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Salvage Surgery for Esophageal Cancer: How to Improve Outcomes?

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ABSTRACT

Background. Locoregional recurrence rates after definitive chemoradiotherapy (dCRT) for locally advanced esophageal cancer (EC) are high. Salvage surgery (SALV) is considered the best treatment option in case of persistent or recurrent disease for operable patients, but SALV has been associated with increased morbidity and mortality. The aim of this study is to identify factors linked to outcomes after SALV to better select candidates and to optimize perioperative care.

Study Design. We retrospectively analyzed data from 308 consecutive SALV patients from a large multicenter European cohort. Univariate and multivariate analyses were performed to identify factors associated with in-hospital postoperative morbidity, anastomotic leakage (AL), and overall survival (OS).

Results. The in-hospital postoperative mortality and morbidity rates were 8.4 and 34.7%, respectively. Squamous cell histology ($p = 0.040$) and radiation dose $\geq$ 55 Gy ($p = 0.047$) were independently associated with major morbidity. The AL rate was 12.7%, and cervical anastomosis was independently associated with AL ($p = 0.002$). OS at 5 years was 34.0%. Radiation dose $\geq$ 55 Gy ($p = 0.003$), occurrence of postoperative complications ($p = 0.006$), ypTNM stage 3 ($p = 0.019$), and positive surgical margins ($p < 0.001$) were linked to poor prognosis.

Conclusions. SALV is a valuable option for patients with persistent or recurrent disease after dCRT and offers long-term survival. Factors such as radiation dose and anastomosis location identified here will help to optimize outcomes after SALV, which may be considered a standard treatment in the EC therapeutic armamentarium.

Collaborators of the FREGAT (French Eso-Gastric Tumors working group) – FRENCH(Fédération de Recherche en Chirurgie) – AFC (Association Française de Chirurgie) Working Groups are listed in "Acknowledgment".

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Esophageal cancer (EC) is the seventh leading cause of cancer-related death in the US male population.[1] Surgery is frequently combined with neoadjuvant chemo(radio)therapy, and is associated with significant morbidity and mortality.[2] Randomized trials have shown an equivalent 2-year survival rate in patients with esophageal squamous cell carcinoma treated by

neoadjuvant chemoradiotherapy plus surgery or definitive chemoradiotherapy (dCRT).[3,4] European Society of Medical Oncology (ESMO) and French guidelines state that dCRT without surgery is an alternative to neoadjuvant chemoradiotherapy plus surgery for locally advanced squamous cell carcinoma.[5,6] However, locoregional control is poor after dCRT, with locoregional recurrence rates ranging from 27 to 83%.[7] Salvage surgery (SALV) appears to be a promising curative therapeutic option in case of persistent or recurrent disease without distant metastasis. SALV was found to be associated with increased mortality, morbidity, and anastomotic leak (AL) in a recent metaanalysis of 11 retrospective studies involving a total of 563 SALV patients.[8] A study showed that 5-year survival rates ranged from 25 to 35%.[9]

Available data regarding SALV are derived from small retrospective series. Because SALV may have an increasing role in the EC therapeutic armamentarium, improving outcomes is a major issue. The aim of this study is to identify factors associated with postoperative mortality, morbidity, and survival in a large multicenter European cohort of patients treated with SALV.

METHODS

Study Population

We retrospectively collected data from 2944 consecutive adult patients undergoing surgical resection for biopsy-proven EC (including Siewert type I and II junctional tumors) with curative intent in 30 French-speaking European centers between January 2000 and December 2010. All data were collected through a dedicated website (http://www.chirurgie-viscerale.org). An independent monitoring team audited the data capture to minimize lost data and to control concordance and the inclusion of consecutive patients. Missing or inconsistent data were obtained via e-mail exchanges or telephone calls. We selected patients who had undergone dCRT and then SALV for persistent or recurrent esophageal adenocarcinoma (ADC) or squamous cell carcinoma (SCC) ($n = 308$).

The study was approved by the regional institutional review board on 15 July 2013. The database was registered on the Clinicaltrials.gov website under the identifier NCT 01927016.

