Interval Between Neoadjuvant Chemoradiotherapy and Surgery for Squamous Cell Carcinoma of the Thoracic Esophagus

Does Delayed Surgery Have an Impact on Outcome?

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Objective: Aim of this study was to evaluate whether delayed surgery after neoadjuvant chemoradiotherapy (CRT) affects postoperative outcomes in patients with locally advanced squamous cell carcinoma (SCC) of the thoracic esophagus.

Background: Esophagectomy is usually recommended within 4 to 6 weeks after completion of neoadjuvant CRT. However, the optimal timing of surgery is not clearly defined.

Methods: A total of 129 consecutive patients with locally advanced esophageal cancer, treated between 1998 and 2007, were retrospectively analyzed using prospectively collected data. Patients were divided into 3 groups on the basis of timing to surgery: group 1, ≤30 days (n = 17); group 2, 31 to 60 days (n = 83); and group 3, 61 to 90 days (n = 29). Subsequently, only 2—numerically more consistent—groups were studied, using the median value of timing intervals as a cutoff level: group A, ≤46 days (n = 66); and group B, >46 days (n = 63).

Results: Groups were comparable in terms of patient and tumor characteristics, type of neoadjuvant regimen, toxicity, postoperative morbidity and mortality rates, tumor downstaging, and pathologic complete responses. The overall 5-year actuarial survival rate was 0% in group 1, 43.1% in group 2, and 35.9% in group 3 ($P = 0.13$). After R0 resection (n = 106), the 5-year actuarial survival rate was 0%, 51%, and 47.3%, respectively ($P = 0.18$). Tumor recurrence after R0 resection seemed to be inversely related, even if not significantly ($P = 0.17$), to the time interval between chemoradiation and surgery: 50% in group 1, 40.6% in group 2, and 21.7% in group 3. When considering only 2 groups, the overall 5-year survival was 33.1% in group A and 42.7% in group B ($P = 0.64$); after R0 resection, the 5-year survival was 37.8% and 56.3%, respectively ($P = 0.18$). The rate of tumor recurrence was significantly lower in group B (25%) than in group A (48.3%) ($P = 0.02$).

Conclusion: Delayed surgery after neoadjuvant chemoradiation does not compromise the outcomes of patients with locally advanced SCC of the esophagus. Delaying surgery up to 90 days offers relevant advantages in the clinical management of the patients, can reduce tumor recurrences, and may improve prognosis after complete R0 resection surgery.

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Surgical resection remains an essential cornerstone in the treatment of fit patients with resectable squamous cell carcinoma (SCC) of the esophagus.[1] Surgery alone is curative in patients with early-stage tumors, but most patients present with dysphagia and have a locally advanced disease. The prognosis for these patients is poor, and surgery alone resulted in 5-year survival rates of 10% to 20%.[2] Consequently, attention has been focused on the use of neoadjuvant chemoradiotherapy (CRT) in an effort to reduce tumor burden, increase the rate of complete resections, eradicate micrometastases, decrease cancer cell dissemination, and prolong survival.[1,2]

During the past 2 decades, neoadjuvant CRT has been tested in numerous phase II and III trials,[3] and even if a significant improvement in survival compared with surgical resection alone has not been definitely demonstrated, subgroup analysis has suggested that patients who obtain a complete pathologic response (pCR) have an improved survival compared with those who have residual disease at the time of surgery.[4] Thus, preoperative CRT has become a standard component of multimodal treatment of locally advanced SCC of the esophagus. In the 8 randomized phase III trials of neoadjuvant CRT versus surgery alone, cited in the metaanalyses,[3] patients are scheduled for surgery within 2 to 6 weeks after completion of CRT. However, to date the issue of the optimal timing of surgery after neoadjuvant CRT has not been addressed to. Many surgeons prefer to allow resolution of the acute inflammatory response to CRT before surgery. On the other hand, longer CRT-surgery intervals may potentially allow tumor regrowth, and dissection may become more difficult as fibrosis becomes more established.

Therefore, we retrospectively analyzed our prospectively assembled database with the aim of evaluating whether the interval between completion of neoadjuvant CRT and surgery may affect outcomes in patients with locally advanced SCC of the thoracic esophagus.

MATERIALS AND METHODS

Study Population

This is a retrospective review of a prospectively assembled Esophageal Cancer Database. The study population was drawn from all patients who had an esophagectomy for SCC of the thoracic esophagus from 1998 to 2007. Informed consent was obtained from each patient before CRT and surgery. Assessment of the extent of disease before treatment included upper endoscopy, barium swallows x-ray, chest and abdominal computed tomographic (CT) scan, videolaryngoscopy, tracheobronchoscopy, endoscopic ultrasonography (since 2000), and PET-CT scan (since 2005). In the absence of visceral metastases, patients were considered to have a locally advanced disease when there was evidence of full-thickness involvement (cT3) or infiltration of adjacent structures (cT4) or enlarged nodes (N1 or M1lym), that is, stage T2, N1, M0-M1lym or T3-4, N0-1, M0-Mlym.

A total of 287 consecutive patients with locally advanced SCC of the thoracic esophagus underwent first-line CRT with

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neoadjuvant intent. Of these patients, 3 died of treatment-related toxicity, 8 received only 1 cycle of chemotherapy due to severe toxicity, 15 did not have enough data to be included for further analysis, 21 did not undergo surgery within 3 months, and 111 subsequently received only palliation or supportive care because of an unresectable tumor, distant metastasis, and/or poor general condition contraindicating surgery. Excluding these 158 patients, the remaining 129 patients, who represent the study population, were analyzed and divided into 3 groups on the basis of the time interval between completion of CRT and surgery: group 1, ≤30 days (n = 17); group 2, 31 to 60 days (n = 83); and group 3, 61 to 90 days (n = 29). In addition, only 2—numerically more consistent—groups were studied, using the median value of CRT-surgery intervals as a cutoff level: group A, ≤46 days (n = 66); and group B, >46 days (n = 63).

