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ORIGINAL REPORT

Phase III Trial of Protracted Compared With Split-Course Chemoradiation for Esophageal Carcinoma: Fédération Francophone de Cancérologie Digestive 9102

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
Chemoradiotherapy (CRT) is an alternative to surgery for resectable locally advanced esophageal carcinoma (RLA-EC). We investigated the heterogeneity of the treatment benefits across subgroups of patients, defined according to the radiation scheme.

Patients and Methods
Between February 1993 and December 2000, 451 patients were enrolled. The following two schemes were allowed: protracted radiotherapy (P-RT), which scheduled 46 Gy over 4.5 weeks or split-course radiotherapy (SC-RT) with two 1-week courses of 15 Gy. Two courses of cisplatin and fluorouracil were delivered concomitantly. In case of exclusive CRT, a further course of 20 Gy over 2 weeks in the P-RT group and one 1-week course of 15 Gy in the SC-RT group were delivered with three courses of chemotherapy. SC-RT and P-RT were administered to 285 patients (64%) and 161 patients (36%), respectively.

Results
For P-RT versus SC-RT, the response rate to induction CRT was 67% *v* 68%, respectively ($P = .09$), and 2-year local relapse-free survival rate was 76.7% *v* 56.8%, respectively ($P = .002$). Shorter tumor length and P-RT were associated with better local control in multivariate analysis ($P = .002$ for both). After a median follow-up time of 47.4 months, 2-year overall survival rate was 37.1% for P-RT compared with 30.5% for SC-RT ($P = .25$). Independent prognostic factors on survival were tumor diameter ($P = .02$), weight loss of 10% or less ($P = .05$), and response to induction CRT ($P = .002$).

Conclusion
Patients with RLA-EC treated with P-RT had better local control than patients treated with SC-RT. Response to induction CRT is a determinant prognostic factor on survival.

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INTRODUCTION

Esophageal cancer (EC) is a highly aggressive disease with a poor prognosis, even after a curative resection. Data from the Eurocare III study indicate a 5-year relative survival rate of approximately 10% for all patients for the period of 1990 to 1994.[1] For locally advanced EC, the standard treatment is the Radiation Therapy Oncology Group 85-01 scheme, which delivers 50 Gy in 25 fractions of 2 Gy over 5 weeks, combined with cisplatin/fluorouracil chemotherapy.[2,3] This treatment scheme showed reproducible results in terms of survival, with a 2-year survival rate of approximately 40%.[2-4] Similar survival rates are observed with surgery alone.[5] Preoperative chemoradiotherapy (CRT) decreases the rate of local failure and increases the rate of curative resection but also increases morbidity rates.[6-8] Although individual randomized trials failed to demonstrate any survival benefit, four meta-analyses showed a survival benefit over surgery alone that appeared at 3 years.[9-12] The efficacy of this regimen led to studies about the place of surgery in patients with resectable locally advanced EC (RLA-EC) treated with preoperative CRT. The Fédération Francophone de Cancérologie Digestive (FFCD) investigated, in a phase III study (FFCD 9102), the benefit of surgical removal of the tumor for patients with a T3, N0-1 tumor of the thoracic esophagus responding to CRT. This study concluded that exclusive CRT in responders showed similar median survival and quality of life whether patients were resected or not.[13,14] The aim of this ancillary study was to compare outcomes according to both

schemes of radiotherapy allowed by the protocol (split-course radiotherapy [SC-RT] *v* protracted radiotherapy [P-RT]) among all included patients and to explore prognostic factors on local control and survival related to patient, tumor, and treatment characteristics.

PATIENTS AND METHODS

Eligibility Criteria

Patients were eligible if they had invasive, resectable, T3, N0-1 squamous cell or adenocarcinoma of the thoracic esophagus and clinical and biologic eligibility for surgery or CRT. Noninclusion criteria were tumors less than 18 cm from the dental ridge or infiltrating the gastric cardia, tracheobronchial involvement, visceral metastases or supraclavicular lymph nodes, weight loss of more than 15%, symptomatic coronary heart disease, cirrhosis of Child-Pugh class B or C, and respiratory insufficiency.

