Significance of Microscopically Incomplete Resection Margin After Esophagectomy for Esophageal Cancer

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Objective: The objectives of this study were to establish if R1 resection margin after esophagectomy was (i) a poor prognostic factor independent of patient and tumor characteristics, (ii) a marker of tumor aggressiveness and (iii) to look at the impact of adjuvant treatment in this subpopulation.

Methods: Data were collected from 30 European centers from 2000 to 2010. Patients with an R1 resection margin (n = 242) were compared with those with an R0 margin (n = 2573) in terms of short- and long-term outcomes. Propensity score matching and multivariable analyses were used to compensate for differences in baseline characteristics.

Results: Independent factors significantly associated with an R1 resection margin included an upper third esophageal tumor location, preoperative malnutrition, and pathological stage III. There were significant differences between the groups in postoperative histology, with an increase in pathological stage III and TRG 4–5 in the R1 group. Total average lymph node harvests were similar between the groups; however, there was an increase in the number of positive lymph nodes seen in the R1 group. Propensity matched analysis confirmed that R1 resection margin was significantly associated with reduced overall survival and increased overall, locoregional, and mixed tumor recurrence. Similar observations were seen in the subgroup that received neoadjuvant chemoradiation. In R1 patients adjuvant therapy improved survival and reduced distant recurrence however failed to affect locoregional recurrence.

Conclusions: This large multicenter European study provides evidence to support the notion that R1 resection margin is a prognostic indication of aggressive tumor biology with a poor long-term prognosis.

Keywords: esophageal cancer, morbidity, resection margin, surgery, survival

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The incidence of esophageal cancer is rapidly increasing, representing 7% of all gastrointestinal malignancies internationally and this disease annually affects 482,300 people worldwide.[1–3] Improvements in perioperative care in recent years, along with centralization of esophageal cancer surgical services to high volume

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centers and minimal access techniques have led to substantial reductions in postoperative mortality and morbidity.[4] After these improvements in short-term outcomes, increasing attention has been given to improving long-term survival from esophageal cancer.

A recent systematic review of 19 studies identified positive circumferential margin to be associated with overall poor survival and in subset analysis worse survival in stage T3 disease.[5] However, the limitations of this analysis were inherent given the standard published literature on this subject to date. First, the median sample size was 157 patients (range 50–329 patients), suggesting the studies included were small and underpowered. Furthermore, analysis revealed evidence of substantial publication bias as determined by Begg rank correlation and Egger linear regression and heterogeneity identified by the I^2 statistic that limit the conclusions of this study. Third microscopically (R1) and macroscopically (R2) incomplete resections were grouped together, leaving the relative prognostic significance of an R1 resection under evaluated. Related to the prognostic impact of R1 resection, the benefit of adjuvant chemo(radio)therapy is still debated, with some studies suggesting a survival benefit,[6,7] and some others not.[8] Finally, whereas R1 resection is usually considered as a failure of surgery to control disease locally, recent studies in rectal and pancreatic carcinomas have suggested that R1 status may be more related to the tumoral aggressiveness rather than to a suboptimal surgical resection.[9,10] The aim of this study was consequently to establish if R1 resection margin after esophagectomy was (1) a poor prognostic factor independent of patient and tumor characteristics, (2) a marker of tumor aggressiveness, and (3) to look at the impact of adjuvant treatment in this subpopulation.

METHODS

Patient Eligibility Criteria

Data from 2944 consecutive adult patients undergoing surgical resection for esophageal cancer (including Siewert type I and II junctional tumors) with curative intent in 30 French-speaking European centers between 2000 and 2010 were retrospectively collected through a dedicated Web site (http://www.chirurgie-viscerale.org), with an independent monitoring team auditing data capture to minimize missing data and to control concordance, and inclusion of consecutive patients. Data collected included demographic parameters, details with regard to perioperative and surgical treatments, postoperative outcomes, and histopathological analysis. Missing or inconsistent data were obtained from e-mail exchanges or phone calls with the referral center.

