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Original Research

Surgically treated oesophageal cancer developed in a radiated field: Impact on peri-operative and long-term outcomes

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KEYWORDS
Oesophageal cancer;
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Abstract ***Background:*** The objectives of this study were to compare peri-operative and long-term outcomes from oesophageal cancer (EC) (i) that arose in a previously radiated field (ECRF) versus primary (PEC) and among ECRF patients and (ii) radiotherapy-induced (RIEC) versus non-radiotherapy–induced EC (NRIEC).

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Radiotherapy-induced neoplasm;
Survival;
Breast cancer

Methods: Data were collected from 30 European centres from 2000 to 2010. Two thousand four hundred eighty nine EC patients surgically treated were included in the PEC group and 136 in the ECRF group, NRIEC group (n = 61) and RIEC group (n = 75). Propensity score matching analyses were used to compensate for differences in baseline characteristics.
Results: Compared to the PEC group, the ECRF group was characterised by less use of neoadjuvant chemoradiotherapy (0% versus 29.5%; P < 0.001), less pathological stage III/IV (31.6% versus 39.2%, P = 0.036), greater incidence of R1/2 margins (21.3% versus 10.9%; P < 0.001), increased in-hospital mortality (14.0% versus 7.1%; P = 0.003) and overall morbidity (68.4% versus 56.4%, P = 0.006). After matching, 5-year overall (28.8% versus 50.5%; hazard ratio [HR] = 1.53, 95% confidence interval [CI]: 1.15–2.04; P = 0.003) and event-free (32.2% versus 42.5%; HR = 1.56, 95% CI: 1.18–2.05; P = 0.002) survivals were significantly reduced in the ECRF group. There were no significant differences in incidence or pattern of tumour recurrence. Comparing RIEC and NRIEC groups, there were no significant differences in short- or long-term outcomes before and after matching.
Conclusions: ECRF is associated with poorer long-term survival related to a reduced utilisation of neoadjuvant chemoradiotherapy and an increased incidence of tumour margin involvement at surgery. Outcomes appear to be dictated by the limitations related to previous radiotherapy administration more than the radiotherapy-induced carcinogenesis.

1. Introduction

The multimodality approach integrating surgery, radiotherapy and chemotherapy, for the treatment of cancer has substantially improved survival patterns from many cancers including oesophageal, head and neck, breast cancers and lymphoma [1–6]. The focus of much research has been the short-term side-effects of radiotherapy especially radiation pneumonitis and pericarditis [7]. Despite the prognostic benefits for the primary cancer, the long-term adverse effects of radiotherapy to the radiated field and in particular the development of secondary cancers have been studied to only a limited degree previously [8,9].

Oesophageal cancer (EC) can arise in a previously irradiated field following treatment of (i) another cancer type or (ii) previous EC with a substantial interval between cancers [10,11]. Previous studies have suggested that EC can be a radiation dose-related complication of radiotherapy for breast cancer and Hodgkin's lymphoma [12–16]. Despite a limited number of studies identifying an increased risk of EC in a previously irradiated field (ECRF), very little is known regarding the prognosis of this type of EC. As patients live longer following primary cancer treatment, secondary ECRF is likely to become an increasing common problem, with little data available regarding diagnosis, treatment and outcome.

The aims of the present study were to evaluate the short- and long-term outcomes of ECRF, with subgroup analysis of specifically radiotherapy-induced EC (RIEC).

2. Methods

2.1. FREGAT database

A dedicated website (http://www.chirurgie-viscerale.org) was used to capture data from 2944 consecutive adult patients undergoing surgical resection for EC (including Siewert type I and II junctional tumours) with curative intent in 30 French-speaking European centres between 2000 and 2010. Based on a standardised report file, all consecutive cases operated on during the study period were retrospectively collected through a dedicated website. An independent team monitored and audited data capture to minimise missing data and to control concordance, as well as ensure inclusion of consecutive patients. Missing or inconsistent data were clarified from e-mail exchanges or phone calls with the referral centre. No missing data were noted regarding data used in the present article, except specifically mentioned. Patient malnutrition was defined by weight loss of more than 10% over a 6-month period prior to surgery. High volume centres were defined as performing >8 resections per year during the 10-year study period [17]. As recommended by French national guidelines [18], approach to clinical staging used a combination of endoscopic ultrasound for transversable tumours, computerised tomography and, on demand, positron emission tomography. The study was accepted by the regional institutional review board on July 15th, 2013, and the database was registered on the Clinicaltrials.gov website under the identifier NCT01927016.

2.2. Data collection and definitions

Patient demographic and tumour related data were collected. Complications were defined based on the definitions used in the 'Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial' (MIRO) trial protocol [19]. The Clavien–Dindo scale was used to grade severity of all postoperative morbidity [20]. Histologic staging of tumours was based on the 7th edition of the Union Internationale Contre le Cancer (UICC)/TNM classification [21]. Patients' cancer history details are reported in Appendix 1.

2.3. Patient eligibility criteria

Among the 2944 consecutive surgically treated patients collected in the database, were excluded patients with metastatic disease (n = 28), synchronous cancer at diagnosis (n = 28) or history of cancer not fulfilling the inclusion criteria below (n = 263), leaving 2625 patients.

