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Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

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ABSTRACT

Purpose
The aim of this large multicenter study was to assess the impact of salvage esophagectomy after definitive chemoradiotherapy (SALV) on clinical outcome.

Patients and Methods
Data from consecutive adult patients undergoing resection for esophageal cancer in 30 European centers from 2000 to 2010 were collected. First, groups undergoing SALV (n = 308) and neoadjuvant chemoradiotherapy followed by planned esophagectomy (NCRS; n = 540) were compared. Second, patients who benefited from SALV for persistent (n = 234) versus recurrent disease (n = 74) were compared. Propensity score matching and multivariable analyses were used to compensate for differences in some baseline characteristics.

Results
SALV versus NCRS groups: In-hospital mortality was similar in both groups (8.4% *v* 9.3%). The only significant differences in complications were seen for anastomotic leak (17.2% *v* 10.7%; $P = .007$) and surgical site infection, which were both more frequent in the SALV group. At 3 years, groups had similar overall (43.3% *v* 40.1%; $P = .542$) and disease-free survival (39.2% *v* 32.8%; $P = .232$) after matching, along with a similar recurrence pattern. Persistent versus recurrent disease groups: There were no significant differences between groups in incidence of in-hospital mortality or major complications. At 3 years, overall (40.9% *v* 56.2%; $P = .046$) and disease-free survival (36.6% *v* 51.6%; $P = .095$) were lower in the persistent disease group.

Conclusion
The results of this large multicenter study from the modern era suggest that SALV can offer acceptable short- and long-term outcomes in selected patients at experienced centers. Persistent cancer after definitive chemoradiotherapy seems to be more biologically aggressive, with poorer survival compared with recurrent cancer.

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INTRODUCTION

Esophageal cancer is the seventh leading cause of cancer-related death in the US male population.[1,2] Meta-analyses have demonstrated improved survival associated with a combination of neoadjuvant chemoradiotherapy (CRT) and surgery (NCRS), when compared with surgery alone.[3-5] Despite the survival benefits of this combined approach, esophagectomy remains a highly invasive procedure that confers a significant rate of morbidity and mortality and can adversely affect long-term quality of life.[6-8]

Current National Comprehensive Cancer Network and French guidelines state definitive CRT (dCRT) without surgery is an alternative to surgical resection for locally advanced esophageal squamous cell carcinoma.[9] Previous randomized controlled trials have demonstrated equivalence in 2-year survival for patients with esophageal squamous cell carcinoma treated with NCRS and those treated with dCRT.[10,11] However, local recurrence rates are between 40% and 75% after dCRT.[12-14] These groups of patients with persistent or recurrent disease are selectively considered for salvage esophagectomy (SALV). dCRT can adversely affect patient performance status,[15,16] and together with the effects of high radiation doses on thoracic tissue as well radiation effects on cardiac and pulmonary functions, this can make SALV a significant challenge. A meta-analysis of eight retrospective studies involving 254 patients suggested SALV was associated with increases in mortality, anastomotic leak, pulmonary

complications, and length of hospital stay when compared with NCRS.[17] However, with the total number of patients undergoing SALV ranging from 14 to 65 in the included studies, it may be suggested this analysis was based on small series of patients from historical studies, calling into question the relevance of these findings to current practice.

The primary aim of our large multicenter study was to assess the impact of SALV after dCRT on clinical outcome in comparison with NCRS. The secondary aim of this study was to compare outcomes, including survival with SALV, among those with persistent and recurrent esophageal cancers.

PATIENTS AND METHODS

Patient Eligibility Criteria

Data from 2,944 consecutive adult patients undergoing surgical resection for esophageal cancer 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 control concordance, as well as inclusion of consecutive patients. Missing or inconsistent data were obtained from e-mail exchanges or telephone calls with the referral center. The first step was to compare patients who received SALV (n = 308) with those who underwent NCRS (n = 540). The second step was to focus on the SALV group and compare patients who benefited from SALV for persistent (PERS; n = 234) or recurrent disease (REC; n = 74). The study was approved by the regional institutional review board on July 15th, 2013, and the database was registered on the Clinicaltrials.gov website under the identifier NCT 01927016. All patients were evaluated by a multidisciplinary team and treated with curative intent according to French national guidelines[18] (Appendix, online only).

Definition of SALV

SALV was defined as removal of the esophagus for persistent or recurrent disease within the tumor and/or locoregional lymph nodes after dCRT. PERS was defined as presence of cancer on endoscopic or radiologic investigation with histologic confirmation within 3 months of dCRT. REC was defined as presence of cancer within the tumor or locoregional nodes after 3 months of dCRT. There were no differences in operative approach, including extent of nodal dissection, between the SALV and NCRS groups, with all patient having benefited from esophagectomy and two-field lymphadenectomy.

