The Impact of Preoperative Radiochemotherapy on Survival in Advanced Esophagogastric Junction Signet Ring Cell Adenocarcinoma

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Background. **Signet ring cell (SRC) tumors have a worse prognosis when compared with non-SRC tumors, and neoadjuvant chemotherapy has been suggested to be an ineffective treatment strategy. Preoperative radiochemotherapy, of already proven efficacy for esophagogastric junction adenocarcinomas (EGJA), could be an alternative neoadjuvant strategy for SRC EGJA. The aim of this retrospective study was to evaluate the survival impact of preoperative radiochemotherapy on patients with advanced resectable SRC EGJA.**

Methods. **Of 3,010 patients registered in 21 French centers between January 1997 and January 2010, 2,670 underwent surgical resection, of whom 97 patients had a stage III SRC EGJA treated by either neoadjuvant radiochemotherapy followed by surgery (group RCT, n = 23) or primary surgery (group S, n = 74).**

Results. **Groups were comparable by age, sex, American Society of Anesthesiologists score, malnutrition, and cTNM stage. There was evidence of significant tumoral ($p = 0.003$), nodal ($p < 0.001$), and pTNM ($p < 0.001$) downstaging after radiochemotherapy. In group RCT and group S, 3-year overall survival was 51% and 21% ($p = 0.002$), respectively, with disease recurrence rate of 30.4% versus 59.5% ($p = 0.015$), respectively. In multivariate analysis the sole independent favorable prognostic factor identified was the administration of neoadjuvant radiochemotherapy (hazard ratio 0.41, $p = 0.020$).**

Conclusions. **In the setting of locally advanced SRC EGJA, neoadjuvant radiochemotherapy is responsible for tumoral downstaging, reduced disease recurrence, and improved patient survival. A strategy of preoperative radiochemotherapy should be implemented in clinical practice to treat advanced SRC EGJA.**

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A dramatic increase in the incidence of the diffuse form of esophagogastric adenocarcinoma (EGA), particularly signet ring cell (SRC) tumors, has been observed in Western countries [1-4]. Because of their infiltrating character, SRC tumors are often discovered at an advanced stage, with greater propensity for peritoneal dissemination and lymph node invasion [4]. That these tumors may harbor innate chemoresistance has been suggested [4-6].

At present, in Europe, the gold standard of treatment for resectable EGA is perioperative chemotherapy [7, 8]. However, both trials that have established the survival benefit for perioperative chemotherapy have provided no subgroup analysis of the efficacy of such a strategy for SRC cancers. In 2010, to investigate these observations and establish more reliable data with regard to SRC tumors, our FREGAT (French Eso-Gastric Tumors) Working Group carried out a retrospective multicenter study in France of all consecutive EGA treated in 21 centers between 1997 and 2010 (clinicaltrials.gov identifier NCT01249859). Among patients with SRC tumors (n = 1,050), those who received neoadjuvant chemotherapy were compared with those treated with primary surgery. Despite similar pretherapeutic characteristics, survival was significantly shorter in the perioperative chemotherapy group, a variable identified as an independent predictor of poor survival and providing evidence of chemoresistance for SRC EGA [3].

An alternative treatment strategy is consideration of neoadjuvant radiochemotherapy (RCT) [9], offering in recent publications a survival benefit when compared with surgery alone [10, 11]. Whether the same benefit accrues for SRC tumors remains not established. The aim of this study was to evaluate whether preoperative RCT is beneficial for oncologic outcomes in SRC tumors. As preoperative RCT is not recommended in the current French guidelines to treat gastric adenocarcinoma (ADC), this study confines its analysis to SRC tumors of the EGJ.

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Patients And Methods

Patient Eligibility Criteria

A multicenter database for EGA in 21 French centers from 1997 to 2010 was established with an independent monitoring team auditing data capture to minimize missing data and to control concordance, as well as inclusion of consecutive patients. As the French guidelines do not recommend preoperative radiotherapy for stage I and II tumors of the EGJ, criteria for inclusion in the study were patients with pretherapeutic clinical TNM (cTNM) stage III tumors, considered for curative treatment, and with histologic proof of SRC cancer.