Treatment

Neoadjuvant CRT

All the patients underwent platinum-based neoadjuvant CRT: the most common chemotherapy regimen consisted of cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2 per day in continuous infusion (CI) from day 1 to day 5, for 4 cycles. Weekly cisplatin 30 mg/m^2 combined with paclitaxel 60 mg/m^2 or weekly oxaliplatin 85 mg/m^2 combined with 5-fluorouracil 200 mg/m^2 daily CI and folinic acid were the 2 other regimens used less frequently. Radiotherapy was administered in daily fractions of 1.8 Gy for a total dose of 45 to 50.4 Gy, usually starting concomitant with the third cycle of chemotherapy, according to our local policy.

Surgery

After restaging workup, fit patients with adequate tumor downstaging were operated on, possibly within 40 days after completion of CRT. All the operations were performed, either personally or under their direct supervision, by 3 senior surgeons (A.R., C.C., and E.A.) who have been working together, in the same surgical unit, since the 1980s. All the operative reports were personally written and signed by these 3 surgeons.

Esophagectomy was performed with an Ivor–Lewis procedure, through a laparotomy and right thoracotomy, for mid to lower esophageal tumors. A 3-stage McKeown procedure, with an additional left cervical incision, was reserved for tumors in the upper esophagus. At least 6 to 8 cm of healthy esophagus were resected above the proximal edge of the tumor to avoid neoplastic involvement of the proximal resection margin. In patients undergoing resection with a curative intent, en bloc lymph node dissection was performed, including the periesophageal, infracarinal, posterior mediastinal, and paracardial lymph nodes, and those located along the lesser gastric curvature, the origin of the left gastric artery, the celiac trunk, the common hepatic artery, and the splenic artery; in addition, the cervical, recurrent laryngeal chains, and paratracheal nodes were resected for cancers of the upper thoracic esophagus. In few selected patients evaluated as having a high surgical risk, esophagectomy was performed via a transhiatal approach as described by Orringer et al.[5]

The alimentary tract was reconstructed immediately, preferably with the gastric pull-up technique. If the stomach was unavailable, a colon interposition was performed. Anastomoses were performed with a circular stapling device in the thoracic cavity, usually at the apex of the chest, and a double layer of hand-sewn running suture in the neck.

Analysis of Postoperative Data and Pathologic Findings

All surgical reports were reviewed by 3 staff surgeons (A.R., C.C., and M.C.) and the technical difficulty of surgical dissection was graded as follows: grade 1 = normal periesophageal dissection planes; grade 2 = presence of some periesophageal fibrosis; grade 3 = presence of dense periesophageal fibrosis; grade 4 = presence of very dense periesophageal fibrosis, requiring demanding sharp dissection; and grade X = presence of periesophageal tumor infiltration.

Postoperative mortality included all in-hospital and 30-day deaths. Postoperative morbidity included any minor or major medical or surgical complication. Anastomotic complications (ie, necrosis of the esophageal substitute and anastomotic leaks) included both symptomatic and small asymptomatic leaks detected on routine postoperative radiological examination.

The stage of the tumor was classified according to the sixth edition (2002) of the *AJCC Staging System*. Pathologic tumor regression was graded according to Mandard's TRG classification.[6] *Pathologic complete response* (pCR) was defined as the absence of residual tumor in both the esophagus (ypT0) and lymph nodes (ypN0).

Patients were followed by the operating surgeon within a disease-dedicated multidisciplinary team at regularly scheduled intervals: every 3 to 4 months for the first 2 years, every 6 months up to 5 years, and yearly thereafter. At each visit, clinical examination was performed, eating difficulties and body weight problems were investigated, and routine blood chemistry results were obtained. Endoscopy, barium swallow, and CT scans of the chest and abdomen were obtained every 6 to 12 months or more frequently when clinically indicated.

Statistical Analysis

Data are expressed as median and interquartile range or number of patients with percentage in parenthesis. Categorical data were compared using the Fisher exact test. Continuous variables were compared using Wilcoxon-Mann-Whitney nonparametric test and Kruskal-Wallis test. Survival estimates included hospital deaths and were calculated by the Kaplan–Meier method. Survival comparisons were performed using the log-rank test. Cox proportional hazard models were used to identify independent predictors of survival. A $P < 0.05$ was considered significant. Statistical analysis was performed using SAS 9.1 software.

RESULTS

The study population was composed of 129 patients (99 men and 30 women) with a median age of 60.4 years (IQR 54.3–66.6). At the time of operation, 9 (7%) patients were found to have grossly unresectable disease and the resection was not performed, and 14 (10.9%) patients had an incomplete R1 or R2 resection. Therefore, a complete R0 resection was achieved in 106 patients: by a transthoracic approach in 96 patients (90.6%) and by a transhiatal approach in 10 patients (9.4%).

First Step of the Analysis

For the first part of the analysis, the study population was divided into 3 groups on the basis of timing to surgery after completion of CRT: group 1, ≤30 days (n = 17); group 2, 31 to 60 days (n = 83); and group 3, 61 to 90 days (n = 29). The 3 groups did not differ significantly in terms of sex ratio, age, Karnofsky performance status, comorbidities, anesthesiologic risk (ASA) score, clinical TNM stage, neoadjuvant CRT regimen, and treatment-related toxicity (Table 1). The degree of clinical response, the completeness of resection, and the difficulty of surgical dissection were similar for all groups, as shown in Table 2. The overall postoperative mortality was 3.9% (5/129), with no significant differences among groups (none in group 1; 2 in group 2, 2.4%; 3 in group 3, 10.3%; $P = 0.11$). The overall morbidity rate was 41.8% (54/129): 6 in group 1, 35.3%; 35 in group 2, 42.2%; and 13 in group 3, 44.8% ($P = 0.81$). Also, the

TABLE 1. Demographic and Clinical Characteristics of 129 Patients Who Underwent Neoadjuvant CRT and Surgery. Data are Expressed as n (%)