2.4. The ECRF group included

(i) Patients having developed an EC within the field of previous radiotherapy given for breast, ENT, bronchopulmonary, lymphoma or
(ii) Patients with a second EC (after a delay of at least 5 years between the two ECs to eliminate local recurrence) with a histology of the second primary tumour different from the first (to exclude metastases).

The tumoural location within the RT field has been controlled based on the RT plan from the primary cancer.

The primary EC group (PEC) included all others patients surgically treated for EC irrespective of the peri-operative strategy, primary surgery or neoadjuvant and/or adjuvant chemo(radio)therapy.

Within the ERCF group, a subgroup of patients was identified with a probable radiotherapy-induced EC (RIEC group) based on a latency period between irradiation exposure and second primary cancer of more than 5 years. Patients among the ECRF group not fulfilling the RIEC criteria were included in the non-radiotherapy-induced EC group (NRIEC), based on a latency period between irradiation exposure and second primary cancer of less than 5 years.

2.5. Study objectives

The primary objective of the present study was to compare overall and event-free survivals from ECRF (n = 136), with PEC (n = 2489). The secondary objectives were to compare tumour pathology, treatment approach and postoperative outcomes between these two groups. Within the ECRF group, a subset comparison has been undertaken evaluating short- and long-term outcomes from patients with RIEC (n = 75) versus NRIEC (n = 61).

2.6. Follow-up – survival and recurrence

All patients were followed until death or the time of database closure (2013). During follow-up, clinical examination, thoracoabdominal CT every 6 months for 5 years was recommended, with upper gastrointestinal endoscopy at 2 years [18]. In cases of suspected recurrence, thoracoabdominal CT scan and upper gastrointestinal endoscopy were performed. Histological, cytological or unequivocal radiological proof was required before a diagnosis of recurrence was made, and using this disease-free survival was calculated.

2.7. Statistical analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS, Chicago, IL) or using the SAS software package, release 9.3 (SAS Institute, Cary, NC). Data are presented as prevalence (percentage), median (range) and for survival as median (95% confidence interval [CI]). Continuous variables are expressed as the mean ± standard deviation or the median [range] and categorical variables as a percentage. A Mann–Whitney test was used for intergroup comparisons of continuous variables, whereas a χ^2 test or Fisher test was used to compare categorical data. Overall and disease-free survivals were estimated using the Kaplan–Meier method. The time for disease-free survival was defined from date of surgery and the earliest occurrence of disease progression resulting from locoregional recurrence or distant dissemination, or death from any cause. The log rank test was used to compare survival curves. The median follow-up was 54.0 (0.5–156.7) months. In order to reduce the effects of potential confounding factors in the comparisons of short- and long-term outcomes between the study groups (ECRF versus PEC and RIEC versus NRIEC), we calculated a propensity score to assemble well-balanced groups. Propensity score was estimated using a multivariable logistic regression model, with the study groups as the dependent variables and all potential confounders as covariates. The covariates were chosen as previous research has demonstrated their prognostic influence [17]. Specific cofounders included as covariates were; surgery after 2006, age ≥60 years, male incidence, American Society of Anesthesiologists (ASA) score, malnutrition, high centre volume (≥80), clinical TNM stage, tumour location, neoadjuvant chemotherapy, surgical technique, and histological subtype. All patients in PEC group were matched 2:1 to patients in ECRF group according to the propensity score using the global optimum method. The short- and long-term outcomes were compared between the matched groups using a generalised linear mixed (logistic regression) model or a

Cox's regression model using the robust sandwich estimate for matched sets. We derived from these models, odds ratio (ORs) and hazard ratio (HRs) as effect size measures, with their 95% CIs. Regarding the small sample size in RIEC group, the comparisons between groups NRIEC and RIEC were adjusted for propensity score rather than using a matching process. Adjustment was done using multivariable logistic regression or Cox's regression model including the propensity score as a covariate. All statistical tests were two-sided, with the threshold of significance set at a P value < 0.05.

3. Results

3.1. Comparison of ECRF and PEC groups (Tables 1 and 2)

The median dose of external radiotherapy received on the tumour site was 54 [25–75] Gy and the median delay between the primary cancer and the oesophageal cancer developed in the radiotherapy field (ECRF) was 10 [1–39] years.