Therapeutic Strategy

The pretreatment investigations were standard and followed national guidelines[6] that are reported elsewhere.[10] The cTNM was based on endoscopic ultrasonography and/or computed tomography (CT) scan and was completed by positron emission tomography (PET) scan in several patients. All patients were evaluated by a multidisciplinary team and treated with curative intent with either neoadjuvant chemoradiotherapy plus surgery or dCRT to treat locally advanced squamous cell carcinoma in operable patients following the publication of the FFCD9102 trial.[4] The dCRT patients, included in the present study, were scheduled to receive a combination of 5-fluorouracil (800–1000 mg/m^2) from day 1 to 4 and a platinum-based regimen (cisplatin 75–100 mg/m^2 or oxaliplatin 75–85 mg/m^2 day 1) for two to four cycles. The chemotherapy was given with concomitant radiotherapy (50.4 Gy over 5 weeks) and two adjuvant cycles of chemotherapy at the physician's discretion. After dCRT, patients were restaged based on clinical evaluation combined with endoscopy with biopsies and CT scan.

SALV was defined as removal of the esophagus for persistent or recurrent disease within the tumor and/or the locoregional lymph node after dCRT. Tumor persistence was defined as presence of cancer on endoscopic or radiologic investigation with histologic confirmation within 3 months of dCRT. Tumor recurrence was defined as presence of cancer within the tumor or locoregional nodes 3 months after dCRT. Follow-up included clinical examination, upper endoscopy with biopsies, and thoracoabdominal CT scan every 3 months for the first year and every 6 months for 4 additional years. Other examinations such as PET scan were performed on demand. Details of the surgical resection have been described elsewhere.[11]

Data Collection

Demographic data related to the patients and the tumors were collected, and complications were defined based on the definitions used in the MIRO trial.[12] The Clavien–Dindo scale was used to grade the severity of postoperative morbidity, and only complications with Clavien–Dindo score $\geq$ III were reported.[13] Histological tumor staging was based on the seventh edition of the Union Internationale Contre le Cancer/TNM classification.[14] Tumor resection was designated R0 when removal was complete both macroscopically and microscopically. Resection was considered R1 in cases with microscopically positive resection margins, and R2 in cases with macroscopically positive resection margins.

Study Endpoints

The primary endpoint was to identify independent factors associated with in-hospital postoperative morbidity. The secondary objectives included identification of factors associated with AL and overall survival (OS).

Statistical Analysis

Data are expressed as prevalence (percentage), mean (± standard deviation), median (range), and median survival (95% confidence interval). Student *t* test or Mann–Whitney *U*-test was used for intergroup comparisons of continuous data. χ^2 test or Fisher's exact test was used to compare categorical data. Binary logistic regression was used to identify predictors for postoperative morbidity and AL. Survival estimates were calculated by Kaplan–Meier method from day of SALV, and log-rank test was used to compare survival curves. Patient survival status was ascertained in May 2012. Follow-up was complete in all cases, and median follow-up was 52.7 (1.8–145.4) months for survivors. A Cox regression model was used to identify predictors of mortality. Variables with $p < 0.10$ on univariate analysis were integrated in the multivariate model. All tests were two-sided, and the threshold for statistical significance was $p < 0.050$. Statistical analysis was performed using SPSS® version 19.0 software (SPSS, Chicago, IL, USA).

RESULTS

Demographics of the Study Population

Study population characteristics ($n = 308$) are summarized in Table 1. Median patient age at surgery was 59 (26–81) years. The male/female ratio was 5.3/1. The tumors were mostly locally advanced (64.6% cTNM stage III/IV) and located at the lower two-thirds of the esophagus (80.8%). The majority of tumors were SCC (62.7%). The median radiation dose was 50 (25–75) Gy, and 17.5% of patients received ≥ 55 Gy. The patients received a median of 2 (1–20) cycles of chemotherapy. The median delay from dCRT completion to SALV was 8.6 (1–45) months, being 2 (1–4) months in the persistent group and 10 (3–45) months in the recurrence group. Transthoracic surgical approach was the most frequent procedure (93.8%), and R0 resection was obtained in 87.3% of cases. The median number of resected lymph nodes was 14 (1–49), and the mean number of invaded nodes was 1.1 ± 2.0.