	Group 1 (n = 17)	Group 2 (n = 83)	Group 3 (n = 29)	*P*
CRT-surgery interval, d	≤30	31–60	61–90	
Sex, male/female	11/6	66/17	22/7	0.41
Median age, years* [IQR]	60.8 [52.5–66.6]	60 [54.8–66.9]	60.9 [58.8–66.1]	0.99
Karnofsky status > 90%	16 (94.1)	78 (94)	26 (89.7)	0.77
Weight loss > 10%	4 (23.5)	17 (20.5)	7 (24.1)	0.86
Presence of comorbidities				
Cardiovascular	5 (29.4)	34 (41)	13 (44.8)	0.07
Pulmonary	2 (11.8)	13 (15.7)	4 (13.8)	0.99
Hepatic	3 (17.7)	16 (19.3)	3 (10.3)	0.61
Metabolic	0	4 (4.8)	1 (3.5)	0.99
Other	1 (5.9)	6 (7.2)	2 (6.9)	0.99
ASA risk score				0.13
1–2	16 (94.1)	59 (71.1)	21 (72.4)	
3–4	1 (5.9)	24 (28.9)	8 (27.6)	
cTNM stage				0.44
2B	2 (11.8)	7 (8.4)	5 (17.2)	
3–4A	15 (88.2)	76 (91.6)	24 (82.8)	
Platinum-based CRT regimen				0.12
5FU-cisplatin	14 (82.4)	75 (90.4)	28 (96.6)	
5FU-oxaliplatin-folinic acid	3 (17.6)	3 (3.6)	1 (3.4)	
cisplatin-paclitaxel	0	5 (6)	0	
Treatment-related toxicity†				0.19
Low: WHO grade 0–2	13 (92.9)	56 (70)	21 (77.8)	
High: WHO grade 3–4	1 (7.1)	24 (30)	6 (22.2)	

*Data are expressed as median, "IQR".
†Data were not available for 8 patients.

TABLE 2. Surgical Data for Each Group

	Group 1 (n = 17)	Group 2 (n = 83)	Group 3 (n = 29)	*P*
CRT-surgery interval, days	≤30	31–60	61–90	
Clinical response				0.80
Complete response + partial response	15 (88.2)	66 (79.5)	24 (82.8)	
No change + progressive disease	2 (11.8)	17 (20.5)	5 (17.2)	
Type of resection, R0/R1–2*	14/2 (82.3/11.8)	69/7 (83.2/8.4)	23/6 (79.3/20.7)	0.25
Difficulty of surgical dissection†:				0.82
Grade 1–2	7 (41.2)	35 (42.2)	10 (34.5)	
Grade 3	6 (35.3)	24 (28.9)	10 (34.5)	
Grade 4	1 (5.9)	5 (6.0)	4 (13.8)	
Grade X	3 (17.6)	19 (22.9)	5 (17.2)	
Postoperative‡ mortality	0	2 (2.4)	3 (10.3)	0.11
Postoperative morbidity	6 (35.3)	35 (42.2)	13 (44.8)	0.81
Type of complication:				0.57
Medical complications only	2 (33.3)	12 (34.3)	7 (53.8)	
Surgical complications only	3 (50.0)	17 (48.6)	3 (23.1)	
Both medical/surgical complications	1 (16.7)	6 (17.1)	3 (23.1)	
Anastomotic complications	1/16 (6.25)	6/76 (7.9)	1/29 (3.5)	0.87

Data are expressed as n (%).
*At the time of operation, 9 (7%) patients had a grossly unresectable disease and the resection was not performed.
†Technical difficulty of surgical dissection: grade 1: normal periesophageal dissection planes; grade 2: presence of some periesophageal fibrosis; grade 3: presence of dense periesophageal fibrosis; grade 4: very dense periesophageal fibrosis, requiring demanding sharp dissection; grade X: presence of periesophageal tumor infiltration.
‡Postoperative mortality includes all in-hospital and 30-day deaths.

rate of anastomotic complications was comparable, independent of the CRT-surgery interval (Table 2).

A pCR was documented in 31.1% (33/106) of the patients who underwent a complete R0 resection and was similarly distributed in the 3 groups. The number of lymph nodes removed per patient, ypT, ypN, and ypStage were similar in all groups. Details of tumor characteristics and final pathology are shown in Table 3.

The overall median follow-up was 26.7 months (IQR, 12.9–51). By intention-to-treat analysis, the overall 3- and 5-year actuarial survival rate was 46% and 38.2%, respectively. Comparing the 3 groups, the overall 5-year actuarial survival rate was 0% in group 1, 43.1% in group 2, and 35.9% in group 3 ($P = 0.13$) (Fig. 1A). The overall 5-year actuarial survival rate after R0 resection (n = 106) was 46.6% and comparable in the 3 groups (Fig. 1B).

The pattern of failure and median time to recurrence are shown in Table 4. After R0 resection, recurrence of any type occurred in 40 of 106 (37.7%) patients, at a median of 12 months (IQR, 5–19) after surgery; the recurrence rate was 50% (7/14) in group 1, 40.6% (28/69) in group 2, and 21.7% (5/23) in group 3 ($P = 0.45$).

TABLE 3. Tumor Characteristics and Pathology Data of the 106 Patients Who Underwent R0 Resection

