Journal of Gastrointestinal Surgery (2019) 23:11–22
https://doi.org/10.1007/s11605-018-3958-8

2018 SSAT PLENARY PRESENTATION

Outcomes of Radiation-Associated Esophageal Squamous Cell Carcinoma: The MSKCC Experience

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Received: 4 June 2018 / Accepted: 29 August 2018 / Published online: 13 September 2018

Abstract

Objective Esophageal squamous cell carcinoma (ESCC-R) is a rarely encountered sequela of chest radiation. Treatment is limited by toxicity with reirradiation and complex surgical dissection in a previously radiated field. The clinical presentation, prognosis, and treatment selection of ESCC-R remain undefined.

Methods A retrospective review of patients with esophageal squamous cell carcinoma at a single institution between 2000 and 2017 was performed to identify patients with previous radiation therapy (≥ 5 years delay). Clinicopathologic characteristics, treatment, and outcomes of ESCC-R ($n = 69$) patients were compared to patients with primary esophageal squamous cell carcinoma (ESCC) ($n = 827$). Overall survival (OS) and cumulative incidence of recurrence (CIR) were compared using log-rank and Gray's tests, respectively.

Results Median time from radiation to ESCC-R was 18.2 years. The majority of ESCC-R patients were female and presented with earlier disease and decreased behavioral risk factors. ESCC-R treated with surgery alone had worse OS than ESCC (5-year 15 vs 33%; $p = 0.045$). Patients with ESCC-R who received neoadjuvant treatment had higher risk of postoperative in-house mortality (16.7 vs 4.2%; $p = 0.032$). Patients with ESCC-R treated with surgery alone and definitive chemoradiation had higher recurrence risk than those with neoadjuvant + surgery (5-year recurrence 55 and 45 vs 15%; $p = 0.101$).

Conclusion Neoadjuvant chemotherapy or chemoradiation should be used whenever possible for ESCC-R as it is associated with lower risk of recurrence. The improved survival benefits of aggressive treatment must be weighed against the higher associated postoperative risks.

Keywords Esophageal squamous cell carcinoma · Reirradiation · Treatment selection · Neoadjuvant therapy

Introduction

Increasing use of radiotherapy has resulted in improved survival for many cancer types, and consequently, the number of cancer survivors with a history of radiation exposure is rising.[1,2] The observed survival benefits associated with radiation must be weighed against the risks associated with this treatment.[3–5] Esophageal squamous cell carcinoma (ESCC-R) arising in a previously radiated field has been previously described as a rare long-term sequela following treatment of diseases of the neck and mediastinum, such as breast cancer and lymphoma.[6–8] The literature is predominantly limited to large epidemiologic studies, and the clinical presentation, tumor behavior, and optimal treatment of this disease remain largely undefined.

Presented at the Digestive Disease Week, Washington, DC: June 5th, 2018.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-018-3958-8) contains supplementary material, which is available to authorized users.

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Previous studies have suggested that development of ESCC-R is dependent on radiation dose and time, with the risk of disease increasing significantly at 10 years after initial treatment.[8–10] Locally advanced ESCC-R presents a unique challenge to clinical decision-making as treatment options are limited by concerns of toxicity associated with reirradiation and the increased complexity of surgical dissection in a previously radiated field. The only study to date that compared the prognosis of ESCC-R to patients with primary esophageal cancer has observed increased postoperative morbidity and reduced overall long-term survival in 136 patients with previous radiation therapy.[11]

ESCC-R is rare; however, it is feasible that its incidence will rise with increasing indications for use of radiation therapy. The optimal therapeutic approach for this disease has yet to be identified. We therefore performed this study to describe the clinical presentation, treatment, and outcomes of a large cohort of patients with ESCC-R in order to better guide clinical management of these patients.

Methods

Patients who presented to Memorial Sloan Kettering Cancer Center with esophageal squamous cell carcinoma between January 2000 and August 2017 were identified from a prospectively maintained institutional database. Only patients with available treatment information were included in our analysis. Clinicopathologic, cancer-related, and treatment data were collected as approved by the institutional IRB.

In the first part of the study, clinical presentation was described. Patients were grouped by previous radiation exposure. As described in the literature, ESCC-R was defined as development of esophageal squamous cell carcinoma within a field previously radiated for the treatment of breast, head and neck, lung, mediastinum, or esophagogastric disease with latency of ≥5 years from radiation exposure to esophageal cancer diagnosis.[7,9,11] Of 896 patients identified with esophageal squamous cell carcinoma that were eligible for inclusion, 69 patients met criteria for ESCC-R (Fig. 1). Data on previous cancer, previous radiation dose, and interval time from initiation radiation to diagnosis of esophageal cancer were abstracted from patient charts. Demographics, clinical staging, and treatment selection were collected and compared between all patients with ESCC-R and ESCC. Clinical staging used a combination of EGD, EUS, CT and PET scans, as is the standard at our institution. Continuous variables were presented as median and interquartile range, and categorical variables were presented as prevalence with percentage. The Wilcoxon rank sum test was used to compare continuous variables between groups. Fisher's exact test or Chi-square was used to compare categorical variables.

In the second part of the study, outcomes were compared in patients with ESCC-R and ESCC who received treatment with curative intent. Our objective was to reflect the specific challenges associated with treating patients with ESCC-R. Patients with stage I disease do not meet criteria for chemoradiation according to current treatment standards in the United States, and furthermore, many may be managed with endoscopic interventions alone; as such, they were not included in our analysis.[12] Additionally, patients with stage IV disease or those who received palliative care only were not included. Patients with concurrent second primary cancers at time of treatment for esophageal cancer were excluded to eliminate potential bias. The final analysis group for overall survival and cumulative incident time to recurrence included patients with locoregional disease (AJCC 7th edition stage II/III) with ESCC-R ($n = 50$) and ESCC ($n = 563$) who received curative

