The impact of neoadjuvant immunotherapy on perioperative outcomes and survival after esophagectomy for esophageal cancer

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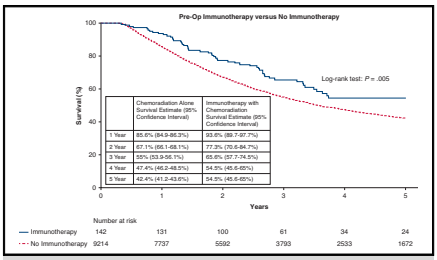
ABSTRACT

Objective: Immunotherapy for esophageal cancer is relatively novel but increasingly used. This study evaluated the early use of immunotherapy as an adjunct to neoadjuvant chemoradiotherapy before esophagectomy for locally advanced disease.

Methods: Perioperative morbidity (composite of mortality, hospitalization ≥21 days, or readmission) and survival of patients with locally advanced (cT3NoMo, cT1-3N + Mo) distal esophageal cancer in the National Cancer Database from 2013 to 2020 who underwent neoadjuvant immunotherapy plus chemoradiotherapy or chemoradiotherapy alone followed by esophagectomy were evaluated using logistic regression, Kaplan–Meier curves, Cox proportional hazards methods, and propensity-matched analysis.

Results: Immunotherapy was used in 165 (1.6%) of 10,348 patients. Younger age (odds ratio, 0.66; 95% confidence interval, 0.53-0.81; $P < .001$) predicted immunotherapy use, which slightly delayed time from diagnosis to surgery versus chemoradiation alone (immunotherapy 148 [interquartile range, 128-177] days vs chemoradiation 138 [interquartile range, 120-162] days, $P < .001$). There were no statistically significant differences between the immunotherapy and chemoradiation groups for the composite major morbidity index (14.5% [24/165] vs 15.6% [1584/10,183], $P = .8$). Immunotherapy was associated with a significant improvement in median overall survival (69.1 months vs 56.3 months, $P = .005$) and 3-year overall survival in univariate analysis (65.6% [95% confidence interval, 57.7-74.5] vs 55.0% [53.9-56.1], $P = .005$), and independently predicted improved survival in multivariable analysis (hazard ratio 0.68 [95% confidence interval, 0.52-0.89], $P = .006$). Propensity-matched analysis also showed that immunotherapy use was not associated with increased surgical morbidity ($P = .5$) but was associated with improved survival ($P = .047$).

Conclusions: Neoadjuvant immunotherapy use before esophagectomy for locally advanced esophageal cancer did not lead to worse perioperative outcomes and shows promising results on midterm survival. (JTCVS Open 2023;14:547-60)



Use of immunotherapy before esophagectomy is associated with improved survival in esophageal cancer.

CENTRAL MESSAGE

Neoadjuvant immunotherapy use before esophagectomy for locally advanced esophageal cancer did not lead to worse perioperative outcomes and shows promising results on midterm survival.

PERSPECTIVE

Immunotherapy has traditionally been studied in advanced or metastatic disease, or in the adjuvant setting. Our study seeks to use a national database to explore the impact of immunotherapy use, in addition to standard chemoradiation regimens, in the preoperative setting in locally advanced, resectable esophageal cancer.

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The incidence of esophageal cancer continues to increase, with an estimate of more than 20,000 new cases in the United States in 2022.[1] Survival of those with esophageal cancer has improved but remains disappointing at approximately 20% overall currently (Fig. 1).[1-3] One reason for improved prognosis is recognition of the benefit of neoadjuvant chemoradiation before esophagectomy for resectable but locally advanced disease, most definitively shown by the CROSS trial.[4] However, that gold standard therapy only improves 5-year survival to 47% compared

Abbreviations and Acronyms
CI = confidence interval
LOS = length of stay
NCDB = National Cancer Database
OS = overall survival

with 33% with surgery alone.[4] Improved treatment options are clearly needed.[5]

A significant general oncologic advance over the past decade has been the ability to "target" therapy based on specific tumor characteristics. Immunotherapy is one area of targeted therapy increasingly used in esophageal cancer, where monoclonal antibodies inhibit cell growth by blocking receptors that mediate cytotoxic T-cell damage to tumor cells.[5,6] Adjuvant nivolumab is now standard of care for patients with locally advanced esophageal cancer who have residual disease after chemoradiation.[7,8] The use of immunotherapy with chemoradiation in the neoadjuvant setting also holds theoretical promise for esophageal cancer, because upregulation of immunotherapy markers by chemoradiation and activation of immune responses by radiation-induced immunologic cell death may increase the potential oncologic benefit of immunotherapy.[6] Neoadjuvant immunotherapy has been used in several phase 2 trials and is currently being investigated in at least 5 other trials.[9-14]