We excluded 129 patients who either had an R2 resection margin or metastatic disease, therefore 2815 patients were included in the final analysis. Among this population, the focus of this study was to compare patients with an R0 resection (group R0; n = 2573) to those with an R1 resection (group R1; n = 242). The study was accepted by the regional institutional review board on July 15, 2013, and the database was registered on the Clinicaltrials.gov Web site under the identifier NCT 01927016.

R1 Resection Margin Definition and Data Collection

R1 resection margin was defined according to the College of American Pathologists criteria,[11] as microscopic residual tumor present at the vertical or circumferential resection margins of the surgical specimen. All pathology specimens were examined by 2 pathologists, at least 1 being a senior gastrointestinal pathology, which was standard practice among the participating institutions. Patient demographic and tumor related data were collected. Patient malnutrition was defined by weight loss of more than 10% over a 6-month period before surgery. Complications were defined based upon the definitions used in the MIRO trial protocol.[12] The Clavien-Dindo scale was used to grade severity of all postoperative morbidity.[13] Histologic staging of tumors was based on the seventh edition of the Union Internationale Contre le Cancer (UICC)/TNM classification.[14] Information with regard to the neoadjuvant and adjuvant therapeutic regimes is given in the Appendix.

Follow-up: Survival and Recurrence

During follow-up, clinical examination, thoracoabdominal CT every 6 months for 5 years was recommended, with upper gastrointestinal endoscopy at 2 years.[15] In cases of suspected recurrence, thoracoabdominal CT scan and upper gastrointestinal endoscopy were carried out. Histological, cytological, or unequivocal radiological proof was required before a diagnosis of recurrence was made. The first site of recurrence was used to define whether a locoregional or distant relapse had occurred. Locoregional recurrence comprised cancer relapse within the area of resection including local anastomotic sites. Distant recurrence included solid organ metastases, peritoneal recurrence, and nodal metastases beyond the regional lymph nodes. Mixed recurrence was used to describe the situation when locoregional and distant recurrences were discovered simultaneously.

Statistical Analysis

Statistical analysis was carried out using SPSS version 19.0 software (SPSS, Chicago, IL). 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 U 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 log rank test was used to compare survival curves.

In a second step, we carried out a propensity score matching analysis to compensate for the differences in baseline characteristics between the R0 and R1 groups in the assessment of outcomes. First we compared all available patient and tumor variables using a χ^2 test, and then a propensity score was calculated using logistic regression using the unbalanced variables. Finally, all patients in-group R1 were matched 1:3 according to propensity scores to group R0 patients, leading to an even distribution of potential confounding factors to the treatment groups. A subset analysis was carried out for R1 patients who did or did not receive adjuvant therapy. A new propensity score was estimated using a multivariable logistic regression model, with the presence or absence of adjuvant treatment study groups as the dependent variables and all potential confounders as covariates. To maximize the number of cases, comparisons were here adjusted for propensity score and malnutrition rather than using a matching process. All statistical tests were 2-sided with the threshold of significance set at a $P < 0.05$.

RESULTS

Characteristics of the R1 Population

Analysis of the unmatched population demonstrated no significant difference between the groups in patients ages 60 years or older, sex, or American Society of Anesthesiology (ASA) grade, however there was an increased incidence of preoperative malnutrition in the R1 group (28.5% vs 19.1%) (Table 1). The R1 group also presented with more advanced tumors with a greater proportion of pT3+4 (77.3% vs 22.8%) and pN+ (70.2% vs 44.3%). The R1 group had a greater proportion of upper third esophageal tumors, and a reduced utilization of neoadjuvant chemo- and chemoradiotherapy, however adjuvant therapy was used more commonly. Mandard tumor

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TABLE 1. Comparison of Demographic, Therapeutic and Pathological Characteristics of Patients With R0 and R1 Resection Margins

