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ORIGINAL ARTICLE

[AQ1]

Impact of Neoadjuvant Chemoradiotherapy on Postoperative Outcomes After Esophageal Cancer Resection

Results of a European Multicenter Study

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Objectives: To assess the impact of neoadjuvant chemoradiotherapy (NCRT) on anastomotic leakage (AL) and other postoperative outcomes after esophageal cancer (EC) resection.

Background: Conflicting data have emerged from randomized studies regarding the impact of NCRT on AL.

Methods: Among 2944 consecutive patients operated on for EC between 2000 and 2010 in 30 European centers, patients treated by NCRT after surgery (n = 593) were compared with those treated by primary surgery (n = 1487). Multivariable analyses and propensity score matching were used to compensate for the differences in some baseline characteristics.

Results: Patients in the NCRT group were younger, with a higher prevalence of male sex, malnutrition, advanced tumor stage, squamous cell carcinoma, and surgery after 2005 when compared with the primary surgery group. Postoperative AL rates were 8.8% versus 10.6% ($P = 0.220$), and 90-day postoperative mortality and morbidity rates were 9.3% versus 7.2% ($P = 0.110$) and 33.4% versus 32.1% ($P = 0.564$), respectively. Pulmonary complication rates did not differ between groups (24.6% vs 22.5%; $P = 0.291$), whereas chylothorax (2.5% vs 1.2%; $P = 0.020$), cardiovascular complications (8.6% vs 0.1%; $P = 0.037$), and thromboembolic events (8.6% vs 6.0%; $P = 0.037$) were higher in the NCRT group. After propensity score matching, AL rates were 8.8% versus 11.3% ($P = 0.228$), with more chylothorax (2.5% vs 0.7%; $P = 0.030$) and trend toward more cardiovascular and thromboembolic events in the NCRT group ($P = 0.069$). Predictors of AL were high American Society of Anesthesiologists scores, supracarinal tumoral location, and cervical anastomosis, but not NCRT.

Conclusions: Neoadjuvant chemoradiotherapy does not have an impact on the AL rate after EC resection (NCT 01927016).

Keywords: anastomotic leakage, chemoradiotherapy, esophageal cancer, morbidity, mortality, surgery

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The mortality associated with anastomotic leakage (AL) after esophageal cancer (EC) resection has decreased in the last decades because of improvement in surgical technique, perioperative care, and patient selection.[1,2] Despite this, AL remains an important cause of patient morbidity and impaired quality of life.[3]

The incidence of AL varies widely from 0% to 35%,[4,5] with various risk factors having been identified. These include both patient and tumoral characteristics [an American Society of Anesthesiologists (ASA) score of ≥III, malnutrition, cardiovascular disease, tobacco consumption, steroid use, chronic renal failure, and tumoral location] and perioperative factors (cervical or hand-sewn anastomosis, positive longitudinal resection margins, and operative time >5 hours) as also administration of neoadjuvant therapy.[6–9]

Although the evidence that neoadjuvant chemoradiotherapy (NCRT) provides a survival benefit in EC is increasing,[10,11] there is still some controversy on its impact on AL,[12–15] with some trials having shown a deleterious impact[16] and others not.[11,17–19] None of these trials were designed and powered to study the relationship of NCRT and such a rare event as AL. The aim of our study was therefore to assess the impact of NCRT on postoperative outcomes after EC resection, particularly the AL rate, in a large European multicenter database.

STUDY POPULATION

Data from 2944 consecutive adult patients operated on for EC (including Siewert I and II junctional tumors) with curative intent in 30 French-speaking European centers, between 2000 and 2010, were collected retrospectively through a dedicated Web site (http://www.chirurgie-viscerale.org). Data collected included demographic parameters, details regarding perioperative and surgical treatment, and postoperative outcomes. When missing, additional data were obtained from e-mail exchanges or phone calls with the referral center. Patients were not included if surgical and/or tumoral data required for the analysis were missing. In addition, only patients with squamous cell carcinomas (SCC) or adenocarcinomas were included. Patients receiving definitive chemoradiotherapy and

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neoadjuvant chemotherapy were excluded. Among the remaining population (n = 2080), those patients who received NCRT (n = 593) were compared with those who underwent primary surgery (PS, n = 1487). The study was accepted by the regional institutional review board on July 15, 2013, and the database was registered on the Clinicaltrials.com Web site under the identifier NCT 01927016.