The safety of esophagectomy after immunotherapy has been assessed by only a few small studies. Esophagectomy is already a complex procedure with typically higher potential morbidity than most other cancer surgeries, and surgical resection is necessary for cure in patients with locally advanced disease. Thus, ensuring that induction immunotherapy does not worsen surgical outcomes such that any oncologic benefit is negated is critically important.[8,15,16] Existing literature is growing regarding immunotherapy for esophageal cancer but has been largely focused on use in advanced or metastatic esophageal cancer, rather than resectable disease.[17,18] Thus, the impact of immunotherapy use as an adjunct to standard neoadjuvant chemoradiotherapy before esophagectomy for locally advanced esophageal cancer is not well defined, particularly outside of highly specialized centers. This study aims to analyze a national dataset to evaluate the impact of neoadjuvant immunotherapy use on perioperative and oncologic outcomes. Our hypothesis is that perioperative outcomes after neoadjuvant immunotherapy with chemoradiation is similar to outcomes after neoadjuvant chemoradiation alone.

MATERIALS AND METHODS

Data Source

The National Cancer Database (NDCB) is a comprehensive collection of cancer diagnoses from more than 1500 facilities in the United States. Patients are de-identified in the database; thus, this study was exempt from Stanford Institutional Review Board approval (Protocol 35,143, approved 3/7/2017).

Patient Selection

Patients with Seventh Edition American Joint Committee on Cancer cT3N0M0 or cT1-3N + M0 adenocarcinoma or squamous cell carcinoma of the mid to distal esophagus diagnosed from 2013 to 2020 and treated with neoadjuvant immunotherapy plus chemoradiotherapy or just neoadjuvant chemoradiotherapy alone followed by esophagectomy were included for analysis (Figure E1). The study period was chosen because preliminary analysis of the NCDB esophageal cancer dataset showed only 1 patient who received immunotherapy in 2012 and no patients who received immunotherapy before that year. In the overall analysis, we included patients without missing histology, tumor location, or TNM stage; patients with known use and sequence of surgery, chemotherapy, and radiation; and patients with survival data. Patients with previous malignancies and incompletely recorded follow-up data were not included. The used NCDB dataset only provides follow-up data for patients treated up to the year 2019, so the survival analyses did not include patients treated in 2020.

Postoperative Major Morbidity Definition

The NCDB does not have intraoperative and postoperative details such as operation time, estimated blood loss, rate of transfusion, or cardiac and pulmonary complications. However, it does provide hospital length of stay (LOS), readmission, and 30-day mortality after surgery. Therefore, a definition of postoperative morbidity was constructed using these available parameters, based on a study of the Society of Thoracic Surgeons General Thoracic Surgery Database that showed a mean LOS of 10.6 days for patients with uncomplicated esophagectomy versus a mean LOS of 25.6 days for patients with perioperative complications.[19] The occurrence of major morbidity in our study was thus defined as the occurrence of 30-day death, a hospital stay after surgery more than 20 days, or readmission.

Perioperative and Survival Analyses

We estimated independent predictors of receiving preoperative immunotherapy using multivariable logistic regression, looking at variables such as age, sex, race, insurance, Charlson comorbidity index, income, education, distance to facility, tumor histology, clinical T stage, clinical N stage, tumor location, and facility type. Perioperative outcomes were analyzed stratifying the entire cohort into 1 group that had neoadjuvant immunotherapy plus chemoradiation and another group that just received neoadjuvant chemoradiation. Univariate analysis was performed to compare the rates of major morbidity and mortality, as well as hospital LOS, readmission rates, nodes examined, T and N pathological staging, margins, and adjuvant treatment. Independent predictors of major morbidity were evaluated with multivariable logistic regression, considering age, sex, race, insurance, Charlson comorbidity index, income, education, distance to facility, tumor histology, clinical T stage, clinical N stage, tumor location, facility type, and immunotherapy use. Patients who had missing data for any of the potential predictor variables were excluded from these regression analyses.

Survival was evaluated using Kaplan–Meier curves, log-rank test, and Cox proportional hazards methods. The primary end point was 3-year overall survival (OS). This midterm survival period was chosen given the recent years of the study precluded longer-term follow-up for many of the included patients. Variables chosen a priori for inclusion in the Cox model were patient (age, sex, comorbidities) and tumor/oncologic characteristics (histology, location, T stage, nodal involvement, adjuvant systemic therapy) previously shown or clinically expected to be potentially associated with survival, along with the study variable of interest: exposure to preoperative immunotherapy. The Cox models were adjusted for clustering by hospital by including the specific facility in the model as a random effect.