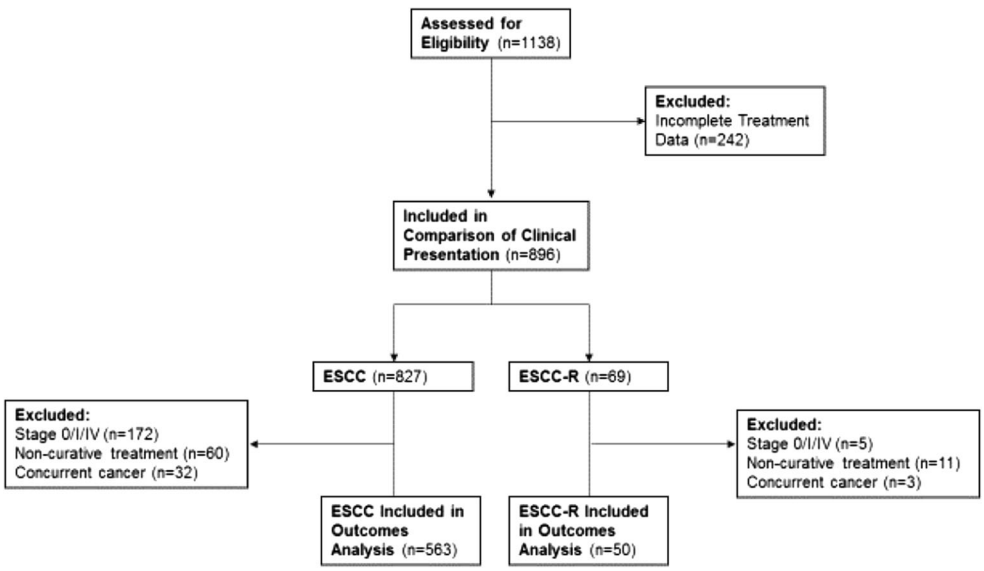


Fig. 1 Included study population

Table 1 Comparison of clinicopathologic characteristics among all patients with ESCC-R and ESCC ($N = 896$)

Characteristic N (%)	Overall ($N = 896$)	ESCC ($N = 827$)	ESCC-R ($N = 69$)	p
Age	65.43 (58.3, 73.9)	65.41 (58.03, 73.93)	66.44 (60, 73.87)	0.493
BMI median (IQR)	23.05 (20.19, 26.34)	23.11 (20.15, 26.7)	22.41 (20.49, 25.19)	0.321
Gender				
Male	536 (59.8)	512 (61.9)	24 (34.8)	< 0.001
Female	360 (40.2)	315 (38.1)	45 (65.2)	
Alcohol use	645 (72)	608 (73.5)	37 (53.6)	< 0.001
Tobacco use	657 (73.3)	617 (74.6)	40 (58)	0.003
Comorbidities				
Cardiac	468 (52.2)	424 (51.3)	44 (63.8)	0.06
Pulmonary	111 (12.4)	101 (12.2)	10 (14.5)	0.57
Diabetes	80 (8.9)	77 (9.3)	3 (4.3)	0.192
Concurrent cancer	47 (5.2)	44 (5.3)	3 (4.3)	1
Family cancer history	490 (54.7)	449 (54.3)	41 (59.4)	0.529
Clinical grade				
0	12 (1.3)	11 (1.3)	1 (1.4)	0.129
1	21 (2.3)	19 (2.3)	2 (2.9)	
2	405 (45.2)	367 (44.4)	38 (55.1)	
3	325 (36.3)	308 (37.2)	17 (24.6)	
NA	133 (14.8)	122 (14.8)	11 (15.9)	
Clinical stage				
0	15 (1.7)	13 (1.6)	2 (2.9)	0.002
1	44 (4.9)	42 (5.1)	2 (2.9)	
2	265 (29.6)	230 (27.8)	35 (50.7)	
3	452 (50.4)	425 (51.4)	27 (39.1)	
4	101 (11.3)	98 (11.9)	3 (4.3)	
NA	19 (2.1)	19 (2.3)	0 (0)	
Location				
Cervical	77 (8.6)	68 (8.2)	9 (13)	0.361
Upper thoracic	175 (19.5)	160 (19.3)	15 (21.7)	
Mid thoracic	312 (34.8)	287 (34.7)	25 (36.2)	
Distal thoracic/GEJ	325 (36.3)	305 (36.9)	20 (29)	
NA	7 (0.8)	7 (0.8)	0 (0)	

treatment with either definitive chemoradiation or surgical resection, either alone or in combination with neoadjuvant chemotherapy and/or radiation.

Overall survival (OS) time, calculated from date of diagnosis until the date of death or last follow-up, was estimated by the Kaplan–Meier method. Cumulative incidence of recurrence (CIR) was calculated from date of diagnosis until the date of recurrence or last follow-up. In patients that did not undergo surgical resection (i.e., received definitive chemoradiation), recurrence was defined by observed disease progression as clinical complete response may not be correlated with a true absence of disease. Death without a recurrence was considered a competing risk. Analysis of these endpoints started from the date of diagnosis in order to include patients with unavailable or incomplete treatment start dates, as some patients presented to our institution for follow-up after treatment at outside hospitals. The interval from diagnosis until start of treatment in the available data had a median of 38 days (range 0–184) for ESCC and 39 days (7, 167) for ESCC-R ($p = 0.86$), suggesting that there were similar and minimal waiting periods. OS and CIR were compared between ESCC and ESCC-R groups by the log-rank and Gray's tests, respectively. Analyses were stratified by clinical stage to account for different baseline risks. Patients with ESCC-R are less likely to undergo reirradiation due to concern with associated toxicity, and as such, they have higher frequency of treatment with surgery alone and neoadjuvant therapy with chemotherapy alone. To determine whether differences in treatment selection had different effects, OS and CIR were further compared between ESCC-R and ESCC within treatment groups: definitive chemoradiation, neoadjuvant therapy (chemotherapy and/or radiation) + surgery, and

surgery alone. Postoperative complication rates were also compared between ESCC and ESCC-R patients who underwent surgical resection.

Finally, in the subset of patients with locoregional ESCC-R, OS and CIR were estimated to describe their long-term outcomes and assess for differences across treatment groups. Clinicopathologic features were analyzed for association with treatment groups to explore characteristics associated with treatment selection for this population.