Pretreatment Workup

Pretreatment investigations were standard following national guidelines (www.tncd.org) and reported elsewhere.[20] Pretherapeutic clinical tumor, node, metastasis (cTNM) classification was based on endoscopic ultrasonography and/or a CT scan in cases where tumor stenosis precluded a full endoscopic ultrasonography examination.

Therapeutic Strategy

All patients were evaluated by a multidisciplinary team and treated with a curative intent according to French national guidelines (www.tncd.org).

Neoadjuvant Chemoradiotherapy

Briefly, NCRT was used for patients with cT3/T4 tumors and/or [AQ2] cN+ disease. Neoadjuvant chemoradiotherapy, combining usually 5-fluorouracil and platinum salt administration for 2 to 4 cycles with concomitant 45 Gy of radiotherapy, and was used for locally advanced tumors where preoperative staging suggested an R0 resection, appeared questionable and in SCCs.

Surgical Resection

Surgical resection was performed approximately 6 to 8 weeks after the completion of NCRT. Details of the surgical resection have been described elsewhere.[21] Briefly, curative surgical resection consisted of a transthoracic en bloc esophagectomy, including an abdominal and a mediastinal lymphadenectomy. The anastomotic location was dictated by tumoral location and not by the extent of the radiotherapy field. For supracarinal tumors, cervical lymphadenectomies were performed and anastomosis was placed in the neck. A transhiatal esophagectomy without thoracotomy was performed, with an abdominal and inferior mediastinal lymphadenectomy, for patients with respiratory insufficiency, small tumors of the lower third esophagus, and no evidence of lymph node metastasis.

Histopathological Analysis

Histological staging of tumors was based on the seventh edition of the International Union Against Cancer TNM classification.[22] Resections were designated R0 when removal was complete both macroscopically and microscopically—R1 in case of a microscopically positive resection margin and R2 in case of a macroscopically positive resection margin. All patients with pTNM stage IV were considered to have an R2 resection. Tumors showing a complete pathological response were graded as pTNM stage 0.

Endpoints of the Study

The primary objective was to evaluate the impact of NCRT on AL. Secondary objectives were to analyze the impact of NCRT on 90-day postoperative morbidity and mortality, and on the following postoperative events: pulmonary complications, plasty necrosis, chylothorax, bleeding, cardiovascular complications, thromboembolic events, sepsis, and reoperation.

Definitions of Complications

The definition of each studied complication has been previously reported.[23] Briefly, AL was defined as a symptomatic (mediastinal abscess, mediastinitis, or enteric contents in chest drainage) or asymptomatic disruption of the anastomosis (diagnosed by water-soluble contrast swallow or endoscopy). Severity of complications was assessed according to the Dindo-Clavien classification, and only grade III/IV complications were considered for the analysis.[24]

Statistical Analysis

Quantitative variables are expressed as the mean ± standard deviation or the median (range), and qualitative variables as a percentage. A Student *t* test or Mann-Whitney test was used for intergroup comparisons of quantitative variables, whereas a χ^2 test or Fisher test was used to compare categorical data. A binary logistic regression was used to identify predictors of AL. In a second step, because of the retrospective nature of the study exposing to selection bias and the fact that ~~nCRT~~ is usually proposed to patients with more advanced tumors, we conducted a propensity score matching analysis to compensate for the differences in some baseline characteristics between the 2 treatment groups. First, we compared all available patient and tumor variables using a χ^2 test. Next, a propensity score (the probability that a patient is assigned to the ~~nCRT~~ or PS group as a consequence of the individual profile of these factors in a nonrandomized patient population, range of 0%–100%) was calculated using a logistic regression with the aforementioned imbalanced variables. Finally, all patients in the NCRT group were matched one-to-one according to propensity scores to PS patients, leading to an even distribution of potential confounding factors to the treatment groups. All tests were 2-sided, and the threshold for statistical significance was set to $P < 0.05$. Analyses were performed with SPSS® version 19.0 software (SPSS, Chicago, Illinois).

RESULTS

Demographic Characteristics

The characteristics of the overall population (n = 2080) are summarized in Table 1. The patients' ASA score was I and II in 73.9% [T1] of cases. The patients' median age was 61 years (range, 20–93), with a male-to-female ratio of 4.6:1.0. Tumors were mostly staged cTNM III (42.9%) and located in the lower two thirds of the esophagus (85.0%). The median dose of radiotherapy received was 45 Gy (range, 12–45), with a median number of chemotherapy cycles received of 3 (range, 1–20). An Ivor Lewis procedure was performed in 73.7% of cases. Patients in the NCRT group (n = 1487) were younger, with a higher prevalence of male sex, malnutrition, advanced tumor stage, SCC, and surgery after 2005 when compared with the PS group (n = 593) ($P < 0.05$).