The work-up procedure has been described previously.[13] Written informed consent was required.

Treatment

Radiotherapy. Two techniques were allowed in the protocol, a P-RT regimen and an SC-RT regimen (Fig 1). Conventional P-RT was delivered in 5 daily fractions of 2 Gy each week over 4.5 weeks for a total dose of 46 Gy before random assignment and over 2 weeks after random assignment for a total dose of 66 Gy. SC-RT was delivered in two 1-week courses separated by 2 weeks before random assignment and one 1-week course after random assignment. During each course of 15 Gy, 5 daily fractions of 3 Gy were delivered. Thus, the total cumulative dose was 45 Gy. Irradiation techniques and treatment volumes have been reported previously.[13]

Chemotherapy. Two cycles were delivered before random assignment, starting on day 1 and day 22. In case of exclusive CRT, three cycles were administered, starting on days 43, 64, and 92. Cisplatin was administered either at a dose of 15 mg/m^2 from day 1 to day 5 or 75 mg/m^2 on day 2. Fluorouracil was administered at a dose of 800 mg/m^2 daily as a continuous venous infusion from days 1 to 5 of each cycle. Modifications in chemotherapy doses and timing have been described previously.[13]

Surgery. In the combined treatment group, surgery was planned to take place between day 50 and day 60. No surgical procedure was specified.

Follow-Up

Follow-up evaluation started 2 months after resection in the surgical group. In all patients, whatever the treatment arm, an evaluation was performed 4 months after the beginning of treatment, then every 3 months during the first 2 years, and then every 6 months thereafter.

Random Assignment and Statistical Analysis

This pragmatic study was based on the first step of the FFCD 9102 trial,[13] which was constructed with a two-step design; thus, all patients who received induction radiotherapy were considered. After checking the eligibility criteria, the first sequence of CRT comprising two courses of chemotherapy combined with radiation was administered before random assignment. Patients were then evaluated by esophagogram, abdominal ultrasonography, chest x-ray, and, if possible, endoscopic ultrasound. A clinical complete response (CR) was defined as the absence of both dysphagia and visible tumor on the esophagogram, and a partial response (PR) corresponded to an improvement in dysphagia and a decrease of more than 30% in tumor length on the esophagogram, according to WHO criteria.[15] According to the results of the previously described protocols for radiation delivery, the patients were divided into the following two subgroups: responders (CR + PR) to the first CRT course (corresponding to randomly assigned patients) and nonresponders (treatment decided by each investigator). If CRT had not been tolerated, surgery was recommended. Calculation of sample size and random assignment for the main objectives of this trial have been described elsewhere.[13,14] For the present study, analyses were performed strictly on the intent-to-treat principle for all of the included patients receiving induction radiotherapy (n = 446). Exploratory analyses were also performed among randomly assigned patients (n = 259) and among both randomization arms (surgery, n = 129; or exclusive CRT, n = 130). Baseline characteristics were compared according to the two radiotherapy groups using the *t* test or the Mann-Whitney *U* test for continuous variables and the χ^2 test or Fisher's exact test for categoric variables.[16] Local relapse-free survival (LRFS) was defined as the time interval between the first day of induction radiotherapy and local or regional failure or was censored at the last follow-up or death. Disease-free survival (DFS) was defined as the time interval between the first day of induction radiotherapy and local failure or distant failure, second cancer, or death, whichever occurred first, or was censored at the last follow-up. Overall survival (OS) was defined as the time interval between the first day of induction radiotherapy and death or last follow-up. Survival was estimated using the