Variable	Overall Incidence (n = 2815) (%)	Before Matching			After Matching		
		R0 (n = 2573) (%)	R1 (n = 242) (%)	*P*	R0 (n = 726) (%)	R1 (n = 242) (%)	*P*
Age ≥ 60 yr*	1466 (52.1)	1341 (52.1)	125 (51.7)	0.890	394 (54.3)	125 (51.7)	0.503
Male incidence*	2317 (82.3)	2111 (82.0)	206 (85.1)	0.230	629 (86.6)	206 (85.1)	0.553
ASA score*							
1	463 (16.5)	423 (16.4)	40 (16.5)	0.982	118 (16.3)	40 (16.5)	0.685
2	1636 (58.1)	1498 (58.2)	138 (57.0)		440 (60.6)	138 (57.0)	
3	684 (24.3)	623 (24.2)	61 (25.2)		158 (21.8)	61 (25.2)	
4	32 (1.1)	29 (1.2)	3 (1.3)		10 (1.4)	3 (1.3)	
Malnutrition*	561 (19.9)	492 (19.1)	69 (28.5)	0.002	106 (29.5)	69 (28.5)	0.158
Tumor location*							
Upper	382 (13.6)	317 (12.3)	65 (26.9)	<0.001	155 (21.4)	65 (26.9)	0.207
Middle	934 (33.2)	868 (33.7)	66 (27.3)		210 (28.9)	66 (27.3)	
Lower	1499 (53.2)	1388 (54.0)	111 (45.8)		361 (49.7)	111 (45.8)	
Neoadjuvant chemotherapy*	1272 (45.2)	1183 (46.0)	89 (36.8)	0.006	244 (33.6)	89 (36.8)	0.390
Neoadjuvant chemoradiotherapy*	788 (28.0)	738 (28.7)	50 (20.7)	0.008	116 (16.0)	50 (20.7)	0.116
Surgical technique*							0.864
Ivor Lewis	2105 (74.8)	1938 (75.3)	167 (69.0)	0.088	514 (70.8)	167 (69.0)	
3-stage	318 (11.3)	286 (11.1)	32 (13.2)		92 (12.7)	32 (13.2)	
Transhiatal	392 (13.9)	349 (13.6)	43 (17.8)		120 (16.5)	43 (17.8)	
Histology*							
SCC	1294 (46.0)	1182 (45.9)	112 (46.3)	0.919	311 (42.8)	112 (46.3)	0.350
Adenocarcinoma	1521 (54.0)	1391 (54.1)	130 (53.7)		415 (57.2)	130 (53.7)	
pT classification*							
pT1+2	1642 (55.3)	1587 (61.7)	55 (22.7)	<0.001	166 (22.9)	55 (22.7)	0.965
pT3+4	1173 (41.7)	986 (38.3)	187 (77.3)		560 (77.1)	187 (77.3)	
pN classification*							
pN0	1504 (53.4)	1432 (55.7)	72 (29.8)	<0.001	211 (29.1)	72 (29.8)	0.838
pN+	1311 (46.6)	1141 (44.3)	170 (70.2)		515 (70.9)	170 (70.2)	
pTNM stage							
0	285 (10.1)	284 (11.0)	1 (0.4)	<0.001	3 (0.4)	1 (0.4)	0.876
I	848 (30.1)	818 (31.8)	30 (12.4)		92 (12.7)	30 (12.4)	
II	656 (23.3)	609 (23.7)	47 (19.4)		140 (19.3)	47 (19.4)	
III	1026 (36.5)	862 (33.5)	164 (67.8)		491 (67.6)	164 (67.8)	
TRG Mandard†	n = 788	n = 738	n = 50		n = 117	n = 50	
TRG1	258 (32.7)	257 (34.8)	1 (2.0)	<0.001	12 (10.3)	1 (2.0)	0.220
TRG2	120 (15.2)	116 (15.7)	4 (8.0)		11 (9.4)	4 (8.0)	
TRG3	141 (17.9)	129 (17.5)	12 (24.0)		34 (29.1)	12 (24.0)	
TRG4	159 (20.2)	139 (18.8)	20 (40.0)		39 (33.3)	20 (40.0)	
TRG5	75 (9.5)	64 (8.7)	11 (22.0)		18 (15.4)	11 (22.0)	
Not reported	35 (4.4)	33 (4.5)	2 (4.0)		3 (2.6)	2 (4.0)	
Lymph nodes harvest‡	18.0 ± 10.2	18.0 ± 9.9	18.8 ± 12.7	0.330	19.5 ± 10.4	18.8 ± 12.7	0.190
Positive lymph nodes harvested‡	2 ± 3.7	1.8 ± 3.5	4.2 ± 5.4	<0.001	3.1 ± 4.2	4.2 ± 5.4	0.031