Primary Endpoint: Factors Associated with in-Hospital Postoperative Morbidity

The 30-day and in-hospital postoperative mortality rates were 6.2 and 8.4%, respectively. The in-hospital postoperative morbidity rate was 34.7% (Table 2). The results of univariate analysis are presented in Table 1. Multivariate analysis revealed that SCC histology [odds ratio (OR) 1.89, 95% confidence interval (CI) 1.03–3.47, $p = 0.040$] and radiation dose ≥ 55 Gy (OR 1.96, 95% CI 1.01–3.79, $p = 0.047$) were independently associated with in-hospital postoperative morbidity (Table 1).

Factors Associated with Anastomotic Leakage

AL was diagnosed in 39 patients (12.7%). The results of univariate analysis are presented in Table 3. Multivariate analysis showed that cervical location of the anastomosis (OR 3.54, 95% CI 1.57–7.95, $p = 0.002$) was independently associated with AL.

Factors Associated with Overall Survival

Median OS was 25.9 (18.7–32.9) months, and the 3- and 5-year OS rates were 43.3 and 34.0%, respectively. The patients with R0 resection had median OS of 30.2 (21.9–38.6) months. The 3- and 5-year OS rates of R0 patients were 48.0 and 38.0%, respectively. The OS was 6.3 (2.8–9.7) months after R1/R2 resection. The 3- and 5-year OS rates of R1/R2 patients were 10.8 and 5.4%, respectively ($p < 0.001$). Comparison of SALV for persistent versus recurrent disease revealed median OS rates of 23.3 and 39.1 months, respectively. The 3-year OS rates were 39.1 and 56.2%, respectively. The 5-year OS rates were 31.6 and 41.6%, respectively ($p = 0.054$). The following factors were associated with OS: American Society of Anesthesiologists (ASA) score ($p < 0.001$), cTNM stage ($p = 0.039$), radiation dose ($p = 0.029$), postoperative complication ($p < 0.001$), ypTNM stage ($p < 0.001$), and surgical margins ($p < 0.001$) (Table 4). Multivariate analysis showed that the poor prognosis factors were radiation dose ≥ 55 Gy [hazard ratio (HR) 1.80, 95% CI 1.22–2.64, $p = 0.003$], occurrence of postoperative complications (HR 1.64, 95% CI 1.15–2.34, $p = 0.006$), ypTNM stage 3 (HR 2.10, 95% CI 1.28–4.98, $p = 0.019$), and R1 (HR 2.03, 95% CI 1.18–3.50) or R2 (HR 4.55, 95% CI 2.10–9.89) resection ($p < 0.001$).

Subgroup Analysis of Patients Receiving Radiation Dose ≥ 55 Gy

The patients receiving radiation dose greater or less than 55 Gy were comparable in terms of demographic information and tumor parameters (data not shown). However, when we compared patients receiving radiation dose < 55 Gy with patients treated with ≥ 55 Gy, we found the following results for high-radiation patients: increased in-hospital postoperative mortality rate (27.8% vs. 4.3%, $p < 0.001$), increased in-hospital postoperative morbidity rate (51.9% vs. 31.1%, $p = 0.004$), increased AL rate (20.4% vs. 11.0%, $p = 0.061$), increased AL-related death (54.5% vs. 14.3%, $p = 0.017$), similar R0 resection rate

TABLE 1 Factors influencing in-hospital postoperative morbidity after salvage esophagectomy