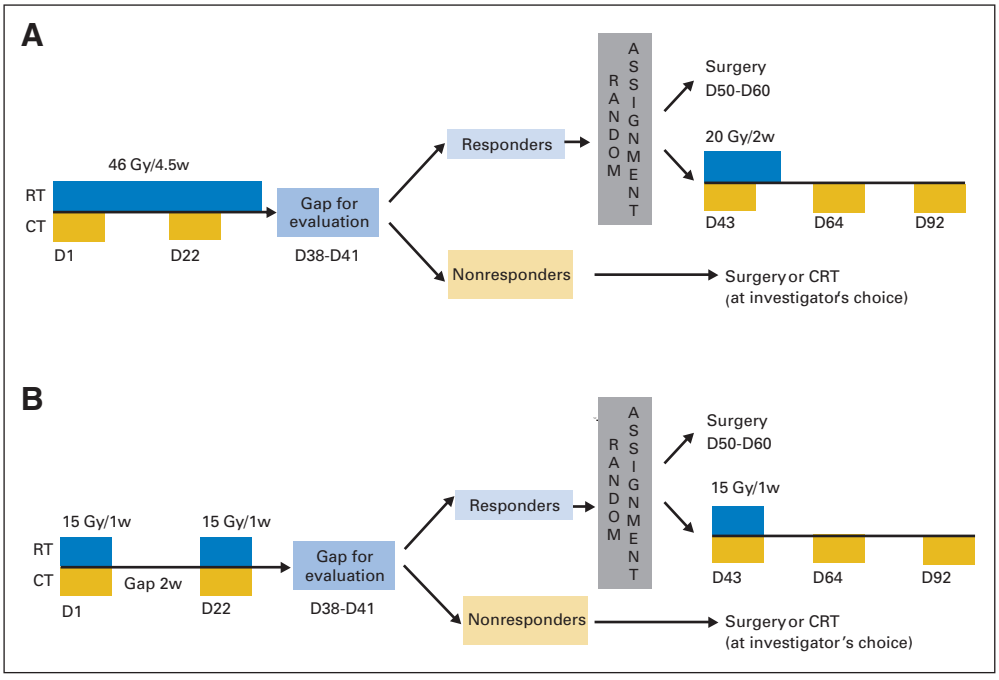

Fig 1. Treatment schedule. First sequence involved protracted radiotherapy (P-RT) 46 Gy over 4.5 weeks or split-course radiotherapy (SC-RT; two courses of 15 Gy over 1 week with a break of 2 weeks) before random assignment. In case of chemoradiotherapy (CRT) continuation, 20 Gy over 2 weeks was delivered in the P-RT group, whereas a third course of 15 Gy over 1 week was delivered in the SC-RT group. RT, radiotherapy; CT, chemotherapy; D, day; w, week.

Kaplan-Meier method and compared using the log-rank test.[17] The Cox proportional hazards model was used to calculate univariate and multivariate hazard radios (HR) and 95% CIs.[18]

Multivariate analyses of LRFS and OS were performed including all variables with univariate $P \leq .1$ or variables of interest, such as radiation scheme (P-RT *v* SC-RT), sex, age, length and diameter of the tumor, weight loss, quality of life evaluated by the Spitzer index,[19] length of hospital stay, N stage as determined by computed tomography, dysphagia, number of patients included per center, and response after the first sequence. All *P* values are two-sided, and analyses were performed using STATA V8 (STATA Corp, College Station, TX).

Role of the Funding Sources

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

RESULTS

Patients

From February 1993 to December 2000, 451 patients were enrolled; seven patients were not eligible, and 185 patients were not randomly assigned.[13] Although six patients did not receive the complete induction CRT among nonrandomized patients, we only excluded the five patients who did not receive any induction radiotherapy. Thus, 446 patients were included; 285 patients (64%) were treated according to the SC-RT regimen, and 161 patients (36%) were treated according to the P-RT regimen. With regard to the main characteristics of the patients and the disease, the two treatment groups were well balanced except for age (Table 1); the patients treated with P-RT were slightly younger than SC-RT patients (mean age, 57 *v* 59 years, respectively; $P = .03$). A response to induction CRT was observed for 195 patients (68%) with SC-RT and for 108 patients (67%) with P-RT ($P = .09$; Table 1). The cutoff date was June 30, 2001. At the time of analysis, median follow-up time was 47.4 months.