Data Collection

Patient and tumor demographic data were collected, and complications were defined based on the definitions used in the MIRO (Minimally Invasive Resection for Oesophageal Cancer) trial[19] (Appendix, online only). The Clavien-Dindo scale was used to grade severity of postoperative morbidity.[20] Histologic staging of tumors was based on the seventh edition of the Union Internationale Contre le Cancer/TNM classification.[21]

Follow-Up: Survival and Recurrence

During follow-up clinical examination, thoracoabdominal computed tomography every 6 months for 5 years was recommended, with upper GI endoscopy at 2 years.[18] In case of complete clinical response, endoscopy with biopsies was recommended every 6 months for 2 years. In cases of suspected recurrence, thoracoabdominal computed tomography and endoscopy with biopsy—and in the more recent, periodic positron emission tomography scanning—were performed. Histologic, cytologic, or unequivocal radiologic proof was required before a diagnosis of recurrence was made. The first site of recurrence was used to define whether 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 performed using SPSS software (version 19.0; SPSS, Chicago, IL). Continuous variables are expressed as mean ± standard deviation (SD) or median and range, and categorical variables as number and percentage. Mann-Whitney *U* test was used for intergroup comparisons of continuous variables, whereas χ^2 or Fisher's test was used to compare categorical data. Overall and disease-free survival were estimated using the Kaplan-Meier method.

To reduce the effects of potential confounding factors in the comparison of short- and long-term outcomes between the study groups (SALV *v* NCRS and PERS *v* REC), 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. All patients in the SALV group were matched at a ratio of 1:1 to patients in the NCRS group according to propensity score using the global optimum method. Short- and long-term outcomes were compared between the matched groups using a generalized linear mixed (logistic regression) model or Cox regression model using the robust sandwich estimate for matched sets. We derived from these models odds ratios (ORs) and hazard ratios (HRs) as effect-size measures, with 95% CIs. Regarding the small sample size in the REC group, comparisons between the PERS and REC groups were adjusted for propensity score rather than using a matching process. Adjustment was performed using multivariable logistic regression or Cox regression models including propensity score as a covariate. All statistical tests were two sided, with the threshold of significance set at $P < .05$.

RESULTS

Demographics and Study Population

A total of 848 patients were included in the study: 308 in the SALV group and 540 in the NCRS group. Of the 308 patients who underwent SALV, 234 had persistent and 74 had recurrent disease. The percentage of patients age ≥ 60 years was 45.2%; 85.3% were male; 59.8% had American Society of Anesthesiologists (ASA) grade 2 status; 30.2% showed evidence of preoperative malnutrition. A majority of patients underwent surgery at high-volume centers (80.9%), with Ivor-Lewis esophagectomy being the most commonly used surgical approach (76.7%). Clinical stage III disease was seen in 62.1% of patients, with squamous cell carcinoma being the most common histologic subtype (60.7%). Complete pathologic response was seen in 22.9% of patients; however, > 10% of patients had an R1/2 resection margin. Comparisons of the SALV and NCRS groups are summarized in Tables 1 and 2.

Analysis of patient demographics revealed no significant differences between the groups in patients age ≥ 60 years, sex, ASA grade, malnutrition, histologic subtype, or clinical TNM stage. However, there was an increase in the proportion of SALV performed after 2006 when compared with the NCRS group. Median total radiation dose was 50 Gy (range, 25 to 75 Gy) in the SALV group and 45 Gy (range, 25 to 45 Gy) in the NCRS group. Mean delay (± SD) between the end of chemoradiotherapy and surgery was 1.6 ± 0.5 months in the NCRS group and 5.5 ± 2.3 months in the SALV group. However, there was no difference in the oncologic quality of surgical resection between the groups, with a similar R0 resection margin rate (SALV, 87.3% *v* NCRS, 90.2%), similar median number of lymph nodes retrieved (SALV, 14 *v* NCRS, 15), and similar mean number of invaded lymph nodes (SALV, 1.1 *v* NCRS, 1.4) in both groups. There were no significant differences between the groups in histologic subtype or pathologic stage status.

Table 1. Comparison of Demographic and Therapeutic Characteristics of SALV and NCRS Groups