Histopathological Results

Significant downstaging was observed after NCRT with significantly more patients with pTNM 0 disease in the NCRT group (22.4% vs 2.2%; $P < 0.001$), as well as both a reduced number of resected and invaded lymph nodes (Table 2). However, no significant [T2] downsizing was observed before matching, with R0 resection rates of 90.0% versus 87.8% ($P = 0.152$) in the NCRT and PS groups, respectively, probably because of larger tumors in the NCRT group at diagnosis.

Predictors for Anastomotic Leakage

Postoperative AL rates were 8.8% versus 10.6% ($P = 0.220$) (Table 3). The reoperation rate was significantly higher in patients [T3] with AL (64.1% vs 9.3%; $P < 0.001$), as was the 90-day postoperative mortality rate (26.3% vs 5.7%; $P < 0.001$). Anastomotic leakage was associated with a significant increase in length of stay (42 days vs 18 days; $P < 0.001$) and delay in recommencing oral feeding (15 days vs 7 days; $P < 0.001$). It was also associated with higher rates

TABLE 1. Comparison of Demographic and Therapeutic Characteristics in the Overall Population and According to Treatment Groups Before and After Propensity Score Matching

		Before Matching			After Matching		
Characteristics	**Overall Population (n = 2080)**	**NCRT Group (n = 593)**	**PS Group (n = 1487)**	***P***	**NCRT Group (n = 593)**	**PS Group (n = 593)**	***P***
Year of intervention, n (%)*							
Before 2005	1047 (50.3)	263 (44.4)	784 (52.7)	0.010	263 (44.4)	288 (48.6)	0.010
After 2005	1033 (49.7)	330 (55.6)	703 (47.3)		330 (55.6)	305 (51.4)	
Age,* n (%)							
<60 yrs	982 (47.2)	319 (53.8)	663 (44.6)	<0.001	319 (53.8)	311 (52.4)	0.393
≥60 yrs	1098 (52.8)	274 (46.2)	824 (55.4)		274 (46.2)	282 (47.6)	
Sex, n (%)*							
Male	1710 (82.2)	510 (86.0)	1200 (80.7)	0.004	510 (86.0)	499 (84.1)	0.192
Female	370 (17.8)	83 (14.0)	287 (19.3)		83 (14.0)	94 (15.9)	
ASA score, n (%)*							
I	316 (15.2)	98 (16.5)	218 (14.7)	0.098	98 (16.5)	99 (16.7)	0.400
II	1220 (58.7)	361 (60.9)	859 (57.8)		361 (60.9)	345 (58.2)	
III	521 (25.0)	130 (21.9)	391 (26.3)		130 (21.9)	146 (24.6)	
IV	23 (1.1)	4 (0.7)	19 (1.2)		4 (0.7)	3 (0.5)	
Tumor location, n (%)*							
Upper	311 (15.0)	97 (16.4)	214 (14.3)	0.141	97 (16.4)	99 (16.7)	0.810
Mid	713 (34.3)	215 (36.2)	498 (33.5)		215 (36.2)	207 (34.9)	
Lower	1056 (50.7)	281 (47.4)	775 (52.2)		281 (47.4)	287 (48.4)	
Pretherapeutic cTNM stage, n (%)*							
I	641 (30.8)	48 (8.1)	593 (39.9)	<0.001	48 (8.1)	48 (8.1)	1.000
II	546 (26.3)	174 (29.3)	372 (25.0)		174 (29.3)	174 (29.3)	
III	893 (42.9)	371 (62.6)	522 (35.1)		371 (62.6)	371 (62.6)	
Histology, n (%)*							
SCC	1084 (52.1)	358 (60.4)	726 (48.8)	<0.001	358 (60.4)	355 (59.9)	0.705
ADC	996 (47.9)	235 (39.6)	761 (51.2)		235 (39.6)	238 (40.1)	
Malnutrition, n (%)†							
No	1265 (60.8)	304 (63.3)	961 (81.9)	<0.001	304 (63.3)	363 (78.1)	<0.001
Yes	388 (18.6)	176 (36.7)	212 (18.1)		176 (36.7)	101 (21.9)	
Unknown	427 (20.6)	113 (19.1)	314 (21.1)		113 (19.1)	129 (21.8)	
Surgical procedure, n (%)							
TT 2 fields	1532 (73.7)	476 (80.3)	1056 (71.0)	<0.001	476 (80.3)	469 (79.1)	0.711
TT 3 fields	233 (11.2)	85 (14.3)	148 (10.0)		85 (14.3)	89 (15.0)	
Transhiatal	315 (15.1)	32 (5.4)	283 (19.0)		32 (5.4)	35 (5.9)	
Anastomotic location, n (%)				<0.001			
Thoracic	1532 (73.7)	476 (80.3)	1056 (71.0)		476 (80.3)	469 (79.1)	0.814
Cervical	548 (26.3)	117 (19.7)	431 (29.0)		117 (19.7)	124 (20.9)	