Because of the method of patient selection for the cohort, none of the patients had missing data in the variables considered in the Cox analysis, although the survival analysis did not include patients in the cohort who were diagnosed in the year 2020 (n = 992), because follow-up data were not recorded for these patients.

Propensity Matching Analysis

Patients were matched based on propensity scores using a 3:1 nearest neighbor algorithm (R software: MatchIt-Nonparametric Preprocessing for Parametric Casual Inference) with the immunotherapy group consisting of 165 patients and the matched no immunotherapy group consisting of 495 patients. The following covariates were used for matching: age, gender, race, education, income, comorbidity profile, insurance, tumor histology, tumor location, T stage, nodal status, and facility type. After propensity matching, balance was assessed between groups based on standardized differences (R software: Nonrandom-Stratification and matching by the propensity score). Major morbidity between groups was compared using the chi-square test, and survival between groups was assessed with the Kaplan–Meier method and log-rank test.

Statistical Analysis

The data were analyzed using R version 3.6.1 (R Foundation for Statistical Computing). Baseline demographic and preoperative clinical characteristics between groups were compared with the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test for discrete variables. The Fisher exact test was used for those discrete variables with fewer than 5 outcomes.

RESULTS

Patient Cohort and Characteristics Stratified by Immunotherapy Use

Of the 10,348 patients who met inclusion criteria, preoperative immunotherapy was used in 165 patients (1.6%) (Table 1). There were no statistically significant differences between patients who did or did not receive immunotherapy regarding sex, race, Charlson comorbidity index, or clinical T stage in univariate analysis. However, younger age, having clinically positive nodal disease, living in a census tract with higher education levels, adenocarcinoma histology, and distal tumor location were all associated with immunotherapy use in univariate analysis. Facility esophagectomy volumes were also higher for patients who received immunotherapy. Younger age, adenocarcinoma histology, and treatment at a research/academic facility were all independent predictors of neoadjuvant immunotherapy in multivariable analysis (Table 2). Use of immunotherapy was associated with a longer interval between diagnosis and surgery (148; interquartile range, 122-177) days in the immunotherapy group vs 138 [interquartile range, 120-162] days in the chemoradiation group ($P < .001$).

Impact of Immunotherapy on Perioperative Esophagectomy Outcomes

Table 3 shows perioperative outcomes stratified by whether or not neoadjuvant immunotherapy was given before esophagectomy. Use of immunotherapy was associated with higher rates of complete pathologic response and nodal downstaging, but did not impact the occurrence of positive margins. There were no statistically significant differences between the immunotherapy and chemoradiation groups for both the composite major morbidity index (14.5% [24/165] vs 15.6% [1584/10,183], $P = .8$) and individual hospital LOS (9 vs 9 days, $P = .4$), unplanned readmission (6.7% vs 5.3%, $P = .5$), 30-day mortality (1.4% vs 2.9%, $P = .4$), and 90-day mortality (3.6% vs 6.9%, $P = .17$). The immunotherapy group was more likely to receive adjuvant systemic therapy (31.5% vs 5.9%, $P < .001$).

Table 4 illustrates the multivariable analysis performed to assess potential predictors of a complicated perioperative course for patients to further evaluate the potential independent impact of immunotherapy use on short-term outcomes. Immunotherapy did not have an association with morbidity (odds ratio, 0.92; 95% confidence interval [CI], 0.54-1.57; $P = .76$). Older age, Charlson comorbidity index 2 or greater, clinical T2 status, and treatment at an academic or research facility showed increased perioperative risk of a complicated perioperative course, whereas living in a census tract with income levels above the median was protective against perioperative complications.

Survival Stratified by Immunotherapy Use

Figure 2 illustrates survival stratified by neoadjuvant immunotherapy plus chemoradiation use versus neoadjuvant chemoradiation alone. Immunotherapy was associated with a significant improvement in median survival (69.1 months vs 56.3 months, $P = .005$) and 3-year OS (65.6% [95% CI, 57.7-74.5] vs 55.0% [95% CI, 53.9-56.1], $P = .005$) in univariate analysis. Neoadjuvant immunotherapy was also associated with better survival in the Cox model hazard ratio (0.68 [95% CI, 0.52-0.89], $P = .006$) (Table 5). Older age, higher T stage, clinical nodal involvement, increasing comorbidity status, mid-esophageal location, and adjuvant systemic therapy were all associated with worse survival, whereas female sex and squamous cell carcinoma histology were associated with improved survival.