There were no significant differences between the groups in the percentage of patients aged 60 years or older, preoperative malnutrition, operated on in high volume centres, operated on after 2006 or utilisation of adjuvant therapy (Table 1). In the ECRF group, there was a lesser percentage of male patients (49.3% versus 83.8%; P < 0.001) and a greater percentage of ASA grade 3/4 (33.8% versus 24.1%; P = 0.004), clinical stage 1 (36.0% versus 23.7%; P < 0.001) and upper third tumour location (48.5% versus 11.9%; P < 0.001). The utilisation of neoadjuvant chemoradiotherapy was significantly decreased in the ECRF group (0% versus 29.5%; P < 0.001), with a three-stage procedure used more commonly (23.5% versus 10.9%; P < 0.002). Analysis of pathology showed a greater proportion of squamous cell cancers (86.0% versus 42.7%; P < 0.001), less pathological stage III (30.9% versus 37.7%; P = 0.036) and a greater incidence of R1/2 margins (21.3% versus 10.9%; P < 0.001) in the ECRF group, with a vertical margin more commonly involved (11.0% versus 4.3%; P = 0.001). There was no significant difference in lateral margin involvement between the groups (10.3% versus 6.8%; P = 0.295). Analysis of postoperative outcomes showed significantly increased in-hospital (14.0% versus 7.1%; P = 0.003) and 90 d (14.0% versus 6.9%; P = 0.002) mortality, overall morbidity (68.4% versus 56.4%; P = 0.006) and specifically surgical site infection (22.8% versus 14.5%; P = 0.009) and neurological complications (17.6% versus 4.7%; P < 0.001), and an increased median length of hospital stay (29.3 versus 24.9 d; P = 0.019) in the ECRF group.

After matching there were no significant differences between ECRF and PEC groups in in-hospital mortality or morbidity, with the exception of neurological complications that were increased in the ECRF group. Importantly, after matching, there was also an increased incidence of R1/R2 resection margin in the ECRF group (21.3% versus 14.7%; P = 0.036). Five-year overall (28.8% versus 50.5%; HR = 1.53, 95% CI: 1.15–2.04; P = 0.003; Fig. 1), event-free (32.2% versus 42.5%; HR = 1.56, 95% CI: 1.18–2.05; P = 0.002) and cancer-specific survivals (46.1% versus 52%; HR = 1.47, 95% CI: 1.04–2.06; P = 0.027) were significantly reduced in the ECRF group. There were no significant differences between the groups in the incidences of overall (31.6% versus 40.5%; HR = 0.98, 95% CI: 0.58–1.66; P = 0.937), locoregional (12.3% versus 22.9%; HR = 1.01, 95% CI 0.44–2.38; P = 0.967), distant (18.8% versus 11.8%; HR = 1.59, 95% CI: 0.71–3.6; P = 0.263) and mixed (4.0% versus 12.4%; HR = 0.43, 95% CI: 0.12–1.53; P = 0.193) tumour recurrence after R0 resection.

3.2. Comparison of RIEC and NRIEC groups (Tables 3 and 4)

In the RIEC group, the median dose of radiotherapy received was 45 (25–66) Gy, and the median delay between the primary cancer and the RIEC was 13 (6–39) years. In the NRIEC group, the median dose of radiotherapy received was 55 (45–75) Gy and the median delay between the primary cancer and the NRIEC was 6 [1–25] years. In the RIEC group, there was a greater proportion of patients aged 60 years or older (61.3% versus 32.8%; P < 0.001), clinical stage III cancers (44.0% versus 19.7%; P = 0.011), lower third tumour location (22.7% versus 6.6%; P = 0.009) and adenocarcinoma histological subtype (20.0% versus 6.6%; P = 0.025). When comparing RIEC and NRIEC groups, there were no significant differences in surgical approach, in tumour differentiation, pathological stage or incidence of R1/2 margin involvement and specifically the vertical (13.1% versus 9.3%; P = 0.529) or lateral (8.2% versus 12%; P = 0.741) margin involvement. Neoadjuvant chemotherapy was used more commonly in the RIEC group (25.3% versus 11.5%; P = 0.041). Analysis of postoperative outcomes showed significantly reduced in-hospital (8% versus 21.3%; P = −0.026) mortality in the RIEC group, with no significant differences between the groups in overall or specific postoperative morbidities.

After adjustment on propensity score, there were no significant differences between RIEC and NRIEC groups in postoperative mortality or morbidity or resection margin involvement. There were no significant differences between the RIEC and NRIEC groups in 5-year overall (42.2% versus 29%; P = 0.482; Fig. 2), event-free (36.4% versus 27.5%; P = 0.619) or cancer-specific (49.2% versus 41.5%; P = 0.169) survivals. Similarly, there were no significant differences between

Table 1
Comparison of patient demographics and pathology between patients who developed oesophageal cancer in ECRF and patients with PEC.