Of 3,202 patients in this database, 2,670 patients underwent surgical resection and 1,171 patients were identified as having a SRC. From this population, 135 patients were identified as having a stage III SRC tumor of the EGJ, of whom 23 underwent preoperative RCT (group RCT) and 74 underwent primary surgical resections (group S). Patients treated with preoperative chemotherapy alone were excluded (n = 38; Fig 1). Preoperative patient malnutrition was defined by weight loss of 10% or more of baseline body mass over a 6-month period, and postoperative mortality as any death within 30 days of surgery. Early postoperative morbidity included events within 30 days of surgery and late morbidity and mortality events up until 90 days after surgery. Surgical morbidity was defined as occurring in the surgical field as a direct consequence of the surgical technique. The Clavien-Dindo scale was used to grade severity of all postoperative morbidity.

Pretreatment Work-Up

Pretherapeutic investigations included physical examination, standard biologic tests, thoracoabdominal

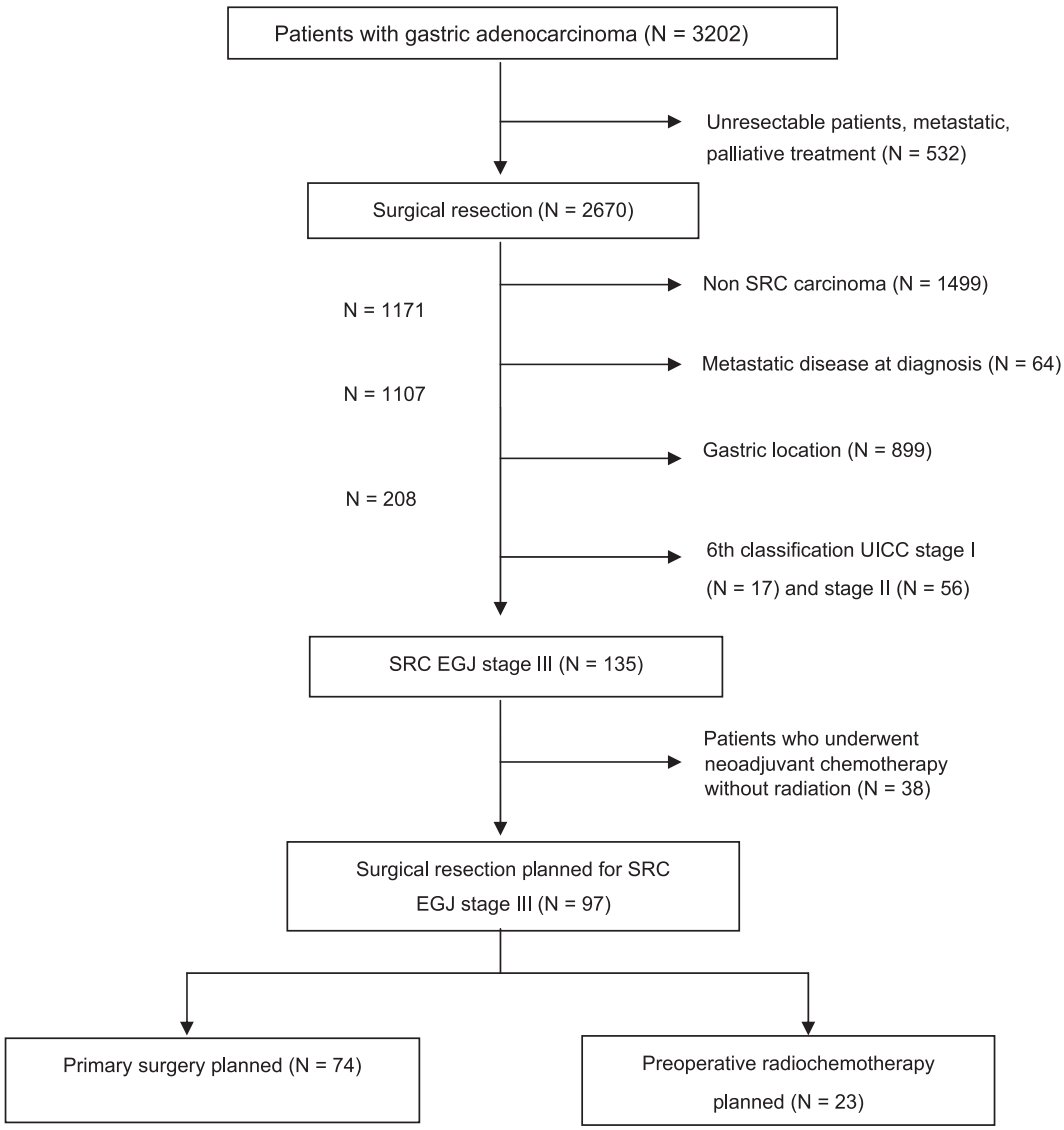

Fig 1. Flow chart of the study. (EGJ = esophagogastric junction; SRC = signet ring cell adenocarcinoma; UICC = Union Internationale Contre le Cancer.)