Two-sided $p < 0.05$ was considered significant. All statistical analyses were compared using R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Patients Presenting with ESCC-R

There were 1138 with esophageal squamous cell carcinoma treated at our institution during the study period. After exclusion of 242 patients with incomplete treatment information, 896 patients remained in the study cohort (Fig. 1). ESCC-R comprised 7.7% of the study population (69/896). Median interval time from previous radiation to esophageal cancer was 18.2 years (IQR 10.8–30). Median previous radiation dose was 6200 cGy (IQR 4995–6600). The most common indications for previous radiation included breast cancer 22 (31.9%), head and neck cancer 21 (30.4%), and lymphoma 12 (17.4%). The remaining cancers included 7 lung (10.1%) and 7 other (10.1%).

Results of the comparison between all patients with ESCC and ESCC-R are presented in Table 1. The median age of presentation with esophageal cancer was 65.4 years, and it did not differ between groups ($p = 0.49$). Patients in the ESCC-R group were more likely to be female (65.2 vs 38.1%; $p < 0.001$) and less likely to have history of smoking or alcohol use ($p < 0.01$). Patients with ESCC-R presented with earlier stage disease than those with ESCC (50.7% stage II vs 28.5%; $p = 0.002$). There was no difference in tumor location or grade.

Treatment Outcome Comparison Between ESCC and ESCC-R

Comparison of clinicopathologic characteristics between ESCC ($n = 563$) and ESCC-R ($n = 50$) patients with stage II/III disease who received curative treatment demonstrated similar clinicopathologic trends as in the analysis of the overall cohort (Supplemental Table 1). More patients with ESCC presented with stage III disease (63.2 vs 44%; $p = 0.01$). Patients with ESCC-R received surgery alone more frequently (20 vs 7.3%) and definitive chemoradiation less often (52 vs 65.9%) than patients with ESCC ($p = 0.012$). Use of neoadjuvant + surgery was similar between groups.

Stratified analysis of overall survival, allowing for different baseline risks according to clinical stage, was not significantly different between ESCC and ESCC-R patients ($p = 0.165$; median follow-up 2.9 years) (Fig. 2). Risk of recurrence also did not significantly differ between groups ($p = 0.21$) (Fig. 3). Pairwise comparisons of OS and CIR for ESCC and ESCC-

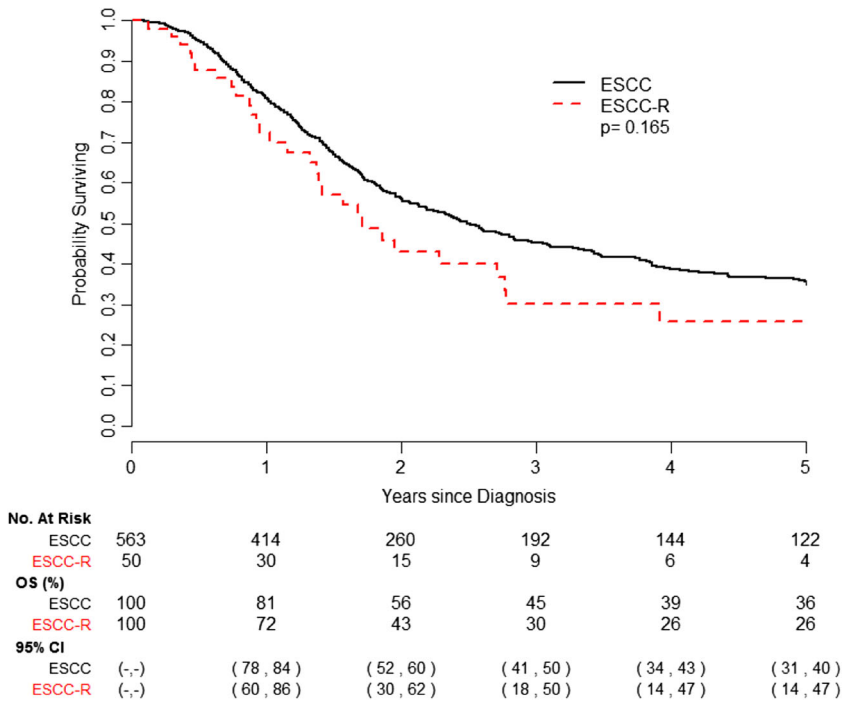


Fig. 2 Overall survival by previous radiation status, stratified by stage and treatment selection

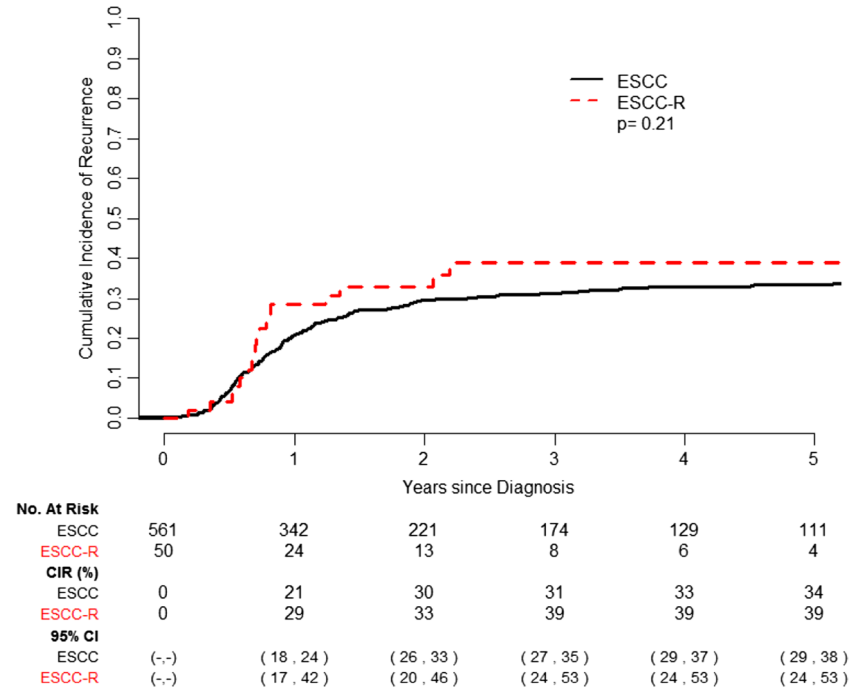


Fig. 3 Cumulative incidence of recurrence by previous radiation status

R are plotted by treatment (surgery alone, definitive chemoradiation, neoadjuvant + surgery) and presented in Fig. 4a–c. As shown in Fig. 4a, ESCC-R patients treated with surgery alone had lower overall survival in the surgery alone group compared to ESCC (5-year OS of 15 vs 33%; $p = 0.045$). Although not significant, patients with ESCC-R also trended towards higher risk of recurrence (55 vs 25%; $p = 0.076$). Among patients treated with definitive chemoradiation (Fig. 4b), no difference was observed in overall survival. However, there appeared to be a trend towards higher risk of recurrence (5-year 45 vs 38%; $p = 0.401$). In the neoadjuvant + surgery group, the ESCC-R patients appeared to have a trend towards lower survival although this was not significant (5-year OS 19 vs 50%; $p = 0.117$) (Fig. 4c). There were too few events to observe a pattern in risk of recurrence.

