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ORIGINAL REPORT

# Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102

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## ABSTRACT

### Purpose
Uncontrolled studies suggest that chemoradiation has similar efficacy as surgery for esophageal cancer. Therefore, a randomized trial was carried out to compare, in responders only, chemoradiation alone with chemoradiation followed by surgery in patients with locally advanced tumors.

### Patients and Methods
Eligible patients had operable T3N0-1M0 thoracic esophageal cancer. Patients received two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. Patients with response and no contraindication to either treatment were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy). Chemoradiation was considered equivalent to surgery if the difference in 2-year survival rate was less than 10%.

### Results
Of 444 eligible patients, 259 were randomly assigned; 230 patients (88.8%) had epidermoid cancer, and 29 (11.2%) had glandular carcinoma. Two-year survival rate was 34% in arm A versus 40% in arm B (hazard ratio for arm B *v* arm A = 0.90; adjusted $P = .44$). Median survival time was 17.7 months in arm A compared with 19.3 months in arm B. Two-year local control rate was 66.4% in arm A compared with 57.0% in arm B, and stents were less required in the surgery arm (5% in arm A *v* 32% in arm B; $P < .001$). The 3-month mortality rate was 9.3% in arm A compared with 0.8% in arm B ($P = .002$). Cumulative hospital stay was 68 days in arm A compared with 52 days in arm B ($P = .02$).

### Conclusion
Our data suggest that, in patients with locally advanced thoracic esophageal cancers, especially epidermoid, who respond to chemoradiation, there is no benefit for the addition of surgery after chemoradiation compared with the continuation of additional chemoradiation.

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## INTRODUCTION

Until now, surgery has been the mainstay of curative treatment in patients with thoracic esophageal cancer.[1] However, after preoperative chemoradiation, 18% to 25% of the tumors are sterilized.[2,3] With chemoradiation alone, a median survival time of 11 to 22 months was observed,[4-6] and the 5-year survival rate reached 27% with chemoradiation in a randomized study,[7] which is similar to the rate after surgery.[1] Furthermore, nonrandomized studies in patients treated with chemoradiation found similar survival rates with or without additional surgery.[8,9] The Fédération Francophone de Cancérologie Digestive (FFCD) was thus prompted to carry out a randomized trial comparing chemoradiation alone with chemoradiation followed by surgery in patients with esophageal cancer. The aim was to demonstrate the equivalence of the overall survival after chemoradiation alone or chemoradiation followed by surgery in patients responding to initial chemoradiation.

## PATIENTS AND METHODS

### *Eligibility Criteria*

Inclusion criteria were resectable T3N0-1M0 (International Union Against Cancer criteria, 1987)[10] epidermoid or adenocarcinoma of the thoracic esophagus and

clinical and biologic eligibility for surgery or chemoradiation. Exclusion criteria were tumor within 18 cm from the dental ridge or infiltrating the gastric cardia, tracheobronchial involvement, visceral metastases or supraclavicular nodes, weight loss more than 15%, symptomatic coronary heart disease, cirrhosis Child-Pugh B or C, and respiratory insufficiency.

Staging was based on computed tomography (CT). T3 tumors were defined by a diameter $\geq$ 3 cm, without invasion of adjacent structures.[11] Work-up included clinical examination, gastroscopy with biopsies, esophagogram, bronchoscopy, supraclavicular ultrasonography, thoracoabdominal CT scan, and endoscopic ultrasonography when available. Written informed consent was required.

### Design and Random Assignment

All eligible patients were registered and received chemoradiation (Fig 1). They were then evaluated by esophagogram, abdominal ultrasonography, chest x-ray, and, if possible, endoscopic ultrasonography. Indeed, for ethical reasons, only patients responding to induction chemoradiation were considered for the randomized part of the trial. A clinical complete response was defined by the absence of dysphagia and of visible tumor on esophagogram; a partial response was defined as a decrease of more than 30% of the tumor length on esophagogram, which is the WHO definition of partial response for unidimensionally measurable lesions,[12] and improvement of dysphagia. In the absence of objective response or in case of contraindication to surgery, the treatment was decided by the investigator. If chemoradiation had not been tolerated, surgery was recommended. The remaining patients were randomly assigned by telephone at the FFCD Data Center through a minimization program either to arm A (surgery) or arm B (continuation of chemoradiation); patients were stratified according to institution, sex, histology (epidermoid *v* glandular), differentiation (well or moderately differentiated *v* poorly or undifferentiated), and response to induction treatment (complete *v* partial). Toxicity was graded according to the WHO criteria.