*Variables used for propensity matching process.
†Evaluated in patients treated by neoadjuvant chemoradiation.
‡Mean ± SD.
ASA indicates American Society of Anesthesiology grade; TRG, tumor regression grade.

regression grading showed a greater incidence of poor responders (TRG4–5) to neoadjuvant chemoradiotherapy in the R1 group (62.0% vs 27.5%). The risk for vertical margin involvement was 21.9% when the lateral margin was involved compared with 3.2% in absence of lateral margin involvement ($P < 0.001$).

Multivariate logistic regression demonstrated an upper third esophageal tumor location [odds ratio (OR) 4.75; 95% CI, 3.15–7.18; $P < 0.001$], preoperative malnutrition (OR 1.47; 95% CI, 1.06–2.04; $P = 0.02$), and advanced pathological stage III (OR 20.83; 95% CI, 19.84–21.91, $P = 0.003$) were independently associated with R1 resection margin status.

Impact of R1 Margin on Postoperative Outcomes

To minimize biases, postoperative outcomes were studied in the matched population. Increases in total morbidity rate (65.7% vs 55.2%) and specifically pulmonary complications (44.6% vs 35.5%) were observed in the R1 group (Table 2). Furthermore, although there was a similar average lymph node harvest for the groups, there was an increase in the mean number of positive lymph nodes observed in the R1 group (4.2 ± 5.4 vs 3.1 ± 4.2).

Impact of R1 Margin on Long-term Oncological Outcomes (Table 3)

In multivariable Cox regression analysis carried out in the unmatched population, R1 resection margin was an independent poor prognostic factor. Other factors significantly and independently associated with poor overall survival included age 60 years or older, male sex, ASA grade 3 and 4, absence of neoadjuvant chemoradiotherapy, postoperative complication, squamous cell subtype, and pathological stage III.

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TABLE 2. Comparison of Postoperative Outcomes of Patients With R0 and R1 Resection Margins

Outcome	Overall Incidence (n = 2815) (%)	Before Matching			After Matching		
		R0 (n = 2573) (%)	R1 (n = 242) (%)	*P*	R0 (n = 726) (%)	R1 (n = 242) (%)	*P*
In-hospital mortality	189 (6.7)	169 (6.6)	20 (8.3)	0.313	48 (6.6)	20 (8.3)	0.416
In-hospital morbidity	1620 (57.5)	1461 (56.8)	159 (65.7)	0.007	401 (55.2)	159 (65.7)	0.003
Complications							
Anastomotic leak	375 (13.3)	334 (13.0)	41 (16.9)	0.083	104 (14.3)	41 (16.9)	0.321
Pulmonary	1068 (37.9)	960 (37.3)	108 (44.6)	0.025	258 (35.5)	106 (44.6)	0.013
Cardiovascular	319 (11.3)	284 (11.0)	35 (14.5)	0.108	91 (12.5)	35 (14.5)	0.459
Clavien-Dindo (n = 1620)	n = 1620	n = 1461	n = 159	0.220	n = 401	n = 159	0.145
I	221 (13.6)	202 (13.8)	19 (11.9)		55 (13.7)	19 (11.9)	
II	532 (32.8)	477 (32.6)	55 (34.6)		128 (31.9)	55 (34.6)	
IIIa	152 (9.4)	134 (9.2)	18 (11.3)		36 (9.0)	18 (11.3)	
IIIb	190 (11.7)	173 (11.8)	17 (10.7)		39 (9.7)	17 (10.7)	
IVa	279 (17.2)	255 (17.5)	24 (15.1)		76 (19.0)	24 (15.1)	
IVb	57 (3.5)	51 (3.5)	6 (3.8)		19 (4.7)	6 (3.8)	
V	189 (11.7)	169 (11.6)	20 (12.6)		48 (12.0)	20 (12.6)	
Reoperation	404 (14.4)	366 (14.2)	38 (15.7)	0.531	106 (14.6)	38 (15.7)	0.677
Adjuvant therapy	587 (20.9)	501 (19.5)	86 (35.5)	<0.001	199 (27.4)	86 (35.5)	0.016