Factor	Study population ($n = 308$) (%)	No postoperative complication Clavien > II ($n = 201$) (%)	Postoperative complication Clavien > II ($n = 107$) (%)	p-value univariate	OR (95% CI)	p-value multivariate
Age						
< 60 years	135 (43.8)	89 (44.3)	46 (43.0)	0.828		
≥ 60 years	173 (56.2)	112 (55.7)	61 (57.0)			
Gender						
Male	259 (84.1)	170 (84.6)	89 (83.2)	0.749		
Female	49 (15.9)	31 (15.4)	18 (16.8)			
ASA score						
I	43 (14.0)	34 (16.9)	9 (8.4)	0.066		0.128
II	182 (59.1)	118 (58.7)	64 (59.8)			
III	79 (25.6)	48 (23.9)	31 (29.0)			
IV	4 (1.3)	1 (0.5)	3 (2.8)			
Esophageal tumor location						
Upper third	59 (19.2)	33 (16.4)	26 (24.3)	0.043		0.876
Middle third	126 (40.9)	78 (38.8)	48 (44.9)			
Lower third	123 (39.9)	90 (44.8)	33 (30.8)			
cTNM stage						
I	17 (5.5)	13 (6.5)	4 (3.7)	0.071		0.083
II	92 (29.9)	55 (27.3)	37 (34.6)			
III	190 (61.7)	130 (64.7)	60 (56.1)			
IV	9 (2.9)	3 (1.5)	6 (5.6)			
Radiation dose						
< 55 Gy	254 (82.5)	175 (87.1)	79 (73.8)	0.004	1	0.047
≥ 55 Gy	54 (17.5)	26 (12.9)	28 (26.2)		1.96 (1.01–3.79)	
Indication for salvage						
Persistence	234 (76.0)	150 (74.6)	84 (78.5)	0.448		
Recurrence	74 (24.0)	51 (25.4)	23 (21.5)			
Surgical procedure						
Ivor–Lewis	216 (70.1)	153 (76.1)	63 (58.9)	0.004		0.075
Three-field	73 (23.7)	36 (17.9)	37 (34.6)			
Transhiatal	19 (6.2)	12 (6.0)	7 (6.5)			
Histology						
ADC	115 (37.3)	88 (43.8)	27 (25.2)	0.001	1	0.040
SCC	193 (62.7)	113 (56.2)	80 (74.8)		1.89 (1.03–3.47)	
ypTNM stage						
0	68 (22.1)	47 (23.4)	21 (19.6)	0.151		
I	62 (20.1)	43 (21.4)	19 (17.8)			
II	84 (27.3)	54 (26.9)	30 (28.0)			
III	86 (27.9)	55 (27.3)	31 (29.0)			
IV	8 (2.6)	2 (1.0)	6 (5.6)			
Surgical margins						
R0	269 (87.3)	180 (89.5)	89 (83.2)	0.109		
R1/R2	39 (12.7)	21 (10.5)	18 (16.8)			

ASA American Society of Anesthesiologists, *cTNM* clinical tumor node metastasis classification, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *ypTNM* pathological tumor node metastasis classification after chemoradiation, *OR* odd ratio, *95% CI* 95% confidence interval. Only grade III and higher postoperative complications were recorded

TABLE 2 Details of in-hospital postoperative morbidity after salvage esophagectomy

Variable	Study population ($n = 308$) (%)
Death	26 (8.4)
Surgical complication	
Anastomotic leakage	39 (12.7)
Conduit necrosis	4 (1.3)
Surgical-site infection	42 (13.6)
Chylothorax	9 (2.9)
Postoperative bleeding	3 (1.0)
Gastroparesis	3 (1.0)
Medical complication	
Pulmonary	78 (25.3)
Cardiovascular	26 (8.4)
Thromboembolic	7 (2.5)
Neurologic	5 (1.6)

(85.2% vs. 87.8%, $p = 0.600$), and shorter median OS (11.7 vs. 28.2 months, $p = 0.029$).

DISCUSSION

SALV is an important issue in the field of EC multimodal management because it may represent a promising curative therapeutic option for patients with persistent or recurrent locoregional disease after dCRT. Previously, patients were directed to palliative chemotherapy, but SALV may offer a cure to well-selected patients. In published series, median survival of resected patients varied from 12.1 to 33.3 months. They had high rates of morbidity (27–77%), AL (6.0–39.0%), and mortality (3.1–22.2%) (Table 5).[15–37]

A comparison of this same cohort and a cohort with planned neoadjuvant chemotherapy, published by Markar et al. in 2015, showed equivalent in-hospital mortality, but higher rates of anastomotic leakage and operative-site infection after SALV.[43] It seems essential to identify factors that impact outcomes after SALV to better select candidates and to optimize perioperative care.

We report this cohort of 308 SALV from a multicenter experience with homogeneous data collection based on standardized definitions of complications and SALV.