### Treatment

*Radiotherapy.* Radiotherapy included the macroscopic tumor and lymph nodes, with a 3-cm proximal and distal margin and a 2-cm radial margin. The use of three or four fields and daily treatment of all fields were required. Initially, the following two techniques were allowed, according to the initial choice of the investigator for all of his or her included patients: split-course or conventional radiotherapy (Fig 1). Split-course radiotherapy was delivered in daily fractions of 3 Gy, including two sequences (days 1 to 5 and 22 to 26; 30 Gy) before random assignment and one sequence (days 43 to 47; 15 Gy) after random assignment in arm B (total, 45 Gy). Each sequence was separated by a 2-week rest period. Conventional radiotherapy was delivered in 5 daily fractions per week of 2 Gy during the 4.5 weeks before random assignment (46 Gy) and the 2 weeks after random assignment (20 Gy), for a total of 66 Gy. Beginning January 1999, an amendment based on the results of a randomized study permitted only conventional radiotherapy.[13]

*Chemotherapy.* Two cycles of chemotherapy were delivered before random assignment, starting on days 1 and 22, and three cycles were administered after random assignment in arm B, starting on days 43, 64, and 92. Fluorouracil (FU) 800 mg/m$^2$ daily was administered as a continuous intravenous (IV) infusion (days 1 to 5). Cisplatin 15 mg/m$^2$ (days 1 to 5) was delivered during a 1-hour IV infusion, preceded and followed by a 2-hour IV infusion of normal saline 1 L. If serum creatinine was more than 15 mg/L, chemotherapy was delayed for up to 2 weeks. If serum creatinine remained elevated, cisplatin was discontinued. In cases of angina-like pain or cerebral ischemia during FU infusion, FU was discontinued.

*Surgery.* Surgery was to be performed between days 50 and 60 in arm A (Fig 1). No type of surgery was recommended. The pathology assessment indicated whether the resection was curative and whether there was no residual tumor, microscopic remnants, or a macroscopic tumor.

### Follow-Up

In both arms, follow-up was planned 4 months after starting the treatment (ie, in arm A, 2 months after resection, and in arm B, 3 weeks after the end of chemotherapy). The status was assessed by endoscopy with biopsies, esophagogram, thoracoabdominal CT scan, and, if available, endoscopic ultrasonography. Follow-up was carried out every 3 months for 2 years and then every 6 months thereafter. Dysphagia was scored from 1 (asymptomatic) to 5 (no swallowing at all) according to the O'Rourke criteria[14]; patterns of first recurrence (locoregional, distant, or both, or second cancer), hospitalizations,

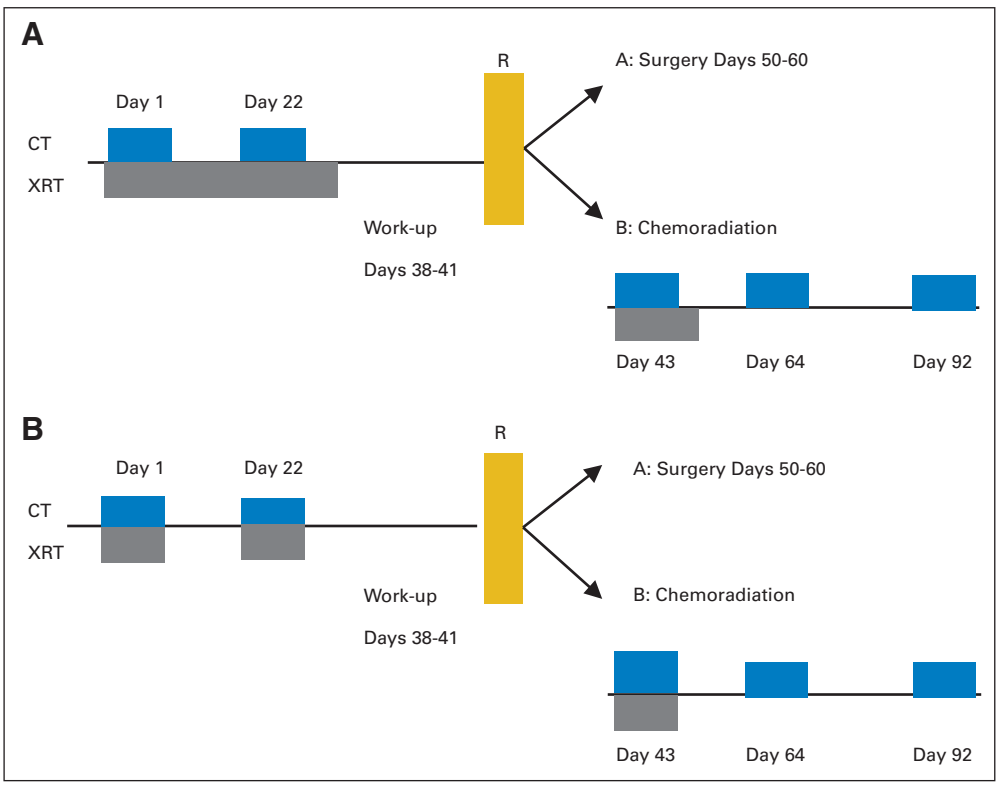


**Fig 1.** Treatment Design of the Fédération Francophone de Cancérologie Digestive 9102 trial. CT, chemotherapy; XRT, radiotherapy; R, random assignment.

and palliative procedures against dysphagia were reported. Quality of life was evaluated by the Spitzer quality-of-life index, which establishes a score from 0 (worst) to 10 (best) after answering five items in the areas of activity, daily life, health perception, social support, and behavior.[15] The Spitzer quality-of-life index was assessed by the clinician before treatment and at each follow-up point in both arms.

### End Points

The main end point was overall survival. Secondary end points were duration of hospital stay, quality of life, type of recurrence, and procedures against dysphagia. The protocol was approved by the regional ethics committee.