TABLE 3. Comparison of Survival and Recurrence of Patients With R0 and R1 Resection Margins

Outcomes	Before Matching			After Matching		
	R0	R1	*P*	R0	R1	*P*
Overall survival						
Median	45.3 mo	17.4 mo	<0.001	28.0 mo	17.4 mo	<0.001
(95% CI)	(40.5–50.0)	(14.6–20.1)		(25.1–30.4)	(14.6–20.1)	
At 3 yr	55.1%	27.1%		40.0%	27.1%	
Recurrence rate at 3 yr						
Overall	36.0%	70.8%	<0.001	58.2%	70.8%	<0.001
Locoregional	12.7%	41.2%	<0.001	26.1%	41.2%	<0.001
Distant	17.6%	28.9%	0.003	28.3%	28.9%	0.664
Mixed	10.2%	26.7%	<0.001	19.4%	26.7%	0.018

After matching, R1 resection margin remained an independently poor prognostic factor (Fig. 1) as shown by a reduction in overall survival (HR 1.57; 95% CI, 1.29–1.91; $P < 0.001$) and an increase in overall recurrence (HR 1.56; 95% CI, 1.25–1.95; $P < 0.001$) especially locoregional (HR 2.07; 95% CI, 1.46–2.93; $P < 0.001$) and mixed (HR 1.56; 95% CI, 1.01–2.42; $P = 0.048$) recurrence. The poor prognosis associated with R1 resection margin was observed both in the pN0 and in the pN+ subgroups with median survivals of 66.0 versus 24.4 months ($P = 0.003$) and 23.0 versus 16.6 months ($P = 0.002$), respectively.

In patients having received neoadjuvant chemoradiation, R1 resection margin was an independent predictor of poor prognosis (HR 1.51, 95% CI, 1.06–2.14, $P = 0.021$) by multivariable analysis and was associated with an increase overall (HR 2.54; 95% CI, 2.25–2.95; $P < 0.001$), locoregional (HR 2.17; 95% CI, 1.67–2.83; $P < 0.001$), distant (HR 1.87; 95% CI, 1.29–2.65; $P = 0.004$), and mixed (HR 1.53; 95% CI, 0.98–2.22; $P = 0.062$) recurrence. The risk for vertical margin involvement was 36.4% when the lateral margin was involved compared with 3.5% in absence of lateral margin involvement ($P < 0.001$).

Impact of Adjuvant Treatment in the R1 Population

Because R1 status has been shown to be a marker of tumoral aggressiveness and R1 patients received more frequently adjuvant chemo(radio)therapy, the impact of adjuvant treatment on survival and recurrence in the R1 population was further assessed using adjustment on a dedicated propensity score and malnutrition. Three-year overall survival was significantly improved through the use of adjuvant therapy (34.1% vs 25.8%; $P = 0.015$) (Fig. 2), with a trend in reduction of overall (69.7% vs 76.8%; $P = 0.087$) and distant recurrence (25.7% vs 37.9%; $P = 0.058$), but without significant effect upon locoregional (37.5% vs 48.6%; $P = 0.851$) or mixed (28.4% vs 22.8%; $P = 0.245$) recurrence. Adjuvant (chemo)radiation did not offer a survival benefit over adjuvant chemotherapy alone in the subgroup of R1 patients that did not receive neoadjuvant chemoradiotherapy ($P = 0.431$).