Variable	Overall incidence (n = 2625, %)	Before matching			After matching		
		PEC group (n = 2489, %)	ECRF group (n = 136, %)	P value	PEC group (n = 272, %)	ECRF group (n = 136, %)	P value
Surgery after 2006[a]	1315 (50.1)	1243 (49.9)	72 (52.9)	0.495	140 (51.5)	72 (52.9)	0.779
Age ≥ 60 years[a]	1338 (51.0)	1272 (51.1)	66 (48.5)	0.559	129 (47.4)	66 (48.5)	0.833
Male incidence[a]	2154 (82.1)	2087 (83.8)	67 (49.3)	<0.001	134 (49.3)	67 (49.3)	1.000
ASA score[a]							
1	452 (17.2)	442 (17.8)	10 (7.4)	0.004	20 (7.4)	10 (7.4)	0.959
2	1528 (58.2)	1448 (58.2)	80 (58.8)		167 (61.4)	80 (58.8)	
3	613 (23.4)	570 (22.9)	43 (31.6)		80 (29.4)	43 (31.6)	
4	32 (1.2)	29 (1.2)	3 (2.2)		5 (1.8)	3 (2.2)	
Malnutrition[a]	531 (20.2)	510 (20.5)	21 (15.4)	0.349	71 (26.1)	21 (15.4)	0.314
Centre volume (≥80)[a]	1562 (59.5)	1484 (59.5)	78 (57.4)	0.080	164 (60.3)	78 (57.4)	0.813
Clinical TNM stage[a]							
1	638 (24.3)	589 (23.7)	49 (36.0)	<0.001	99 (36.4)	49 (36.0)	0.996
2	699 (26.6)	657 (26.4)	42 (30.9)		84 (30.9)	42 (30.9)	
3	1288 (49.1)	1243 (49.9)	45 (33.1)		89 (32.7)	45 (33.1)	
Tumour location[a]							
Upper	361 (13.8)	295 (11.9)	66 (48.5)	<0.001	129 (47.4)	66 (48.5)	0.959
Middle	855 (32.6)	806 (32.4)	49 (36.0)		102 (37.5)	49 (36.0)	
Lower	1409 (53.7)	1388 (55.8)	21 (15.4)		41 (15.1)	21 (15.4)	
Neoadjuvant therapy							
Chemoradiotherapy	735 (28.0)	735 (29.5)	0 (0)	<0.001	0 (0)	0 (0)	–
Chemotherapy[a]	1197 (45.6)	1171 (47.0)	26 (19.1)	<0.001	53 (19.5)	26 (19.1)	0.929
Surgical technique[a]							
Ivor Lewis	1964 (74.8)	1888 (75.9)	76 (55.9)	<0.001	156 (57.4)	76 (55.9)	0.577
3-stage	303 (11.5)	271 (10.9)	32 (23.5)		71 (26.1)	32 (23.5)	
Transhiatal	358 (13.6)	330 (13.3)	28 (20.6)		45 (16.5)	28 (20.6)	
Histological subtype[a]							
Squamous cell cancer	1181 (45.0)	1064 (42.7)	117 (86.0)	<0.001	239 (87.9)	117 (86.0)	0.600
Adenocarcinoma	1444 (55.0)	1425 (57.3)	19 (14.0)		33 (12.1)	19 (14.0)	
Tumour differentiation							
Good	789 (30.1)	742 (29.8)	47 (34.6)	0.048	107 (39.3)	47 (34.6)	0.133
Average	911 (34.7)	859 (34.5)	52 (38.2)		87 (32.0)	52 (38.2)	
Poor	436 (16.6)	412 (16.6)	24 (17.6)		35 (12.9)	24 (17.6)	
Data missing	489 (18.6)	476 (19.1)	13 (9.6)		43 (15.8)	13 (9.6)	
pT stage							
pT0	315 (12.0)	307 (12.3)	8 (5.9)	<0.001	18 (6.6)	8 (5.9)	0.834
pT1a	317 (12.1)	299 (12.0)	18 (13.2)		41 (15.1)	18 (13.2)	
pT1b	350 (13.3)	317 (12.7)	33 (24.3)		68 (25.0)	33 (24.3)	
pT2	503 (19.2)	475 (19.1)	28 (20.6)		51 (18.8)	28 (20.6)	
pT3	1004 (38.2)	962 (38.7)	42 (30.9)		87 (32.0)	42 (30.9)	
pT4a	107 (4.1)	105 (4.2)	2 (1.5)		5 (1.8)	2 (1.5)	
pT4b	29 (1.1)	24 (1.0)	5 (3.7)		2 (0.7)	5 (3.7)	
pN stage							
pN0	1376 (52.4)	1295 (52.0)	81 (59.6)	0.005	163 (59.9)	81 (59.6)	0.710
pN1	606 (23.1)	567 (22.8)	39 (28.9)		73 (26.8)	39 (28.9)	
pN2	379 (14.4)	369 (14.8)	10 (7.4)		19 (7.0)	10 (7.4)	
pN3	264 (10.1)	258 (10.4)	6 (4.4)		17 (6.3)	6 (4.4)	
Pathological stage							
0	260 (9.9)	253 (10.2)	7 (5.1)	0.036	24 (8.8)	7 (5.1)	0.296
I	750 (28.6)	706 (28.4)	44 (32.4)		110 (40.4)	44 (32.4)	
II	597 (22.7)	555 (22.3)	42 (30.9)		68 (25)	42 (30.9)	
III	980 (37.3)	938 (37.7)	42 (30.9)		68 (25)	42 (30.9)	
IV	38 (1.4)	37 (1.5)	1 (0.7)		2 (0.7)	1 (0.7)	
Resection margin							
R0	2324 (88.5)	2217 (89.1)	107 (78.7)	<0.001	232 (85.3)	107 (78.7)	0.036
R1/R2	301 (11.5)	272 (10.9)	29 (21.3)		40 (14.7)	29 (21.3)	
Adjuvant therapy	573 (21.8)	547 (22.0)	26 (19.1)	0.432	50 (18.4)	26 (19.1)	0.789
Chemoradiotherapy	160 (6.1)	157 (6.3)	3 (2.2)		8 (2.9)	3 (2.2)	
Chemotherapy	384 (14.6)	365 (14.7)	19 (14.0)		35 (12.9)	19 (14.0)	
Radiotherapy	29 (1.1)	25 (1.0)	4 (2.9)		9 (3.3)	4 (2.9)	

Abbreviations: ASA, American Society of Anesthesiologists; PEC: primary oesophageal cancer; ECRF: oesophageal cancer arising in a previously radiated field.