A comparison of surgical pathology and outcomes is presented in Table 2. Among surgical patients, there was no difference in patient age or ASA score. ESCC-R patients were less likely to receive any neoadjuvant therapy (58.3 vs 78.6%; $p = 0.039$) and, specifically, were much less likely to receive neoadjuvant chemoradiation therapy (29.2 vs 72.9%; $p < 0.001$). None of the patients with ESCC-R in the surgery alone group received adjuvant therapy compared to 29% of the patients with ESCC. Surgical pathology demonstrated higher frequency of pathologic complete response in patients with ESCC (38.5% ypT0 vs 16.7%; $p = 0.024$). There was no difference in nodal positivity, lymphovascular invasion, or margin status; however, patients with ESCC-R had a higher rate of neural invasion (61 vs 25.4%; $p = 0.001$). There was no difference in complication rate between groups, although patients with ESCC-R had a significantly higher rate of in-house mortality (16.7 vs 4.2%; $p = 0.032$). Of the 4 ESCC-R patients who expired in-house, 2 had bowel necrosis which necessitated a reoperation but ultimately succumbed to multi-system organ failure, 1 died from respiratory failure, and 1 from septic complications of an anastomotic leak. Among the 8 ESCC patients who died in the hospital, 5 had septic complications from anastomotic leak and 2 from respiratory failure in the setting of likely aspiration pneumonia. One had a prolonged postoperative course complicated by subsequent resection of a cranial mass that turned out to be a glioblastoma, but ultimately expired due to persistent postoperative respiratory failure.

Observed Trends in Treatment Selection for ESCC-R

Patient demographic and clinical characteristics were summarized by treatment type for ESCC-R patients with stage II/III disease to describe factors that may be associated with treatment selection (Supplemental Table 2). With the small sample size, the power to detect differences is limited. Definitive chemoradiation patients may be slightly older compared to surgery alone and neoadjuvant + surgery (median 66 years vs. 62 and 61; $p = 0.1$), and have more cardiac comorbidities (81% vs. 40 and 57%; $p = 0.05$). Comparison of overall survival between treatment groups is presented in Fig. 5. Although not significant, patients with surgery alone had lower survival compared to neoadjuvant + surgery and definitive chemoradiation ($p = 0.194$). Risk of recurrence also did not differ between treatment groups ($p = 0.101$); however, patients with surgery alone and definitive chemoradiation had higher recurrence (5-year CIR of 55 and 45%, respectively) compared to patients with neoadjuvant + surgery (15%) ($p = 0.101$) (Fig. 6).