SALV provided 5-year OS of 34%, which increased to 38% after R0 resection. There are several already well-known factors for poor prognosis, such as locally advanced disease and incomplete tumor resection.[38] Additionally, occurrence of a postoperative complication graded Clavien–Dindo $\geq$ III (HR 1.64, 95% CI 1.15–2.34, $p = 0.006$) and radiation dose $\geq$ 55 Gy (HR 1.96, 95% CI 1.01–3.79, $p = 0.047$) were associated with poor prognosis.

High radiation dose was also independently associated with postoperative morbidity and was responsible for higher postoperative mortality and AL rates.

Median radiation dose was 50 Gy in the SALV group, substantially lower than in the majority of published studies (Table 5). This difference may explain the 34.7% rate of major postoperative morbidity, which is similar to rates reported after neoadjuvant chemoradiation.[37,39,43] Of the 54 patients treated with radiation dose $\geq$ 55 Gy, 51.8% experienced severe postoperative morbidity. The cut-off value of 55 Gy was chosen based on previous report.[16] It should be noted that, presently, there is no published evidence to support high radiation dose $>$ 50 Gy in patients receiving dCRT. A phase III trial published in 2002 showed no significant advantage of 64.8 Gy compared with a 50-Gy dCRT regimen with respect to median survival (13 vs. 18.1 months) or locoregional control of the disease.[40] This result suggests 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, as recommended by National Comprehensive Cancer Network (NCCN) guidelines.[41] An ongoing phase II trial is testing the impact of an escalation dose of radiotherapy up to 66 Gy on the primary tumor and nodes in locally advanced or inoperable carcinoma of the esophagus (NCT 01348217). The rationale for this approach is that most toxicity-related deaths in the experimental high-dose arm of the INT-0123 phase III trial occurred $<$ 50 Gy and that RT techniques have evolved since the publication of Minsky.[40] While waiting for those results, it seems that no radiation dose $>$ 50 Gy should be offered outside of prospective studies based on currently published data.

The major AL ($>$ II) rate was 12.7% in the present study and was independently associated with cervical anastomosis location. Cervical anastomosis is a well-known risk factor[39] of AL, but it is usually considered of lower severity compared with thoracic leakage. Our results do not support this statement. Systematic placement of the anastomosis in the neck to prevent severe AL after SALV is not a way to lower major morbidity. The AL rate within the thorax is similar to rates reported after neoadjuvant chemoradiation or primary surgery.[42] The choice of the location of the anastomosis has to be made based on tumor site and not preferably in the neck. The AL rate was higher in patients receiving radiation dose $\geq$ 55 Gy than in patients receiving $<$ 55 Gy (20.4% vs. 11.0%, $p = 0.061$). AL-related death rates were 54.5% after $<$ 55 Gy versus 14.3% after $\geq$ 55 Gy ($p = 0.017$). These findings support the reported higher postoperative morbidity rate and