DISCUSSION

From this large multicenter study the incidence of R1 resection margin status was 8.6%. Independent predictors of R1 resection margin included an upper third esophageal tumor location, preoperative malnutrition, and advanced pathological stage. R1 resection margin was associated with an increased incidence of postoperative morbidity, was an indicator of aggressive disease, and was associated with a poor prognosis in both the total and the neoadjuvant chemoradiation populations, irrespective of the lymph node status. Adjuvant therapy did improve overall survival and reduce distant recurrence but failed to significantly affect locoregional recurrence.

The results of the present study highlight the importance of R1 resection margin status as a prognostic factor independent of patient and tumor characteristics including histological subtype. These results parallel similar findings with regard to the prognostic significance of an R1 margin seen in other cancers including pancreatic, colorectal, and liver.[16–19] Given the strong association of R1 resection margin with upper third esophageal tumor location after

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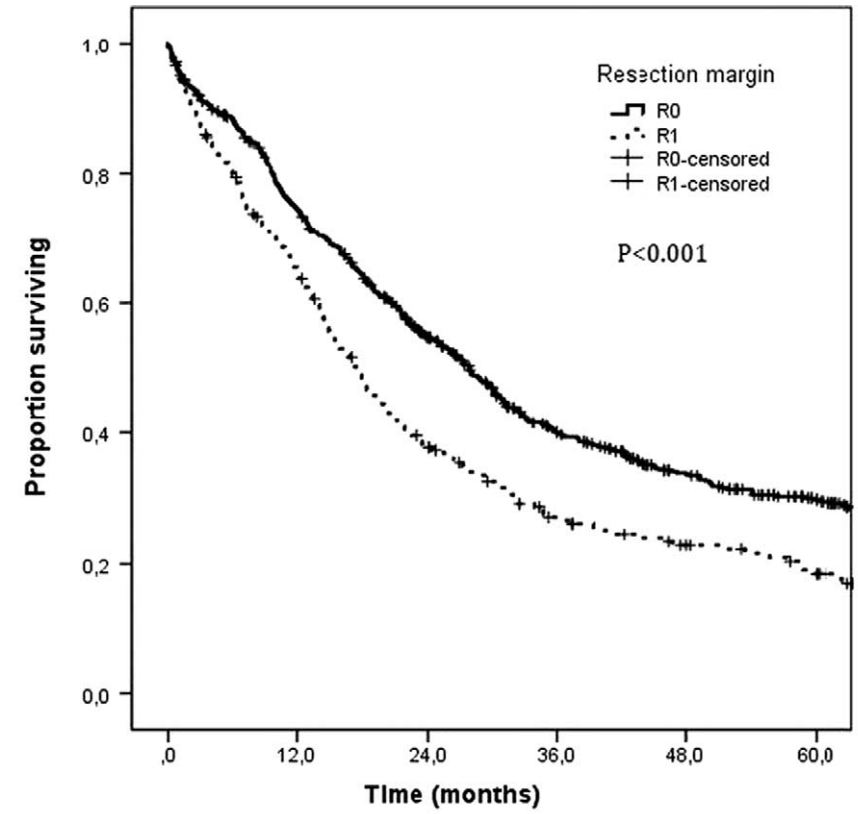

R0	726	515	355	226	164	117
R1	242	148	83	53	39	27

FIGURE 1. Comparison of overall survival in propensity-matched patients with R0 and R1 resection margin. The number of patients at risk at each interval is shown in the table at the bottom of the graph.