computed tomography (CT), upper gastrointestinal endoscopy with biopsies, and endoscopic ultrasonography. The cTNM stage was evaluated before treatment from endoscopic ultrasonography results in conjunction with the CT scan. A staging laparoscopy was not systematically performed.

Preoperative Radiochemotherapy

Indication of neoadjuvant RCT was decided by a multidisciplinary team in each center, with an increased use with time after the growing evidence for its survival benefit for junctional tumors (Table 1). Patients treated with RCT received 45 Gy radiotherapy delivered in 25 fractions of 1.8 Gy over a period of 5 weeks with two courses of concomitant chemotherapy by 5-fluorouracil 800 mg/m^2 on days 1 to 4 and on days 29 to 32 combined with cisplatin 75 mg/m^2 on day 1 or 2 and on day 29 or 30.

Surgical Strategy

Details of the surgical approach to resection have been previously described [3]. Briefly, an esophagectomy was performed for Siewert type I junctional tumors; for type II tumors either a total gastrectomy or esophagectomy was performed depending upon surgeon preference. For Siewert type III tumors, a total gastrectomy was routinely performed. When gastric resection was extended to the esophagus, this was performed by either a transthoracic or transhiatal approach with a dedicated mediastinal lymphadenectomy. Lymphadenectomy was classified according to the number of lymph nodes resected (fewer than 15 lymph nodes, between 15 and 24 lymph nodes, and 25 or more lymph nodes). When a total gastrectomy was performed, a D2 lymphadenectomy was standard, without systematic splenectomy or distal pancreatectomy [9]. Extended resections were performed in cases of neoplastic invasion of adjacent structures (liver, spleen, pancreas, colon). Patients without metastatic disease at diagnosis but who were found to have metastases at the time of surgery were included in the analysis.

Histopathologic Analysis

Histologic staging of tumors was based on the 6th edition of the Union International Contre le Cancer (UICC)/TNM classification being the classification in use at time of study accrual, and SRC tumors were defined by the World Health Organization classification as those with more than 50% of the tumor consisting of isolated or small groups of malignant cells containing intracytoplasmic mucins [12]. A radical resection, with macroscopically and microscopically tumor free margins, was considered as a R0 resection; a R1 resection indicated a microscopically positive resection margin; and a R2 resection indicated a macroscopically positive resection margin. The pT0 category was defined as no microscopic tumoral residue on tumor site.

Follow-Up

All patients surviving operation were followed until death or time of database closure (March 2010). During follow-up, patients underwent clinical examination, abdominal endoscopic ultrasonography or CT, and chest radiography every 6 months for 5 years. In cases of suspected recurrence, thoracoabdominal CT scan and upper gastrointestinal endoscopy were performed. Histologic, cytologic, or unequivocal radiologic proof was required before a diagnosis of recurrence was made. In R0 patients the first site of recurrence was used to define whether locoregional or distant relapse had occurred. Locoregional relapse included cancer recurrence within the area of resection, local anastomotic sites, or peritoneal recurrence. Distant recurrence included solid organ metastases and nodal metastases beyond the regional lymph nodes. Mixed recurrences included both locoregional and distant relapses.

Endpoints of the Study

The primary endpoint of this study was to evaluate whether neoadjuvant RCT had a favorable impact on 3-year overall survival (OS) for EGJ SRC cancers. Secondary endpoints were to evaluate disease recurrence, tumor and lymph node response to RCT, resection margin positivity, need for adjuvant therapy, and postoperative morbidity and mortality rates.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL). Data are shown as the prevalence, mean (standard deviation), or median (range). Continuous data were compared using the Mann-Whitney *U* test. Ordinal data were compared using the χ^2 test or the Fisher exact test as appropriate. Survival was estimated using the Kaplan-Meier method. All causes of death were considered for OS estimation whereas only EGJ cancer related deaths were considered for disease-specific survival. The log rank test was used to compare survival curves. The predictive factors of survival were analyzed by Cox proportional hazard regression analysis using a stepwise procedure; the 0.1 level was defined for entry into the model. All statistical tests were two-sided, with the threshold of significance set at p less than 0.050. The study was accepted by the regional Institutional Review Board, and the database was previously registered at clinicaltrials.gov (NCT01249859).