[a] Variables used for propensity-matching process.

Table 2
Unmatched and adjusted comparison of postoperative outcomes between patients who developed oesophageal cancer in a previously radiated field (ECRF) and patients with primary oesophageal cancer (PEC).

Outcome	Overall incidence (n = 2625)	Before matching				After matching			
		PEC group (n = 2489, %)	ECRF group (n = 136, %)	OR (95% CI)	P value	PEC group (n = 272, %)	ECRF group (n = 136, %)	OR (95% CI)	P value
Outcomes									
In-hospital mortality	195 (7.4)	176 (7.1)	19 (14.0)	0.47 (0.28–0.78)	0.003	24 (8.8)	19 (14.0)	0.23 (0.07–0.56)	0.128
In-hospital morbidity	1496 (57.0)	1403 (56.4)	93 (68.4)	0.60 (0.41–0.87)	0.006	169 (62.1)	93 (68.4)	0.35 (0.16–0.59)	0.211
Complications									
Anastomotic leak	340 (13.0)	315 (12.7)	25 (18.4)	0.64 (0.41–1.01)	0.053	50 (18.4)	25 (18.4)	0.43 (0.20–0.7)	0.61
Surgical site infection	393 (15.0)	362 (14.5)	31 (22.8)	0.58 (0.38–0.87)	0.009	59 (21.7)	31 (22.8)	0.38 (0.18–0.63)	0.359
Chylothorax	63 (2.4)	59 (2.4)	4 (2.9)	0.80 (0.29–2.24)	0.672	6 (2.2)	4 (2.9)	0.2 (0.01–0.85)	0.437
Gastroparesis	35 (1.3)	34 (1.4)	1 (0.7)	1.87 (0.25–13.76)	0.532	2 (0.4)	1 (0.7)	NA[a]	NA[a]
Pulmonary	980 (37.3)	919 (36.9)	61 (44.9)	0.72 (0.51–1.02)	0.063	111 (40.8)	61 (44.9)	0.39 (0.21–0.62)	0.346
Cardiovascular	301 (11.5)	284 (11.4)	17 (12.5)	0.90 (0.53–1.52)	0.698	35 (12.9)	17 (12.5)	0.38 (0.13–0.71)	0.505
Thromboembolic	69 (2.6)	67 (2.7)	2 (1.5)	1.85 (0.45–7.65)	0.386	7 (3.4)	2 (1.5)	0.78 (0.11–0.99)	0.404
Neurological	140 (5.3)	116 (4.7)	24 (17.6)	0.23 (0.14–0.37)	<0.001	12 (4.4)	24 (17.7)	0.05 (0.01–0.2)	<0.001
Reintervention	373 (14.2)	346 (13.9)	27 (19.9)	0.65 (0.42–1.01)	0.053	49 (18.0)	27 (19.9)	0.24 (0.09–0.51)	0.074
Clavien–Dindo									
I	203 (7.6)	191 (7.6)	12 (7.4)	–	0.015	19 (7.0)	12 (7.4)	NA[a]	NA[a]
II	491 (18.7)	465 (18.7)	26 (19.1)			55 (20.2)	26 (19.1)		
IIIa	131 (5.0)	122 (4.9)	9 (6.6)			19 (7.0)	9 (6.6)		
IIIb	185 (7.0)	172 (6.9)	13 (9.6)			26 (10.0)	13 (9.6)		
IVa	240 (9.1)	225 (9.0)	15 (11.0)			25 (9.2)	15 (11.0)		
IVb	54 (2.1)	52 (2.1)	2 (1.5)			1 (0.4)	2 (1.5)		

Abbreviations: PEC: primary oesophageal cancer; ECRF: oesophageal cancer arising in a previously radiated field; OR: odds ratio; 95% CI: 95% Confidence Interval.
[a] NA, not applicable because of low numbers.

the groups in overall (35.3% versus 27.2%; P = 0.376), locoregional (11.3% versus 14.9%; P = 0.844), distant (23.3% versus 11.8%; P = 0.262) or mixed (4.6% versus 3.0%; P = 0.751) tumour recurrence.

4. Discussion

The results from this large multi-centre study suggest that ECRF is associated with a significantly increased incidence of positive resection margin at surgery and a poor long-term prognosis with reduced overall and event-free survivals. Furthermore, in unmatched comparison, the ECRF group had a significantly increased 30 d postoperative mortality compared to the PEC group.

