 (37)	ns
Any local	15 (79)	12 (63)	ns
Any distant	13 (68)	14 (78)	ns

ns: Not significant.
[a] Values in parentheses are the percentages of patients who had treatment failure.

TABLE 4
Final Outcome of All Registered Patients Who Were Evaluated on an Intention-to-Treat Basis According to Treatment Group

Outcome	No. of patients (%) Surgery (n = 47)	Chemotherapy plus surgery (n = 47)	*P* value
Treatment-related death	2 (4.2)[a]	2 (4.2)	ns
No evidence of tumor	17 (36)	17 (36)	ns
Tumor progression or recurrence	29 (62)[a]	28 (59)	ns
Failure pattern[b]			
Locoregional only	10 (34)	9 (32)	ns
Distant only	4 (14)	7 (25)	ns
Local plus distant	15 (52)	12 (43)	ns
Any local	25 (86)	21 (75)	ns
Any distant	19 (66)	19 (68)	ns

ns: not significant.
[a] One patient who died from postoperative complications 3 months after an R2 resection also had both local and distant tumor recurrence.
[b] Values in parentheses are the percentages of patients who experienced treatment failure.

the hypopharynx after 48 months. Both tumors were treated with combined chemoradiotherapy, obtaining a complete clinical response. Of two patients who, after preoperative chemotherapy and surgery, showed a complete response of the primary tumor but positive lymph nodes (pT0 N1), one patient is alive with no evidence of failure after 96 months, whereas the other patient died after 39 months with locoregional recurrence plus bone and brain metastases. Of two patients who showed microscopic in situ carcinoma (pTis N0 M0), one patient died disease free from acute necrotizing pancreatitis after 11 months, and the other patient died with locoregional failure plus distant metastases after 60 months.

Four patients in Arm A developed metachronous malignancies after undergoing esophagectomy: of the oral cavity after 24 months, of the tongue after 26 months, of the prostate after 30 months, and of the oral cavity after 60 months. Three patients in Arm B developed four malignancies: of the rectum after 36 months, of the larynx after 24 months and the hypopharynx 48 after months, and of the hypopharynx 80 after months.

DISCUSSION

Surgery remains the mainstay of treatment for patients with nonmetastatic esophageal carcinoma who are fit medically for surgery,[1,2,18] but their long term prognosis remains unsatisfactory even after they undergo complete R0 resections.[3] However, the use of preoperative chemotherapy or chemoradiotherapy outside of an investigational setting cannot be recommended to date.[18]

Previous Phase II studies of preoperative chemotherapy showed encouraging results in patients with squamous cell carcinoma of the esophagus: Major responses with cisplatin-based combination chemotherapy have been documented in 15–60% of patients, with a complete pathologic response obtained in 4–7% of patients.[1,2] To date, few randomized, controlled trials have been performed, and their findings were not conclusive.[1,2,10,11] These studies reported an overall complete or partial response rate of approximately 50% (range, 38–71%), with no increase in the curative resection rate and no significant increase in postoperative morbidity and mortality. Complete histopathologic response after preoperative chemotherapy was reported in 5–10% of patients who underwent resection. The overall survival rate, based on the intention-to-treat analysis, was not improved, even though compiled data suggested a trend toward improved long term survival for patients who were treated with preoperative chemotherapy compared with those who were treated with surgery alone.[1,2]

High-volume referral centers that see many patients with esophageal carcinoma every year guarantee more updated and standardized diagnostic and therapeutic procedures and are reported to offer significantly lower treatment-related morbidity and mortality rates than other centers where these surgical procedures seldom are carried out.[19] Although it would be desirable to perform a randomized trial of combined therapy modalities for patients with esophageal carcinoma within a single, high-volume referral center, we failed to enroll sufficiently large numbers of patients in a short recruitment period because of the

strict eligibility criteria and because of the many comorbidity factors that affect patients with esophageal carcinoma: In our study, < 25% of the patients who were observed during the study period could be enrolled. Less than 100 patients[11,20–22] or less than 150 patients[4,23] were studied in all but one of the other randomized trials that compared preoperative chemotherapy with surgery alone in patients with epidermoid carcinoma of the esophagus. The only published report that studied 204 patients with epidermoid carcinoma of the esophagus was a multiinstitutional, randomized trial that involved 123 institutions, i.e., with a mean contribution of 1.6 patients per institution![18] Therefore, it is advisable that, in the future, several high-volume referral centers join multiinstitutional, randomized trials of neoadjuvant chemoradiotherapy.

Despite the fact that our study was interrupted after 6 years without reaching the proposed number of patients, some considerations can be drawn. In our study, which adopted one of the most common combinations of chemotherapeutic agents used in the treatment of patients with esophageal carcinoma,[12,14,24] the preoperative chemotherapy plus surgery regimen was tolerated reasonably well. The resection rate and the postoperative mortality and morbidity rates were comparable in patients who received preoperative chemotherapy and those who underwent immediate surgery. In patients who received preoperative chemotherapy, the pathologic complete response rate, based on the intention-to-treat analysis, was 12.7%.