adjustment on other confounding variables, such as tumoral stage and histology, we can hypothesize that this association is most likely to be due to the technical challenges associated with a high tumor location placing the margin at risk. The utilization of neoadjuvant chemoradiotherapy seems to reduce the incidence of R1 resection margins in univariate analysis, which is consistent with the published literature on the subject.[20,21] Despite these benefits, some patients fail to respond to neoadjuvant chemoradiotherapy with a poor response as classified by Mandard regression grade correlated with R1 resection margin status. This may explain why absence of neoadjuvant chemoradiotherapy was not an independent predictor of R1 resection margin in multivariate analysis. Given the prognostic significance of R1 resection margin status, this study further highlights the importance of future research into pretherapeutic identification of patients less likely to respond to neoadjuvant therapy and further the ongoing research to optimize neoadjuvant treatment and/or testing adaptive strategies for early nonresponders.[22,23]

Malnutrition is shown to be an independent predictor of R1 resection through multivariable analysis, independently from the tumoral stage and other confounding variables. Even if preoperative malnutrition may be partly reflection of aggressive disease, the independent link exhibited between malnutrition and R1 status could be explained by some other mechanisms: (i) malnutrition has been shown to be a predictor of poor response to neoadjuvant treatment response,[24,25] exposing to an increase risk of R1 margin; (ii) hypoalbuminemia induces an increase of unbound platinum, leading to an increase in grade 3–4 toxicities to neoadjuvant treatment,[26] which has been shown to be associated with poorer outcomes.[27]

R1 resection margin seems to be a marker of underling aggressive tumor biology. This is reflected in the R1 margin group by an increased number of positive lymph nodes (4.2 ± 5.4 vs 3.1 ± 4.2), and a higher risk of vertical margin involvement of 36.4% when the lateral margin was involved compared with 3.5% in absence of lateral margin involvement. The suggestion that R1 margin is an indication of aggressive tumors has previously been proposed in the setting of liver metastases,[28] and in rectal[9] and pancreatic[10] cancers. Propensity matching between groups included patient and tumor factors that may influence survival, therefore it seems that R1 resection margin identifies aggressive tumors with a poor long-term prognosis, independently of the lymph nodes status that has frequently been identified as a confounding factor in published series,[5] and the administration of neoadjuvant chemoradiotherapy.

Related to the recognized issue of increased recurrence after an R1 resection margin, we show that adjuvant therapy did significantly improve survival, and reduced distant tumor recurrence but failed to significantly affect locoregional control of disease, questioning the optimal modalities of the adjuvant treatment in this situation.

Previous studies in the setting of esophageal cancer have similarly suggested, in a smaller and homogeneous population, the improved survival of R1 margin patients after adjuvant therapy

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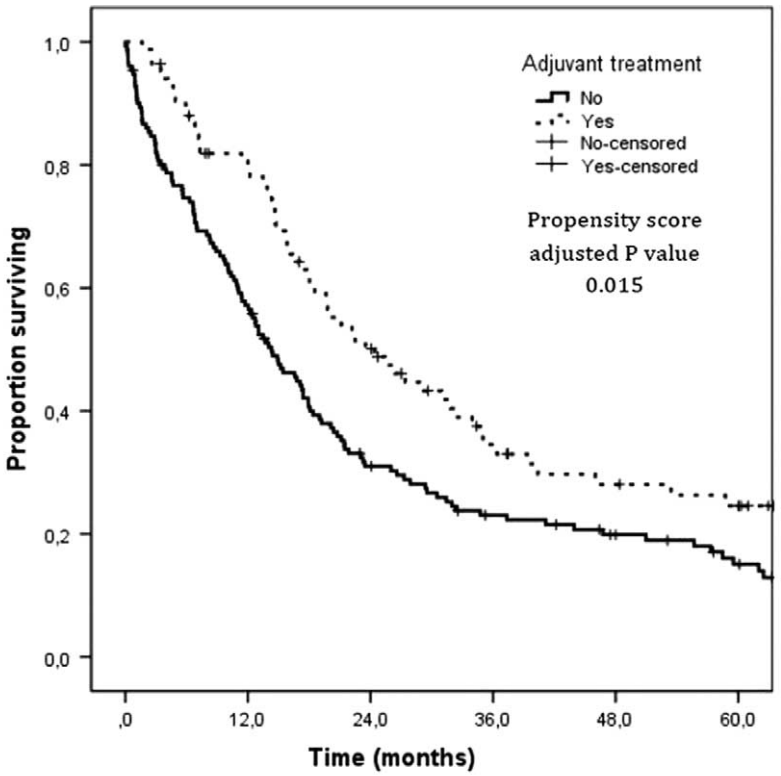

