Impact of Postoperative Radiation after Esophagectomy for Esophageal Cancer

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Introduction: Though postoperative radiation for esophageal cancer is offered in selected cases, there is conflicting evidence as to whether it improves overall survival (OS). We performed a retrospective analysis using the Surveillance Epidemiology and End Results database to analyze the impact of adjuvant radiation in a large cohort of patients.

Methods: From 1998 to 2005, patients diagnosed with stage T3-4N0M0 or T1-4N1M0 esophageal adenocarcinoma (AC) or squamous cell carcinoma (SCC) who were definitively treated with esophagectomy, with or without postoperative radiation, were selected. Kaplan-Meier and Cox regression analysis were used to compare OS and disease-specific survival (DSS).

Results: A total of 1046 patients met the selection criteria: 683 (65.3%) received surgery alone and 363 (34.7%) received postoperative radiation. For American Joint Committee on Cancer stage III esophageal carcinoma (T3N1M0 or T4N0-1M0), there was significant improvement in median and 3-year OS ($p < 0.001$) and DSS ($p < 0.001$), respectively. This benefit was present for both SCC and AC. However, for American Joint Committee on Cancer stages IIA and IIB disease there was no significant differences in OS or DSS. Multivariate analysis revealed that postoperative radiation was the most significant predictor for improved OS (hazard ratio 0.70, 95% confidence interval 0.59–0.83, $p < 0.001$).

Conclusions: This large population-based review supports the use of postoperative radiation for stage III SCC and AC of the esophagus. Given the retrospective nature of this study, until appropriately powered randomized trials confirm these results, caution should be used before broadly applying these findings in clinical practice.

Key Words: Esophageal cancer, Postoperative radiation, Esophagectomy, Survival, Chemotherapy.

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Esophageal Cancer is a relatively uncommon malignancy with 16,470 new cases estimated in 2008, accounting for approximately 1% of all new cancer diagnoses in the United States. However, it is quite lethal with more than 14,000 deaths.[1] The treatment of choice in esophageal cancer typically involves esophagectomy for resectable tumors and concomitant chemoradiation for unresectable tumors. However, the locoregional recurrence rates remain high regardless of treatment modality. The locoregional recurrence rate has been reported to be 30% for an radical resection and 60% for an R1 or R2 resection.[2] The locoregional recurrence has been reported to be 50 to 55% in those treated with definitive chemoradiation.[3] In addition, 5-year survivals are poor at approximately 25% regardless of treatment modality.[2,3]

Seeking a superior alternative to esophagectomy alone, several randomized trials have recently been performed evaluating the role of preoperative chemoradiation.[4–8] Though the data concerning its efficacy are conflicting, use of neoadjuvant chemoradiation has been an increasingly used treatment approach.[9] Phase III studies analyzing the role of postoperative radiation have been conflicting,[10–13] and phase III trials comparing adjuvant chemotherapy to surgery alone have revealed no overall survival (OS) benefit.[14–16] Therefore, in those for whom the primary treatment is surgery, there is no clear indication for adjuvant treatment.

Because of the conflicting data on the role of postoperative radiation in esophageal cancer, we performed a retrospective review using the Surveillance Epidemiology and End Results (SEER) database to analyze whether there is a survival benefit to adjuvant radiation in a large cohort of patients.

MATERIALS AND METHODS

Data Source

The SEER-17 database is a National Cancer Institute program serving as the representative cancer registry of the United States. Data concerning individual patient demographics, diagnosis, treatment, and survival outcomes are collected from 17 regions covering 26% of the US population.[17] Because the individual patient data are de-identified, approval from an ethics committee or institutional review board is not required.

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Study Cohort

From 1998 to 2005, patients diagnosed with stage T3-4N0M0 or T1-4N1M0 esophageal adenocarcinoma (AC) (SEER codes 8140-8389) or squamous cell carcinoma (SCC) (SEER codes 8050-8089) who were definitively treated with esophagectomy were selected. Before 1998 SEER did not have a unique surgical code for esophageal cancer, and therefore, 1998 was chosen as the earliest time period for the cohort. Patients with T1-2N0 disease were excluded.