*Matching variables.
†All tests were adjusted on the malnutrition variable.
ADC indicates adenocarcinoma; TT, transthoracic.

of pulmonary, cardiovascular, and thromboembolic complications [T4] (Table 4).

In univariable analysis, pre- and perioperative factors significantly linked to AL were high ASA scores, supracarinal tumor location, SCC histology, and a cervical anastomosis (Table 4). Predictors of AL identified by multivariable analysis were high ASA scores, supracarinal tumor location, and cervical anastomosis, but not NCRT [T5] (Table 5). In an exploratory subgroup analysis looking at the impact of NCRT separately according to the anastomotic location, the AL rate was not influenced by NCRT in the subgroup of IT anastomosis (6.6% after NCRT vs 9.2% after PS; $P = 0.108$), neither in the subgroup of cervical anastomosis (17.1% vs 13.9%; $P = 0.389$).

Postoperative Course

Ninety-day postoperative mortality and morbidity rates were 9.3% versus 7.2% ($P = 0.110$) and 33.4% versus 32.1% ($P = 0.564$), respectively (Table 3). Pulmonary complication rates did not differ between groups (24.6% vs 22.5%; $P = 0.291$), whereas chylothorax (2.5% vs 1.2%; $P = 0.020$), cardiovascular complications (8.6% vs 0.1%; $P = 0.037$), and thromboembolic events (8.6% vs 6.0%; $P = 0.037$) were higher in the NCRT group. The median length of hospital stay was 19 days (range, 1–261 days), comparable in the NCRT and PS groups ($P = 0.122$). By multivariable analysis, AL was an independent predictor of 90-day postoperative mortality [odds ratio (OR), 2.82; 95% confidence interval (CI), 1.71–4.67; $P < 0.001$], as well as age over 60 years ($P = 0.003$), high ASA scores ($P = 0.002$), pulmonary ($P < 0.001$), and cardiovascular ($P < 0.001$) complications, whereas NCRT was not (OR, 1.12; 95% CI, 0.73–2.02; $P = 0.450$).

Propensity Score Analysis

To compensate for the differences in some baseline characteristics, a propensity score was calculated for each patient, taken into account variables not equally distributed between the 2 treatment groups (year of intervention, age, sex, ASA score, pretherapeutic cTNM stage, and histology) and the variable conditioning the surgical procedure (tumor location). Because of some missing data regarding malnutrition, it was not possible to include this variable in the

TABLE 2. Histopathological Results in the Overall Population and According to Treatment Groups Before and After Propensity Score Matching

		Before Matching			After Matching		
	Overall Population (n = 2080)	**NCRT Group (n = 593)**	**PS Group (n = 1487)**	***P***	**NCRT Group (n = 593)**	**PS Group (n = 593)**	***P***
Resection type, n (%)							
R0	1840 (88.5)	534 (90.0)	1306 (87.8)	0.152	534 (90.0)	492 (83.0)	<0.001
R1/R2	240 (11.5)	59 (10.0)	181 (12.2)		59 (10.0)	101 (17.0)	
pTNM stage, n (%)							
0	165 (7.9)	133 (22.4)	32 (2.2)	<0.001	133 (22.4)	8 (1.3)	<0.001
Ia	515 (24.8)	56 (9.4)	459 (30.8)		56 (9.4)	147 (24.8)	
Ib	186 (8.9)	72 (12.2)	114 (7.7)		72 (12.2)	43 (7.2)	
IIa	238 (11.4)	86 (14.5)	152 (10.2)		86 (14.5)	69 (11.6)	
IIb	228 (11.0)	74 (12.5)	154 (10.4)		74 (12.5)	51 (8.6)	
IIIa	330 (15.9)	77 (13.0)	253 (17.0)		77 (13.0)	113 (19.1)	
IIIb	153 (7.4)	38 (6.4)	115 (7.7)		38 (6.4)	51 (8.6)	
IIIc	237 (11.4)	41 (6.9)	196 (13.2)		41 (6.9)	106 (17.9)	
IV	28 (1.3)	16 (2.7)	12 (0.8)		16 (2.7)	5 (0.9)	
Lymph nodes resected, median (range)	16 (1–72)	15 (1–49)	16 (1–72)	0.003	15 (9–22)	18 (1–72)	<0.001
Lymph nodes involved, median (range)	0 (0–32)	0 (0–21)	0 (0–32)]	<0.001	0 (0–21)	1 (0–32)	<0.001

TABLE 3. Incidence of Postoperative Complications in the Overall Population and According to Treatment Groups Before and After Propensity Score Matching.