Results

Demographic and Perioperative Variables

Table 1 details population characteristics. A total of 97 patients were identified with an EGJ SRC, among whom 23 patients benefited from preoperative RCT. The median age of patients was 64.4 years (range, 19.0 to 81.0); 78.4% of patients had an American Society of Anesthesiology (ASA) score of I or II; and 25.8% of patients had malnutrition at time of diagnosis. Groups RCT and S were comparable in terms of sex, age, ASA score, and prevalence of malnutrition. All included patients had a cTNM stage III tumor of the EGJ. Patients in group RCT received a median of two cycles of chemotherapy (range, 1 to 6)

Table 1. Demographic and Perioperative Variables (n = 97)

Variables	Total n = 97 (%)	Group RCT n = 23 (%)	Group S n = 74 (%)	*p* Value
Sex				
Male	82 (84.5)	18 (78.3)	64 (86.5)	0.339
Female	15 (15.5)	5 (21.7)	10 (13.5)	
Age				
≤60 years	31 (32.0)	9 (39.1)	22 (29.7)	0.398
>60 years	66 (68.0)	14 (60.9)	52 (70.3)	
ASA score				
I	19 (19.6)	5 (21.7)	14 (18.9)	0.185
II	57 (58.8)	16 (69.6)	41 (55.4)	
III	21 (21.6)	2 (8.7)	19 (25.7)	
IV	0 (0.0)	0 (0.0)	0 (0.0)	
Malnutrition[a]				
No	70 (72.2)	16 (69.6)	54 (73.0)	0.606
Yes	25 (25.8)	7 (30.4)	18 (24.3)	
Unknown[b]	2			
Macroscopic aspect of linitis plastica				
No	85 (87.6)	21 (91.3)	64 (86.5)	0.725
Yes	12 (12.4)	21 (91.3)	10 (13.5)	
Study period				
1997–2000	33 (34.0)	3 (13.0)	30 (40.5)	0.032
2001–2005	31 (32.0)	8 (34.8)	23 (31.1)	
2006–2010	33 (34 .0)	12 (52.2)	21 (28.4)	
Surgical approach				
Strategy total gastrectomy	39 (40.2)	6 (26.1)	33 (44.6)	0.114
Subtotal esophagectomy	58 (59.8)	17 (73.9)	41 (55.4)	
Extended resection to neighboring organs				
Yes	11 (11.3)	1 (4.3)	10 (13.5)	0.451
No	86 (88.7)	22 (95.7)	64 (86.5)	
Localized carcinomatosis				
Yes	4 (4.1)	0 (0.0)	4 (5.4)	0.570
No	93 (95.9)	23 (100.0)	70 (94.6)	
Adjuvant treatment				
Chemotherapy				
Yes	14 (14.4)	1 (4.4)	13 (17.6)	0.053
No	83 (85.6)	22 (95.6)	61 (82.4)	
Radiochemotherapy				
Yes	9 (9.3)	1 (4.4)	8 (10.8)	0.681
No	88 (90.7)	22 (95.6)	66 (89.2)	
30-Day postoperative mortality and morbidity				
Postoperative mortality				
Yes	6 (6.2)	2 (8.7)	4 (5.4)	0.625
No	91 (93.8)	21 (91.3)	70 (94.6)	
Postoperative morbidity				
Yes	49 (50.5)	16 (69.6)	33 (44.6)	0.036
No	48 (49.5)	7 (30.4)	41 (55.4)	
Clavien-Dindo grade 3/4 morbidity				
Yes	9 (9.3)	2 (8.7)	7 (9.4)	1.000
No	88 (90.7)	21 (91.3)	67 (90.6)	

[a] Malnutrition indicates weight loss of 10% or more over a 6-month period. [b] Not reported for 2 patients.