### Statistical Analysis

The treatment in arm B was considered equivalent to arm A if the difference in the 2-year survival rate was less than 10%. To reject this hypothesis, with an alpha risk of 5% (bilateral) and an 80% power, 360 randomly assigned patients were required. On the basis of previous studies that found a complete clinical response rate in 71% to 87% of the patients,[4,6] it was estimated that 75% of the registered patients could be randomly assigned, thus increasing the number of required patients to 500. Baseline characteristics of the treatment groups were compared using the *t* test or Mann-Whitney *U* test for continuous variables and the $\chi^2$ or Fisher's exact tests for categoric variables. The probability of survival was estimated using the Kaplan-Meier method. Data were analyzed according to the intent-to-treat principle as well as per protocol (ie, taking into account the treatment actually received). Survival was calculated from the date of registration to the most recent follow-up or death. Results are presented with 95% CIs. The accrual was slower than expected, and according to an amendment approved by the ethics committee, an interim analysis was performed on the first 200 patients (of 259 randomly assigned patients at that time) who had a follow-up of more than 1 year, and the data were examined in November of 2000 by the Independent Data Monitoring Committee. The discontinuation of the study was advised; the analysis favored the nonsurgical arm, and the committee concluded that there was no possibility of rejecting the hypothesis of equivalence with the planned number of patients.

Quality of life was compared between the two arms by analysis of variance. Its longitudinal changes were compared with a general mixed model analysis of variance for repeated measurements.[16]

The following variables were assessed as potential prognostic factors with respect to overall survival in univariate and multivariate (Cox model) analyses: center accrual size, sex, age, length and diameter of the tumor, presence of enlarged (> 1 cm) lymph nodes on CT scan, weight loss, dysphagia, histology, differentiation, and response to the pre–random assignment treatment (partial or complete).

### Role of the Funding Sources

The sponsors had no role in the study design; in the collection, analysis, or interpretation of the data; or in the writing of the report and decision to submit the article for publication.

## RESULTS

### Patients

From February 1993 until December 2000, 444 of 451 registered patients were eligible for the study. Reasons for ineligibility are outlined in Figure 2. Among the 259 responding patients who were randomly assigned (57%), 129 were assigned to surgery (arm A), and 130 were assigned to chemoradiation (arm B). The cutoff date was June 30, 2001. Median follow-up time was 47.4 months. Four patients were lost to follow-up after a median of 15 months. There was no significant difference between treatment groups (Table 1). The reasons for patients not receiving random assignment are detailed in Figure 2. Of eight deaths that occurred before random assignment, seven (1.6%) were possibly related to chemoradiation (three febrile aplasias, one septic shock, two bleedings caused by tumor necrosis, and one acute cardiac insufficiency).

### Compliance With the Allocated Arm

The compliance rates were significantly different (85% in arm A and 97% in arm B; $P = .001$; Fig 2). In arm A, 16 patients received chemoradiation (10 patients refused surgery, three were inoperable after random assignment, and three were explored without resection), and three patients received no treatment. In arm B, one patient underwent surgery (patient demand), and three patients had no treatment (two patients refused, and the cause was unknown in one patient).

### Treatment Characteristics

In arm A, 110 of 129 patients underwent surgery. The types of surgery are listed in Table 2. Curative (R0) resection was achieved in 97 patients (75%). The median delay between start of treatment and surgery was 63 days (interquartile range, 56 to 73 days). In the 110 operated patients, the pathology results were as follows: no residual tumor in 25 patients (23%), microscopic remnants in 18 patients (16%), and macroscopic tumor in 67 patients (61%). Split-course radiotherapy was delivered in 67% of patients in arm A and 65% of patients in arm B ($P = .63$ in intent-to-treat analysis; $P = .96$ in per-protocol analysis).

### Toxicity of Chemoradiation and Therapeutic Mortality in the Randomly Assigned Patients

Before random assignment, the maximal toxicity was grade 3 in 51 (20%) of 259 patients and grade 4 in two (1%) of 259 patients. After random assignment, the maximal toxicity reached grade 3 in 36 (25%) of 142 patients and grade 4 in eight (6%) of 142 patients (Table 3).

During the first 3 months after registration, 12 patients (9%) died in arm A and one patient (1%) died in arm B ($P = .002$). Deaths in arm A were consecutive to surgical complications (n = 6), progressive disease (n = 3), or other causes (n = 3), and the death in arm B was related to herpetic encephalopathy. Six-month mortality rates were 16% in arm A (eight additional patients: surgical complication, n = 4; progressive disease, n = 3; and other, n = 1) and 6% in arm B (seven additional patients: progressive disease, n = 3; and other, n = 4; $P = .015$).