		Before Matching			After Matching*		
	Overall Population (n = 2080)	**NCRT Group (n = 593)**	**PS Group (n = 1487)**	***P***	**NCRT Group (n = 593)**	**PS Group (n = 593)**	***P***
90-d postoperative morbidity, n (%)							
No	1405 (67.5)	395 (66.6)	1010 (67.9)	0.564	395 (66.6)	251 (42.3)	0.236
Yes	675 (32.5)	198 (33.4)	477 (32.1)		198 (33.4)	342 (57.7)	
90-d postoperative mortality, n (%)							
No	1918 (92.2)	538 (90.7)	1380 (92.8)	0.110	538 (90.7)	548 (92.4)	0.225
Yes	162 (7.8)	55 (9.3)	107 (7.2)		55 (9.3)	45 (7.6)	
Anastomotic leakage, n (%)							
No	1871 (90.0)	541 (91.2)	1330 (89.4)	0.220	541 (91.2)	526 (88.7)	0.228
Yes	209 (10.0)	52 (8.8)	157 (10.6)		52 (8.8)	67 (11.3)	
Plasty necrosis, n (%)							
No	2059 (99.0)	590 (99.5)	1469 (98.8)	0.147	590 (99.5)	588 (99.2)	0.410
Yes	21 (1.0)	3 (0.5)	18 (1.2)		3 (0.5)	5 (0.8)	
Chylothorax, n (%)							
No	2048 (98.5)	578 (97.5)	1470 (98.8)	0.020	578 (97.5)	589 (99.3)	0.030
Yes	32 (1.5)	15 (2.5)	17 (1.2)		15 (2.5)	4 (0.7)	
Postoperative bleeding, n (%)							
No	2072 (99.6)	589 (99.3)	1483 (99.7)	0.177	589 (99.3)	592 (99.8)	NA
Yes	8 (0.4)	4 (0.7)	4 (0.3)		4 (0.7)	1 (0.2)	
Pulmonary complication, n (%)							
No	1600 (76.9)	447 (75.4)	1153 (77.5)	0.291	447 (75.4)	447 (75.4)	1.000
Yes	480 (23.1)	146 (24.6)	334 (22.5)		146 (24.6)	146 (24.6)	
Cardiovascular complication, n (%)							
No	1939 (93.2)	542 (91.4)	1397 (93.9)	0.037	542 (91.4)	558 (94.1)	0.067
Yes	141 (6.8)	51 (8.6)	90 (0.1)		51 (8.6)	35 (7.9)	
Thromboembolic event, n (%)							
No	1939 (93.2)	542 (91.4)	1397 (94.0)	0.037	542 (91.4)	558 (94.1)	0.067
Yes	141 (6.8)	51 (8.6)	90 (6.0)		51 (8.6)	35 (7.9)	
Sepsis, n (%)							
No	2062 (99.1)	588 (99.1)	1474 (99.1)	0.945	588 (99.1)	585 (98.7)	0.712
Yes	18 (0.9)	5 (0.9)	13 (0.9)		5 (0.9)	8 (1.3)	
Reoperation, n (%)							
No	1772 (85.2)	520 (87.7)	1252 (84.1)	0.043	520 (87.7)	524 (88.4)	0.331
Yes	308 (14.8)	73 (12.3)	235 (15.9)		73 (12.3)	69 (11.6)	

*All results after matching are given adjusted on the malnutrition variable.
NA indicates not applicable because of very low number of events.