No adjuvant treatment	156	85	44	30	22	15
Adjuvant treatment	86	63	39	23	17	13

FIGURE 2. Comparison of overall survival in R1 patients who did or did not receive adjuvant therapy. The number of patients at risk at each interval is shown in the table at the bottom of the graph.

without influencing locoregional recurrence.[29] In addition some surgeons have suggested the resection of locoregional recurrence or hepatic metastases can improve prognosis,[30] however salvage surgery was not a treatment included in the present study and remains highly questionable given the aggressiveness of the R1 disease highlighted in the present study. The positive impact of neoadjuvant chemoradiotherapy in decreasing the risk of R1 margin combined with the failure of chemoradiotherapy in the adjuvant setting to decrease locoregional recurrence in R1 patients highlights the critical importance of discussion in a multidisciplinary setting with regard to the optimal therapeutic strategy at initial diagnosis to avoid noncurable surgery.[31]

The major strength of this study lies in the large sample size of patients that has allowed for multivariable regression modeling and propensity-matched analysis to adjust for some important confounding factors, and some relevant subgroup analyses, that have strongly limited previous studies.[32–35] However, there are some limitations of this study that must be considered, including its design as a retrospective, observational study. As a large multicenter database study the results generated are dependent upon the reliability of the methodology of data collection. To minimize any bias associated with data collection methodology during this study an independent monitoring team audited data capture to minimize missing data and to control concordance, and 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. Furthermore, there was variation in regimes used for adjuvant therapy, therefore the optimal adjuvant therapy for R1 margin patients remains undetermined by the present study.

This large multicenter European study of 2815 patients has showed that R1 resection margin seems to be a marker of underlying aggressive tumor disease and was significantly associated with reduced overall survival and increased recurrence. Although adjuvant therapy was seen to improve survival it failed to influence locoregional recurrence, therefore the optimal regime remains an important area for future study. Based upon the predictive factors of an R1 margin identified in this study, patients with an upper third tumor location and advanced stage should benefit from neoadjuvant chemoradiotherapy to reduce the risk of an R1 margin. However, if an unexpected R1 margin is discovered at pathological analysis, adjuvant chemotherapy should be discussed with the patient given the survival benefits identified in this study.

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APPENDIX

DESCRIPTION OF NEOADJUVANT AND ADJUVANT THERAPEUTIC REGIMES

All patients were evaluated by a multidisciplinary team and treated with a curative intent according to French national guidelines.[15]

Neoadjuvant Therapy

During neoadjuvant chemoradiotherapy (nCRT), usually patients were scheduled to receive 2 cycles of 5-fluorouracil (800 mg/m^2/24 hours over 4 or 5 days) and cisplatin (75 mg/m^2/24 hours over 1 day, or 15 mg/m^2/24 hours over 5 days), in combination with 45 Gy of concomitant radiotherapy over 5 weeks. After nCRT, curative surgery was proposed regardless of tumor response, with esophagectomy carried out 6 to 8 weeks after treatment completion.

Adjuvant Therapy

From 242 patients with R1 positive margin status 86 patients received adjuvant therapy. The breakdown was as follows: 35 received chemotherapy only, 13 received radiotherapy only, and 38 received nCRT. The regime of adjuvant chemotherapy did vary between the centers included, however, the most common regimes used included 5-fluorouracil (31.4%) and Cisplatin (26.7%).

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