Table 1. Pretreatment Patient and Tumor Characteristics of All Patients Registered According to the Radiotherapy Scheme

Characteristic	SC-RT (n = 285) No. of Patients	SC-RT (n = 285) %	P-RT (n = 161) No. of Patients	P-RT (n = 161) %	*P*
Age, years					.03
Mean	59.33		57.35		
Standard deviation	9.1		9.5		
Spitzer QOL index					.85
Mean	8.36		8.39		
Standard deviation	1.7		1.5		
Sex					.79
Male	264	93	148	92	
Female	21	7	13	8	
Weight loss					.25
≤ 10%	214	75	119	74	
> 10%	63	22	41	25	
Unknown	8	3	1	1	
Dysphagia					.46
Grade 1	18	6	14	9	
Grade 2	118	41	67	42	
Grade 3	110	39	58	36	
Grade 4	29	10	18	11	
Grade 5	6	2	2	1	
Unknown	4	2	2	1	
Length of tumor, cm					.86
Mean	6.77		6.48		
Standard deviation	8.3		4.2		
Tumor maximal diameter, mm					.65
Mean	32.38		31.76		
Standard deviation	11.0		12.7		
Histology in randomly assigned patients	171		88		
Squamous cell	158	92	72	82	.01
Adenocarcinoma	13	8	16	18	
Differentiation					
Well or moderately differentiated	129	75	73	83	
Poorly or undifferentiated	42	25	15	17	
Response rate according to WHO criteria					.09
Complete and/or partial response	195	68	108	67	
Stable and/or progressive disease	79	28	39	24	
Unknown	11	4	14	9	

Abbreviations: SC-RT, split-course radiotherapy; P-RT, protracted radiotherapy; QOL, quality of life.

Pathologic Responses in the Surgery Group

Data were reviewed for 149 operative specimens. A pathologic CR (pCR) was noted for 13 (27%) of 48 patients in the P-RT group and 23 (23%) of 101 patients in the SC-RT group. The patients treated with P-RT were significantly more likely than patients treated with SC-RT to have no viable tumor or a microscopic residual tumor (40% *v* 25%, respectively) and less likely to have a macroscopic residual tumor (27% *v* 50%, respectively; $P = .026$).

Local Failure and LRFS Among All Registered Patients

At the date of analysis, 102 patients (36%) and 27 patients (17%) experienced local relapse on the SC-RT and P-RT regimens, respectively (Table 2). At 2 years, LRFS was significantly higher with P-RT than with SC-RT (76.7% *v* 56.8%, respectively; HR = 0.52; 95% CI, 0.34 to 0.79; $P = .002$; Fig 2A). Moreover, the 2-year LRFS rate was higher with P-RT compared with SC-RT whether patients were resected (82.3% *v* 62.4%, respectively; $P = .06$) or not (72.9% *v* 52.8%, respectively; $P = .02$) Nevertheless, in each group, 2-year LRFS was longer in the surgery group (Table 2).

DFS Among All Registered Patients

At the time of analysis in the SC-RT and the P-RT groups, 36 and 49 patients were alive without disease, respectively, whereas 157 and 62 survivors in the SC-RT and P-RT groups, respectively, had persistent or recurrent disease. No difference was observed between the two radiation regimens for DFS. Two-year DFS rate was 24.6% and 27.6% for SC-RT and P-RT, respectively (HR = 0.93; 95% CI, 0.75 to 1.17; $P = .55$).

OS Among All Registered Patients

At the time of analysis, 233 patients had died in the SC-RT group, and 93 patients had died in the P-RT group. Two-year OS rate was 30.5% and 37.1% for SC-RT and P-RT, respectively (Fig 2B). The OS curves did not differ significantly; median OS time was 15.6 months (range, 13.0 to 18.3 months) and 18.4 months (range, 14.0 to 22.0 months) in the SC-RT and the P-RT groups, respectively (HR = 0.87; 95% CI, 0.68 to 1.11; $P = .25$).