TABLE 4. Factors Associated With Anastomotic Leakage by Univariable Analysis in the Overall Population*

	No AL (n = 1871)	AL (n = 209)	*P*
Year of intervention, n (%)			
Before 2005	946 (90.4)	101 (9.6)	0.540
After 2005	925 (89.5)	108 (10.5)	
Age, n (%)			
<60 yrs	888 (90.4)	94 (9.6)	0.495
≥60 yrs	983 (89.5)	115 (10.5)	
Sex, n (%)			
Male	1540 (90.1)	170 (9.9)	0.728
Female	331 (89.5)	39 (10.5)	
ASA score, n (%)			
I	289 (91.5)	27 (8.5)	0.007
II	1113 (91.2)	107 (8.8)	
III	448 (86.0)	73 (14.0)	
IV	21 (91.3)	2 (8.7)	
Tumor location, n (%)			
Upper	252 (81.0)	59 (19.0)	<0.001
Mid	644 (90.3)	69 (9.7)	
Lower	975 (92.3)	81 (7.7)	
Pretherapeutic cTNM stage, n (%)			
I	580 (90.5)	61 (9.5)	0.127
II	479 (87.7)	67 (12.3)	
III	812 (90.9)	81 (9.1)	
Histology, n (%)			
SCC	956 (88.2)	128 (11.8)	0.005
ADC	915 (91.9)	81 (8.1)	
Malnutrition, n (%)			
No	1142 (90.3)	123 (9.7)	0.627
Yes	347 (89.4)	41 (10.6)	
NCRT, n (%)			
No	1330 (89.4)	157 (10.6)	0.220
Yes	541 (91.2)	52 (87.7)	
Dose of RT received, Gy, median (range)	45 (15–45)	45 (30–45)	0.125
Surgical procedure, n (%)			
TT 2 fields	1403 (91.6)	129 (8.4)	<0.001
TT 3 fields	202 (86.7)	31 (13.3)	
Transhiatal	266 (84.4)	49 (15.6)	
Anastomosis location, n (%)			
Thoracic	1619 (91.5)	150 (8.5)	<0.001
Cervical	252 (81.0)	59 (19.0)	
Resection type, n (%)			
R0	1656 (90.0)	184 (10.0)	0.840
R1/R2	215 (89.6)	25 (10.4)	
pTNM stage, n (%)			
0	148 (89.7)	17 (10.3)	0.808
Ia	468 (90.9)	47 (9.1)	
Ib	167 (89.8)	19 (10.2)	
IIa	209 (87.8)	29 (12.2)	
IIb	199 (87.3)	29 (12.7)	
IIIa	301 (91.2)	29 (8.8)	
IIIb	139 (90.8)	14 (9.2)	
IIIc	214 (90.3)	23 (9.7)	
IV	26 (92.9)	2 (7.1)	
Postoperative bleeding, n (%)			
No	1863 (89.9)	209 (10.1)	1.000
Yes	8 (100)	0 (0)	
Pulmonary complication, n (%)			
No	1519 (94.9)	81 (5.1)	<0.001
Yes	352 (73.3)	128 (26.7)	
Cardiovascular complication, n (%)			
No	1770 (91.3)	169 (8.7)	<0.001
Yes	101 (71.6)	40 (28.4)	
Thromboembolic event, n (%)			
No	1770 (91.3)	169 (8.7)	<0.001
Yes	101 (71.6)	40 (28.4)	

*Percentages are given according to the number of patients per line.
ADC indicates adenocarcinoma; RT, radiotherapy; TT, transthoracic.

TABLE 5. Independent Predictors for Anastomotic Leakage in the Overall Population by Multivariable Analysis Considering Variables Available at the Time of Surgery

	OR (95% CI)	*P*
ASA score		
I	1.0	0.023
II	0.94 (0.60–1.47)	0.774
III	1.53 (0.95–2.45)	0.078
IV	0.73 (0.16–3.33)	0.681
Tumor location		
Upper	1.0	<0.001
Mid	0.52 (0.34–0.79)	0.002
Lower	0.41 (0.26–0.65)	<0.001
Histology		
SCC	1.0	0.329
ADC	0.84 (0.59–1.19)	
NCRT		
No	1.0	0.357
Yes	0.85 (0.61–1.20)	
Anastomosis location		
Thoracic	1.0	0.027
Cervical	1.65 (1.13–2.42)	0.009

ADC indicates adenocarcinoma.

propensity score construction. Consequently, in addition to matching, adjustment on malnutrition was systematically done. After propensity score matching, the NCRT and PS groups were well balanced (Table 1). As expected, significant downsizing and downstaging were observed (Table 2). AL rates were 8.8% versus 11.3% ($P = 0.228$), with more chylothorax (2.5% vs 0.7%; $P = 0.030$) in the NCRT group than in the PS group. A trend toward more cardiovascular and thromboembolic events was observed in the NCRT group ($P = 0.067$) (Table 3).