Variable	Overall (N = 848)	Before Matching			After Matching		
		SALV (n = 308)	NCRS (n = 540)	*P*	SALV (n = 308)	NCRS (n = 308)	*P*
Surgery after 2006, No. (%)*	424 (50)	170 (55.2)	254 (47.0)	.022	170 (55.2)	169 (54.9)	.935
Age ≥ 60 years, No. (%)*	383 (45.2)	135 (43.8)	248 (45.9)	.556	135 (43.8)	119 (38.6)	.190
Male sex, No. (%)*	723 (85.3)	259 (84.1)	464 (85.9)	.469	259 (84.1)	269 (87.3)	.250
ASA score, No. (%)*				.321			.981
1	135 (15.9)	43 (14.0)	92 (17.0)		43 (14.0)	41 (13.3)	
2	507 (59.8)	182 (59.1)	325 (60.2)		182 (59.1)	183 (59.4)	
3	199 (23.5)	79 (25.6)	120 (22.2)		79 (25.6)	81 (26.3)	
4	7 (0.8)	4 (1.3)	3 (0.6)		4 (1.3)	3 (1.0)	
Malnutrition, No. (%)	256 (30.2)	98 (31.8)	158 (29.3)	.373	98 (31.8)	90 (36.4)	.722
Center volume ≥ 80%, No. (%)*	686 (80.9)	240 (77.9)	446 (82.6)	.096	240 (77.9)	244 (79.2)	.695
Tumor location, No. (%)*				.050			.954
Upper	143 (16.9)	59 (19.2)	84 (15.6)		59 (19.2)	62 (20.1)	
Middle	320 (37.7)	126 (40.9)	194 (35.9)		126 (40.9)	125 (40.6)	
Lower	385 (45.4)	123 (39.9)	262 (48.5)		123 (39.9)	121 (39.2)	
Clinical TNM stage, No. (%)*				.239			.919
I	64 (7.5)	17 (5.5)	47 (8.7)		17 (5.5)	17 (5.5)	
II	238 (28.1)	92 (29.9)	146 (27.0)		92 (29.9)	85 (27.6)	
III	527 (62.1)	190 (61.7)	337 (62.4)		190 (61.7)	198 (64.3)	
IV	19 (2.3)	9 (2.9)	10 (1.9)		9 (2.9)	8 (2.6)	
Surgical technique, No. (%)*				.001			.821
Ivor Lewis	650 (76.7)	216 (70.1)	434 (80.4)		216 (70.1)	223 (72.4)	
Three stage	146 (17.2)	73 (23.7)	73 (13.5)		73 (23.7)	67 (21.8)	
Transhiatal	52 (6.1)	19 (6.2)	33 (6.1)		19 (6.2)	18 (5.8)	
Histology, No. (%)*				.550			.776
SCC	515 (60.7)	193 (62.7)	322 (59.6)		193 (62.7)	200 (64.9)	
Adenocarcinoma	319 (37.6)	109 (35.4)	210 (38.9)		109 (35.4)	101 (32.8)	
Other	14 (1.7)	6 (1.9)	8 (1.5)		6 (1.9)	7 (2.3)	
Tumor differentiation, No. (%)				.417			.365
Good	204 (24.1)	84 (27.3)	120 (22.2)		84 (27.3)	66 (21.4)	
Average	259 (30.5)	91 (29.5)	168 (31.1)		91 (29.5)	102 (33.1)	
Poor	131 (15.4)	44 (14.3)	87 (16.1)		44 (14.3)	50 (16.2)	
Data missing	254 (30)	89 (28.9)	165 (30.6)		89 (28.9)	90 (29.2)	
Pathological stage, No. (%)				.917			.991
0	194 (22.9)	68 (22.1)	126 (23.3)		68 (22.1)	72 (22.7)	
I	182 (21.5)	62 (20.1)	120 (22.2)		62 (20.1)	63 (20.5)	
II	223 (26.3)	84 (27.3)	139 (25.7)		84 (27.3)	84 (27.3)	
III	227 (26.7)	86 (27.9)	141 (26.1)		86 (27.9)	82 (26.6)	
IV	22 (2.6)	8 (2.6)	14 (2.6)		8 (2.6)	7 (2.3)	
Resection margin, No. (%)				.403			.720†
R0	756 (89.2)	269 (87.3)	487 (90.2)		269 (87.3)	274 (89.0)	
R1	52 (6.1)	23 (7.5)	29 (5.4)		23 (7.5)	18 (5.8)	
R2	40 (4.7)	16 (5.2)	24 (4.4)		16 (5.2)	16 (5.2)	
Adjuvant therapy, No. (%)	85 (10)	30 (9.7)	55 (10.2)	.836	30 (9.7)	27 (8.8)	.781

Abbreviations: ASA, American Society of Anesthesiologists; NCRS, neoadjuvant chemoradiotherapy followed by planned esophagectomy; SALV, salvage esophagectomy after definitive chemoradiotherapy; SCC, squamous cell carcinoma.
*Variables used for propensity-matching process.
†R1/2 resection margin grouped together in propensity-matched analysis.

Percentages of in-hospital mortality (8.4% *v* 9.3%) and morbidity (63.6% *v* 58.9%) were similar in both groups (Table 2). The only significant differences in complications were seen for anastomotic leak and surgical site infection, which were both increased in the SALV group. There was no significant difference in severity of complications as assessed by the Clavien-Dindo system after SALV. Of the 308 patients in the SALV group, 68 underwent surgery in low- and 240 in high-volume centers. SALV in high-volume centers was associated with a significant reduction in in-hospital mortality (6.3% *v* 16.2%; $P = .009$) and overall morbidity (58.8% *v* 80.9%; $P = .001$). Further subset analysis of patients undergoing SALV who received a total radiation dose ≥ 55 Gy (17.5%) revealed significant increases in in-hospital mortality (27.8% *v* 4.3%; $P < .001$), overall morbidity (75.9% *v* 61%; $P = .039$), anastomotic leak (27.8% *v* 15%; $P = .023$), surgical site infection (29.6% *v* 16.1%; $P = .02$), and pulmonary complications (55.6% *v* 40.2%; $P = .038$), compared with those who received < 55 Gy (82.5%).