### Survival

For the 444 eligible patients, the median survival time from registration was 16.1 months (SE = 1.2 months), whereas the 2-year survival rate was 33.1% ± 2.4%. For the 259 randomly assigned patients, median survival time was 18.6 months (SE = 1.2 months); in arms A and B, the median survival times were 17.7 months (SE = 2.0 months) and 19.3 months (SE = 1.4 months), respectively. Two-year survival rates in arms A and B were 33.6% ± 4.5% and 39.8% ± 4.5%, respectively, in the intent-to-treat analysis and 37.1% ± 5.0% and 36.5% ± 4.2%, respectively, in the per-protocol analysis (Table 4, Fig 3). The survival differences (arm A minus arm B) were −6.2% (95% CI, −18.0 to 5.69) in the intent-to-treat analysis and +0.6% (95% CI, −11.4 to 12.6) in the per-protocol analysis. Thus, the upper limit of the 95% CI of the survival difference did not reach 10% in the intent-to-treat analysis. This means that the 2-year survival rate of patients treated with chemoradiation only could not be inferior by more than 10% to the survival rate of patients treated with surgery ($P = .03$). Despite a higher survival probability in arm B, survival curves did not differ significantly (unadjusted hazard ratio [HR] for arm B *v* arm A = 0.90, $P = .49$; adjusted HR = 0.88, $P = .44$). Eligible patients who

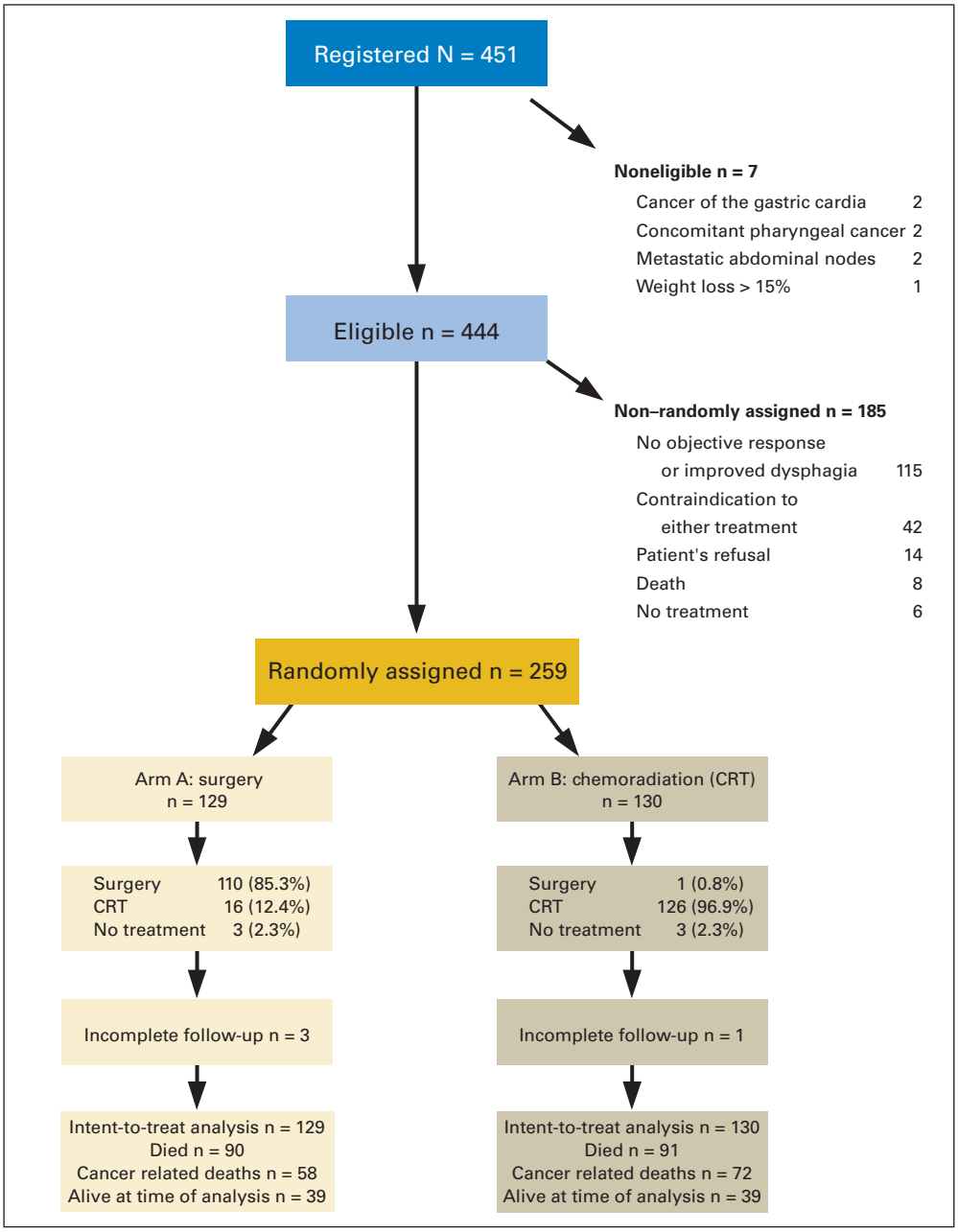


**Fig 2.** Population of the study: eligibility, reasons for patients not receiving random assignment, and compliance to the allocated treatment. CRT, chemoradiation.

were not randomly assigned fared worse, with a median survival time of 11.4 months (SE = 1.5 months). The HR was 1.22 (95% CI, 0.94 to 1.58) in case of insufficient efficacy of the treatment administered before random assignment, 1.39 (95% CI, 0.97 to 1.98) in case of contraindication to any treatment, and 1.63 (95% CI, 0.95 to 2.82) for patients who refused random assignment. In univariate or multivariate analysis, none of the analyzed factors were of prognostic value (Table 5).