Table 2. Patterns of Local Failure According to the Radiotherapy Scheme and 2-Year LRFS by Subgroup Analysis

Local Failure	SC-RT	P-RT	Log-Rank *P*
All eligible patients, No.	285	161	
Locoregional failure			
No.	102	27	
%	36	17	
2-year LRFS, %	56.8	76.7	.002
95% CI	49.5 to 63.5	66.5 to 84.1	
Preoperative CRT group			
Locoregional failure			
No.	34	7	
%	24	13	
2-year LRFS, %	62.4	82.3	.06
95% CI	50.2 to 72.4	63.6 to 92.0	
Exclusive CRT group			
Locoregional failure			
No.	43	10	
%	46	18	
2-year LRFS, %	52.8	72.9	.02
95% CI	41.0 to 63.3	53.8 to 85.1	
Randomly assigned patients, No.	171	88	
Locoregional failure			
No.	70	14	
%	41	16	
2-year LRFS, %	55.2	75.7	.004
95% CI	46.3 to 63.2	60.6 to 85.6	
Preoperative CRT group			
Locoregional failure			
No.	27	5	
%	31	12	
2-year LRFS, %	61.4	79.5	.12
95% CI	47.8 to 72.4	54.6 to 91.7	
Exclusive CRT group			
Locoregional failure			
No.	43	9	
%	51	20	
2-year LRFS, %	49.6	72.7	.01
	37.7 to 60.5	51.8 to 85.6	

Abbreviations: LRFS, local relapse-free survival; SC-RT, split-course radiotherapy; P-RT, protracted radiotherapy; CRT, chemoradiotherapy.