Unmatched and matched comparisons both showed an increased incidence of R1 or R2 resection margins in the ECRF group compared with the PEC group. This is primarily due to an increase in vertical margin tumour involvement in the ECRF group. In the unadjusted analysis, this may be explained by a greater proportion of tumours located in the upper third of the oesophagus. Importantly, propensity matching adjusted for clinical stage and tumour location, both of which can influence margin. The increase in vertical margin involvement may be secondary to a multifocality of disease seen in the radiotherapeutic field. No patient in the ECRF group received neoadjuvant chemoradiotherapy, and there was a significantly reduced utilisation of neoadjuvant chemotherapy (19.1% versus 47%). Previously, it has been shown that utilisation of neoadjuvant chemoradiotherapy reduces the incidence of positive margin involvement in primary EC [22].

ECRF was also associated with significantly reduced overall and event-free survivals. This difference in survival was seen despite the ECRF group actually have a reduced incidence of pathological stage III and IV disease compared with the PEC group. There are two possible explanations for this difference in long-term prognosis between the groups. Firstly, as previously noted, there was a difference in treatment approach with a notable absence of neoadjuvant chemoradiotherapy in the ECRF group. The median total radiation doses used for treatment of the primary cancer were rather high ranging from 40–70 Gy (Appendix 1). Thus radiation oncologists may have concerns regarding radiation toxicity that may be encountered to the key structures in the mediastinum, when given neoadjuvant chemoradiotherapy for secondary EC in a previously radiated field. In an EC patient with no previous history of radiotherapy treatment, the incidence of developing radiation induced pneum onitis or pericarditis is dose-

Table 3
Unmatched comparison of patient demographics between RIEC versus NRIEC in the subpopulation of the 136 patients having developed an oesophageal in the radiotherapy field.

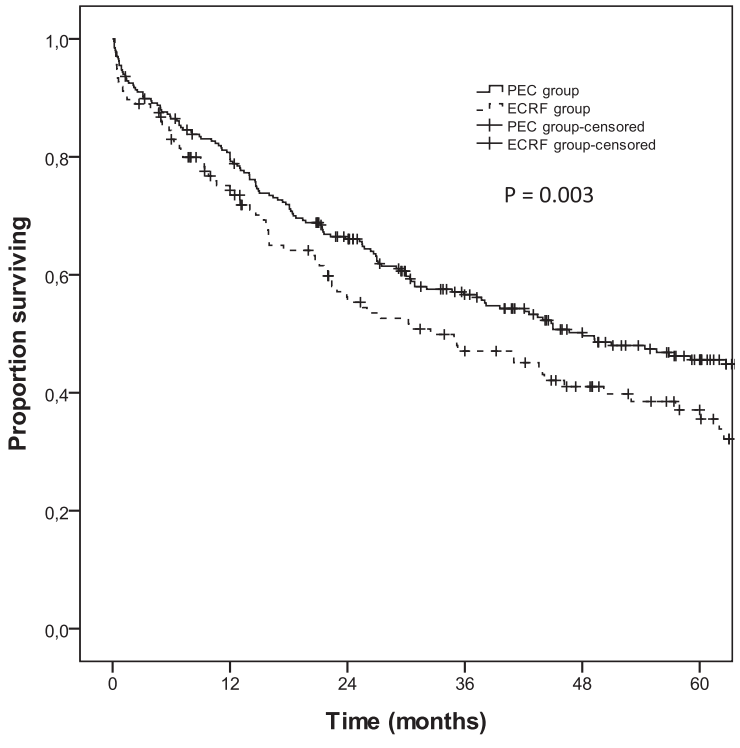
Variable	Overall incidence (n = 136, %)	Unadjusted analysis		
		NRIEC group (n = 61, %)	RIEC group (n = 75, %)	P value
Surgery after 2006[a]	72 (52.9)	28 (45.9)	44 (58.7)	0.138
Age ≥ 60 years[a]	66 (48.5)	20 (32.8)	46 (61.3)	0.001
Male incidence[a]	67 (49.3)	50 (82.0)	17 (22.7)	<0.001
ASA score[a]				
1	10 (7.4)	2 (3.3)	8 (10.7)	0.070
2	80 (58.8)	34 (5.6)	46 (61.3)	
3	43 (31.6)	22 (36.1)	21 (28.0)	
4	3 (2.2)	3 (4.9)	0 (0)	
Malnutrition[a]	21 (15.4)	7 (11.5)	14 (18.7)	0.372
Centre volume (≥80)[a]	78 (57.4)	39 (63.9)	39 (52.0)	0.156
Clinical TNM stage[a]				
1	49 (35.3)	26 (42.6)	23 (30.7)	0.011
2	42 (30.9)	23 (37.7)	19 (25.3)	
3	45 (33.1)	12 (19.7)	33 (44.0)	
Tumour location[a]				
Upper	66 (48.5)	37 (60.7)	29 (38.7)	0.009
Middle	49 (36.0)	20 (32.8)	29 (38.7)	
Lower	21 (15.4)	4 (6.6)	17 (22.7)	
Neoadjuvant therapy				
Chemoradiotherapy	0 (0)	0 (0)	0 (0)	–
Chemotherapy[a]	26 (19.1)	7 (11.5)	19 (25.3)	0.041
Surgical technique[a]				
Ivor Lewis	76 (55.9)	32 (52.5)	44 (58.7)	0.337
3-Stage	32 (23.5)	13 (21.3)	19 (25.3)	
Transhiatal	28 (20.6)	16 (26.2)	12 (16.0)	
Histological subtype[a]				
Squamous cell cancer	117 (86.0)	57 (93.4)	60 (80.0)	0.025
Adenocarcinoma	19 (14.0)	4 (6.6)	15 (20.0)	
Tumour differentiation				
Good	47 (34.6)	21 (34.4)	26 (34.7)	0.231
Average	52 (38.2)	28 (45.9)	24 (32.0)	
Poor	24 (17.6)	7 (11.5)	17 (22.7)	
Data missing	13 (9.6)	5 (8.2)	8 (10.7)	
pT stage				
pT0	8 (5.9)	3 (4.9)	5 (6.7)	0.107
pT1a	18 (13.2)	10 (16.4)	8 (10.7)	
pT1b	33 (24.3)	20 (32.8)	13 (17.3)	
pT2	28 (20.6)	11 (18.0)	17 (22.7)	
pT3	42 (30.9)	13 (21.3)	29 (38.7)	
pT4a	2 (1.5)	2 (3.3)	0 (0)	
pT4b	5 (3.7)	2 (3.3)	3 (4.0)	
pN stage				
pN0	81 (59.6)	38 (62.3)	43 (57.3)	0.566
pN1	39 (28.7)	15 (24.6)	24 (32.0)	
pN2	10 (7.4)	6 (9.8)	4 (5.3)	
pN3	6 (4.4)	2 (3.3)	4 (5.3)	
Pathological stage				
0	7 (5.1)	3 (4.9)	4 (5.3)	0.254
I	44 (32.4)	25 (41.0)	19 (25.3)	
II	42 (30.9)	16 (26.2)	26 (34.7)	
III	42 (30.9)	16 (26.2)	26 (34.7)	
IV	1 (0.7)	1 (1.6)	0 (0)	
Resection margin				
R0	107 (78.7)	47 (77.0)	60 (80.0)	0.676
R1/R2	29 (21.3)	14 (23.0)	15 (20.0)	
Adjuvant therapy	26 (19.1)	7 (11.5)	19 (25.3)	0.041
Chemoradiotherapy	3 (2.2)	0 (0)	3 (4.0)	
Chemotherapy	19 (14.0)	5 (8.2)	14 (18.7)	
Radiotherapy	4 (2.9)	2 (3.3)	2 (2.7)	