ASA = American Society of Anesthesiologists; group RCT = radiochemotherapy followed by surgery; group S = primary surgery.

with a median duration of therapy of 1.2 months (range, 1 to 7) and with a median delay between completion of neoadjuvant therapy and surgery of 1.2 months (range, 0.3 to 8.6).

At time of surgery, no difference occurred between groups in terms of the macroscopic appearance of linitis plastica ($p = 0.725$), the requirement for an extended resection of neighboring organs ($p = 0.451$), and evidence of peritoneal carcinomatosis ($p = 0.570$). No patients had evidence of solid organ metastases at time of surgical exploration. The 4 patients in group S who had evidence of localized carcinomatosis at time of surgery, near to the EGJ, underwent resection with curative intent.

Postoperative Mortality and Morbidity

A total of 6 patients (6.2%) died within 30 days of surgery, with no difference in rates of postoperative mortality between groups ($p = 0.625$). Overall, a total of 48 patients (49.5%) had a 30-day postoperative morbid event, with more 30-day postoperative morbidity occurring in group RCT compared with group S ($p = 0.036$; Table 1). The frequency of Clavien-Dindo grade 3/4 early morbidity did not differ significantly between the groups (8.8% versus 9.4%, respectively; $p = 1.000$), nor was there a difference in either the rates of medical (39.1% versus 25.7%, respectively; $p = 0.214$) or surgical morbidity (39.1% versus 29.7%, respectively; $p = 0.398$). No patients in group RCT were noted to have late morbidity, compared with 11 patients (14.9%) in group S ($p = 0.062$); and there were no late deaths in group RCT compared with 2 in group S ($p = 1.00$).

Histopathologic Assessment of the Resected Specimen

For the population as a whole, the median number of lymph nodes resected was 21 (range, 4 to 59), and the median number of lymph nodes invaded was 6 (range, 0 to 48; Table 2). There was evidence of significant tumoral ($p = 0.003$), nodal ($p < 0.001$), and pTNM ($p < 0.001$) downstaging after RCT. In group RCT, 91.3% of patients underwent an R0 resection compared with 62.2% of patients in group S ($p = 0.155$).

Adjuvant Treatment

There was a trend toward more adjuvant therapy being administered in group S ($p = 0.053$), with 21 of 23 patients who received a postoperative treatment not having received any neoadjuvant therapy. Adjuvant chemotherapy was required for 8.7% of patients in group RCT, compared with 28.4% of patients in group S ($p = 0.053$).

Oncologic Outcomes

The median follow-up was 32.6 months (range, 5.7 to 148.8) and was comparable between group RCT and group S. The 3-year survival and median OS for the population as a whole were, respectively, 29% and 20 months (range, 13.7 to 26.3; Fig 2). Survival was significantly better in group RCT: 3-year OS was 51% in group RCT with a median OS not reached, whereas in group S, 3-year OS was 21% with a median of 16.9 months (range, 11.1 to 22.7; $p = 0.002$; Fig 3). A total of 51 patients were diagnosed with disease recurrence and the rate of disease recurrence was significantly lower in group RCT compared with group S (30.4% versus 59.5%, respectively; $p = 0.015$). Distant recurrences were found in the liver (n = 12), extraabdominal sites (n = 9), and lymph nodes (n = 3). There was a trend to a higher risk of distant