Patients who refused radiation therapy (RT), were coded as unknown regarding radiation treatment or who had neoadjuvant radiation, or any RT other than postoperative external beam RT (postopRT), were excluded. Only patients who survived more than 3 months postsurgery were included in the cohort. This was done to remove possible bias in favor of the postoperative radiation group, because some of the patients who received surgery alone may have died in the perioperative period before receiving adjuvant radiation. Thus, the comparison was strictly limited to those who were treated with definitive esophagectomy with or without adjuvant radiation.

The SEER database does not include the details of radiation delivery, such as total dose, dose distribution, technique, compliance, and overall elapsed treatment time. Systemic therapy information is not available in the SEER registry; thus, analyses based on the presence or absence of chemotherapy were not possible.

Staging

Extent of invasion was determined using the appropriate staging and coding manuals that correlated to patients from 1998 to 2003[18] and from 2004 to 2005.[19] Tumor size and extent is coded primarily from the operative report and pathology reports and therefore likely represents pathologic staging. Extent of nodal disease was determined based on pathologic findings only. This information was used to convert the extent of disease to tumor, node, metastasis staging according to the American Joint Committee on Cancer (AJCC) staging, 6th edition.[20] Table 1 lists the included patients based on their tumor, node, metastasis classification and AJCC stage grouping.

Outcome

The primary endpoints were all-cause mortality and esophageal cancer-specific mortality. Follow-up time was calculated from the month and year of initial diagnosis. Vital status at the date of last contact was available for all patients.

Statistical Analysis

Comparisons of the characteristics between the RT and non-RT groups were made using Pearson Chi Square. Actuarial disease-specific survival (DSS) and OS curves were generated using the Kaplan-Meier method and compared using the log-rank test. Separate queries were performed to analyze both DSS and OS outcomes for all patients. DSS was defined as death from esophageal cancer and was measured from diagnosis until death from esophageal cancer. OS was measured from diagnosis until death from any cause. The 3-year actuarial DSS and OS rates, as well as median survival, were analyzed. Subgroup analysis was also performed to analyze OS and DSS by AJCC stage grouping as well as by histology. On univariate analysis, the covariates analyzed included delivery of postopRT (yes versus no), age, tumor stage (T1-2 versus T3 versus T4), presence of pathologically positive nodes (yes versus no), gender, race (white versus black versus other), and histologic type (AC versus SCC). Multivariate analyses using Cox proportional hazards survival regression analyses were performed to evaluate the influence of covariates on OS. Statis-

TABLE 1. Patient Characteristics Based on TNM Classification and AJCC Stage Grouping

	Stage Grouping	PostopRT	Surgery Alone	Total No. of Patients
T3N0	IIA	69	190	259
T1N1	IIB	26	73	99
T2N1	IIB	37	74	111
T3N1	III	185	253	438
T4N0	III	16	27	43
T4N1	III	30	66	96
Total no. of patients		363	683	1046

TNM, tumor, node, metastases based classification; AJCC, American Joint Committee on Cancer; postopRT, postoperative radiation therapy.

TABLE 2. Comparison of Patient Characteristics by Treatment Assignment

Variable	All Patients (%)	PostopRT Yes	PostopRT No	p^a
Age (yr)				0.095
<66	499 (48)	186 (37)	313 (63)	
≥66	547 (52)	177 (32)	370 (68)	
Histologic type				0.393
AC	688 (66)	245 (36)	443 (64)	
SCC	358 (34)	118 (33)	240 (67)	
Gender				0.006
Female	232 (22)	63 (27)	169 (73)	
Male	814 (78)	300 (37)	514 (63)	
Stage				<0.001
IIA	259 (25)	69 (27)	190 (73)	
IIB	207 (20)	63 (30)	147 (70)	
III	571 (55)	231 (40)	346 (60)	
T classification				0.208
T1–2	210 (20)	63 (30)	147 (70)	
T3	697 (67)	254 (36)	443 (64)	
T4	139 (13)	46 (33)	93 (67)	
LN status				0.005
Negative	302 (29)	85 (28)	217 (72)	
Positive	744 (71)	278 (37)	466 (63)	
Race				0.682
White	906 (87)	310 (34)	596 (66)	
Black	81 (8)	30 (37)	51 (63)	
Other	59 (5)	23 (39)	36 (61)	

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

[a] χ^2 p value.

postopRT, postoperative radiation therapy; AC, adenocarcinoma; SCC, squamous cell carcinoma; LN, lymph node.

tical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago Illinois). Statistical significance was defined as a two-sided p value of 0.05 or less.