### *Length of Hospital Stay*

Length of hospital stay was known during the whole follow-up period in 220 patients (85%; 112 patients in arm A and 108 in arm B), unknown for only one period of follow-up in 32 patients (12%; 15 patients in arm A and 17 in arm B), and totally unknown for seven patients (3%; two patients in arm A and five in arm B). The figures listed in Table 4 relate the cumulative hospital stay. During the therapeutic period (ie, before the first follow-up report), the mean hospital stay was 38.6 days (SE = 2.60 days) in the surgery arm and 24.7 days (SE = 1.25 days) in the chemoradiation arm ($P < .0001$).

### *Dysphagia and Palliative Procedures*

A procedure against dysphagia was required in 24% of the patients in arm A compared with 46% of patients in arm B ($P < .001$; Table 4). Dysphagia before death was rated as grade 1 to 2 for 63% of the patients in arm A compared with 46% of patients in arm B ($P = .04$).

### *Type of First Failure*

At 2 years, the recurrence probability was 56.7% (SE = 5.4%) in arm A and 59.6% (SE = 4.8%) in arm B ($P = .23$; Table 4). The median survival time after recurrence was 4.2 ± 0.4 months

**Table 1.** Characteristics of the 259 Randomly Assigned Patients According to Treatment Group

| Characteristic | Intent-to-Treat Analysis | | | | Per-Protocol Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Surgery (n = 129) | | Chemoradiation (n = 130) | | Surgery (n = 111) | | Chemoradiation (n = 142) | | No Treatment (n = 6) | |
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| Mean, years | | | | | | | | | | |
| Mean | 57.3 | | 59.3 | | 57.2 | | 59.1 | | 58.4 | |
| Two standard deviations | 9.2 | | 8.9 | | 8.2 | | 9.1 | | 13.6 | |
| Center accrual* | | | | | | | | | | |
| Small, < 5 patients | 56 | 43.4 | 56 | 43.1 | 56 | 50.5 | 62 | 43.7 | 6 | 100.0 |
| Medium, 5-10 patients | 40 | 31.0 | 38 | 29.2 | 32 | 28.8 | 53 | 37.3 | 0 | 0.0 |
| Large, > 10 patients | 33 | 25.6 | 36 | 27.7 | 23 | 20.7 | 27 | 19.0 | 0 | 0.0 |
| Sex | | | | | | | | | | |
| Male | 120 | 93.0 | 122 | 93.8 | 104 | 93.7 | 132 | 93.0 | 6 | 100.0 |
| Female | 9 | 7.0 | 8 | 6.2 | 7 | 6.3 | 10 | 7.0 | 0 | 0.0 |
| Length of the tumor | | | | | | | | | | |
| ≤ 5 cm | 58 | 45.0 | 66 | 50.8 | 54 | 48.7 | 68 | 47.9 | 2 | 33.3 |
| > 5 cm | 70 | 54.3 | 64 | 49.2 | 57 | 51.4 | 73 | 51.4 | 4 | 66.7 |
| Diameter of the tumor on CT scan† | | | | | | | | | | |
| ≤ 20 mm | 13 | 10.1 | 23 | 17.7 | 12 | 10.8 | 22 | 15.5 | 2 | 33.3 |
| 21-50 mm | 101 | 78.3 | 96 | 73.9 | 88 | 79.3 | 107 | 75.4 | 2 | 33.3 |
| > 50 mm | 8 | 6.2 | 3 | 2.3 | 6 | 5.4 | 4 | 2.8 | 1 | 16.7 |
| Unknown | 7 | 5.4 | 8 | 6.2 | 5 | 4.5 | 9 | 6.3 | 1 | 16.7 |
| Enlarged lymph nodes on CT scan | | | | | | | | | | |
| Yes | 62 | 48.1 | 52 | 40.0 | 54 | 48.7 | 58 | 40.9 | 2 | 33.3 |
| No | 67 | 51.9 | 76 | 58.5 | 57 | 51.4 | 82 | 57.8 | 4 | 66.7 |
| Unknown | 0 | 0.0 | 2 | 1.5 | 0 | 0.0 | 2 | 1.4 | 0 | 0.0 |
| Weight loss | | | | | | | | | | |
| ≤ 10% | 98 | 76.0 | 101 | 77.7 | 83 | 74.8 | 112 | 78.9 | 4 | 66.7 |
| > 10% | 28 | 21.7 | 27 | 20.8 | 25 | 22.5 | 28 | 19.7 | 2 | 33.3 |
| Unknown | 3 | 2.3 | 2 | 1.5 | 3 | 2.7 | 2 | 1.4 | 0 | 0.0 |
| Dysphagia | | | | | | | | | | |
| Absent | 10 | 7.8 | 13 | 10.0 | 10 | 9.0 | 13 | 9.2 | 0 | 0.0 |
| Solid | 54 | 41.9 | 60 | 46.2 | 48 | 43.2 | 65 | 45.8 | 1 | 16.7 |
| Semiliquid | 43 | 33.3 | 46 | 35.4 | 36 | 32.4 | 50 | 35.2 | 3 | 50.0 |
| Liquid | 18 | 14.0 | 10 | 7.7 | 14 | 12.6 | 13 | 9.2 | 1 | 16.7 |
| Aphagia | 2 | 1.6 | 1 | 0,8% | 1 | 0.9 | 1 | 0.7 | 1 | 16.7 |
| Unknown | 2 | 1.6 | 0 | 0.0 | 2 | 1.6 | 0 | 0.0 | 0 | 0.0 |
| Histology | | | | | | | | | | |
| Epidermoid | 115 | 89.2 | 115 | 88.5 | 100 | 90.1 | 124 | 87.3 | 6 | 100.0 |
| Glandular | 14 | 10.9 | 15 | 11.5 | 11 | 9.9 | 18 | 12.7 | 0 | 0.0 |
| Differentiation | | | | | | | | | | |
| Well/moderately differentiated | 101 | 78.3 | 101 | 77.7 | 89 | 80.2 | 108 | 76.1 | 5 | 83.3 |
| Poorly differentiated/undifferentiated | 28 | 21.7 | 29 | 22.3 | 22 | 19.8 | 34 | 23.9 | 1 | 16.7 |
| Clinical response to treatment before random assignment | | | | | | | | | | |
| Complete | 13 | 10.1 | 14 | 10.8 | 11 | 9.9 | 15 | 10.6 | 1 | 16.7 |
| Partial | 116 | 89.9 | 116 | 89.2 | 100 | 90.1 | 127 | 89.4 | 5 | 83.3 |