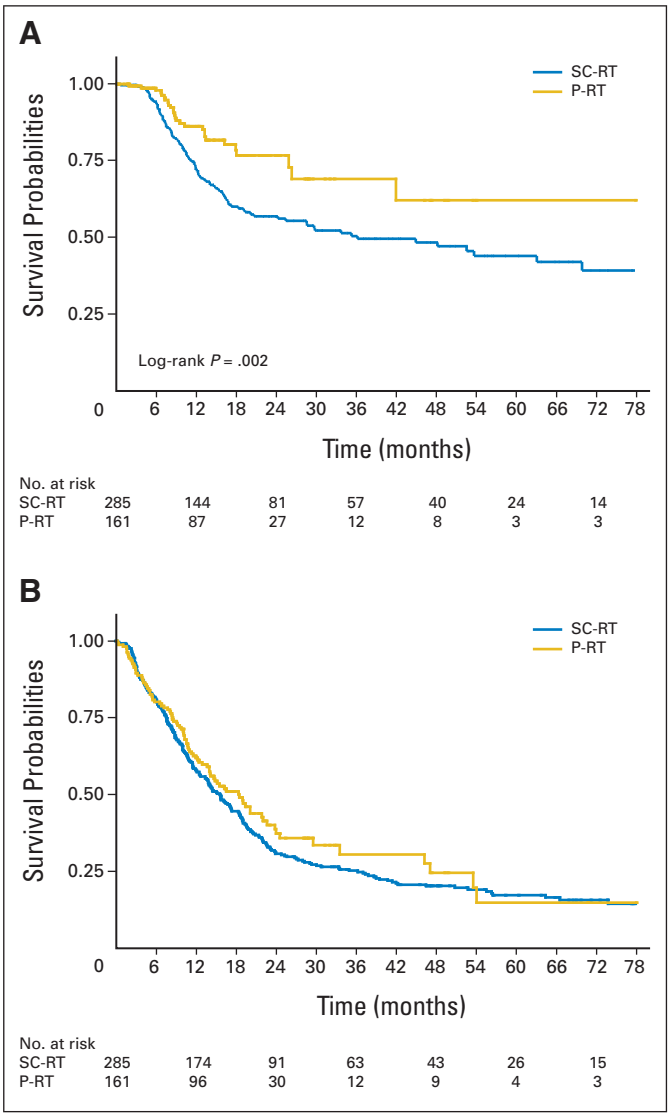

Fig 2. (A) Local relapse-free survival among patients with esophageal cancer treated with protracted radiotherapy (P-RT) versus split-course radiotherapy (SC-RT). Log-rank test, $P = .002$. (B) Overall survival among patients with esophageal cancer treated with P-RT versus SC-RT.

Prognostic Factors Among All Registered Patients

In univariate analysis, local control was significantly more often achieved in patients treated with the P-RT regimen, as evidenced by a shorter tumor length (Table 3). In the subgroup of patients who underwent surgery, patients in whom the tumor was sterilized also had better LRFS (HR = 2.32; 95% CI, 1.11 to 4.83; $P = .025$). After multivariate Cox model analysis, two factors had a favorable impact on LRFS, P-RT and a shorter tumor length ($P = .002$ for both). Patients with a weight loss of 10% or less and responding patients had better OS in univariate analysis. Furthermore, the shorter the length and the smaller the diameter of the tumor, the longer the OS was. In the surgery subgroup, patients with a pCR (HR = 1.85; 95% CI, 1.24 to 2.76; $P = .003$) had better survival in univariate analysis. In multivariate analysis, the maximal diameter of tumor, weight loss of 10% or less, and response to induction CRT had a favorable impact on survival (Table 4).

LRFS Among Randomly Assigned Patients

Among the 259 randomly assigned patients, 70 patients (41%) and 14 patients (16%) experienced local relapse in the SC-RT and P-RT groups, respectively. Local failure in the subgroups is summarized in Table 2.

LRFS at 2 years was significantly improved in the P-RT group compared with the SC-RT group (75.7% *v* 55.2%, respectively; HR = 0.43; 95% CI, 0.24 to 0.77; $P = .004$). In the surgery arm, LRFS did not differ significantly according to the radiotherapy scheme (HR = 0.48; 95% CI, 0.18 to 1.25; $P = .12$). LRFS rates at 2 years were 79.5% in the P-RT group and 61.4% in the SC-RT group.

In the CRT only group, LRFS was significantly longer with P-RT than with SC-RT (HR = 0.40; 95% CI, 0.19 to 0.82; $P = .012$). LRFS rates at 2 years were 72.7% in the P-RT group and 49.6% in the SC-RT group.

Table 3. Univariate and Multivariate Cox Analyses of Local Relapse-Free Survival (intent-to-treat analyses)

Factor	Univariate Cox Analysis (n = 446)			Multivariate Cox Analysis (n = 443)		
	HR	95% CI	*P*	HR	95% CI	*P*
Radiation scheme: P-RT *v* SC-RT	0.52	0.34 to 0.79	.002	0.51	0.33 to 0.79	.002
Weight loss: > 10% *v* ≤ 10%	0.97	0.63 to 1.50	.90			
Sex: male *v* female	1.40	0.80 to 2.45	.23			
Quality of life: Spitzer index	1.08	0.96 to 1.22	.20			
Length of the tumor	1.03	1.01 to 1.05	.001	1.03	1.01 to 1.05	.002
Maximal diameter of the tumor	1.01	0.99 to 1.03	.21			
Age	1.01	0.99 to 1.03	.34			
Invaded nodes at CT	1.00	0.70 to 1.43	.99			
Dysphagia: grade 1-3 *v* grade 4-5	1.09	0.65 to 1.85	.74			
No. of patients included per center: < 10 *v* ≥ 10	0.94	0.65 to 1.34	.71	0.87	0.61 to 1.25	.46
Responding patients	1.25	0.81 to 1.92	.32			

Abbreviations: HR, hazard ratio; SC-RT, split-course radiotherapy; P-RT, protracted radiotherapy; CT, computed tomography.