RESULTS

A total of 1046 patients met the selection criteria: 683 (65.3%) received surgery alone and 363 (34.7%) received postoperative radiation. The median age of all patients was 66 years. The median number of nodes removed was 11. Table 2 lists available patient characteristics and the comparisons for the characteristics by treatment assignment. Patients who received postopRT were more often male and had node positive disease.

OS and DSS

The use of postopRT was associated with significantly improved OS ($p = 0.010$) and DSS ($p = 0.042$). The median OS was 24 months in the group receiving postopRT and 18 months in the group undergoing surgery alone. The addition of postopRT improved OS at 3 years from 31.2 to 34.5% compared with surgery alone. DSS was improved at3 years from 40.5 to 44%. The median DSS was 28 months in the group receiving postopRT and 25 months in the group undergoing surgery alone. On subgroup analysis, the OS and DSS benefit of postopRT was noted to be significant only for AJCC stage III disease and not for AJCC stages IIA and IIB.

Survival by AJCC Stage Grouping

For AJCC stage IIA (T3N0), 190 patients underwent surgery alone and 69 patients received postopRT. There was no significant OS benefit with the use of postopRT. The median and 3-year OS were 27 months and 46.4% in the surgery alone group compared with 46 months and 51.9% in the postopRT group, respectively ($p = 0.245$). Similarly, there was no significant difference in DSS between surgery alone and postopRT ($p = 0.344$).

For AJCC stage IIB (T1N1 or T2N1), 147 patients underwent surgery alone and 63 patients received postopRT. Again, there was no significant OS benefit with the use of postopRT. The median and 3-year OS were 25 months and 41.5% in the surgery alone group compared with 30 months and 42.1% in the postopRT group, respectively ($p = 0.449$). There was also no significant difference in DSS between surgery alone and postopRT ($p = 0.588$).

For AJCC stage III (T3N1 or T4N0-1), 346 patients underwent surgery alone and 231 patients received postopRT. Use of postopRT resulted in an improvement in median OS from 15 months to 19 months and an improvement in 3-year OS from 18.2 to 28.9% ($p < 0.001$) (Figure 1). Similarly, use of postopRT improved the median DSS from 18 months to 24 months and improved 3-year DSS from 27 to 38.1% ($p < 0.001$).

Survival by Histology

Squamous Cell Carcinoma

A total of 240 patients with SCC received surgery alone compared with 118 patients who received postopRT. Median OS was improved from 17 months to 24 months with the