TABLE 3 Risk factors for anastomotic leakage (AL) after salvage esophagectomy

Variable	Study population ($n = 308$) (%)	No AL ($n = 269$) (%)	AL ($n = 39$) (%)	p-value univariate	OR (95% CI)	p-value multivariate
Age						
< 60 years	135 (43.8)	118 (43.9)	17 (43.6)	0.558		
≥ 60 years	173 (56.2)	151 (56.1)	22 (56.4)			
Gender						
Male	259 (84.1)	228 (84.8)	31 (79.5)	0.400		
Female	49 (15.9)	41 (15.2)	8 (20.5)			
ASA score						
I	43 (14.0)	40 (14.9)	3 (7.7)	0.544		
II	182 (59.1)	157 (58.3)	25 (64.1)			
III	79 (25.6)	68 (25.3)	11 (28.2)			
IV	4 (1.3)	4 (1.5)	0 (0.0)			
Esophageal tumor location						
Upper third	59 (19.2)	46 (17.1)	13 (33.3)	0.019		0.841
Middle third	126 (40.9)	109 (40.5)	17 (43.6)			
Lower third	123 (39.9)	114 (42.4)	9 (23.1)			
cTNM stage						
I	17 (5.5)	14 (5.2)	3 (7.7)	0.484		
II	92 (29.9)	78 (29.0)	14 (35.9)			
III	190 (61.7)	170 (63.2)	20 (51.3)			
IV	9 (2.9)	7 (2.6)	2 (5.1)			
Radiation dose						
< 55 Gy	254 (82.5)	226 (84.0)	28 (71.8)	0.061		0.353
≥ 55 Gy	54 (17.5)	43 (16.0)	11 (28.2)			
Indication for salvage						
Persistence	234 (76.0)	207 (76.9)	27 (69.2)	0.292		
Recurrence	74 (24.0)	62 (23.1)	12 (30.8)			
Anastomosis level						
Cervical	92 (29.9)	69 (25.6)	23 (59.0)	< 0.001	3.54 (1.572–7.952)	0.002
Thoracic	216 (70.1)	200 (74.4)	16 (41.0)		1	
Histology						
ADC	115 (37.3)	106 (39.4)	9 (23.1)	0.049		0.514
SCC	193 (62.7)	163 (60.6)	30 (76.9)			
ypTNM stage						
0	68 (22.1)	65 (24.2)	3 (7.7)	0.164		
I	62 (20.1)	53 (19.7)	9 (23.1)			
II	84 (27.3)	73 (27.1)	11 (28.2)			
III	86 (27.9)	72 (26.8)	14 (35.9)			
IV	8 (2.6)	6 (2.2)	2 (5.1)			
Surgical margins						
R0	269 (87.3)	236 (87.7)	33 (84.6)	0.584		
R1/R2	39 (12.7)	33 (12.3)	6 (15.4)			

ASA American Society of Anesthesiologists, *cTNM* clinical tumor node metastasis classification, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *ypTNM* pathological tumor node metastasis classification after chemoradiation, *OR* odd ratio, *95% CI* 95% confidence interval. Only grade III and higher postoperative complications were recorded

TABLE 4 Factors influencing overall survival (OS) after salvage esophagectomy

Variable	Median OS in Months (95% CI)	χ^2	*p*-value univariate	HR (95% CI)	*p*-value multivariate
Age					
< 60 years	26.4 (18.5–34.2)	1.094	0.296		
≥ 60 years	25.0 (11.9–38.1)				
Gender					
Male	27.6 (17.4–37.9)	0.012	0.914		
Female	24.7 (17.8–31.7)				
ASA score					
I	27.7 (15.5–39.7)	23.200	< 0.001		0.533
II	28.6 (17.5–39.7)				
III	19.0 (9.7–28.3)				
IV	0.2 (0–3.0)				
Tumor location					
Upper third	37.7 (21.9–53.5)	5.533	0.063		0.387
Middle third	21.0 (12.2–29.8)				
Lower third	27.6 (12.4–29.8)				
cTNM stage					
I	43.3 (29.0–57.5)	8.339	0.039		0.524
II	30.0 (12.5–47.9)				
III	25.0 (19.7–30.2)				
IV	13.9 (3.5–24.4)				
Radiation dose					
< 55 Gy	28.2 (18.6–37.7)	4.746	0.029	1	0.003
≥ 55 Gy	11.7 (0.4–22.9)			1.80 (1.22–2.64)	
Indication for salvage					
Persistence	23.3 (17.2–29.4)	3.724	0.054		0.516
Recurrence	39.1 (20.3–57.9)				
Surgical procedure					
Ivor–Lewis	26.4 (17.7–35.1)	0.634	0.728		
Three-field	24.7 (14.0–35.3)				
Transhiatal	30.0 (1.4–58.5)				
Postoperative complication					
No	33.2 (21.8–44.7)	12.741	< 0.001	1	0.006
Yes	13.7 (9.7–17.6)			1.64 (1.15–2.34)	
Anastomotic leakage					
No	27.7 (20.1–35.2)	3.033	0.082		0.615
Yes	12.0 (8.6–15.5)				
Histology					
ADC	25.0 (17.0–33.0)	1.824	0.177		
SCC	26.4 (13.9–38.8)				
ypTNM stage					
0	83.6 (27.2–139.9)	53.731	< 0.001	1	0.019
I	43.3 (28.5–58.0)			1.13 (0.68–1.87)	
II	24.9 (13.5–36.4)			1.36 (0.85–2.17)	
III	15.5 (10.0–20.6)			2.10 (1.28–4.98)	
IV	3.0 (0–7.6)			1.57 (0.49–4.98)	
Quality of resection					
R0	30.2 (21.9–38.6)	61.179	< 0.001	1	< 0.001
R1	11.7 (3.7–19.7)			2.03 (1.18–3.50)	
R2	5.2 (4.0–6.4)			4.55 (2.10–9.89)	