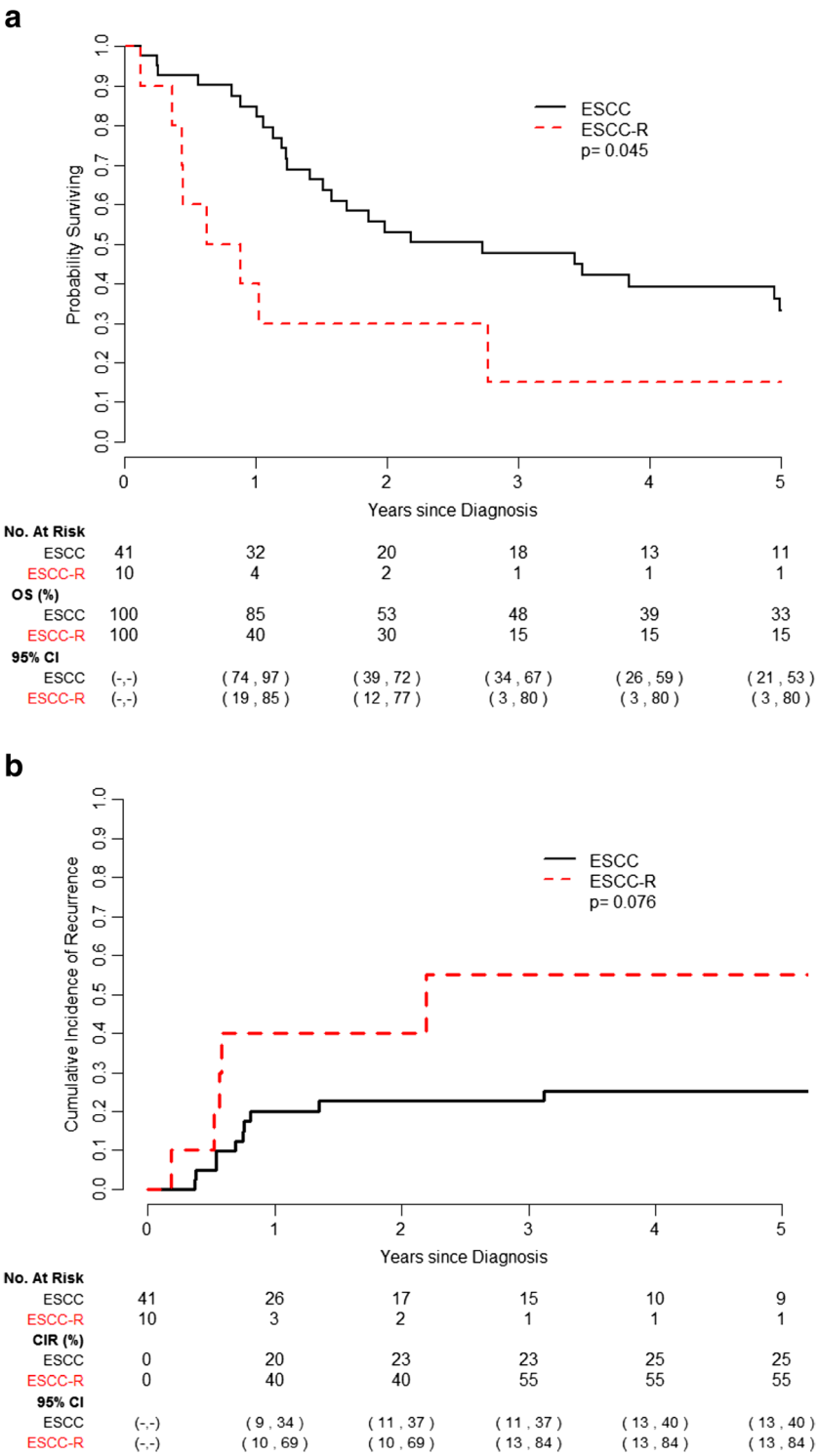


Fig. 4 **a–c** Overall survival and cumulative incidence of recurrence by treatment type for ESCC and ESCC-R. Treatment types included (**a**) surgery alone, (**b**) definitive chemoradiation, and (**c**) neoadjuvant + surgery

Discussion

Esophageal cancer arising in a previously radiated field has been previously described as a complication following radiation therapy.[6,7,9,10] However, the literature is predominantly limited to large epidemiologic studies—the clinical presentation, tumor behavior, and optimal treatment of this disease remain largely undefined. This is the largest single institution series of ESCC-R to date and the first to compare outcomes of different treatment options utilized for this disease. ESCC-R comprised 7.7% of patients diagnosed with esophageal squamous cell carcinoma during the study period. Patients with ESCC-R had lower engagement in high risk behaviors known to be strongly associated with the development of esophageal

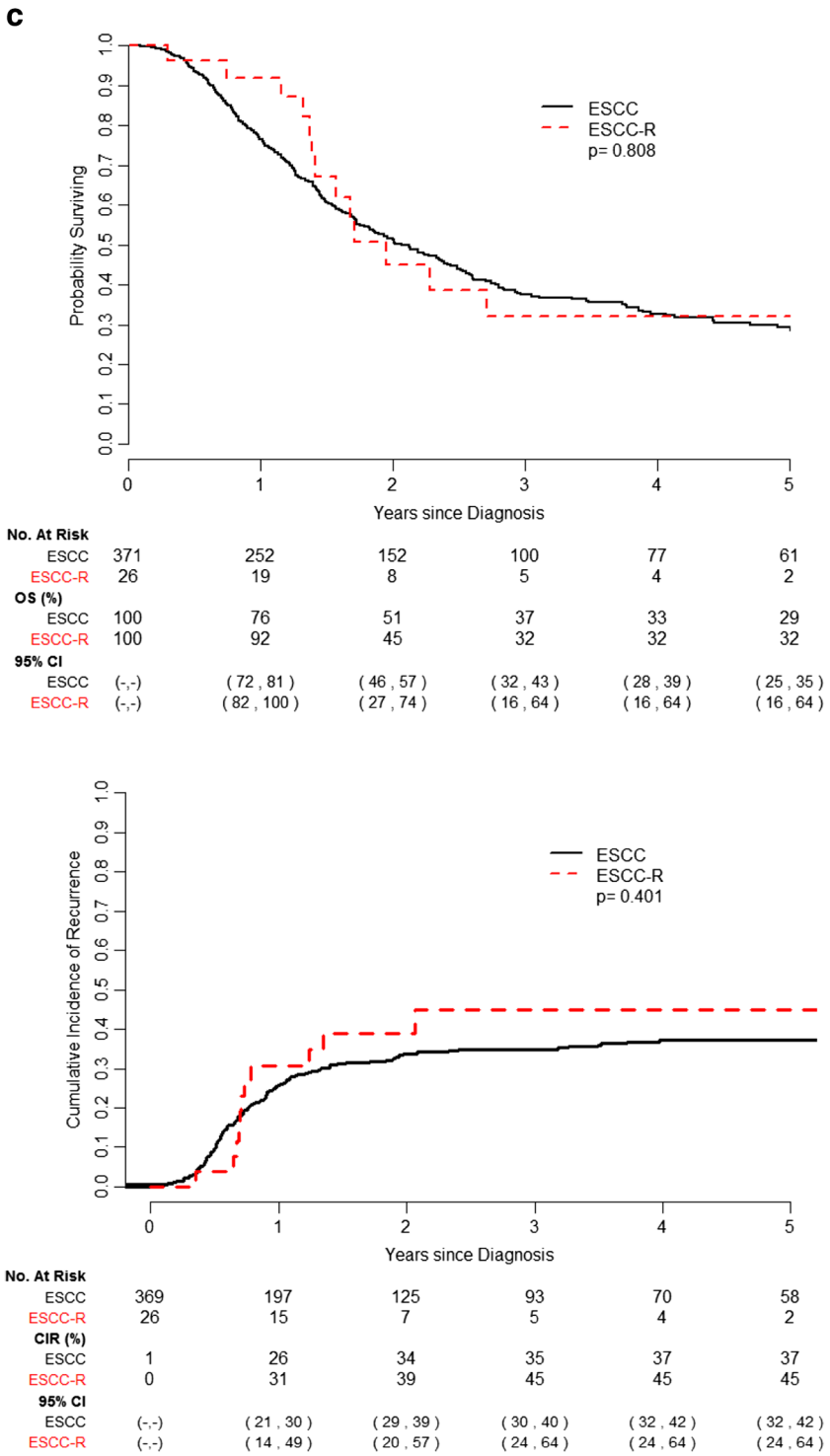


Fig. 4 continued.

squamous cell carcinoma. ESCC-R was often undertreated and appeared to be associated with worse prognosis than ESCC despite presenting with earlier clinical stage.