NOTE. There was no significant difference between arms for any of the characteristics
Abbreviation: CT, computed tomography.
*Center accrual refers to the number of patients entered onto the study.
†Patients with a tumor diameter of less than 30 mm on CT scan were classified as T3 by endoscopic ultrasonography.

(5.0 ± 1.1 months after locoregional recurrence, 4.2 ± 1.0 months after metastatic recurrence, and 2.1 ± 0.7 months after both). Recurrence occurred in 60.6% of the patients within 12 months after registration and in 80.3% of patients within 24 months. The frequency of metastases was not different between the arms (HR for arm B *v* arm A = 0.77; 95% CI, 0.49 to 1.24); however, there were more locoregional relapses after chemoradiation (HR for arm B *v* arm A = 1.63; 95% CI, 1.04 to 2.55; $P = .03$). Considering the treatment actually received, the HRs were 0.80 (95% CI, 0.50 to 1.27) and 2.26 (95% CI, 1.39 to 3.67; $P = .0006$) for metastases and locoregional relapse, respectively.

### *Quality of Life*

In univariate analysis, the mean Spitzer quality-of-life index score was higher in arm B only at the first follow-up period 6 months after inclusion ($P = .01$). The longitudinal quality-of-life study showed no difference between the two arms ($P = .26$).[16]

**Table 2.** Type of Surgery in Operated Patients in Arm A

| Type of Surgery | No. of Patients (n = 110) | % |
|---|---|---|
| Transthoracic esophagectomy | 103 | 93.6 |
| Right thoracotomy and laparotomy | 79 | |
| Three-stage esophagectomy | 20 | |
| Laparoscopy and thoracotomy | 2 | |
| Left thoracophreno laparotomy | 2 | |
| Transhiatal esophagectomy | 4 | 3.6 |
| Exploratory thoracotomy | 2 | 1.8 |
| Exploratory laparotomy | 1 | 0.9 |

## DISCUSSION

Our results suggest that chemoradiation alone and chemoradiation followed by surgery are equivalent in terms of survival and quality of life in responders. Results were given from the start of treatment and not from random assignment because, although the differences were nearly the same, the results from the start of treatment better reflected overall survival. Indeed, the treatment administered before random assignment lasted for more than 1 month. Our study results are consistent with the results from the study by Stahl et al,[17] in which 172 patients with epidermoid esophageal cancer were randomly assigned to either chemoradiation with surgery or chemoradiation without surgery. Median survival time was 16.4 months with surgery compared with 14.9 months without surgery, and 2-year survival rates were 39.9% and 35.4%, respectively (test for equivalence with $\delta = -0.15$, $P = .007$). As in our study, freedom from local progression was longer in the surgery group versus the no surgery group (at 2 years, 64.3% *v* 40.7%, respectively; HR = 2.1; 95% CI, 1.3 to 3.5; $P = .003$). If the patients responding to induction chemotherapy were considered, 3-year survival rates were 58% and 55% in the surgery and no surgery groups, respectively.[17] In the FFCD 9102 study, random assignment was not performed at registration to test the efficacy and tolerance of chemoradiation and, hence, avoid cross over or continuation of an inefficient therapy. A smaller than expected percentage of patients was randomly assigned (57% instead of 75%). The rates of 71% and 87% for complete clinical response, which we based our

**Table 3.** Grade 3 and 4 WHO Toxicities Observed Before Random Assignment and After Random Assignment in the Patients Treated With Chemoradiation (per protocol)

| Toxicity | Before Random Assignment (n = 259) | | | After Random Assignment (n = 142; 16 from surgery arm) | |
|---|---|---|---|---|---|
| | Surgery (No.) | Chemoradiation (No.) | Total (%) | No. | % |
| Leukocytes | 10 | 10 | 8 | 26 | 20 |
| Febrile neutropenia | 0 | 2 | 1 | 3 | 2 |
| Thrombocytes | 2 | 0 | 1 | 9 | 6 |
| Hemoglobin | 5 | 3 | 3 | 3 | 2 |
| Nausea/vomiting | 6 | 10 | 6 | 9 | 6 |
| Diarrhea | 0 | 0 | 0 | 2 | 1 |
| Stomatitis | 2 | 2 | 2 | 1 | 1 |
| Esophagitis | — | — | — | 5 | 4 |
| Cardiovascular | 0 | 2 | 1 | 2 | 1 |
| At least one grade 3 or 4 toxicity | 25 | 28 | 21 | 44 | 31 |