Abbreviations: ASA, American Society of Anesthesiologists; NRIEC: non-radiotherapy–induced oesophageal cancer; RIEC: radiotherapy-induced oesophageal cancer.
[a] Variables used for propensity-matching process.

Table 4
Unmatched and adjusted comparison of postoperative outcomes between radiotherapy-induced (RIEC) versus non-radiotherapy–induced oesophageal cancer (NRIEC) in the subpopulation of the 136 patients having developed an oesophageal in the radiotherapy field.

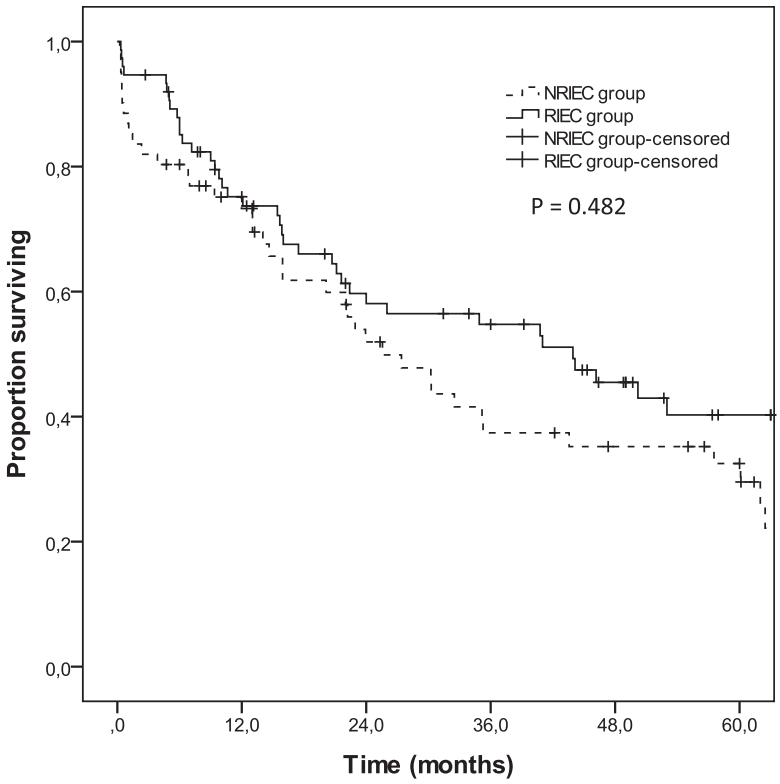
Outcome	Overall incidence (n = 136) (%)	Unadjusted analysis			Adjusted analysis[b]	
		NRIEC group (n = 61, %)	RIEC group (n = 75, %)	P value	OR (95% CI)	P value
Outcomes						
In-hospital mortality	19 (14)	13 (21.3)	6 (8.0)	0.026	0.26 (0.05–1.40)	0.116
In-hospital morbidity	93 (68.4)	44 (72.1)	49 (65.3)	0.396	0.48 (0.08–2.71)	0.273
Complications						
Anastomotic leak	25 (18.4)	12 (19.7)	13 (17.3)	0.726	1.29 (0.28–5.89)	0.742
Surgical site infection	31 (22.8)	16 (26.2)	15 (20.0)	0.389	0.60 (0.15–2.36)	0.467
Chylothorax	4 (2.9)	1 (1.6)	3 (4.0)	NA	NA[a]	NA[a]
Gastroparesis	1 (0.7)	0 (0)	1 (1.3)	NA	NA[a]	NA[a]
Pulmonary	61 (44.9)	30 (49.2)	31 (41.3)	0.360	0.60 (0.15–2.36)	0.467
Cardiovascular	17 (12.5)	7 (11.5)	10 (13.3)	0.745	1.23 (0.22–6.98)	0.813
Thromboembolic	2 (1.5)	1 (1.6)	1 (1.3)	NA	NA[a]	NA[a]
Neurological	24 (17.6)	11 (18.0)	13 (17.3)	0.915	0.49 (0.11–2.15)	0.346
Reintervention	27 (19.9)	14 (23.0)	13 (17.3)	0.414	0.49 (0.12–1.98)	0.314
Clavien–Dindo						
I	10 (7.4)	4 (6.6)	6 (8.0)	0.089	NA[a]	NA[a]
II	25 (18.3)	15 (2.5)	10 (13.3)			
IIIa	9 (6.6)	2 (3.3)	7 (9.3)			
IIIb	13 (9.6)	6 (9.8)	7 (9.3)			
IVa	15 (11.0)	3 (4.9)	12 (16.0)			
IVb	2 (1.5)	1 (1.6)	1 (1.3)			