DFS Among Randomly Assigned Patients

At the time of analysis in the SC-RT and P-RT groups, 110 and 36 patients with persistent or recurrent disease were alive, respectively, whereas 27 and 32 patients were alive without disease, respectively. No difference was observed on DFS between the two radiation regimens. Two-year DFS rate was 29.1% and 28.0% for P-RT and SC-RT, respectively (HR = 0.97; 95% CI, 0.71 to 1.33; $P = .83$). In the surgery group ($P = .83$) and the exclusive CRT group ($P = .87$), DFS did not differ according to radiation scheme.

OS Among Randomly Assigned Patients

At the time of analysis in the SC-RT and P-RT groups, 134 and 48 patients, respectively, had died. Two-year survival rate among randomly assigned patients was 37.3% and 36.2% for P-RT and SC-RT, respectively (HR = 1.01; 95% CI, 0.72 to 1.42; $P = .94$). Among randomly assigned patients, survival was similar for the two radiation protocols in the surgery group ($P = .86$) and the exclusive CRT group ($P = .79$).

DISCUSSION

CRT protocols using an SC-RT scheme were developed to reduce the length of therapy, the cost of treatment, and acute toxicity, and to alleviate the therapeutic burden on the patient.[20] The theoretical advantage is that patients may recover during the rest period and the remaining tumor may become more susceptible to radiation damage as a result of reoxygenation. This approach was tested in phase II trials, which showed reproducible results with acceptable toxicities and a 2-year survival rate varying between 25% and 39%.[20-22] A randomized study from the European Organisation for Research and Treatment of Cancer (EORTC) testing an SC-RT regimen with or without concomitant cisplatin demonstrated an improved outcome with concomitant CRT, with a 2-year survival rate of 20%.[23] The large FFCD-EORTC study investigated the feasibility of an SC-RT regimen in a neoadjuvant setting and showed a pCR rate of 24%, which is similar to the pCR rate found with conventional CRT (range, 15% and 30%).[6,24] We found that P-RT resulted in better local control for patients with RLA-EC, whether the patients underwent resection or not. These results corroborate data from different studies, confirming that a conventional radiation regimen remains a standard approach, although no published randomized data are available.[25] To highlight our results, we recommend distinguishing between exclusive CRT and preoperative CRT and between all included patients and randomly assigned patients.

In case of exclusive CRT, we found that P-RT resulted in better local control. We acknowledge that the total dose of radiation in the

Table 4. Univariate and Multivariate Cox Analyses of Overall Survival (intent-to-treat analyses)

Factor	Univariate Cox Analysis (n = 446)			Multivariate Cox Analysis (n = 388)		
	HR	95% CI	*P*	HR	95% CI	*P*
Radiation scheme: P-RT *v* SC-RT	0.87	0.68 to 1.11	.25	0.83	0.63 to 1.08	.17
Weight loss: > 10% *v* ≤ 10%	1.32	1.03 to 1.71	.03	1.31	1.00 to 1.73	.05
Sex: male *v* female	0.90	0.59 to 1.36	.60			
Quality of life: Spitzer index	0.99	0.93 to 1.07	.91			
Length of the tumor	1.02	1.00 to 1.03	.009	1.01	1.00 to 1.03	.14
Maximal diameter of the tumor	1.01	1.00 to 1.02	.03	1.01	1.00 to 1.02	.02
Age	1.01	1.00 to 1.02	.34			
Invaded nodes at CT	1.00	0.85 to 1.25	.98			
Dysphagia: grade 1-3 *v* grade 4-5	1.22	0.88 to 1.68	.24			
No. of patients included per center: < 10 *v* ≥ 10	0.99	0.80 to 1.25	.95	1.00	0.78 to 1.28	.99
Responding patients	0.70	0.55 to 0.89	.004	0.66	0.50 to 0.85	.002

Abbreviations: HR, hazard ratio; SC-RT, split-course radiotherapy; P-RT, protracted radiotherapy; CT, computed tomography.