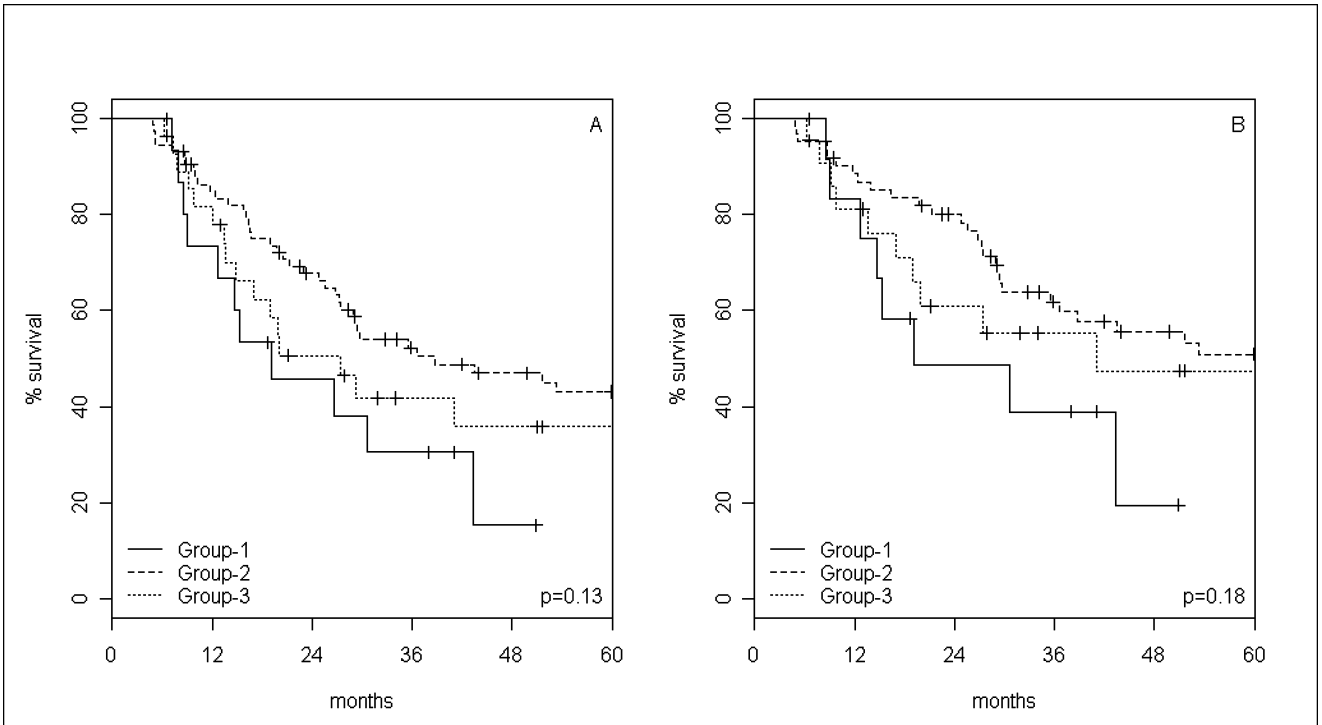
	Group 1 (n = 14)	Group 2 (n = 69)	Group 3 (n = 23)	*P*
CRT-surgery interval, days	≤30	31–60	61–90	
Tumor grading, G1–2/G3–4	9/5	49/20	16/7	0.09
Tumor length,* mm [IQR]	60 [50–80]	50 [40–70]	60 [50–70]	0.77
Harvested nodes* [IQR]	16 [14–18]	18 [14–21]	19 [13–22]	0.86
ypT0/ypT1/ypT2/ypT3/ypT4	5/1/5/2/1	30/6/15/16/2	10/3/5/5/0	0.89
ypN0/ypN1	7/7	51/18	15/8	0.19
ypStage 0-1-2:3-4	8/6	54/15	17/6	0.29
pCR n (%)	2 (14.3)	25 (36.2)	6 (26.1)	0.23
TRG classification 1-2/3-4-5	9/5	41/28	14/9	0.99

*Data are expressed as median, [IQR].

pCR indicates pathologic complete response; TRG, Mandard's Tumor Regression Grade.

Second Step of the Analysis

In addition, the study population was divided into 2 groups by using the median value of CRT-surgery intervals (46 days) as a cutoff level: group A, ≤46 days (n = 66); group B, >46 days (n = 63). The 2 groups did not differ in terms of sex ratio, age, Karnofsky performance status, comorbidities, ASA score, clinical TNM stage, neoadjuvant CRT regimen, and treatment-related toxicity (Table 5). Also, in terms of degree of clinical response and completeness of resection, there were no differences between the 2 groups, with an R0 resection rate of 87.9% (58/66) in group A and 76.2% (48/63)



1A) Patients at risk

Year	0	1	2	3	4	5
Group1	17	16	8	5	2	-
Group2	83	69	52	33	27	22
Group3	29	28	16	8	6	4

1B) Patients at risk

Year	0	1	2	3	4	5
Group1	14	13	7	5	2	-
Group2	69	58	49	33	27	22
Group3	23	22	14	8	6	4

FIGURE 1. Kaplan–Meier survival curves (including postoperative deaths) plotted by intention to treat (n = 129) (A) and R0 resection (n = 106) (B). Patients are stratified according to the 3 CRT-surgery intervals.

TABLE 4. Pattern of Failure and Median Time to Tumor Recurrence After R0 Resection

	Group 1 (n = 7)	Group 2 (n = 28)	Group 3 (n = 5)	*P*
CRT-surgery interval, d	≤30	31–60	61–90	
Median time, median [IQR], mo	4.5 [3–11]	14 [8–24]	6 [3–12]	0.03
Recurrence*				0.45
Local	4 (57.1)	14 (50)	1 (20)	
Systemic	2 (28.6)	10 (35.7)	4 (80)	
Both	1 (14.3)	4 (14.3)	0	

*Data are expressed as n (%).

TABLE 5. Demographic and Clinical Characteristics of 129 Patients Who Underwent Neoadjuvant CRT and Surgery, Stratified According to the Median CRT-Surgery Interval (46 Days)

	Group A (n = 66)	Group B (n = 63)	*P*
CRT-surgery interval, d	≤46 days	>46 days	
Sex, male/female	50/16	49/14	0.84
Median age, years* [IQR]	59.6 [54.5–66.5]	60.9 [54.1–67]	0.47
Karnofsky status >90%	61 (92.4)	59 (93.6)	0.99
Weight loss >10%	14 (21.2)	14 (22.2)	0.99
Presence of comorbidities			
Cardiovascular	24 (36.4)	28 (44.4)	0.37
Pulmonary	10 (15.2)	9 (14.3)	0.99
Hepatic	13 (19.7)	9 (14.3)	0.49
Metabolic	3 (4.6)	2 (3.2)	0.99
Other	3 (4.6)	6 (9.5)	0.32
ASA risk score			0.31
1–2	52 (78.8)	44 (69.8)	
3–4	14 (21.2)	19 (30.2)	
cTNM stage			0.27
2B	5 (7.6)	9 (14.3)	
3–4A	61 (92.4)	54 (85.7)	
Platinum-based CRT regimen			0.99
5FU-cisplatin	59 (89.4)	58 (92.1)	
5FU-oxaliplatin-folinic acid	4 (6.1)	3 (4.8)	
Cisplatin-paclitaxel	3 (4.5)	2 (3.1)	
Treatment-related toxicity†			0.21
Low: WHO grade 0–2	42 (68.9)	48 (80)	
High: WHO grade 3–4	19 (31.1)	12 (20)	