Table 2. Histologic Variables

Variables	Total n = 97 (%)	Group RCT n = 23 (%)	Group S n = 74 (%)	*p* Value
pT category				
pT0	1 (1.0)	1 (4.4)	0 (0)	0.003
pT1	6 (6.2)	5 (21.7)	1 (1.4)	
pT2	20 (20.6)	6 (26.1)	14 (18.9)	
pT3	52 (53.6)	9 (39.1)	43 (58.1)	
pT4	18 (18.6)	2 (8.7)	16 (21.6)	
pN category				
pN0	18 (18.6)	11 (47.8)	7 (9.5)	< 0.001
pN1	24 (24.7)	8 (34.8)	16 (21.6)	
pN2	33 (34.0)	4 (17.4)	29 (39.2)	
pN3	22 (22.7)	0 (0)	22 (29.7)	
pM category				
pM0	88 (90.7)	23 (100)	65 (87.8)	0.109
pM1	9 (9.3)	0 (0)	9 (12.2)	
pTNM stage				
I	10 (10.3)	7 (30.4)	3 (4.0)	< 0.001
II	13 (13.4)	6 (26.1)	7 (9.5)	
III	65 (67.0)	10 (43.5)	55 (74.3)	
IV	9 (9.3)	0 (0)	9 (12.2)	
Lymphadenectomy				
<15	22 (22.7)	9 (39.1)	13 (17.6)	0.043
≥15 to <25	41 (42.3)	10 (43.5)	31 (41.9)	
≥25	34 (35.0)	4 (17.4)	30 (40.5)	
Resection radicality				
R0	64 (66.0)	18 (91.3)	46 (62.2)	0.155
R1 + R2	33 (34.0)	5 (8.7)	28 (37.8)	
Patterns of disease recurrence				
Recurrent disease				
Yes	51 (52.6)	7 (30.4)	44 (59.5)	0.015
No	46 (47.4)	16 (69.6)	30 (40.5)	
Locoregional recurrence				
Yes	11 (11.3)	1 (4.3)	10 (13.5)	0.451
No	86 (88.7)	22 (95.7)	64 (86.5)	
Distant recurrence				
Yes	23 (23.7)	2 (8.7)	21 (28.4)	0.053
No	74 (76.3)	21 (91.3)	53 (71.6)	
Peritoneal recurrence				
Yes	16 (16.5)	2 (8.7)	14 (18.9)	0.344
No	81 (83.5)	21 (91.3)	60 (81.1)	
Mixed recurrence				
Yes	17 (17.5)	4 (17.4)	13 (17.6)	1.000
No	80 (82.5)	19 (82.6)	61 (82.4)	

Group RCT = radiochemotherapy followed by surgery; group S = primary surgery.

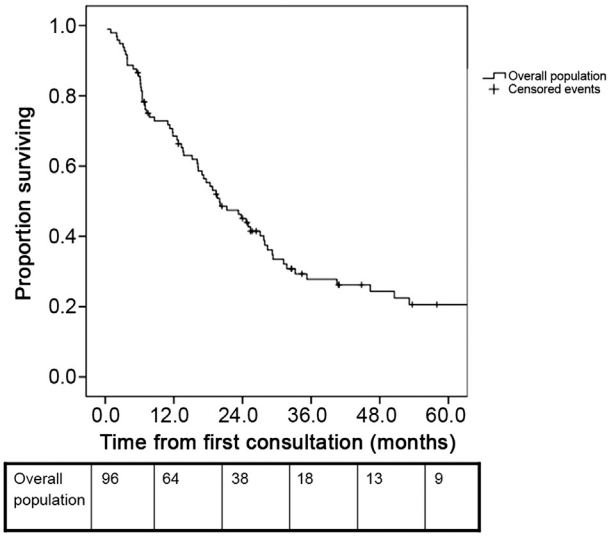

Fig 2. Survival curve in the overall population (hatch marks indicate censored events). The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

recurrence in group S ($p = 0.053$). The risk of peritoneal recurrence was similar between groups ($p = 0.344$).

After having indentified six variables related to survival by univariable analysis (Table 3), the sole independent favorable prognostic factor in multivariable analysis was administration of neoadjuvant RCT ($p = 0.020$), although there was a trend toward R0 resection being of prognostic significance ($p = 0.054$; Table 4).

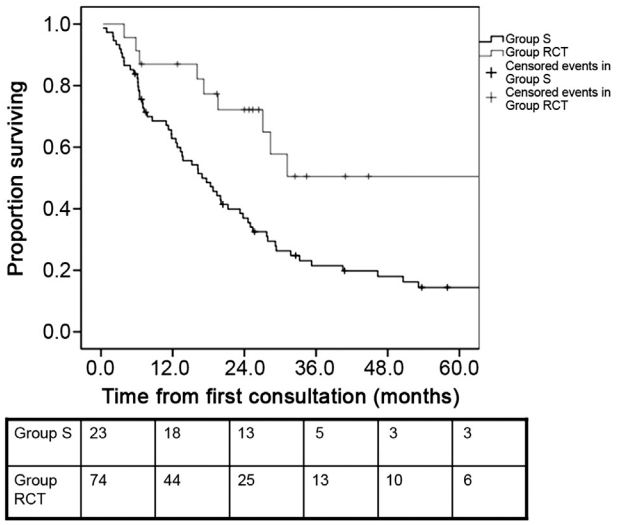

Fig 3. Survival curves after primary surgery (group S [heavy line]; hatch marks indicate censored events in group S) and radiochemotherapy followed by surgery (group RCT [light line]; hatch marks indicate censored evens in group RCT). The number of subjects at risk at each interval is shown in the table at the bottom of the graph.