After matching, there were no significant differences between SALV and NCRS groups in in-hospital mortality or morbidity, with the exception of anastomotic leak (17.2% *v* 10.7%; $P = .015$)

Table 2. Comparison of In-Hospital Mortality and Morbidity in SALV and NCRS Groups

Variable	Overall (N = 848)	Before Matching				After Matching			
		SALV (n = 308)	NCRS (n = 540)	OR (95% CI)	*P*	SALV (n = 308)	NCRS (n = 308)	OR (95% CI)	*P*
Outcome									
In-hospital mortality, No. (%)	76 (9.0)	26 (8.4)	50 (9.3)	0.904 (0.550 to 1.484)	.688	26 (8.4)	35 (11.4)	0.719 (0.414 to 1.250)	.241
In-hospital morbidity, No. (%)	514 (60.6)	196 (63.6)	318 (58.9)	1.222 (0.915 to 1.630)	.174	196 (63.6)	188 (61.0)	1.117 (0.818 to 1.525)	.506
Complications									
Anastomotic leak, No. (%)	111 (13.1)	53 (17.2)	58 (10.7)	1.727 (1.155 to 2.582)	.007	53 (17.2)	33 (10.7)	1.732 (1.110 to 2.703)	.015
Conduit necrosis, No. (%)	6 (0.7)	4 (1.3)	2 (0.4)	—	NA*	4 (1.3)	1 (0.3)	—	NA*
Surgical site infection, No. (%)	123 (14.5)	57 (18.5)	66 (12.2)	1.631 (1.109 to 2.399)	.012	57 (18.5)	38 (12.3)	1.614 (1.058 to 2.461)	.026
Chylothorax, No. (%)	26 (3.1)	10 (3.2)	16 (3.0)	1.099 (0.492 to 2.453)	.818	10 (3.3)	10 (3.3)	1.000 (0.404 to 2.474)	> .999
Postoperative hemorrhage, No. (%)	5 (0.6)	1 (0.3)	4 (0.7)	—	NA*	1 (0.3)	3 (1.0)	—	NA*
Gastroparesis, No. (%)	10 (1.2)	6 (1.9)	4 (0.7)	—	NA*	3 (1.0)	3 (1.0)	—	NA*
Pulmonary, No. (%)	353 (41.6)	132 (42.9)	221 (40.9)	1.083 (0.815 to 1.437)	.583	132 (42.9)	127 (41.2)	1.069 (0.786 to 1.454)	.672
Cardiovascular, No. (%)	115 (13.6)	42 (13.6)	73 (13.5)	1.010 (0.671 to 1.521)	.962	42 (13.6)	43 (14.0)	0.973 (0.612 to 1.547)	.908
Thromboembolic, No. (%)	25 (2.9)	9 (2.9)	16 (3.0)	0.989 (0.443 to 2.324)	.973	9 (2.9)	10 (3.3)	0.900 (0.374 to 2.167)	.814
Neurologic, No. (%)	25 (2.9)	6 (1.9)	19 (3.5)	1.010 (0.687 to 1.235)	.388	5 (1.6)	8 (2.6)	0.998 (0.876 to 1.113)	.405
Clavien-Dindo score, No. (%)				—	.461			—	.201
I	64 (7.5)	21 (6.8)	43 (8.0)			21 (6.8)	30 (9.7)		
II	168 (19.8)	68 (22.1)	100 (18.5)			68 (22.1)	45 (14.6)		
IIIa	51 (6)	20 (6.5)	31 (5.7)			20 (6.5)	21 (6.8)		
IIIb	49 (5.8)	23 (7.5)	26 (4.8)			23 (7.5)	18 (5.8)		
IVa	86 (10.1)	33 (10.7)	53 (9.8)			33 (10.7)	30 (9.7)		
IVb	20 (2.4)	5 (1.6)	15 (2.8)			5 (1.6)	9 (2.9)		
V	76 (9)	26 (8.4)	50 (9.3)			26 (8.4)	35 (11.4)		

Abbreviations: NA, not applicable; NCRS, neoadjuvant chemoradiotherapy followed by planned esophagectomy; OR, odds ratio; SALV, salvage esophagectomy after definitive chemoradiotherapy.
*Because of low number of events.

and surgical site infection (18.5% *v* 12.3%; *P* = .026), which were increased in the SALV group (Table 2). After a median follow-up of 54.4 months, there was no significant difference between the SALV and NCRS groups in 3-year overall (43.3% *v* 40.1%; *P* = .542) (Fig 1) or disease-free survival (39.2% *v* 32.8%; *P* = .232). Furthermore, at 3 years, there were no significant differences between these groups in overall (46.8% *v* 47.9%; *P* = .829), locoregional (18.8% *v* 15.9%; *P* = .544), distant (24.3% *v* 28.1%; *P* = .949), or mixed tumor recurrence (13.0% *v* 13.5%; *P* = .888). Comparisons of PERS and REC groups after SALV are summarized in Tables 3 and 4.

Subset analysis limited to patients who underwent SALV suggested that persistent rather than recurrent disease was the indication in most cases (76% *v* 24%). Analysis of patient demographics showed incidence of malnutrition was increased in the PERS group (35.5% *v* 20.3%). The PERS group showed a greater percentage of stage III (32.5% *v* 13.5%) and IV disease (3% *v* 1.4%) compared with the REC group. There were no significant differences between the groups in incidence of in-hospital mortality or major complications.