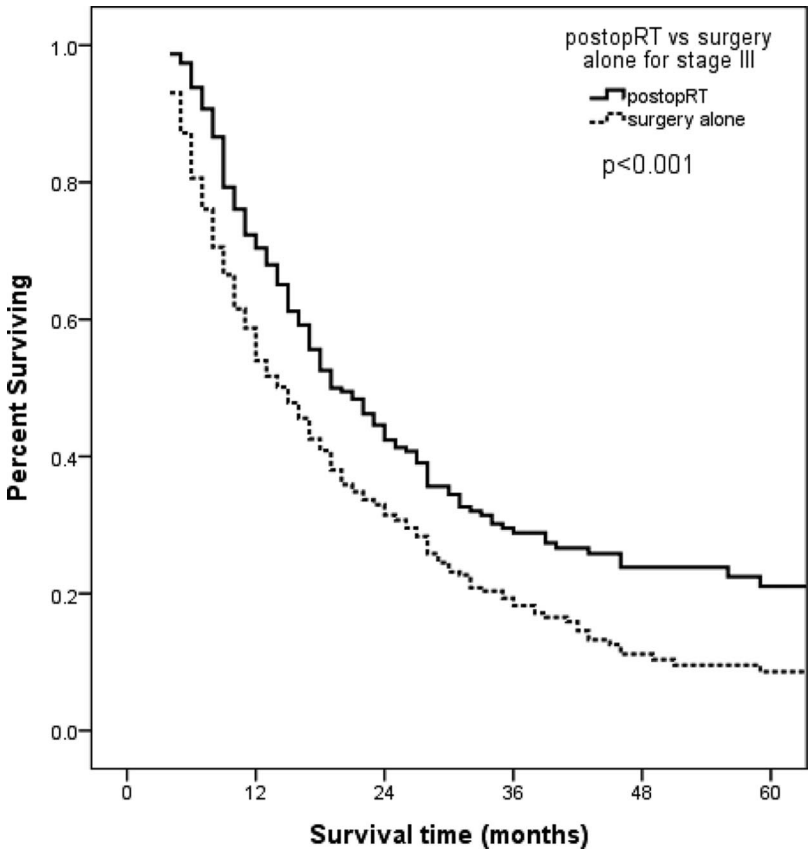

FIGURE 1. Kaplan-Meier estimates for overall survival for patients receiving postopRT compared with surgery alone for AJCC stage III. The median survival was 19 months for postopRT versus 15 months for surgery alone ($p < 0.001$). postopRT, postoperative radiation therapy.

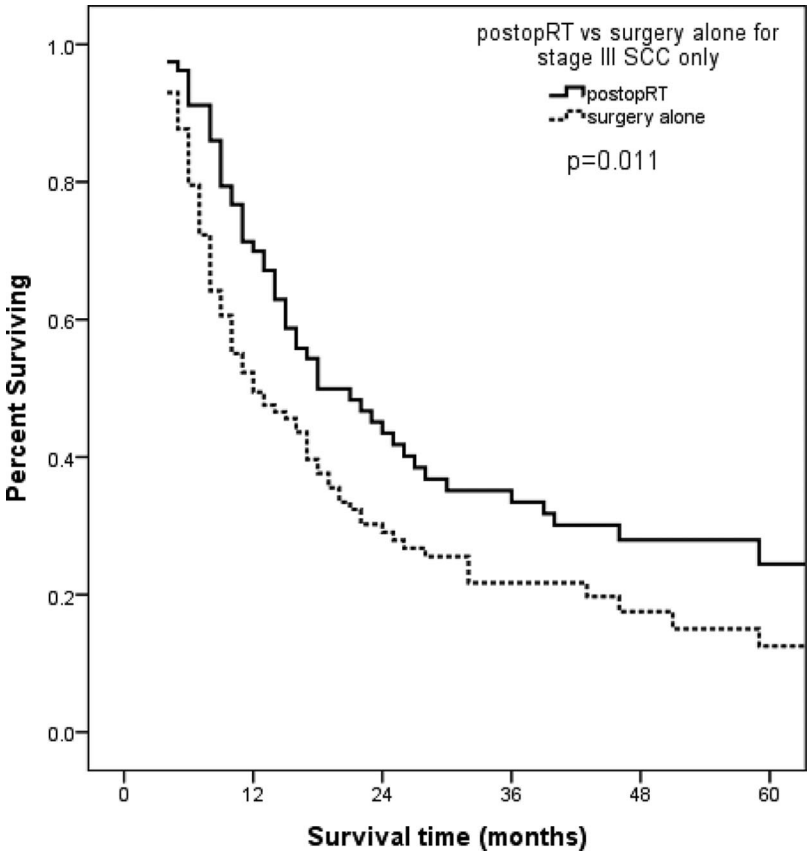

FIGURE 2. Kaplan-Meier estimates for overall survival for patients receiving postopRT compared with surgery alone for AJCC stage III squamous cell carcinoma. The median survival was 18 months for postopRT versus 12 months for surgery alone ($p = 0.011$). AJCC, American Joint Committee on Cancer; postopRT, postoperative radiation therapy.

addition of postopRT as well as an improvement in 3-year OS from 28.4 to 35.7% ($p = 0.049$). When these patients were grouped by AJCC stage, there was no OS benefit for stage IIA or IIB disease ($p = 0.259$ and $p = 0.846$, respectively). For stage III SCC, 114 patients received surgery alone and 79 patients received postopRT. Median OS improved from 12 months to 18 months, and 3-year OS improved from 21.7 to 33.4% ($p = 0.011$) (Figure 2). Similarly, when analyzing DSS, there was no significant differences for stage IIA or IIB disease ($p = 0.751$ and $p = 0.898$, respectively). However, for stage III disease, median DSS improved from 17 months to 27 months, and 3-year DSS improved from 29.6 to 44.7% ($p = 0.019$).