Data are Expressed as n (%).
*Data are expressed as median, [IQR].
†Data were not available for 8 patients.

in group B ($P = 0.17$). The difficulty of surgical dissection, postoperative morbidity (26/66, 39.4% vs 28/63, 44.4%; $P = 0.60$), and mortality rates (1/66, 1.5% vs 4/63, 6.3%; $P = 0.20$) were comparable in group A and group B.

Pathologic complete response was documented in 34.5% (20/58) of patients in group A and in 27.1% (13/48) of patients in group B ($P = 0.53$). The number of lymph nodes removed per patient, ypT, ypN, and ypStage were similar in both groups (Table 6).

The overall actuarial 5-year survival rate was 33.1% in group A and 42.7% in group B ($P = 0.64$) (Fig. 2A) and, considering only the 106 patients with an R0 resection, it was 37.8% and 56.3%, respectively ($P = 0.18$) (Fig. 2B).

TABLE 6. Tumor Characteristics and Pathology Data of the 106 Patients Who Underwent R0 Resection, Stratified According to the Median CRT-Surgery Interval (46 Days)

	Group A (n = 58)	Group B (n = 48)	*P*
CRT-surgery interval, d	≤46	>46	
Tumor grading G1–2/G3–4	42/16	32/16	0.53
Tumor length*	60 [45–70]	50 [40–70]	0.13
Harvested nodes*	17 [15–23]	18 [13–21]	0.80
ypT0/ypT1/ypT2/ypT3/ypT4	26/3/14/14/1	19/7/11/9/2	0.49
ypN0/ypN1	39/19	34/14	0.83
ypStage 0-1-2/3-4	43/15	36/12	0.99
pCR n (%)	20 (34.5)	13 (27.1)	0.53
TRG‡ classification 1-2/3-4-5	35/23	29/19	0.99

*Data are expressed as median, [IQR].
pCR indicates pathologic Complete Response; TRG, Mandard's Tumor Regression Grade.

The median time to recurrence was 11.5 months (range, 6–24) in group A and 12 months (range, 6–24) in group B ($P = 0.83$). The prevalence of recurrence was significantly reduced ($P = 0.02$) in group B (25%) compared with group A (48.3%).

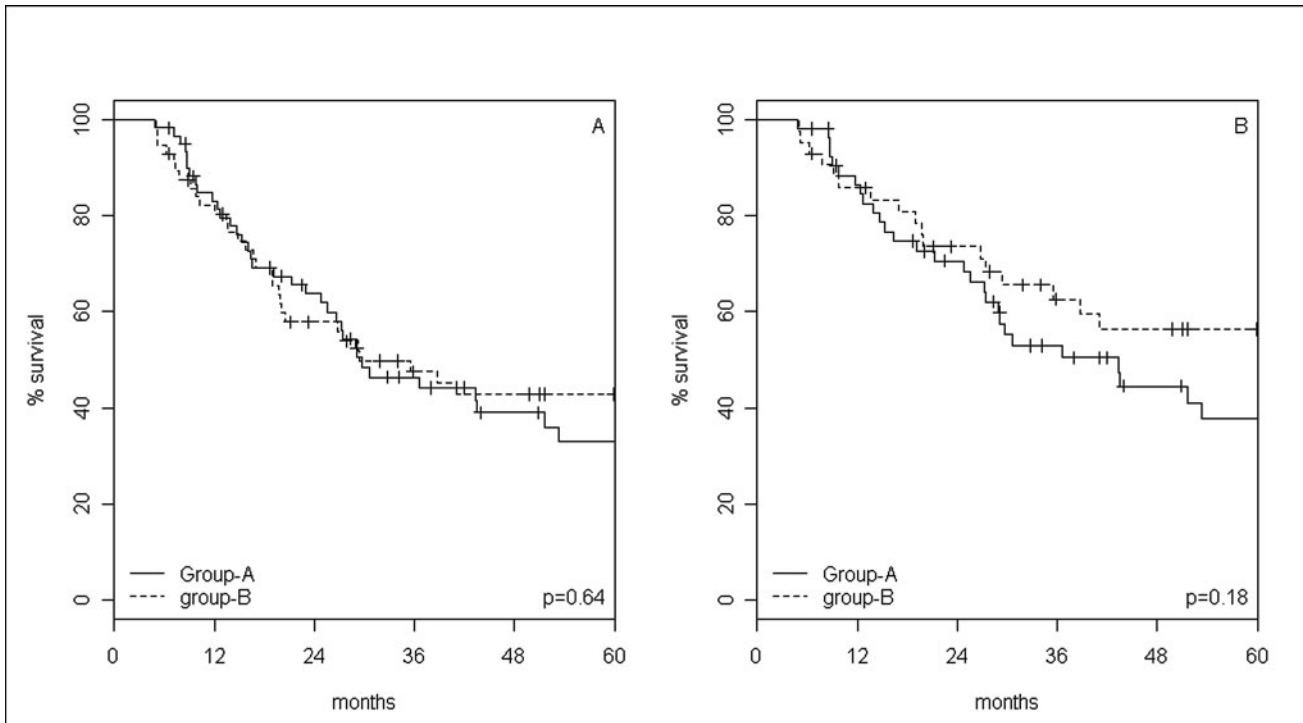
PROGNOSTIC FACTORS

The univariate analysis, calculated on the 106 patients who achieved an R0 resection, identified the following variables associated with survival (Table 7): age ($P = 0.005$), tumor grading ($P = 0.03$), number of harvested nodes ($P = 0.02$), ypT ($P = 0.002$), ypN ($P = 0.006$), ypStage ($P = 0.005$), pCR ($P = 0.002$), and TRG classification ($P = 0.05$). The above parameters were included in Cox regression analysis to assess independent predictors of survival: the presence of a pCR was the strongest predictor of good outcome ($P = 0.003$, HR = 0.33, 95% CI = 0.16-0.68); advanced age ($P = 0.007$, HR = 2.92, 95% CI = 1.34-6.38) and higher tumor grading were significantly related to poor survival ($P = 0.03$, HR = 0.53, 95% CI = 0.30-0.95).