DISCUSSION

Addressing the issue of whether NCRT increases the risk of AL after EC resection is important. If there is no increased risk, compromising oncological outcomes through avoidance of radiotherapy is not justified. In the present study, we did not observe any significant increase in AL rates after NCRT, in either the entire study population or the propensity score-matched cohort. The vast majority of patients benefited from an intrathoracic anastomosis within the field radiation, with the location of the anastomosis being dictated solely by tumoral location. In addition, NCRT was not identified as a predictor for AL.

Several recent studies[13–15,25] and reviews[5,26] have investigated the influence of NCRT on AL in EC, and conflicting data have emerged. This is so for several reasons: the studies are underpowered to study such a rare event, some were not designed to study the incidence of AL, the surgical techniques used vary widely, and in some studies groups are not comparable. In recent randomized studies comparing NCRT with surgery alone, the rate of AL has been

reported to be higher after NCRT (8% vs 0%) in one study,[16] but similar between groups in both the CROSS trial[11] and the FFCD 9901 trial.[19] As reported by others and confirmed in the present large cohort study, high ASA scores,[7] supracarinal tumor location, and cervical anastomosis[9] were independent predictors of AL but not NCRT. In an exploratory subgroup analysis, NCRT did not significantly impact on the AL rate whatever could be the anastomotic location, cervical or intrathoracic. Consequently, our results suggest that NCRT does not preclude an intrathoracic anastomosis for infracarinal tumors. This point is of great importance as the AL rate for a cervical anastomosis ranges from 22% to 30%, as reported in the CROSS trial, but, in the present study, is only 9.3% when an intrathoracic anastomosis is performed.[11]

Another issue is the impact of NCRT on postoperative mortality and morbidity, also a highly debated topic with many conflicting results.[5,13,14,26,27] Our results suggest that NCRT does not have an impact on 90-day postoperative mortality and overall morbidity, including pulmonary complications, but does increase chylothorax rates with a trend toward more cardiovascular and thromboembolic complications.

Neoadjuvant chemoradiotherapy has been frequently correlated with increased pulmonary complications,[5,14,25] whereas the pulmonary complication rates were similar between groups in the present study. It has been suggested that the means of radiotherapy administration and radiotherapy fractionation may minimize lung toxicity and low-dose volume may be more important in the prevention of pulmonary complications than high-dose volume.[5,27] Analysis of this large cohort has allowed us to highlight an increased risk of medical complications such as cardiovascular and thromboembolic complications. Whereas an increased risk of cardiovascular complications after NCRT in EC has been already reported,[11–17] an increased risk of thromboembolic events is an emerging topic. In a recent prospective study, Byrne et al[28] reported an increased activated procoagulant response after NCRT. Moreover, it has been recently shown that platinum salts are responsible for a greater thrombogenic effect than other chemotherapy regimes.[29,30] We identified a 3-fold increased risk of chylothorax after NCRT. It is hypothesized that radiotherapy may induce a fibrotic environment, impairing the surgical dissection.[11,31]

This study has some limitations. As with all retrospective surveys, this study was exposed to selection bias. Collectively, proper selection of the control group is most essential for determining the NCRT effect on short-term outcomes. This prompted us to use propensity score matching to compensate for some differences in baseline characteristics that could have favored the occurrence of AL in the NCRT group. Propensity score matching, taking into account all known variables potentially related to AL, allowed for comparable groups and reinforced the conclusion of the present study. In addition, this statistical technique has been shown to give ORs of the treatment effect very close to the ones obtained in randomized trials.[32] Because of the retrospective nature of our study, no power calculation was done, but the present study represents one of the largest dedicated series published. Even if guidelines were given for appropriate reporting, we cannot ignore that there are some differences regarding the definitions of complications in each individual center. However, having only considered Dindo-Clavien grade III/IV complications strongly mitigated against variation in defining complications.

CONCLUSIONS

Neoadjuvant chemoradiotherapy does not have an impact on the AL rate after EC resection and consequently should not modify the therapeutic strategy.

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DISCUSSANTS

G. Zaninotto (London, United Kingdom):

First, I congratulate the authors for their excellent work and presentation. The main question of this study relates to whether neoadjuvant radiochemotherapy increases the rate of anastomotic leakage after an esophagectomy. To answer this question, the authors selected 500 patients who underwent neoadjuvant radiochemotherapy from their registry, including more than 3000 patients who also underwent an esophagectomy. The registry involves 37 centers and spans over a period of 10 years. To compensate for the differences between the groups, they calculated a propensity score and obtained 2 well-matched groups. Their results showed that neoadjuvant radiochemotherapy does not influence the rate of anastomotic leakage, even if the risk of the complications slightly increases. Anastomotic leakages were affected by a higher ASA score, the supracarinal location of the tumor, and the type of surgery (a 3-field vs a 2-field esophagectomy). I have one short comment and 2 questions.