ASA American Society of Anesthesiologists, *cTNM* clinical tumor node metastasis classification, *ADC* adenocarcinoma, *SCC* squamous cell carcinoma, *ypTNM* pathological tumor node metastasis classification after chemoradiation, *OR* odd ratio, *95% CI* 95% confidence interval. Only grade III and higher postoperative complications were recorded

TABLE 5 Reported experiences of outcomes after salvage esophagectomy in literature

Author	Study period	Patients (n)	Radiation dose (Gy)	Morbidity (%)	Mortality (%)	AL (%)	Median OS (months)	R0 resection (%)
Akutsu[15]	01–12	12	67	38.0	–	–	24.3	–
Borghesi[16]	99–05	10	54	40.0	–	20.0	21.5	30.0
Yoo[17]	03–10	12	41–66	42.0	–	8.0	–	66.7
Chao[18]	97–04	27	30	48,1	22.2	14.8	12.1	62.9
Chen[19]	96–05	51	54–64	27.0	–	6.0	14	80.3
D'Journo[20]	96–06	24	50–75	> 50	20.8	30.0	–	87.5
Farinella[21]	06–14	16	57.7	43	0	25	–	81
Marks[22]	97–10	65	50.4	35.4	3.1	18.5	32	90.8
Miyata[23]	94–07	33	59.8	> 40	12.1	39.0	–	87.8
Morita[24]	94–09	27	> 60	59.3	7.4	37.0	33.3	70.4
Nakamura[25]	92–02	27	50–76	52.0	7.4	22.2	–	66.6
Oki[26]	94–05	14	> 60	50.0	–	28.6	–	50.0
Piessen[27]	94–04	98	30–46	32.7	3.1	7.1	14.2	62.2
Pinto[28]	99–06	15	30–45	71.0	0	13.3	16.4	93.3
Schieman[29]	90–05	12	30–72	41.6	8.0	17.0	21	83.3
Smithers[30]	88–05	14	60	78.6	7.1	14.3	13	–
Sohda[31]	98–15	40	50.4–70	50	5	20	24	75
Swisher[32]	87–00	13	56.7	77.0	15.4	38.5	7	61.5
Tachimori[33]	00–06	59	> 60	–	8.5	30.5	26	84.7
Takeuchi[34]	96–08	25	50–60	–	8.0	24.0	24	80.0
Tomimaru[35]	85–04	24	> 60	50.0	12.5	20.8	–	66.7
Wang[36]	99–12	104	50–70	–	9.0	–	–	–
Watanabe[37]	88–13	63	50–70	65.1	7.9	–	–	73
Markar[43]	00–10	308	50	63.6	8.4	17.2	25.9	87.3

– Not reported, *AL* anastomotic leakage, *OS* overall survival

suggest that this increased risk should be considered before delivering radiation dose $\geq$ 55 Gy.

There are some limitations to this study. As a retrospective multicenter database study, the results generated are dependent on the reliability of data collection. To minimize any data bias, we employed an independent monitoring team that audited data capture to minimize missing data and control concordance. The monitoring team also ensured inclusion of consecutive patients. We cannot comment on the outcomes of patients with cancer recurrence who did not benefit from SALV because of poor physiologic status or advanced tumors. However, previously published data highlight that nonresponders to chemoradiation who did not receive surgery have poor median survival of 5.5 months.[44]

CONCLUSIONS

These findings suggest that SALV is a valuable option for patients with persistent or recurrent disease after definitive chemoradiation. SALV offers long-term survival with acceptable postoperative outcomes. However, the dose of radiation received is a major concern, since higher radiation doses, in excess of 55 Gy, were associated with poorer outcomes.

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