DISCUSSION

The treatment of locally advanced SCC of the thoracic esophagus is demanding, resectability rate is low, and survival is poor. In recent years, the interdisciplinary and multidisciplinary management of patients with esophageal cancer has led to increased resection rates, reduced postoperative morbidity and mortality rates, and improved survival.[1–4] The weight of evidence from several phase II trials, 8 phase III trials, and metaanalyses has suggested that neoadjuvant CRT followed by surgery is an appropriate treatment choice and should be considered the standard treatment for patients with locally advanced esophageal cancer.

In the phase III randomized trials of neoadjuvant CRT for resectable locally advanced esophageal cancer, the CRT-surgery interval was always between 2 and 6 weeks.[3] However, the optimal timing of surgery after neoadjuvant CRT has never been directly evaluated in esophageal cancer clinical trials. A longer CRT-surgery interval may allow for therapy-induced tissue swelling and local inflammation to subside and, theoretically, may be associated with greater degrees of tumor regression (downsizing, downstaging) via apoptosis and necrosis, which may improve tumor resectability and pathologic complete or nearly complete response rates. This must be balanced against the potential risk of tumor regrowth during this time period, or the concern that the late effects of radiotherapy may make surgical dissection



2A) Patients at risk

Year	0	1	2	3	4	5
GroupA	66	59	39	23	17	11
GroupB	63	53	36	23	18	15

2B) patients at risk

Year	0	1	2	3	4	5
GroupA	58	52	37	23	17	11
GroupB	48	41	32	23	18	15

FIGURE 2. Kaplan–Meier survival curves (including postoperative deaths) plotted by intention to treat (n = 129) (A) and R0 resection (n = 106) (B). Comparison between patients operated before and after the median CRT-surgery interval of 46 days.

TABLE 7. Univariate Analysis of the Predictors of Survival in the 106 Patients Who Underwent R0 Resection

	5-Year Survival, %	*P*
Group 1/group 2/group 3	0/51.0/47.3	*0.18*
Group A/group B	37.8/56.3	0.18
Age, <70 years/≥70 years	49.6/19.1	0.005
Sex, male/female	42.3/48.1	0.59
Number of harvested nodes	*	0.02
Grading: G1–2/G3–4	53.5/32.8	0.03
ypT: 0–1-2/3–4	53.7/18.2	0.002
ypN: 0/1	55.9/19.9	0.006
ypStage: 0–1-2/3–4	52.5/27.2	0.005
pCR: yes/no	70.6/34.7	0.002
TRG grade: 1–2/3–5	54.9/30.0	0.05

*Used as continuous variable.

pCR indicates pathologic Complete Response; TRG, Mandard's Tumor Regression Grade.

more difficult as dense fibrosis becomes more established and may worsen surgical outcomes.

Recent studies evaluated the effect of the CRT-surgery interval in locally advanced rectal cancer where surgery is generally recommended within 4 to 6 weeks after completion of CRT. These studies suggest that CRT-surgery intervals of 6 to 12 weeks are safe, do not compromise short-term[7–10] and long-term outcomes,[8,9,11–13] and may improve tumor downstaging,[12,13] pCR rate,[13,14] postoperative morbidity including anastomotic leaks,[15] recurrence rates, and disease-free survival.[14]

In esophageal cancer studies, there is remarkably little variation in the timing of surgery after completion of CRT: the traditional interval of 4 to 6 weeks is well established but not well founded in terms of efficacy or safety relative to longer delays. To our knowledge, this is the first study focused on the impact of the time interval between neoadjuvant CRT and surgery for SCC of the esophagus. The results of the study suggest several important considerations when they are compared with the available randomized trials where patients, with a resectable locally advanced cancer of the esophagus, underwent resection surgery within 6 weeks after completion of CRT.

The study population had a preponderance of locally advanced tumors that were deemed unresectable on the basis of initial staging (ie, cT4). Therefore, only patients with adequate tumor downstaging after CRT could undergo surgery. Even though the expected outcomes after neoadjuvant CRT and surgery were likely to be worse than those reported in prospective phase III randomized studies performed on resectable cancer of the esophagus, both postoperative outcomes and prognosis were comparable. Despite the more advanced stage at presentation, in responding patients who could undergo surgery, the rate of R0 resections was 82.2% and was similar for all CRT-surgery interval groups, suggesting that the benefit of neoadjuvant CRT in terms of tumor downstaging and facilitating a complete resection

was not compromised by a longer CRT-surgery interval. Also the pCR rate was similar in all CRT-surgery interval groups and was comparable with the results of randomized trials that range between 11% and 26%. Therefore, a longer CRT-surgery interval seems not to be associated to a worse pathologic response.

Esophagectomy can be a challenging operation when performed after neoadjuvant CRT. Intuitively, CRT can potentially set the stage for postoperative acute lung injury and anastomotic leaks, and surgical dissection may become more difficult as fibrosis becomes more established. Our study shows that longer CRT-surgery intervals do not increase the technical difficulty of esophageal dissection or the risk of postoperative morbidity. On the other hand, a nonsignificant trend toward increased postoperative mortality was found with longer CRT-surgery intervals. This can possibly be explained by the fact that a nonsignificantly higher prevalence of cardiovascular comorbidities ($P = 0.07$) and ASA 3 to 4 risk ($P = 0.13$) was present in group 3 patients as opposed to group 1.