Abbreviations: NA, not applicable; NRIEC, non-radiotherapy–induced oesophageal cancer; RIEC, radiotherapy-induced oesophageal cancer; OR, odds ratio; 95% CI, 95% confidence interval.
[a] Because of low numbers.
[b] Adjustment was made based on propensity score.



PEC group	272	210	163	123	94	70
ECRF group	136	92	63	50	37	25

Fig. 1. Kaplan–Meier survival analysis for comparison of overall survival from patients who developed oesophageal cancer in a previously radiated field (ECRF) and patients with primary oesophageal cancer (PEC) in the matched cohort.



NRIEC group	61	41	26	18	15	10
RIEC group	75	52	37	32	22	13

Fig. 2. Kaplan Meier survival analysis for comparison of overall survival from patients with radiotherapy-induced (RIEC) versus non-radiotherapy–induced oesophageal cancer (NRIEC) in the subpopulation of the 136 patients having developed an oesophageal in the radiotherapy field.

dependent but is considered to range from 7.7% [23] to 12% [24]. The second possible explanation is that ECRF may represent a more biologically aggressive disease, with an underlying poor prognostic factor that is unmeasured by current methods of pathological staging.

Among ECRF, when comparison was made between RIEC versus NRIEC, there were no significant differences in short- or long-term outcomes. This may suggest that the poor prognosis observed in the ECRF group is less likely to be secondary to more aggressive tumour biology and is more likely to be secondary to a difference in therapeutic approach with less utilisation of neoadjuvant therapy. However, it must be acknowledged that with the small sample size of only 136 patients included in this analysis, it may have been under-powered to truly demonstrate statistical significant results between the groups. One original result is that 20% of RIEC were adenocarcinomas suggesting that RT induced carcinogenesis may not be solely linked with squamous cell carcinomas, as suggested by others [10,11]. Having found significantly more adenocarcinomas in the RIEC compared to the NRIEC group, this may due to an underlying difference in aetiology. As most patients in the NRIEC group had a history of squamous cell EC related to tobacco consumption and thus exposing the upper airways, lungs and oesophagus to a second squamous cancer through the 'cancerisation field' concept [25,26].

There are important limitations that must be considered in interpreting the results of this study, including its design as a retrospective, observational study. To minimise any bias associated with data collection methodology during this study, an independent monitoring team audited data capture to minimise missing data and to control concordance, as well as ensure inclusion of consecutive patients. Despite analysis and control for many important factors that can influence long-term survival and cancer recurrence, there are inevitably other confounding variables that were not studied. The sample size of patients with ECRF is 136 patients, which may be considered small. However, this is the largest series published and represents a substantial contribution to the literature in this area.

In conclusion, this study has demonstrated that ECRF is associated with an increased incidence of tumour margin involvement at surgery and a poorer long-term survival compared with PEC. This is most likely due to a difference in existing therapeutic strategy with a reduced utilisation of neoadjuvant therapy and in particular the absence of neoadjuvant chemoradiotherapy in the ECRF group. Outcomes appear to be influenced by the limitations related to previous radiotherapy

administration to a greater expect than the radiotherapy-induced carcinogenesis.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.12.036.

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