On the basis of adjusted matched analysis, there were no significant differences between the groups in in-hospital mortality or morbidity (Table 4). At 3 years, overall (39.1% *v* 56.2%; *P* = .086; Fig 2) and disease-free survival (35.4% *v* 51.6%; *P* = .090) were reduced in the PERS group. Furthermore, there were nonsignificant increases at 3 years in overall (51.1% *v* 34.9%; *P* = .136), locoregional (20.6% *v* 13.9%; *P* = .233), distant (26.5% *v* 18.7%; *P* = .640), and mixed tumor recurrences (15.5% *v* 6.9%; *P* = .339) in the PERS group. Results remained similar after adjustment for malnutrition (data not shown).

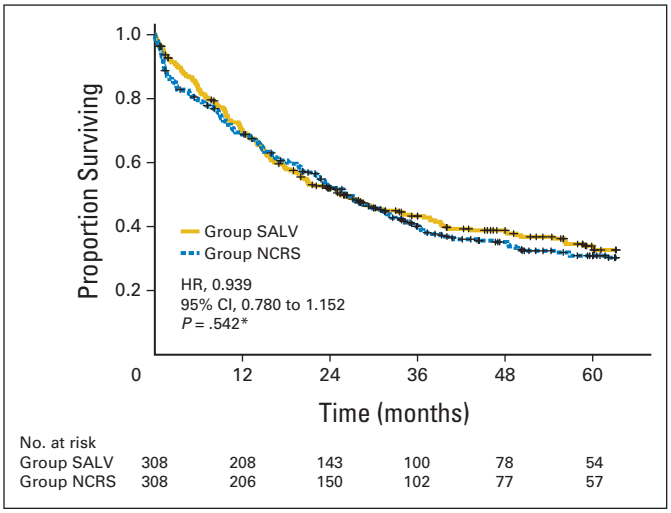

Fig 1. Comparison of overall survival in propensity-matched salvage esophagectomy after definitive chemoradiotherapy (SALV) and neoadjuvant chemoradiotherapy followed by planned esophagectomy (NCRS) groups. No. of patients at risk in each interval is shown in table at bottom of graph. HR, hazard ratio. (*) *P* value and HR calculated using Cox regression model for matched data set.

Table 3. Comparison of Demographic and Therapeutic Characteristics of PERS and REC Disease After Definitive Chemoradiotherapy

Variable	Overall (n = 308)	Salvage Group		P
		PERS (n = 234)	REC (n = 74)	
Surgery after 2006, No. (%)*	170 (55.2)	124 (53.0)	46 (62.2)	.167
Age ≥ 60 years, No. (%)*	135 (43.8)	104 (44.4)	31 (41.9)	.700
Male sex, No. (%)*	259 (84.1)	194 (82.9)	65 (87.8)	.312
ASA score, No. (%)*				.382
1	43 (14)	35 (15.0)	8 (10.8)	
2	182 (59.1)	133 (56.8)	49 (66.2)	
3	79 (25.6)	62 (26.5)	17 (23.0)	
4	4 (1.3)	4 (1.7)	0 (0)	
Malnutrition, No. (%)	98 (31.8)	83 (35.5)	15 (20.3)	.009
Center volume ≥ 80%, No. (%)*	240 (77.9)	179 (76.5)	61 (82.4)	.283
Tumor location, No. (%)*				.067
Upper	59 (19.2)	38 (16.2)	21 (28.4)	
Middle	126 (40.9)	100 (42.7)	26 (35.1)	
Lower	123 (39.9)	96 (41.1)	27 (36.5)	
Clinical TNM stage, No. (%)*				.091
I	17 (5.5)	10 (4.3)	7 (9.5)	
II	92 (29.9)	67 (28.6)	25 (33.8)	
III	190 (61.7)	148 (63.2)	42 (56.8)	
IV	9 (2.9)	9 (3.8)	0 (0)	
Surgical technique, No. (%)*				.402
Ivor Lewis	216 (70.1)	166 (70.9)	50 (67.6)	
Three stage	73 (23.7)	56 (23.9)	17 (23.0)	
Transhiatal	19 (6.2)	12 (5.2)	7 (9.4)	
Histology, No. (%)*				.735
SCC	193 (62.7)	144 (61.5)	49 (66.2)	
Adenocarcinoma	109 (35.4)	85 (36.3)	24 (32.4)	
Other	6 (1.9)	5 (2.2)	1 (1.4)	
Tumor differentiation, No. (%)				.809
Good	84 (27.3)	63 (26.9)	21 (28.4)	
Average	91 (29.5)	68 (29.1)	23 (31.1)	
Poor	44 (14.3)	36 (15.4)	8 (10.8)	
Data missing	89 (28.9)	67 (28.6)	22 (29.7)	
Pathologic stage, No. (%)				.001
0	68 (22.1)	40 (17.1)	28 (37.8)	
I	62 (20.1)	47 (20.1)	15 (20.3)	
II	84 (27.3)	64 (27.4)	20 (27.0)	
III	86 (27.9)	76 (32.5)	10 (13.5)	
IV	8 (2.6)	7 (3.0)	1 (1.4)	
Resection margin, No. (%)				.510
R0	269 (87.3)	202 (86.3)	67 (90.5)	
R1	23 (7.5)	18 (7.7)	5 (6.8)	
R2	16 (5.2)	14 (6.0)	2 (2.7)	
Adjuvant therapy, No. (%)	30 (9.7)	27 (11.5)	3 (4.1)	.071

Abbreviations: ASA, American Society of Anesthesiologists; PERS, persistent; REC, recurrent; SCC, squamous cell carcinoma.
*Variables used for propensity-matching process.