Finally, consistent with the findings of randomized trials, an overall 5-year survival rate of 38.2% was achieved. No significant survival difference was found depending on the length of the CRT-surgery interval. After R0 resection, a positive trend was found in favor of a better survival in the group of patients with a longer CRT-surgery interval: 56.3% in group B versus 37.8% in group A ($P = 0.18$). This finding can be explained by the fact that the prevalence of tumor recurrence was significantly reduced in group B (25%) compared with group A (48.3%) ($P = 0.02$). Therefore, the theoretical belief that a longer CRT-surgery interval may be inappropriate in cases of incomplete tumor response because of the possible risk of tumor regrowth is not confirmed in this study. On the contrary, we can hypothesize that CRT-surgery delays longer than 30 to 40 days may allow the antitumoral effects of preoperative CRT to complete, especially where radiotherapy and chemotherapy have an additional effect, that is, within the irradiation field.

The potential drawback of this study is that it is retrospective and the allocation of the CRT-surgery interval was not random: therefore, a selection bias cannot reasonably be excluded. However, these shortcomings can be of minor significance because comparison between all the CRT-surgery interval groups with regard to demographics, clinical and tumor characteristics, and operative data revealed that they were similar in all parameters. Obviously, only a prospective randomized study could clearly answer the question, but we suspect that such a trial will be rather difficult to organize.

High-volume hospitals have significantly lower operative mortality rates after esophagectomy than low-volume hospitals.[16–18] Significant relationships between hospital volume and long-term survival after esophagectomy are also reported.[17] Therefore, referral to high-volume hospitals has been recommended for complex operations with a demonstrated volume-outcome relationship, such as esophagectomy.[16,18] Actually, esophageal cancer surgery is becoming increasingly centralized, and this centralization has the potential to introduce a capacity problem. To accommodate more patients at high-volume hospitals has resulted in problems in referral, access problems, patient's increased travel burden, and increased operative waiting list.[18] Other reasons for delay include patients' malnutrition or poor physical status, medical conditions such as infections and cardiopulmonary problems, and more thorough and time-consuming preoperative workup.

Whenever possible, patients with esophageal cancer were operated on within 40 days after completion of CRT. However, more than 50% of the patients were referred to our hospital from other Italian regions, where neoadjuvant CRT had been performed. Late referral and operative waiting list may explain why nearly half of the patients were operated on 46 days or more after completion of CRT. The results of our study suggest that delayed surgery does not compromise outcomes. This finding can be of relevant clinical importance for both patients and clinicians because it gives the chance to schedule the operation at a time that may be more convenient, and decrease the urgency to rush a patient to complex preoperative workup and to surgery after he or she had completed CRT and may need some more time to recover.

In summary, this study suggests that compared with a 4- to 6-week interval, delaying surgery up to 6 to 13 weeks after completion of CRT does not negatively affect CRT responses and postoperative outcomes. Furthermore, patients operated on after a CRT-surgery interval of 6 to 13 weeks seem to have a reduced recurrence rate and a positive trend toward increased survival. The retrospective nature of this study mandates caution in interpretation of the results because selection bias cannot reasonably be excluded. Nevertheless, this study may be an important call for the surgical and oncological community: prospective randomized studies are required to gain a more complete understanding of the optimal CRT-surgery interval in patients with locally advanced SCC of the esophagus.

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DISCUSSION

ESA Paper 16: Interval Between Neoadjuvant Chemoradiotherapy and Surgery for Squamous Cell Carcinoma of the Thoracic Esophagus: Does Delayed Surgery Have an Impact on Outcome?

Alberto RUOL (Padova, Italy)

DISCUSSANT

M. Krawczyk (Warsaw, Poland)

We know that treatment of advanced tumors of the esophagus should start with chemoradiation followed by surgery. Dr Ruol et al have attempted to define the most suitable and effective time interval to surgery after chemoradiation, and they concluded that the best time for surgery is 6 weeks after completion of chemoradiation.

It seems that the analyzed data were not homogenous. Three different surgical procedures were performed: esophagectomy with lymphadenectomy and anastomosis in the right thorax, esophagectomy with lymphadenectomy and anastomosis in the neck, and transhiatal esophagectomy. Furthermore, reconstruction of the alimentary tract was performed either by pull-up of the stomach or by using the colon or the jejunum. Thus, one can argue that the series was not homogenous and that the differences between the 3 subgroups may have had some influence on the outcome.

Second, you concluded that differences in postoperative mortality between the 3 groups were not statistically significant but in my opinion there was a visible difference between the groups. Indeed in group 1, the mortality was 0% whereas in group 3 it was 10.3%.

Third, I cannot understand why the 5-year survival rate was 0% in group 1, but 43% in group 2, and 33% in group 3. The basic treatment was the same, chemoradiation and surgical resection. The timing of surgery after chemoradiation is likely to have influenced postsurgical complications and mortality. The mortality and morbidity rates in group 1 were the lowest whereas the 5-year survival rate was the worst and the tumor recurrence rate was the highest in group 1. I think that the explanation for this is based on data. If the resection was R0, the 5-year survival rate is higher than those for R1 and R2 resection. I would be very grateful if you can clarify this matter.

Response From A. Ruol

First of all, Dr Krawczyk suggests that 3 different types of surgical procedure were performed. Actually, whether partial esophagectomy with reconstruction inside the chest or total esophagectomy with anastomosis in the neck was performed depended on the location of the tumor. Of course, when the tumor involved the upper thoracic esophagus, a total esophagectomy and an anastomosis in the neck were a must, which was not the case when the tumor was located below the tracheal bifurcation. The type of operation was simply related to the precise location of the tumor in the thoracic esophagus, either in the upper third or in the mid or lower third. An esophagectomy without thoracotomy was performed in only 10 patients in whom transthoracic esophagectomy was contraindicated. As far as the type of reconstruction is concerned, we performed an esophagogastrostomy in most patients; an esophagocolostomy was performed only when the stomach was not suitable for the reconstruction. No jejunoplasties were performed in this series.