The comment is that the authors did not report any information on the health state of patients, in terms of pulmonary function, cardiovascular disorders, reduced cardiac output, and diabetes; all of these factors could affect the rate of anastomotic leaks, yet only the generic ASA status has been given.

The first question regards the time between the end of radiochemotherapy and surgery. Could it influence the anastomotic leak rate? You reported that patients underwent surgery 6 to 8 weeks after finishing radiochemotherapy. Given the high number of patients included in this study, it can be assumed that some of them underwent surgery after longer intervals. Did the author observe any differences between patients who were operated on early and those who were operated on within 10 to 12 weeks after completing radiochemotherapy?

My second question is, did radiochemotherapy affect the healing process of anastomotic leaks or were the consequences of the anastomotic leak more severe in patients who had had neoadjuvant radiochemotherapy?

Response From C. Mariette (Lille, France):

Thank you for your questions. In response to your first one, we used the ASA score to reflect the global state of the patients, and also because it is a reproducible score, which is required when performing a large retrospective study. With regard to examining compromised pulmonary and cardiac function, I also suggest that it would have been very difficult to obtain reliable data from these 30 centers. This is especially true as the definition of pulmonary and cardiac dysfunction is far from uniform. With regard to your second question, we did not observe any differences when the delay between chemoradiotherapy and surgery was longer, consistent with the data that you previously published (Ruol, *Ann Surg*, 2010). As per your third question, we also did not observe any differences in the severity of the consequences after anastomotic leakage postchemoradiotherapy. The mortality rate was the same within both groups.

N. Senninger (Münster, Germany):

I enjoyed your presentation because it emphasizes that we are on the right path to administering the correct neoadjuvant chemotherapy. Nevertheless, I have one recommendation. You should combine

R1 and R2 together because we all know that there are different types of R1—one is the involvement of the rejection margin, whereas the other is tumor contact to the organ end. I noticed that the direct surgery group had lower tumor stages, whereas the other group had higher ones. Yet, the second group did not have a higher leakage rate. I think that this is a very valuablex result.

My 2 short questions are as follows: (1) Did you differentiate between squamous cell and adenocarcinoma, as we know that these are quite different tumor entities and the patients face different risk factors? (2) I noticed that you had a considerable amount of cases with roughly 10% of stage I tumors in the neoadjuvant treatment group. How come? We do not have any neoadjuvant treatment patients with a stage I tumor; they are all operated on directly. Could you, perhaps, explain this?

Response From C. ~~Mariette~~ (Lille, France):

In answer to your first question, we did not see differences between the 2 histological types. As per your second question, most of the patients with stage I tumors who received neoadjuvant chemoradiotherapy were also included in the FFCD 9901 trial, which studied the impact of this kind of therapy in early-stage esophageal tumors.

C. Bruns (Magdeburg, Germany):

I would like to ask you one final, short question. In your presentation, you stated that chemoradiotherapy was applied with 45 Gy over the last 10 years. Because of protocols that have changed, at least in Germany, the radiation regimen, and in particular, the amount of the radiation dose applied, has been different over the past few years. Could you please comment on this? In other words, since 2000, has the dose of radiation you used always been 45 Gy?

Response From C. ~~Mariette~~ (Lille, France):

Yes, since 2000, in France, Belgium, and Switzerland, the dose of radiation delivered in neoadjuvant chemoradiotherapy has not changed, remaining between 45 and 50 Gy. In other words, since the publication of the CROSS trial, the protocols have not differed.

Queries to Author

Title: Impact of Neoadjuvant Chemoradiotherapy on Postoperative Outcomes After Esophageal Cancer Resection
Author: Caroline Gronnier, Boris Tréchot, Alain Duhamel, Jean-Yves Mabrut, Jean-Pierre Bail, Nicolas Carrere, Jérémie H. Lefevre, Cécile Brigand, Jean-Christophe Vaillant, Mustapha Adham, Simon Msika, Nicolas Demartines, Issam El Nakadi, Guillaume Piessen, Bernard Meunier, Denis Collet, Christophe Mariette

[AQ1]: Author: Please verify the category head.
[AQ2]: Author: "Neoadjuvant chemoradiotherapy, combining usually . . . ": Is this sentence okay as given? Please check.
[AQ3]: Author: Please update Ref 19 with the volume and page numbers.
[AQ4]: Author: Does the edited sentence "My second question is . . . " convey the intended meaning? Please check.