DISCUSSION

Comparison of in-hospital mortality and morbidity demonstrated no differences between the SALV and NCRS groups, with the exception of a higher incidence of anastomotic leak and surgical site infection in the SALV group. Subset analysis of the SALV group showed significant reductions in postoperative mortality and morbidity associated with surgery in high-volume centers and in patients who received a lower radiation dose. Furthermore, overall and disease-free survival, along with recurrence patterns, were similar between these SALV and NCRS groups. There were no significant differences between PERS and REC groups in terms of in-hospital mortality or morbidity after SALV, with a reduction in overall and disease-free survival in the PERS group.

A meta-analysis of small unmatched single-institution series, with only 242 patients in the SALV group, suggested that SALV was associated with increased postoperative mortality, anastomotic leak, and pulmonary complications when compared with NCRS (Table 5). The differences between these results and the results of our study are likely to be multifactorial. In our study, approximately 80% of patients underwent SALV at experienced centers, with discussion at multidisciplinary team meetings ensuring appropriate patient selection and

Table 4. Comparison of In-Hospital Mortality and Morbidity in Patients With PERS and REC Disease After Definitive Chemoradiotherapy

Variable	Overall (n = 308)	PERS (n = 234)	REC (n = 74)	*P*	Adjusted Analysis* OR (95% CI)	*P*
Outcome						
In-hospital mortality	26 (8.4)	23 (9.8)	3 (4.1)	.152	0.438 (0.124 to 1.548)	.200
In-hospital morbidity	196	153 (52.6)	43 (58.1)	.257	0.821 (0.460 to 1.466)	.505
Complications						
Anastomotic leak	53 (17.2)	38 (16.2)	15 (20.3)	.423	1.126 (0.565 to 2.246)	.736
Conduit necrosis	4 (1.3)	3 (1.3)	1 (1.4)	NA†	NA†	
Surgical site infection	57 (18.5)	42 (17.9)	15 (20.3)	.654	1.024 (0.517 to 2.026)	.947
Chylothorax	10 (3.2)	9 (3.8)	1 (1.4)	.461	0.349 (0.042 to 2.913)	.331
Postoperative hemorrhage	1 (0.3)	1 (0.4)	0 (0)	NA†	NA†	
Gastroparesis	6 (1.9)	6 (2.6)	0 (0)	NA†	NA†	
Pulmonary	132 (42.9)	101 (43.2)	31 (41.9)	.847	1.009 (0.582 to 1.747)	.975
Cardiovascular	42 (13.6)	34 (14.5)	8 (10.8)	.416	0.688 (0.296 to 1.602)	.386
Thromboembolic	9 (2.9)	8 (3.4)	1 (1.4)	.692	0.416 (0.049 to 3.543)	.423
Neurologic	6 (1.9)	6 (2.6)	0 (0)	NA†	NA†	
Clavien-Dindo score				.720	—	
I	21 (6.8)	16 (6.8)	5 (6.8)			
II	68 (22.1)	53 (22.6)	15 (20.3)			
IIIa	20 (6.5)	15 (6.4)	5 (6.8)			
IIIb	23 (7.5)	19 (8.1)	4 (5.4)			
IVa	33 (10.7)	23 (9.8)	10 (13.5)			
IVb	5 (1.6)	4 (1.7)	1 (1.4)			
V	26 (8.4)	23 (9.8)	3 (4.1)			

Abbreviations: NA, not applicable; OR, odds ratio; PERS, persistent; REC, recurrent.
*Adjustment was made based on propensity score; consistency of results was verified after adjustment on nutritional status.
†Because of low number of events.

standardized perioperative care pathways to optimize postoperative recovery. This point is further emphasized by the significantly lower rates of postoperative mortality and morbidity with SALV observed in high-volume centers. Furthermore, the median radiation dose was 50 Gy in the SALV group, which was substantially lower than those in the majority of studies included in the previously mentioned meta-analysis (Table 5). Given the substantial increases in adverse outcomes observed in patients who received radiation dose $\geq$ 55 Gy, this may further explain in part the differences seen in mortality and morbidity between our study and the meta-analysis. Currently, there is no evidence in terms of locoregional control or survival benefit to support a high total radiation dose ($>$ 50 Gy) in patients receiving dCRT.[14] Together with the findings presented in our study, this would suggest that an upper threshold of 50 Gy should be used in these patients to optimize the benefits of dCRT without compromising the safety of SALV if required.