Table 3. Univariable Survival Analysis

Variables	Median Survival (Months)	95% CI	*p* Value
ASA score			
I	19.6	15.5–23.7	0.151
II	25.4	17.4–33.4	
III	12.5	3.4–21.7	
Sex			
Female	24.6	15.6–33.7	0.773
Male	19.4	13.1–25.7	
Age, years			
≤60	20.0	10.4–29.6	0.957
>60	19.6	12.2–27.0	
Malnutrition at diagnosis			
Yes	12.5	6.1–19.0	0.080
No	23.8	18.1–29.5	
Macroscopic linitis plastica			
Yes	8.6	2.2–15.0	0.241
No	20.1	13.6–26.6	
Study period			
1997–2000	23.8	17.4–30.2	0.616
2001–2005	18.8	14.4–23.2	
2006–2010	19.6	13.7–26.3	
Surgical variables			
Surgical strategy total gastrectomy	28.2	18.7–37.6	0.239
Subtotal esophagectomy	45.2	29.7–60.6	
Extended resection			
Yes	12.5	10.7–14.4	0.019
No	23.8	16.8–30.7	
Resection radicality			
R0	27.1	22.1–32.0	0.005
R1	8.6	2.4–14.8	
R2	13.3	3.2–23.5	
Lymphadenectomy extent			
<15	25.4	9.7–41.6	0.301
15–25	23.3	16.3–30.3	
>25	16.1	12.6–19.6	
Histopathology			
pT category			
pT0–pT1	NR[a]	–	0.208
pT2	28.4	1.1–55.6	
pT3	18.3	12.7–23.9	
pT4	16.9	9.7–24.1	
pN category			
pN0	NR[a]	–	0.004
pN1	23.3	8.1–38.5	
pN2	20.0	8.7–31.2	
pN3	11.8	8.9–14.8	
pM category			
pM0	23.8	17.8–29.8	0.006
pM1	7.7	5.6–9.8	
pTNM stage			
I	NR[a]	–	0.008

(*Continued*)

Table 3. Continued

Variables	Median Survival (Months)	95% CI	*p* Value
II	27.1	–	
III	21.3	14.5–28.0	
IV	7.7	5.6–9.9	
Postoperative morbidity and adjuvant treatment			
30-day postoperative morbidity			
Yes	17.2	3.7–30.7	0.643
No	21.3	14.0–28.5	
Late morbidity[b]			
Yes	7.2	3.7–10.7	0.032
No	21.3	15.1–27.4	
Adjuvant radiochemotherapy			
No	19.6	13.5–25.6	0.455
Yes	29.3	28.9–29.7	
Adjuvant chemotherapy			
No	19.6	12.1–27.1	0.987
Yes	20.1	11.6–28.6	

[a] Not reached. [b] Postoperative morbidity events up from 30 to 90 days after surgery.

ASA = American Society of Anesthesiologists; CI = confidence interval; group RCT = radiochemotherapy followed by surgery; group S = primary surgery.

Comment

Differing pretherapeutic strategies have been shown to enhance survival of patients with EGA, leading to diverse treatment recommendations depending on both tumoral and geographical location. European treatments have been largely been based on preoperative and perioperative chemotherapy [7, 8] but to date, none of the trials establishing therapeutic benefit for such strategies has provided a subgroup analysis of the efficacy of these treatments for SRC tumors. A large retrospective multicentric study carried out by our Working Group FREGAT provided evidence of chemoresistance for SRC EGA [3]. Consequently, alternative treatment strategies need to be urgently assessed for SRC cancers, a tumor subgroup that affects patients at an early age, is typically diagnosed at a more advanced tumor stage, and carries a worse prognosis [4].

Preoperative RCT is one such alternative treatment strategy for SRC EGJ tumors [2]. This treatment strategy has been validated in several randomized trials in the setting of tumors of the esophagus and EGJ compared with surgery alone [9], with none of them considering its efficacy for the subgroup of SRC tumors.