The paucity of clinical research studies on patients with ESCC-R may reflect the low observed incidence of this disease. Similar to other limited series, patients with ESCC-R comprised a small portion of patients who presented to our institution.[11,13,14] The relationship between radiation and subsequent esophageal cancer appears to be dose- and time-dependent.[6–10] In a multicenter-nested case–control study, Morton et al.[9] demonstrated that the odds of developing esophageal squamous cell carcinoma were 780% greater in breast cancer survivors who received ≥ 3500 cGY in radiation compared to those who had not received any radiation. In

Table 2 Comparison of perioperative clinicopathologic characteristics and outcomes between ESCC and ESCC-R with stage II/III disease that underwent surgery

Characteristic *N* (%)	Overall (*N* = 216)	ESCC (*N* = 192)	ESCC-R (*N* = 24)	*p*
Neoadjuvant therapy				
Any	165 (76.4)	151 (78.6)	14 (58.3)	0.039
Chemo alone	13 (6)	6 (3.1)	7 (29.2)	< 0.001
Chemoradiation	147 (68.1)	140 (72.9)	7 (29.2)	< 0.001
ASA				
2	79 (36.6)	73 (38)	6 (25)	0.22
3	127 (58.8)	110 (57.3)	17 (70.8)	
4	4 (1.9)	3 (1.6)	1 (4.2)	
NA	6 (2.8)	6 (3.1)	0 (0)	
Minimally invasive surgery	23 (10.6)	19 (9.9)	4 (16.7)	0.317
Procedure				
Ivor-Lewis	106 (49.1)	95 (49.5)	11 (45.8)	0.157
3-Hole	71 (32.9)	63 (32.8)	8 (33.3)	
Transhiatal	12 (5.6)	11 (5.7)	1 (4.2)	
Pharyngo-/laryngo-esophagectomy	4 (1.9)	3 (1.6)	1 (4.2)	
Aborted	4 (1.9)	2 (1)	2 (8.3)	
NA	19 (8.8)	18 (9.4)	1 (4.2)	
Vascular invasion	39 (18.1)	32 (16.7)	7 (29.2)	0.143
Neural invasion	41 (19)	30 (15.6)	11 (45.8)	0.001
R0 resection	178 (82.4)	160 (83.3)	18 (75)	1
pT stage				
0 (pathologic complete response)	78 (36.1)	74 (38.5)	4 (16.7)	0.024
1	24 (11.1)	23 (12)	1 (4.2)	
2	25 (11.6)	24 (12.5)	1 (4.2)	
3	70 (32.4)	56 (29.2)	14 (58.3)	
4	7 (3.2)	6 (3.1)	1 (4.2)	
NA	12 (5.6)	9 (4.7)	3 (12.5)	
pN stage				
0	134 (62)	123 (64.1)	11 (45.8)	0.401
1	49 (22.7)	41 (21.4)	8 (33.3)	
2	16 (7.4)	15 (7.8)	1 (4.2)	
3	3 (1.4)	3 (1.6)	0 (0)	
NA	14 (6.5)	10 (5.2)	4 (16.7)	
Length of stay, days Median (IQR)	13 (6, 119)	13 (6, 119)	16 (6, 71)	0.22
30-Day complications				
Any	107 (49.5)	95 (49.5)	12 (50)	1
Serious	59 (27.3)	50 (26)	9 (37.5)	0.803
Leak	28 (13)	24 (12.5)	4 (16.7)	1
30-Day reoperation	27 (12.5)	23 (12)	4 (16.7)	0.756
30-Day readmission	10 (4.6)	10 (5.2)	0 (0)	0.614
30-Day mortality	6 (2.8)	4 (2.1)	2 (8.3)	0.136
In-house mortality	12 (5.6)	8 (4.2)	4 (16.7)	0.032

addition, several studies have reported increased incidence with increasing latency period.[6,9–11] In a retrospective cohort study of 220,806 breast cancer survivors, Ahsan and Neugut[10] demonstrated a 305% increase in risk of esophageal cancer in