Anastomotic leak was increased in the SALV group in both the meta-analysis and our study, even more so in patients who received total radiation dose $\geq$ 55 Gy, suggesting the detrimental effects of definitive levels of radiotherapy on gastric microcirculation and conduit perfusion. Given recent data suggesting the impact of anastomotic leak on oncologic outcome,[30] great caution with conduit handling and anastomotic formation in these patients is particularly recommended. The overall mortality rate in both groups parallels previous results from the FFCD (Fédération Francophone de Cancérologie Digestive) 9901 trial,[31] but is greater than that published in CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study).[5] The reasons for this are multifactorial. In contrast with the CROSS trial, patients in FFCD 9901 were unselected, with an ASA score of 2 to 3; they were frequently malnourished; 60% had squamous cell carcinoma; $>$ 50% of tumors were located in the upper or middle third of the esophagus; and all patients were treated with a combination fluorouracil-platinum regimen plus a higher dose of radiation.[5,32]

Our study demonstrated a similar survival and recurrence pattern for the SALV and NCRS groups, potentially validating an approach of dCRT with reserved SALV for persistent or recurrent disease. Importantly, there were no differences in oncologic safety of surgery, including extent of nodal dissection, between the SALV and NCRS groups, indicating that standard surgery can be performed safely in patients undergoing SALV. Recent data have suggested that 50% of patients with a complete response to dCRT will experience tumor recurrence,[33] with a survival benefit for upfront surgery.[7] Other studies support a strategy of surveillance with selective surgery for patients with residual or recurrent disease.[34] There is an urgent need for data on randomly assigning patients with a complete clinical response to either immediate surgery or surveillance with salvage surgery on demand.

Persistent disease after CRT was associated with poorer long-term prognosis compared with recurrent disease, which may suggest persistent cancer is associated with more aggressive and resistant tumor biology. Identification of tumors not responding to CRT to allow early surgical treatment is clearly an important area for future investigation. Some authors have used positron emission tomography scanning at 2 weeks after initiation of chemotherapy[35]; however, the validity of this approach in the setting of CRT remains unknown.

Table 5. Review of Published Literature of Short-Term Outcomes After SALV Versus NCRS

Study	SALV Radiation Dose (Gy)	Patients		Postoperative Mortality		Anastomotic Leak		Pulmonary Complications	
		SALV	NCRS	SALV	NCRS	SALV	NCRS	SALV	NCRS
Chao et al,[22] No. (%)	30	27 (12.4)	191 (87.6)	6 (22.2)	15 (7.9)	4 (14.8)	2 (1.0)	9 (33.3)	22 (11.5)
Marks et al,[23] No. (%)		65 (50)	65 (50)	2 (3.1)	3 (4.6)	12 (18.5)	12 (18.5)	15 (23.1)	12 (18.5)
Mean	50								
SD	4								
Miyata et al,[24] No. (%)		33 (22.8)	112 (77.2)	5 (15.2)	4 (3.6)	13 (39.4)	25 (22.3)	10 (30.3)	25 (22.3)
Median	> 50								
Range	50 to 68								
Morita et al,[25] No. (%)		27 (10.8)	197 (89.2)	2 (7.4)	4 (2.0)	10 (37.0)	46 (23.4)	8 (29.6)	29 (14.7)
Range	60 to 90								
Nakamura et al,[26] No. (%)		27 (49.1)	28 (50.9)	2 (7.4)	1 (3.6)	6 (22.2)	3 (10.7)	6 (22.2)	4 (14.3)
Median	60								
Range	50 to 76								
Smithers et al,[27] No. (%)	60	14 (20.9)	53 (79.1)	1 (7.1)	0 (0)	2 (14.3)	4 (7.5)	8 (57.1)	16 (30.2)
Takeuchi et al,[28] No. (%)		25 (38.5)	40 (61.5)	2 (8.0)	2 (5.0)	6 (24.0)	10 (25.0)	11 (44.0)	10 (25.0)
Median	60								
Range	50 to 60								
Tomimaru et al,[29] No. (%)		24 (48.0)	26 (52.0)	3 (12.5)	0 (0)	5 (20.8)	2 (7.7)	5 (20.8)	3 (11.5)
Mean	62								
SD	6								
Total, No. (%)		242 (25.4)	712 (74.6)	23 (9.5)	29 (4.1)	58 (24.0)	103 (14.5)	72 (29.8)	121 (17.0)

Abbreviations: NCRS, neoadjuvant chemoradiotherapy followed by planned esophagectomy; SALV, salvage esophagectomy after definitive chemoradiotherapy; SD, standard deviation.

There are some limitations in our study. As a retrospective multicenter database study, the results generated are dependent on the reliability of data collection. To minimize any bias, an independent monitoring team audited data capture to minimize missing data and control concordance, as well as ensure inclusion of consecutive patients. Despite analysis and control for many important factors that can influence oncologic outcome, there are inevitably other confounding variables (measured or unmeasured) that cannot be ruled out, even after propensity score adjustment. The unknown influence of medical comorbidities on selection for salvage esophagectomy is an important limitation. Regarding the study sample size and the low incidence in several outcomes, we could not rule out that some differences could have been overlooked because of the lack of adequate statistical power. In a posterior power calculation, we calculated, for the main comparison, the smallest significant between-group difference (expressed as effect size using OR) that our study sample size allowed us to detect with 80% power. Assuming an incidence of outcome of 10% and 50% in the reference group, we could detect an OR of 2.56 and 1.59 (or 0.39 and 0.63 for protective effects), respectively, with 308 patients per group. We did not adjust for multiple comparisons, given the exploratory nature of the research; therefore, we could not exclude false-positive findings. We cannot comment on the outcomes of patients with cancer recurrence who did not benefit from SALV because of poor physiologic status or advanced-tumor disease. However, previously published European data highlight that nonresponders to CRT who do not receive surgery have a poor 3-year survival of 9.4%.[36] Furthermore, data from a large-volume institution included in our study showed that even in patients with a complete clinical response (25%) to CRT, 5-year survival was only 33.4%, with a high locoregional recurrence rate of 46.7%.[7] A recent study suggested approximately only one third of patients with locoregional recurrence will undergo salvage treatment, with a vastly improved median overall survival compared with those who do not (58.6 *v* 9.5 months).[33] Some patients receiving NCRS may have experienced toxic adverse effects and prolonged delay before undergoing surgery, leading to homogenization of the groups. However, we believe this effect to be minimal, given the mean delay (± SD) between the end of CRT and surgery was 1.6 ± 0.5 months in the NCRS group and 5.5 ± 2.3 months in the SALV group.