**Table 4.** Results Concerning the Main End Point (intent-to-treat and per-protocol analyses) and Secondary End Points (intent-to-treat analysis) in the Surgery Arm (arm A) and the Chemoradiation Only Arm (arm B)

| End Point | Surgery (arm A) | Chemo-radiation (arm B) | Difference Between Arms (arm A minus arm B) | *P* |
|---|---|---|---|---|
| Intent-to-treat analysis | | | | |
| No. of patients | 129 | 130 | | |
| 2-year survival probability, %* | | | | |
| Rate | 33.6 | 39.8 | | |
| SE | 4.5 | 4.5 | | |
| Difference in 2-year survival, % | | | | .03† |
| Rate | | | −6.2 | |
| 95% CI | | | −18.0 to 5.7 | |
| Per-protocol analysis | | | | |
| No. of patients | 111 | 142 | | |
| 2-year survival probability, %* | | | | |
| Rate | 37.1 | 36.5 | | |
| SE | 5.0 | 4.2 | | |
| Difference in 2-year survival, % | | | | .06† |
| Rate | | | 0.6 | |
| 95% CI | | | −11.4 to 12.6 | |
| Intent-to-treat analysis | | | | |
| Cumulative hospital stay, days | | | | .015 |
| Mean | 68 | 52 | | |
| SE | 5 | 4 | | |
| Hospital stay ≤ 5 days per month of survival, % | 61 | 75 | | .008 |
| Therapeutic mortality within 3 months after registration | | | | .0003 |
| No. of patients | 12 | 1 | | |
| % | 9.3 | 0.8 | | |
| Palliative intervention for dysphagia | | | | .0002 |
| No. of patients | 31 | 60 | | |
| % | 24.0 | 46.2 | | |
| Dilatation | | | | |
| No. of patients | 24 | 18 | | |
| % | 18.6 | 13.8 | | |
| Stent | | | | |
| No. of patients | 7 | 42 | | |
| % | 5.4 | 32.3 | | |
| Dysphagia < grade 3‡ at last follow-up before death§ | | | | .04 |
| No. of patients/No. of dead patients | 38/60 | 36/79 | | |
| % | 63.3 | 45.6 | | |
| 2-year recurrence probability, % | | | | .23 |
| Rate | 56.7 | 59.6 | | |
| SE | 5.4 | 4.8 | | |
| Locoregional probability, % | | | | .0014 |
| Rate | 33.6 | 43.0 | | |
| SE | 5.3 | 4.9 | | |
| Metastatic probability, % | | | | .24 |
| Rate | 39.1 | 29.0 | | |
| SE | 5.3 | 4.7 | | |

*Survival rates are calculated from registration.
†Test for noninferiority.
‡Asymptomatic or eats solids with some dysphagia.
§Information was available in 67% of the deceased patients in arm A and 87% of the deceased patients in arm B.

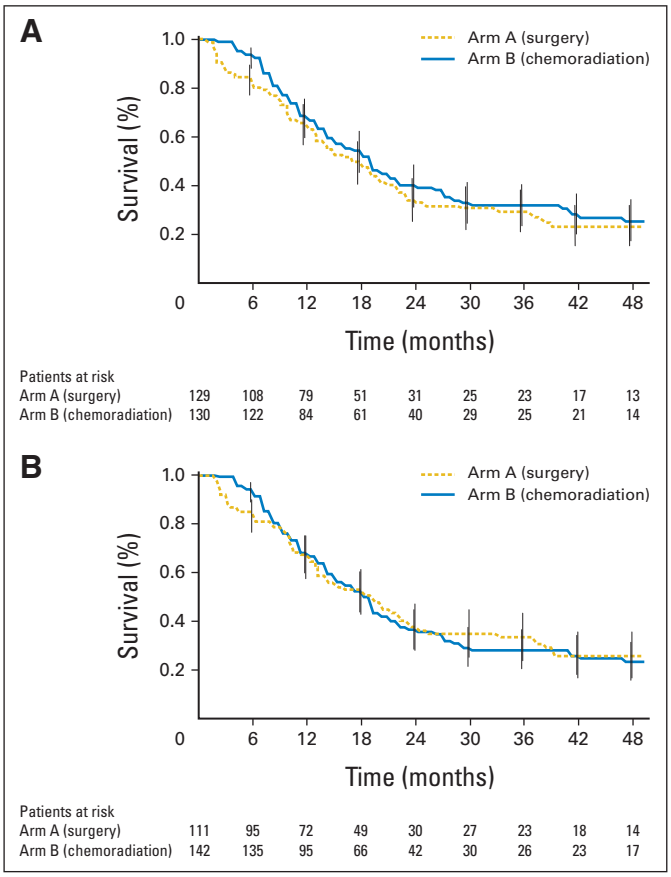


**Fig 3.** Overall survival of the patients with esophageal cancer responding to induction chemoradiation who were randomly assigned to either surgery (arm A) or continuation of chemoradiation (arm B). (A) Survival in intent-to-treat analysis. (B) Survival in per-protocol analysis. The 95% CIs of the survival rates are indicated on the figures.