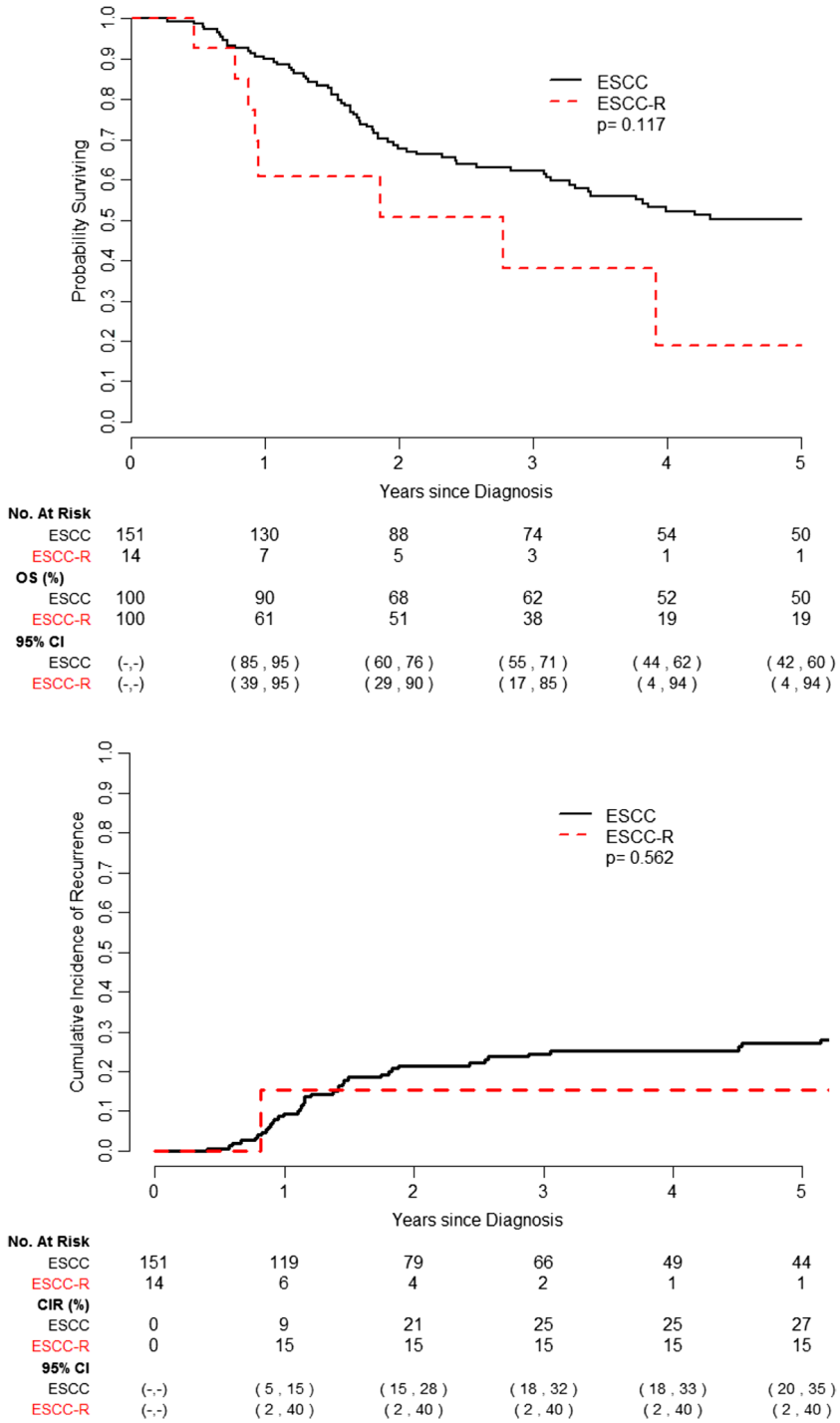
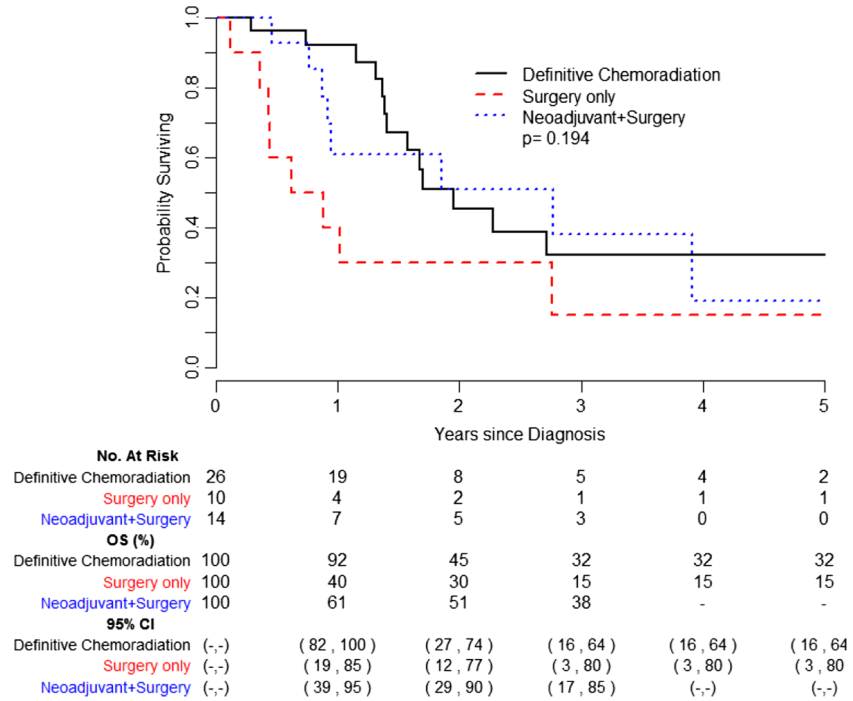


Fig. 5 Overall survival by treatment type in patients with ESCC-R. Comparison of overall survival by treatment types in 50 patients with ESCC-R who received treatment with curative intent

patients who received previous radiation when comparing a < 5-year follow-up to ≥ 15 years. In our cohort, the overall mean time from end of treatment to ESCC-R was 18.2 years. Patients with head and neck cancers received the highest median radiation dose (6600 cGY) and had the shortest median time to development of cancer (10.7 years). Currently available studies predominantly focus on risk of ESCC-R in breast cancer survivors.[6,8–10] It remains unknown whether increased radiation dose or younger age at radiation may predict shorter time to ESCC-R development. This information may help better guide long-term surveillance recommendations in patients who have a history of previous radiation therapy.

Our study demonstrated that the "profile" of patients with ESCC-R differs from the expected clinical presentation of patients with esophageal squamous cell carcinoma. ESCC-R patients were predominantly female and had significantly



No. At Risk						
Definitive Chemoradiation	26	19	8	5	4	2
Surgery only	10	4	2	1	1	1
Neoadjuvant+Surgery	14	7	5	3	0	0
OS (%)						
Definitive Chemoradiation	100	92	45	32	32	32
Surgery only	100	40	30	15	15	15
Neoadjuvant+Surgery	100	61	51	38	-	-
95% CI						
Definitive Chemoradiation	(-,-)	(82 , 100)	(27 , 74)	(16 , 64)	(16 , 64)	(16 , 64
Surgery only	(-,-)	(19 , 85)	(12 , 77)	(3 , 80)	(3 , 80)	(3 , 80
Neoadjuvant+Surgery	(-,-)	(39 , 95)	(29 , 90)	(17 , 85)	(-,-)	(-,-)

Fig. 6 Cumulative incidence of recurrence by treatment type in patients with ESCC-R. Comparison of cumulative incidence of recurrence by treatment types in 50 patients with ESCC-R who received treatment with curative intent

lower rates of alcohol and tobacco use than ESCC patients. The high percentage of females likely parallels the observed relationship between breast cancers treated with radiation and subsequent ESCC-R development. Interestingly, patients with ESCC-R presented with earlier clinical stage disease compared to ESCC. Patients with previous malignancy are likely in more frequent contact with healthcare providers and are enrolled in surveillance programs; consequently, their cancer may be identified earlier, prior to progression. These results suggest that high clinical suspicion should remain for several decades after completion of radiation therapy and that absence of known risk factors should not deter further diagnostic evaluation.

The question of whether ESCC-R is a more aggressive disease than ESCC remains controversial. The only study to date that has attempted to address this question is an evaluation of 2489 patients from 30 European institutions that underwent esophageal resection for esophageal cancer. The authors found that patients with previous radiation had worse disease-free and overall survival; however, their results are limited by their inclusion criteria as patients with history of radiation ≤ 5 years prior to EC diagnosis are included in the previous radiation group and patients with adenocarcinoma are also analyzed.[11] In this study, no patients with previous radiation received neoadjuvant treatment, and the authors concluded that this was the likely etiology of the worse prognosis observed in this group. Our results support the observation that differences in survival between ESCC-R and ESCC may reflect the role of undertreatment rather than a more aggressive disease.