SC-RT group cannot be strictly compared with that in P-RT group and that our results could be criticized or misinterpreted. Assuming either an α/β ratio of 10 (regarding tumor and early reactions) or 3 (regarding late reactions), the total dose in the SC-RT group was always lower than the 66 Gy delivered in the P-RT group. However, the Radiation Therapy Oncology Group 85-01 trial and the Intergroup 0123 trial demonstrated that increasing the total dose to 64.8 Gy, at 2 Gy per fraction, did not improve either local control or survival but increased toxicity.[4] Thus, with the same local failure rates, a conventional radiation regimen delivering 50 Gy, at 2 Gy per fraction, combined with two concomitant courses of cisplatin and fluorouracil remains the standard scheme. Our results are in line with these studies because survival, although not local control, was similar, thus putting into question the role of fractionation rather than the total dose.

In preoperative CRT patients, we observed a significantly lower local failure rate with P-RT (13%) compared with SC-RT (24%), but these rates were lower than in the nonoperative group of patients (Table 2). The local failure rate with preoperative CRT was low (9%), and pCR was achieved for approximately one third of patients.[6,24] In the FFCD-EORTC trial, which tested preoperative CRT for patients with resectable esophageal squamous cell cancers, this approach led to an improvement in local control rate (60% for CRT plus surgery *v* 40% for surgery alone) and 3-year DFS rate (68% for CRT plus surgery *v* 53% for surgery alone).[6] The radiation scheme tested consisted of a preoperative SC-RT regimen delivered in two 1-week courses separated by 2 weeks. Because this study is the only large randomized study to demonstrate an improvement in both local control and DFS in resectable tumors, it should be admitted that the absence of any impact on OS was a result of excessive postoperative mortality related to the high dose per fraction (3.7 Gy). We found that preoperative SC-RT with a dose per fraction of 3 Gy improved neither local control nor survival. Moreover, our results show similar local recurrence rates in resected patients with P-RT versus SC-RT for both all patients and responding patients (13% and 12% *v* 24% and 31%, respectively; Table 2). This raises the question of whether it is necessary to select responding patients before random assignment. In a German randomized trial, testing the role of surgery for T3-4, N0-1 EC, patients were randomly assigned at registration.[26] An analysis of prognostic factors was performed and showed that the clinical response to induction chemotherapy was the sole factor having an impact on OS, according to multivariate analysis (3-year survival rate > 50%, regardless of the treatment group). In the nonresponders who achieved R0 resection after the CRT sequence, the 3-year survival rate increased to 32%. The analysis of treatment-related variables we performed is in agreement with the results of the German trial because we found that patients who responded well to induction CRT (CR and PR) had better survival ($P = .002$).

Finally, in the surgery group, we found that pCR rates were similar for the P-RT and SC-RT groups (27% *v* 23%, respectively). These rates are similar to those observed in randomized studies, varying between 20% and 35%.[6,7,24,26] Nevertheless, patients in the P-RT arm were more likely to have no viable tumor or only a microscopic residual tumor.

In conclusion, our data suggest that CRT with P-RT significantly improves LRFS and pathologic response compared with SC-RT, whether patients were selected as responders or not. As expected, DFS and OS did not differ statistically because the fractionation regimen did not impact on the systemic disease. Our results confirm that weight loss and tumor size are independent prognostic factors for survival. Response to induction treatments has a favorable impact on survival for patients with RLA-EC. This new information will need to be considered in future randomized studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Administrative support: Laurent Bedenne
Provision of study materials or patients: Karine Peignaux, Tan Dat N'guyen, Xavier Mirabel, Christian Marchal, Pierre Verrelle, Bernard Roullet, Franck Bonnetain, Laurent Bedenne
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Manuscript writing: Gilles Crehange, Philippe Maingon, Franck Bonnetain, Laurent Bedenne
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