Adenocarcinoma

A total of 443 patients with AC received surgery alone and 245 patients received postopRT. The median OS and 3-year OS were 25 months and 33.8% for those who received postopRT compared with 19 months and 32.3% for those who received surgery alone ($p = 0.086$). When these patients were grouped by AJCC stage, there was no OS benefit for stage IIA or IIB disease ($p = 0.632$ and $p = 0.517$, respectively). For stage III, 152 patients received postopRT and 232 received surgery alone. The median OS improved from 15 months to 20 months, and the 3-year OS improved from 16.5 to 26.3% with the addition of postopRT ($p = 0.002$) (Figure 3). Similarly, when analyzing DSS, there was no significant differences for stage IIA or IIB disease ($p = 0.371$ and $p = 0.531$, respectively). However, for stage III disease, median DSS improved from 19 months to 24 months, and 3-year DSS improved from 25.7 to 34.8% ($p = 0.010$).

Univariate and Multivariate Analyses

On univariate analysis, postopRT (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.69–0.95, $p = 0.011$) was associated with improved survival. Higher T stage, positive lymph nodes, and black race were all associated with decreased OS (Table 3).

On multivariate analysis, use of postopRT was again associated with improved survival (HR 0.70, 95% CI 0.59–0.83, $p < 0.001$), as was female gender (HR 0.78, 95% CI 0.63–0.95, $p = 0.013$). Positive lymph nodes and higher T stage were again associated with decreased survival (Table 4).

DISCUSSION

The results of this large population-based study reveal that the addition of postopRT is associated with significantly improved OS and DSS for AJCC stage III esophageal cancer. Use of postopRT significantly improved median OS by 4 months ($p < 0.001$) and the median DSS by 6 months ($p < 0.001$). When stratifying by stage and by histology the survival benefit associated with postopRT remains for stage III SCC and AC.

Because of the previously mentioned high rate of locoregional recurrence after surgery alone, several institutions treated these patients adjuvantly with radiation, reporting an

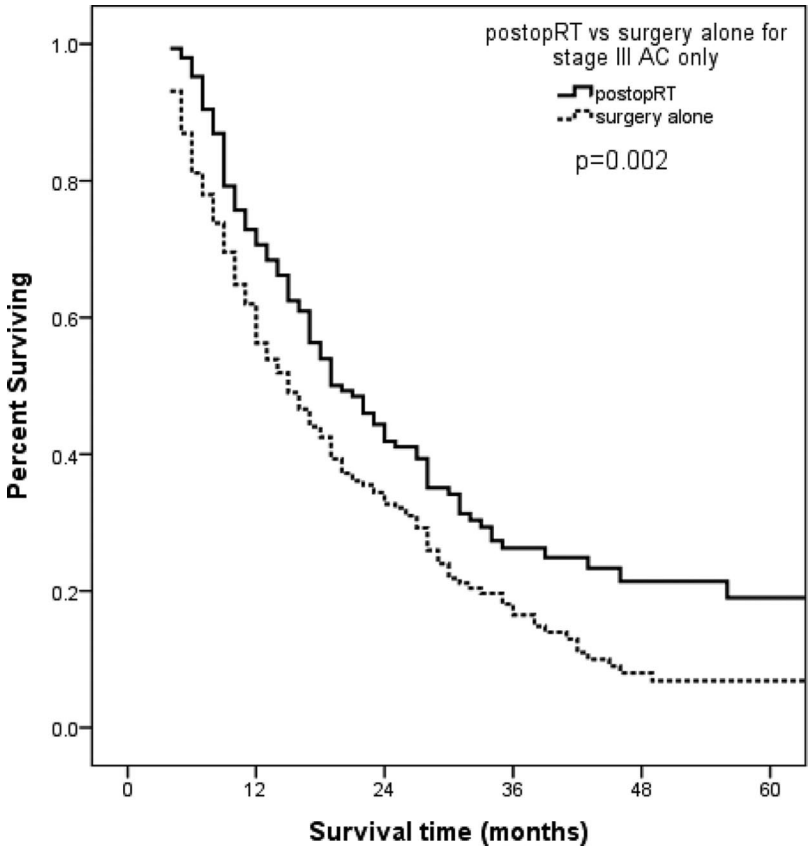

FIGURE 3. Kaplan-Meier estimates for overall survival for patients receiving postopRT compared with surgery alone for AJCC stage III adenocarcinoma. The median survival was 20 months for postopRT versus 15 months for surgery alone ($p = 0.002$). AJCC, American Joint Committee on Cancer; postopRT, postoperative radiation therapy.