With regard to your second point, you are right: postoperative deaths were relatively more frequent in group 3. Actually, 2 of these 3 deaths were of very high-risk patients, who received only the esophagectomy and died of pulmonary plus cardiovascular complications before planned staged reconstruction. We do not usually perform delayed reconstructions, and we reserve delayed reconstruction only for very high-risk patients. So these very high-risk patients were allowed as much time as possible to recover after chemoradiation, before being operated on. This is the reason why they were all in group 3, but unfortunately they died after surgery.

What about the differences in the 5-year survival rate? Actually, it is difficult for me to explain why the prognosis was better after longer intervals between completion of chemoradiation and surgery. One possible explanation could be that when we operate on patients immediately after completion of chemoradiation, it is possible that vital tumor cells may be disseminated by surgical maneuvers. When we wait longer, the effects of chemoradiation have maximized and perhaps dissemination of tumors cells is reduced. Another possible answer is that both group 1 and group 3 were small, therefore the results may be biased by the small number of patients evaluated.

DISCUSSANT

J.J.B. Van Lanschot (Rotterdam, the Netherlands)

It is hard to understand why waiting longer leads to better results. As you indicated, it is not a randomized trial but it suggests a nice hypothesis that even after the end of radiotherapy, radiotherapy continues to work and it might be detrimental to operate too early. Do you think that after chemoradiotherapy it might be best to just wait and see, especially in patients who are responding, and that you should operate only after you prove that patients have residual or recurrent disease, either by biopsy from the esophagus or by FNA FNA stands for Fine Needle Aspiration from a positive lymph node?

Response From A. Ruol

Unfortunately, as yet, nobody knows the correct answer. However, whenever possible, we prefer to operate after chemoradiation independent of the degree of the clinical response, because more than 30% of the patients who apparently show a complete clinical response actually have residual tumor in the operative specimen when they undergo surgery.

To answer your question a little better, let us look at those patients we have not operated on within 90 days after completion of chemoradiation. Fifteen patients were operated on 200 or more days after completion of chemoradiation. These patients received chemoradiation elsewhere, in other hospitals, and were referred to us only when, after an initial complete clinical response, they developed tumor recurrence. In these 15 patients, we performed 3 explorations because the tumor was no longer resectable, 2 R1 resections, and 10 R0 resections. There was no postoperative mortality. Of the 10 patients who underwent an R0 resection, 4 died between 7 and 90 months, 5 were alive between 42 and 111 months and 1 was lost to follow-up. Maybe these promising data on patients operated only for recurrence after an initial complete clinical response can partially answer your question. The risk, though, is that when we decide to operate on a recurrent tumor, it may no longer be resectable.

DISCUSSANT

J. Izbicki (Hamburg, Germany)

What exactly was the reason for delaying surgery in those patients? Was radiochemotherapy given as a definitive treatment and

when did you decide otherwise? Also, I did not quite get the distribution of various risk factors in your 3 groups, but I think there was a serious imbalance of ASA I–II cases in group A and in groups B and C.

Response from A. Ruol

In this study, we considered only patients operated upon earlier than 90 days after completion of chemoradiation. What were the reasons for more delayed surgery? Some patients' physical status was poor, or they suffered from severe side effects of chemoradiation and so it was necessary to wait for the patient to recover from these problems. Another problem is that many patients underwent chemoradiation in other hospitals elsewhere in Italy, and then they were referred to our hospital to be operated upon. Thus, if the referring hospital sent us a patient 30 or 40 days after completion of chemoradiotherapy, that is a problem of late referral, which, of course, may delay surgery even longer than 90 days. The other patients, who were operated on more than 200 days after completion of chemoradiation, represent a completely different problem. These patients experienced a complete clinical response, and the oncologist, radiotherapist, and/or the patient himself or herself decided to exclude surgery after chemoradiation; later on, they were referred to our hospital for surgery, when they experienced tumor recurrence.

The figures for the anesthetic risk scores show that there were more high-risk patients in groups 2 and 3, compared with group 1. Of course, patients with higher ASA scores needed more physiotherapy and more time to recover before being operated on. The difference was not significant, at least with the number of patients in our study, but maybe, with a greater number of patients, this difference may become significant.

DISCUSSANT

N. Senninger (Munster, Germany)

It was definitely worthwhile to group your patients according to risk scores; it makes the differences more understandable. Concerning long-term survival, how many of the patients received additional adjuvant therapy, or maybe palliative therapy later on, that might have influenced the survival curves? Second, it is a pity that you did not evaluate the data of the 21 patients who were referred to you more than 90 days afterward, because, according to your theory, if waiting longer is even better, these patients should have survived maybe forever. Do you have any data on that?

Response From A. Ruol

We generally do not give any form of adjuvant treatment to patients with squamous cell carcinoma because it has not been shown to be worthwhile in terms of improved survival. Adjuvant treatments are usually given to patients with squamous cell carcinoma of thoracic esophagus only when a palliative resection has been performed, so after R1 or R2 resections. Another possible indication for adjuvant treatment is in a young patient with significant negative prognostic factors, such as the presence of many metastatic lymph nodes, extra capsular invasion, and so on.

With regard to the clinical data for the patients operated on after more than 90 days after completion of chemoradiation, 6 patients were operated on between 90 and 200 days: because of late referral in 4, severe hematologic toxicity in 1, and tumor recurrence after an initial complete clinical response in 1. Five R0 resections and 1 R1 resection were performed, with no postoperative deaths. Four patients died between 7 and 26 months, and 1 patient is alive after 118 months.

Fifteen patients were operated on later than 200 days, because of tumor recurrence after an initial complete clinical response. Three patients underwent only exploration because the tumor was not resectable; 2 had an R1 resection, and 10 had an R0 resection. No postoperative deaths were recorded. Of the 10 patients who underwent an R0 resection, 4 died between 7 and 90 months, 5 were alive between 42 and 111 months, and 1 was lost to follow-up. These patients were not included in the analysis of the present study because they represent a completely different population.