In view of both SRC chemoresistance and the suggestion of the deleterious nature of delaying surgery in favor of pursuing neoadjuvant chemotherapy, we excluded from the present study patients who underwent perioperative chemotherapy. The study population is derived from a large national database of 2,670 patients undergoing resection for EGJ ADC, which offers a unique opportunity to look at the role of neoadjuvant RCT in the subgroup of SRC EGJ tumors. This study provides evidence of the efficacy of the addition of radiotherapy to preoperative chemotherapy for advanced stage III EGJ SRC cancers, with patients treated with RCT having a significant survival benefit and a significantly lower incidence of overall disease recurrence when compared with patients treated with surgery alone. Additionally, neoadjuvant RCT was found to be the sole independent prognostic variable identified by multivariate analysis with a clinically relevant hazard ratio of 0.41 (95% confidence interval: 0.19 to 0.87). Significant tumoral, nodal, and pathologic downstaging were apparent after RCT, with a trend toward a higher R0 resection rate. These results suggest that, contrary to preoperative chemotherapy [3], neoadjuvant RCT offers a significant survival benefit through downstaging and downsizing of SRC EGJ tumors.

Only one previous smaller study has suggested that a survival advantage may exist after RCT for EGJ SRC tumors [2]. These data are largely consistent with our current findings, and in combination they suggest that if SRC cancers of the EGJ can be accurately identified at diagnosis, then these patients should receive trimodality therapy rather than neoadjuvant or perioperative chemotherapy alone. As diagnostic biopsies have been shown recently reliable in making the diagnosis of a SRC [13] they may therefore also be relied upon to tailor the therapeutic strategy.

Preoperative RCT has the advantage of downstaging tumoral and nodal disease before surgical tumor extirpation and hypothetically may also decrease intraoperative spillage of tumor cells, one mechanism for the reduced rates of disease recurrence we observed. Whether adjuvant RCT may also be an efficient therapeutic option is questionable. A strategy of postoperative RCT compared with surgery alone has been evaluated in the Intergroup 0116 phase III trial in patients after gastric and EGJ tumor resection. The 10-year follow-up of this study, of a population in which 20% of tumors were EGJ ADC, showed that, in contrast to non-SRC ADC, SRC tumors do not benefit from postoperative RCT [14]. That

Table 4. Multivariable Survival Analysis

Variables	χ^2	Hazard Ratio (95% Confidence Interval)	*p* Value
Neoadjuvant radiochemotherapy	5.385	0.41 (0.19–0.87)	0.020
Non-R0 resection	3.698	1.58 (0.99–2.53)	0.054
Pretherapeutic malnutrition	1.791	1.50 (0.83–2.72)	0.181
pTNM stage	1.229	1.28 (0.83–1.99)	0.268
Late morbidity[a]	1.006	1.50 (0.68–3.33)	0.316
Extended resection	0.345	1.27 (0.57–2.85)	0.557

[a] Postoperative morbidity events up from 30 to 90 days after surgery.

leads us to suggest the real clinical impact of our results comes from the limitation of the metastatic potential by preoperative RCT in combination with the important tumor downstaging in a tumor subgroup known to have resection margins that are more frequently positive when compared with non-SRC ADC [4]. As we propose the intensification of locoregional treatment by neoadjuvant RCT, it seems to be reasonable to first perform a laparoscopic exploration to be sure of the absence of peritoneal carcinomatosis at initial diagnosis.

This study has some limitations. Bias comes from the retrospective nature of the study and the evolving treatment practices over the course of the study. The very large sample size, however, offers a unique opportunity to study a subgroup of SRC EGJ tumors. Moreover, its multicentric nature helps to overcome the selection bias due to treatment habits of individual centers. The relatively small numbers in our overall population is due to the strict selection of patients. We cannot exclude the possibility that some SRC patients who had progressive disease during neoadjuvant RCT may have been excluded from the analysis. The database has, however, been constructed on an intent to treat basis, limiting such selection bias [3]. Even if the study period might have introduced a selection bias, our findings are strengthened by the finding that RCT is the sole independently prognostic factor identified in multivariate analysis, independently from the study period, confirming its strong clinical importance over usual prognostic factors.

The current study provides evidence for improved survival and decreased disease recurrence after treatment with preoperative RCT for advanced EGJ SRC cancers. Future trials evaluating neoadjuvant therapeutic strategies for EGJ tumors need to include a stratification on SRC histology to prospectively confirm our major observations.

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