TABLE 3. Univariate Analysis for Survival

Variable	CHR	95% CI	*p*
Age (continuous)	1.00	0.99–1.01	0.687
Gender			
Female	0.85	0.71–1.03	0.092
Male	1		
Postoperative radiation			
Yes	0.81	0.69–0.95	0.011
No	1		
Histology			
Squamous cell carcinoma	1		
Adenocarcinoma	0.91	0.77–1.06	0.233
T-stage			
T1–2	1		
T3	1.32	1.07–1.63	0.008
T4	1.69	1.29–2.21	<0.001
Positive lymph nodes			
Yes	1.60	1.33–1.92	<0.001
No	1		
Race			
Black	1.38	1.05–1.81	0.022
Other	0.86	0.61–1.21	0.379
White	1		

95% CI, 95% Confidence Interval; CHR, Cox hazard ratio.

TABLE 4. Multivariate Analysis for Survival

Variable	CHR	95% CI	*p*
Age (continuous)	1.00	0.99–1.01	0.591
Gender			
Female	0.78	0.63–0.95	0.013
Male	1		
Postoperative radiation			
Yes	0.70	0.59–0.83	<0.001
No	1		
Histology			
Adenocarcinoma	1		
Squamous cell carcinoma	1.17	0.96–1.41	0.116
T-stage			
T1–2	1		
T3	1.73	1.40–2.15	<0.001
T4	2.11	1.60–2.77	<0.001
Positive lymph nodes			
Yes	1.94	1.59–2.35	<0.001
No	1		
Race			
Black	1.34	0.99–1.81	0.055
Other	0.87	0.61–0.95	0.43
White	1		

95% CI, 95% Confidence Interval; CHR, Cox hazard ratio.

improvement in local control.[21,22] In an attempt to further clarify the impact of postopRT in a prospective fashion, several randomized studies were performed comparing postopRT with surgery alone. However, the majority of the evidence has revealed that postopRT does not confer any survival benefit over surgery alone.

Ténière et al.[10] evaluated 221 patients with epidermoid carcinoma of the middle to lower third of the esophagus who were randomized to postopRT to a dose of 45–55 Gy versus observation. They found that although local control improved from 15 to 30%, there was no survival benefit with the addition of postopRT. Fok et al.[11] also randomized 130 patients with esophageal carcinoma (SCC or AC) to observation versus postopRT to a dose of 49.5 Gy in 3.5 Gy fractions. They found that although local failure was reduced from 31 to 15% ($p = 0.06$), median OS was actually worse in the postopRT arm (8.7 months versus 15.2 months, $p = 0.02$). This trial has been criticized, however, for the high-dose per fraction that may have led to increased mortality in the radiation containing arm. Zieren et al.[12] randomized 68 patients with SCC to either postopRT or surgery alone and found that postopRT significantly increased the fibrotic stricture rate and did not improve OS or disease free survival. Malthaner et al.[23] performed a meta-analysis of 995 patients from five randomized trials of postopRT versus observation. They found that there was no OS benefit with the addition of postopRT, with a risk ratio for death at 1 year of 1.23 (95% CI 0.95–1.59, $p = 0.11$). Therefore, it has been suggested that there are little data to suggest that postopRT affords any survival benefit.[24]

However, all of the aforementioned trials did not stratify the patients based on their stage and likely were not large enough to detect an improvement in survival only for those patients with stage III disease. In addition, both Ténière et al.[10] and Zieren et al.,[12] included patients with positive celiac nodes (stage M1a). These patients are excluded from our study and represent a cohort at much higher risk for distant failure and therefore are less likely to benefit from postopRT. Finally, the meta-analysis included the above flawed trials, but also did not analyze outcome of these patients based on their stage grouping which may obscure the potential benefit of postopRT in patients with stage III disease.