In conclusion, our results suggest that SALV after dCRT can be performed in experienced esophageal cancer centers with low mortality and morbidity rates and result in good survival. Persistent tumors after CRT seem to have poorer survival prognosis than recurrent tumors. There remains an urgent need for randomized controlled trials comparing patients with a complete clinical response to CRT allocated to surgery or surveillance.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

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Therapeutic Strategy

All patients were evaluated by a multidisciplinary team and treated with curative intent according to French national guidelines.[18] These guidelines propose either neoadjuvant chemoradiotherapy (CRT) or definitive CRT for locally advanced squamous cell carcinomas even in operable patients according to center expertise and following the publication of the FFCD (Fédération Francophone de Cancérologie Digestive) 9102 trial.[11]

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

For definitive CRT, generally patients were scheduled to receive two cycles of fluorouracil (1,000 mg/m^2 every 24 hours over 4 days) and cisplatin (75 mg/m2 every 24 hours over 1 day), in combination with concomitant radiotherapy (50.4 Gy over 5 weeks) and at discretion two adjuvant cycles of chemotherapy. All patients underwent standardized radiotherapy; gross tumor volume was determined on the basis of clinical examination, planning computed tomography, endoscopy, and endoscopic ultrasonography. All patients were treated with conformational three-dimensional radiotherapy, with x-ray $>$ 6 MV. Dose distribution was calculated by treatment planning system. Portal imaging was made once per week.

Surgical Complications

Anastomotic leak was defined as any esophagogastric anastomosis dehiscence that was clinically symptomatic (abscess, mediastinitis, digestive liquid externalizing drainage) or asymptomatic detected by contrast study. In case of doubt, diagnosis was confirmed by gastroscopy without insufflation performed by an experienced physician. Surgical site infection was defined as superficial pus expressed

from the abdominal or thoracic or drain incision sites, requiring surgical debridement and antibiotic treatment. Chylothorax was suspected when major pleural effusion was seen in the first postoperative week on resumption of feeding and was defined by the presence of pleural or abdominal fluid, rich in chylomicrons and lymphocytes. Postoperative hemorrhage was defined as blood loss requiring endoscopic or surgical intervention. Gastoparesis was defined by the occurrence of vomiting after removal of the nasogastric tube or distension of the gastric conduit on plain radiograph after day 5 postoperatively, requiring repositioning of the nasogastric tube despite prokinetic treatment.

Medical Complications

Pulmonary complications included bronchial congestion, disorders of ventilation, atelectasis, pneumonia, respiratory failure, and acute respiratory distress syndrome. Cardiovascular complications included angina, myocardial infarction, arrhythmia, and cardiac insufficiency. Thromboembolic complications included deep venous thrombosis and pulmonary embolism. Neurologic complications included temporospatial disorientation, transient ischemic attack, and cerebrovascular accident.

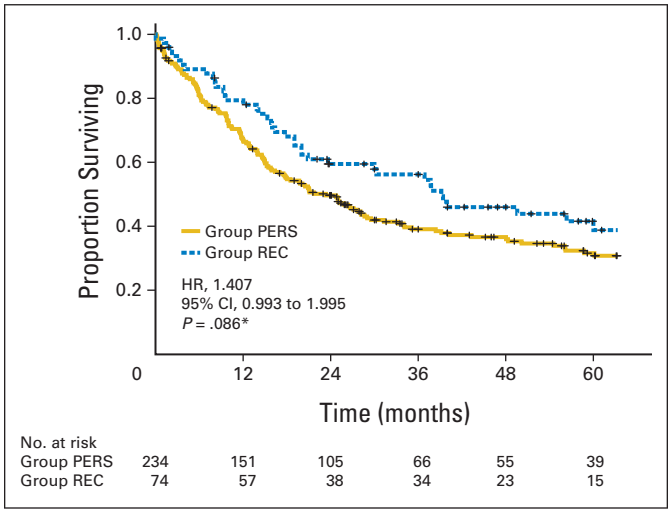

Fig A1. Comparison of overall survival in salvage surgery patients for persistent (PERS) and recurrent (REC) esophageal cancer groups. No. of patients at risk in each interval is shown in table at bottom of graph. HR, hazard ratio. (*) *P* value and HR calculated using Cox regression model adjusted for propensity score.