**Table 5.** Multivariate Analysis of Potential Prognostic Factors in the Randomly Assigned Patients (n = 259)

| Factor | Relative Risk | 95% CI | *P* |
|---|---|---|---|
| Sex | | | |
| Male | 1 | | .23 |
| Female | 0.65 | 0.31 to 1.37 | |
| Age, years | | | |
| < 65 | 1 | | .07 |
| ≥ 65 | 1.39 | 0.98 to 1.97 | |
| Enlarged lymph nodes on computed tomography scan | | | |
| No | 1 | | .54 |
| Yes | 1.10 | 0.80 to 1.51 | |
| Weight loss | | | |
| ≤ 10% | 1 | | .35 |
| > 10% | 1.22 | 0.81 to 1.82 | |
| Differentiation | | | |
| Well/moderately differentiated | 1 | | .99 |
| Poorly differentiated/undifferentiated | 0.99 | 0.68 to 1.46 | |
| Response to treatment administered before random assignment | | | |
| Complete | 1 | | .66 |
| Partial | 0.88 | 0.52 to 1.51 | |
| Radiotherapy | | | |
| Split course | 1 | | .46 |
| Conventional | 1.15 | 0.79 to 1.68 | |
| Arm | | | |
| Surgery, arm A | 1 | | .44 |
| Chemoradiation, arm B | 0.88 | 0.64 to 1.31 | |

NOTE. The model is adjusted on center accrual, length and diameter of the tumor, histology, and dysphagia.

calculations on, were drawn from phase II studies that included tumors that were not always locally advanced.[4,6] Moreover,14 patients refusing surgery and 10 patients not fit for surgery were not randomly assigned. Thus, 24 more patients were eligible for chemoradiation (ie, 64%).

A significant difference in therapeutic mortality was observed, and one could consider that chemoradiation increased the postoperative mortality rate, hence undercutting the benefit of surgery. However, a significantly higher operative mortality rate was reported only in two randomized studies comparing preoperative chemoradiation with surgery alone (9% *v* 4%, respectively, for Walsh et al[18]; 12% *v* 4%, respectively for Bosset et al[19]). In the latter study, the high dose per fraction (3.7 Gy) was probably responsible. In contrast, Le Prise et al,[20] Urba et al,[21] and Burmeister et al[22] observed similar mortality rates in both the chemoradiation and surgery arms (9% *v* 7%, 2% *v* 4%, and 5% *v* 6%, respectively). Conversely, the benefit of chemoradiation may have been undercut in the first period of the trial by split-course chemoradiation, which was later demonstrated to be inferior to conventional protraction in a randomized study.[13]

The dose of 66 Gy used in our trial seems excessive considering the conclusion of the INT 0123 study that a dose of 64.8 Gy is not superior to 50.4 Gy.[23] However, our study design was different and permitted the delivery of three cycles of concomitant chemoradiation instead of two cycles, as in the INT 0123 trial. Regarding adjuvant chemotherapy, although previous studies were negative,[24] the Medical Research Council OE 02 trial concluded that two preoperative cycles of FU plus cisplatin resulted in a better survival than surgery alone without increasing operative mortality.[25] This raises the question of which of the following is the optimal preoperative treatment: chemotherapy or chemoradiation. Actually, several trials testing preoperative chemoradiation versus surgery showed a trend favoring chemoradiation,[20-22,26] and in a recent series, preoperative chemoradiation was predictive of R0 resection, which was a positive prognostic factor.[27] Meta-analyses suggest that preoperative chemoradiation improves 3-year survival and decreases locoregional recurrence rate, although no such beneficial effects are observed after preoperative chemotherapy.[28-30] However, it is difficult to conclude about the best neoadjuvant treatment because another meta-analysis demonstrated opposite results concerning 2-year survival.[31] In our study, no specific type of surgery was proposed, and this could have produced heterogeneity. However, 94% of the patients had transthoracic esophagectomies, and 4% had transhiatal operation. Moreover, randomized studies or meta-analyses have not demonstrated the superiority of one technique.[1,32]

In this study, chemoradiation alone prevented 46% of the patients from having high-grade dysphagia until death, compared with previously reported rates of 60% to 67%.[14] Nevertheless, dysphagia was better improved after surgery (63% mild or absent before death).

In conclusion, this study suggests that therapeutic strategies with or without surgery result in similar survival rates for locally advanced thoracic esophageal cancer patients responding to chemoradiation.

This study applies especially to patients with epidermoid tumors, who represented almost 90% of the patients, although no difference with adenocarcinomas was observed in multivariate analysis. However, chemoradiation alone entailed fewer early deaths and a shorter hospital stay but more locoregional relapses. Because clinical prognostic factors do not help in choosing between both strategies, further studies comparing surgery and chemoradiation should search for new predictive factors and evaluate new tools to detect early responders. Positron emission tomography scan was reported to discriminate responders from nonresponders as early as 14 days after starting chemoradiation and should be re-evaluated in future studies.[33]

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

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### *Acknowledgment*

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

### *Appendix*

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