Adding credence to this argument is the results of the largest trial presented in the meta-analysis, which found a survival benefit only for those with stage III disease. Xiao et al.[13] randomized 495 patients with esophageal SCC to radical resection alone versus postopRT to a total dose of 50−60 Gy in 2 Gy fractions. Once again, there was no survival benefit for the entire cohort with the addition of postopRT, with a 5-year OS of 31.7% for surgery alone versus 41.3% for postopRT ($p = 0.4474$). However, when stratifying based on stage, there was a significant survival benefit with postopRT for stage III patients, with an improvement in 5-year OS from 13.1 to 35.1%, ($p = 0.0027$) but not for stage II patients. However, this trial has been criticized for not adhering to intent-to-treat principles. They excluded 54 patients in the postopRT arm from their analysis who did not complete the treatment as prescribed. In addition, informed consent was not obtained prior to enrolling in this study. These questions have led to significant concerns regarding the validity of these data.[24]

Similar to the findings by Xiao et al., our study revealed that postopRT significantly improved OS for patients with stage III disease only. Additionally, although Xiao et al. only evaluated patients with squamous cell carcinoma, we found in our study that postopRT is beneficial for both stage III SCC and AC. The benefit of adjuvant radiation for esophageal AC has not been previously reported in the literature.

The National Comprehensive Cancer Network (NCCN) does recommend postoperative chemoradiation for stages II–III esophageal AC.[25] This recommendation is based on a randomized phase III trial by Macdonald et al.[26] that found that postoperative chemoradiation improved 3-year OS from 41 to 50% in ACs of the stomach and gastroesophageal junction. However, this trial is criticized because 54% of patients had a suboptimal lymph node dissection, and therefore, it is not clear whether the adjuvant treatment compensated for inadequate surgery. Furthermore, although the NCCN uses this trial as the basis for recommending adjuvant treatment, tumors of the thoracic esophagus were not included in this study.

There are several limitations of this study that require comment. One limitation is the lack of chemotherapy data from the SEER database. Adjuvant chemotherapy has been evaluated in three randomized trials, as well as one meta-analysis, and have not revealed an OS benefit.[14–16,27] Therefore, it is unclear whether the inclusion of these data would alter the significance of our findings. Neoadjuvant chemotherapy has been evaluated in multiple randomized trials, as well as two meta-analyses, with conflicting results. Thirion et al.[28] recently performed a meta-analysis on nine randomized trials and 2102 patients. They found an absolute survival benefit of 4% with the addition of neoadjuvant chemotherapy. Gebski et al.[29] reported a meta-analysis on eight randomized trials and 1724 patients and found an absolute survival benefit of 7%, but only in those with ACs. There was no benefit in those with squamous cell carcinomas. However, these studies did not include patients who received postopRT, and it is unclear how neoadjuvant chemotherapy would have affected the outcome in these patients. Nevertheless, without having access to the chemotherapy data, we cannot say for certain that it had no impact on the outcome reported here, and therefore does remain a limitation and potential source of bias in this study.

Other limitations include the lack of information regarding performance status of the patients, margin status, radiation dose, and radiation fields that were used. In an attempt to account for bias in selecting treatment based on performance status, we excluded all patients who survived 3 months or less after surgery was completed. Therefore, patients with poor performance status, who were more likely to die during the perioperative period, were likely excluded from this analysis.

Margin status is also likely to be an important negative prognostic factor and is missing from this database. However, traditionally, it is these patients that would be more likely to have been referred for postopRT, causing a bias toward worse outcome in the patients receiving radiation compared with those undergoing surgery alone. In addition, on univariate

and multivariate analysis, having positive lymph nodes was significantly associated with worse outcome (Tables 3, 4). However, it was those patients with positive lymph nodes who were significantly more likely to receive postopRT (Table 2), likely providing a further bias against improved survival in the postopRT patients. Despite these negative prognostic factors, postopRT is associated with a survival benefit for stage III disease.

The NCCN recommends upfront surgery only for select patients with clinical T1 disease. For all other stages, chemoradiation, preoperative chemoradiation, or preoperative chemotherapy is recommended.[25] Although our results do support the use for postopRT in stage III esophageal cancer, we do not feel that this data provides evidence that primary surgery followed by postopRT should replace the current NCCN recommendations for treatment of this disease.

In conclusion, for those who do undergo primary surgery, the results of this retrospective population-based analysis reveals that there is an association of improved OS and DSS with postopRT for stage III esophageal AC and squamous cell carcinoma. No significant differences were noted for stage IIA or IIB disease, though given the retrospective nature of this analysis, these results may have been underpowered to detect this difference. Given the retrospective nature of this study, until appropriately powered randomized trials confirm these results, caution should be used before broadly applying these findings in clinical practice.

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