In our study, comparison of ESCC and ESCC-R by treatment selection suggested that patients with ESCC-R who received definitive chemoradiation had similar overall survival compared to those with ESCC; however, patients treated with surgery appeared to have worse prognosis. In the surgery alone group, patients with ESCC-R had significantly lower overall survival than those with ESCC. A similar survival trend is noted in the neoadjuvant + surgery group, although this sub-analysis failed to reach significance. Patients with ESCC-R who received surgery alone also appeared to have higher risk of recurrence; however, there were too few events in the neoadjuvant + surgery group to identify a similar trend. These observations are likely the result of failure to pursue aggressive treatment in the ESCC-R group. For example, none of the patients in the ESCC-R surgery alone group received subsequent adjuvant treatment compared to 28.6% of the ESCC patients. Furthermore, only 29% of the ESCC-R patients received neoadjuvant therapy including both chemotherapy and radiation compared to 72% of the patients with ESCC. Although our findings are limited by small sample size, they suggest that undertreatment of ESCC-R may result in worse overall survival and earlier recurrence compared to ESCC.

The treatment of ESCC-R presents a unique challenge for clinicians. In order to help guide therapeutic clinical decision-making, we compared treatment outcomes in ESCC-R patients alone. Observed trends for risk of recurrence and overall survival suggest that patients treated with surgery alone and definitive chemoradiation have faster time to recurrence than those who received neoadjuvant + surgery, despite the low frequency of administration of neoadjuvant radiation in this

group. Concerns related to operating in a previously radiated field and negative sequelae of reirradiation likely resulted in reduced use of surgical resection and neoadjuvant therapy with radiation. As such, patients in the ESCC-R group more frequently received inappropriate treatment with surgery alone. However, the benefits of neoadjuvant chemoradiation must be weighed against the associated risks. Patients with ESCC-R had a higher rate of in-hospital postoperative mortality. Of the 4 deaths among ESCC-R patients who had surgery, 2 had received reirradiation. As demonstrated by the higher 5-year survival compared to surgical modalities, definitive chemoradiation likely represents the safest option as the risks of surgery are avoided. However, it is possible that not all ESCC-R patients are eligible to receive a curative radiation dose. These findings highlight the dilemma of treatment of patients with ESCC-R and the importance of careful patient selection when pursing aggressive treatment. As operating on ESCC-R patients is more complex than routine esophagectomy, surgery should be performed at specialty centers. A multidisciplinary discussion should be considered on a case-by-case basis to determine which treatment option is most feasible.

There are several limitations that should be considered in the interpretation of our results. First, this was a retrospective, observational study. There is no concrete way to determine whether esophageal squamous cell carcinoma arising in a previously radiated field in the patients is the result of radiation. We opted to use a latency period of ≥ 5 years as previously described in the literature to better control for incident primary disease.[11] As occurrence of ESCC-increases, it will be important to identify better ways to define this condition. Lower rates of behavioral risk factors in ESCC-R patients have been demonstrated elsewhere and further support the likelihood that the cancer is more likely the result of previous radiation than primary.[9] The total sample size of the ESCC-R group in the outcomes analysis was only 50 patients and may have been under-powered to demonstrate statistically significant results. Although our study contained a small number of cases, the observed trends support the conclusion that undertreatment of ESCC-R may yield worse prognosis. As this disease has a low incidence, we included a long study period of 18 years to obtain a sufficient sample size. During this period, there have been changes to methods of radiation delivery. ESCC-R has a long latency period, and as such, it remains unknown what the long-term effects of current therapies will be. Although newer radiation treatments aim to reduce the amount of healthy tissue exposed to high radiation doses, larger fields may result in a greater volume of normal tissue receiving low radiation doses, and it is possible that even lower doses may pose a risk of ESCC-R.[9,15,16] As such, ESCC-R is likely to continue to present as a sequela of radiation therapy. Additionally, there have been significant improvements to the medical and surgical treatment of esophageal cancer as well as in diagnostic techniques with increased use of modalities such as endoscopic ultrasound and minimally invasive surgery. Any changes over time should impact both study groups in a similar fashion; for example, as demonstrated in our sub-analysis of patients that underwent surgery, surgical approach did not differ between ESCC and ESCC-R. Furthermore, any misclassification of clinical staging would be consistent between ESCC and ESCC-R over time.

Conclusions

ESCC-R represents a rare but important long-term consequence of radiation therapy that will likely increase in incidence over time. Patients with ESCC-R may present decades following initial radiation treatment, and as such, clinicians must maintain a high index of suspicion. Our study suggests that poor prognosis in ESCC-R is primarily a function of undertreatment rather than an inherently more aggressive disease process. Patients with ESCC-R who received neoadjuvant treatment with surgical resection had lower disease recurrence but a higher rate of in-hospital mortality. Neoadjuvant chemotherapy or chemoradiation should be used whenever possible for ESCC-R; however, the improved survival benefits of aggressive treatment must be weighed against the higher associated postoperative risks.

Acknowledgements The authors would like to thank Furio Nick Savone, lymphoma and esophageal cancer survivor, for inspiring the design and development of this study.

Funding Sources This study was supported, in part, by the National Institutes of Health/National Cancer Institute Cancer Support Grant P30 CA008748. Tamar Nobel is supported, in part, by a grant from the American Cancer Society.

Author Contributions Tamar Nobel, Arianna Barbetta, David Jones, and Daniela Molena contributed to the conception and design of the work. Tamar Nobel, Arianna Barbetta, Tiffany Pinchinat, Franscisco Schlottman, Manjit Bains, Geoffrey Ku, Abraham Wu, and Marco G. Patti contributed to the acquisition and interpretation of data. Meier Hsu and Kay See Tan contributed to the analysis and interpretation of data. Tamar Nobel, Meier Hsu, Kay See Tan, and Daniela Molena wrote the manuscript with critical revision from all other authors. All authors are in agreement to be accountable for ensuring the accuracy and integrity of the work.

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