Of 47 evaluable patients in Arm A, 6 patients (13%) had an unresectable tumor at thoracotomy, and 6 patients (13%) underwent incomplete resections: This indicates the inability of preoperative staging to discriminate accurately between clinical T3 and T4 disease. However, despite the fact that patients in Arm B had the same chance of having their tumor understaged clinically, only 3 of 47 patients (6%) underwent incomplete resections, and 2 patients (4%) had an unresectable tumor at surgery. Endoscopic ultrasonography was not used routinely in the clinical staging of our patients, although it is the best available method to assess the T classification and, although it is less accurate, also to assess lymph node status.[25] However (and this also was true for us), endoscopic ultrasonography is not generally and/or always available in institutions worldwide.[26] Because the accuracy of preoperative staging may be severely limited by the lack of preoperative endoscopic ultrasonography, we strongly recommend the inclusion of endoscopic ultrasonography assessment in future studies.

The overall survival based on the intention-to-treat analysis and the survival of patients who underwent a complete R0 resection were comparable in patients who were treated with preoperative chemotherapy plus surgery and those who underwent surgery alone. This is in agreement with the results reported in other prospective, randomized, controlled trials comparing preoperative chemotherapy and surgery with surgery alone.[11,18,20–23,27] However, few other randomized trials reported a significant advantage for patients who were treated with preoperative chemotherapy.[4,28] In the trial reported by Kok et al.,[4] 160 patients with squamous cell esophageal carcinoma were randomized either to receive cisplatin-etoposide chemotherapy followed by surgery or to undergo surgery alone: The median survival of patients who received preoperative chemotherapy and surgery was 18.5 months compared with 11 months for patients who underwent surgery alone ($P = 0.002$). These positive results, which may be related to a greater efficacy of the cisplatin-etoposide regimen compared with cisplatin-fluorouracil, are difficult to evaluate, because they were reported only in abstract format, and a detailed, full paper has never been published.

More recently, because of the contrasting and suboptimal results obtained with preoperative chemotherapy, preoperative chemoradiotherapy was used to offer the greatest potential for increasing cure rates: This combined modality treatment resulted in a marked increase in the pathologic complete response rate (15–40%)[10] but at the expense of increased postoperative morbidity and mortality rates, which exceeded 20% in some studies.[21,29] No significant survival advantage was reported by some randomized, controlled trials comparing preoperative chemoradiotherapy and surgery with surgery alone.[21,29–32] Other randomized trials reported a significant survival advantage for patients who were treated with preoperative chemoradiotherapy;[6–9] however, it should be pointed out that the studies reported by Urba et al.[7,8] and Walsh et al.[9] were performed almost exclusively on patients with adenocarcinoma of the esophagus and that, in the study by Walsh et al., the 5-year survival rate of patients undergoing surgery alone was an uncommon, remarkably low 6%.[9] To date, none of the available trials has convincingly demonstrated an overall improvement in the overall survival of patients with esophageal carcinoma who undergo preoperative treatments.

The most important finding that emerges from our trial, although its value may be limited due to the small number of patients considered, is that patients who respond to preoperative chemotherapy and undergo a complete R0 resection have a significantly better long term survival compared with both nonresponders and patients who undergo an R0 resection

without preoperative chemotherapy. To date, the six patients who were treated with preoperative chemotherapy and who had a pathologic complete response documented on the operative specimen are alive and disease free after a median of 55.5 months. However, because this finding can be a result of patient selection (i.e., response to chemotherapy may be a means of selecting those with potential long term survival), it cannot be used as an argument to offer preoperative chemotherapy to all patients with potentially resectable squamous cell carcinoma of the esophagus.

Other reports support our findings, with 5-year survival rates for complete responders after preoperative chemoradiotherapy that range between 42% and 70%.[33–41] A significant survival advantage appears to be limited only to patients who show a complete response to preoperative treatments and subsequently undergo curative resection.[35,36,38,39] Unfortunately, nonresponders fare worse than patients who undergo surgery alone[2] and have to face the costs and potential toxicity of preoperative treatments without any benefit. Therefore, major efforts should be undertaken to identify before treatment those patients who are likely to respond to preoperative cytoreductive treatments. Because, in the literature, it is reported that 21–62% of clinical complete responders actually do not have a pathologic complete response,[35,38] surgical resection should be considered an indispensable component of multimodality treatments for patients with esophageal carcinoma.

In conclusion, improved long term survival was obtained in patients with clinically resectable squamous cell carcinoma of the esophagus who underwent preoperative chemotherapy and obtained a pathologic complete response. It remains unclear whether patients who respond to preoperative chemotherapy have a potential for long term survival or whether preoperative chemotherapy actually contributes to long term survival. This is of the utmost importance in light of the potential harm to all patients, including nonresponders. Therefore, major efforts should be undertaken both to identify patients before treatment who are likely to respond to preoperative treatments and to increase the percentage of responders by using new preoperative treatments with less toxicity and greater efficacy.

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