Propensity Score Analysis

Propensity score matching led to groups that were well matched as a comprehensive cohort (Table E1). The previously statistically significant increase in rate of adjuvant systemic therapy use in the immunotherapy group was no longer present in the matched groups (Table E2). As described in the primary analysis, there were no statistically significant differences between the groups in terms of the morbidity composite as well as the individual outcomes of 30-day mortality, readmission, and hospital LOS. Neoadjuvant immunotherapy patients did have a slightly longer interval between diagnosis and surgery compared with chemoradiation alone (148 vs 140 days, $P = .006$), although

TABLE 1. Characteristics of entire cohort and stratified by neoadjuvant immunotherapy plus chemoradiotherapy or just chemoradiotherapy alone

	Total (n = 10,348)	Preoperative immunotherapy (n = 165)	Chemoradiotherapy only (n = 10,183)	*P* value
Age, median [IQR]	63 (57-69)	61 (54-67)	63 (57-69)	<.001
Female	1621 (15.7%)	24 (14.5%)	1597 (15.7%)	.771
Race				.193
White	9598 (93.4%)	157 (95.2%)	9441 (93.4%)	
Black	376 (3.7%)	2 (1.2%)	374 (3.7%)	
Other	304 (3%)	6 (3.6%)	298 (2.9%)	
Insured	10,051 (98.3%)	157 (96.9%)	9894 (98.4%)	.198
Charlson comorbidity index				.367
0	7299 (70.5%)	124 (75.2%)	7175 (70.5%)	
1	2134 (20.6%)	27 (16.4%)	2107 (20.7%)	
2+	915 (8.8%)	14 (8.5%)	901 (8.8%)	
Income above median	5451 (62.3%)	88 (68.8%)	5363 (62.2%)	.152
Education above median	5518 (63%)	93 (72.1%)	5425 (62.9%)	.039
Distance to facility, median [IQR]	17.6 (7.2-45.4)	18.6 (9.6-52.9)	17.6 (7.2-45.4)	.131
Tumor histology				.001
Adenocarcinoma	8861 (85.6%)	156 (94.5%)	8705 (85.5%)	
Squamous cell carcinoma	1487 (14.4%)	9 (5.5%)	1478 (14.5%)	
Location				.027
Distal esophagus	9236 (89.3%)	156 (94.5%)	9080 (89.2%)	
Mid esophagus	1112 (10.7%)	9 (5.5%)	1103 (10.8%)	
Clinical T stage				.815
1	225 (2.2%)	3 (1.8%)	222 (2.2%)	
2	1298 (12.5%)	23 (13.9%)	1275 (12.5%)	
3	8825 (85.3%)	139 (84.2%)	8686 (85.3%)	
Clinical N stage				.018
0	2992 (28.9%)	34 (20.6%)	2958 (29%)	
1	7356 (71.1%)	131 (79.4%)	7225 (71%)	
Facility type				.059
Community program	479 (4.7%)	5 (3.1%)	474 (4.7%)	
Comprehensive community	2926 (28.6%)	34 (21.4%)	2892 (28.8%)	
Integrated network program	1873 (18.3%)	27 (17%)	1846 (18.4%)	
Research/academic program	4935 (48.3%)	93 (58.5%)	4842 (48.2%)	
Facility esophagectomy volume (median [IQR])	3.000 [1.75-6.000]	5.25 [2.250-11.875]	3.000 [1.75-6.000]	<.001
Minimally invasive surgical approach	3994 (38.6%)	72 (43.6%)	3922 (38.5%)	.18
Days from diagnosis to surgery	138 (120-162)	148 (128-177)	138 (120-162)	<.001

IQR, Interquartile range.

this 8-day difference is not likely to be clinically meaningful. Immunotherapy also had a statistically significant association with improved survival in the matched groups (median survival of 67.7 months vs 58.3 months ($P = .047$) and 3-year OS 65.6% [95% CI, 57.7-74.5] vs 56.9% [95% CI, 52.2-61.9]) (Figure E2).

DISCUSSION

Immunotherapy is an exciting topic in oncology, specifically in esophageal cancer. This current study of the early use of neoadjuvant immunotherapy combined with chemoradiation before esophagectomy supports continuing investigations in esophageal cancer care. Our results demonstrate that preoperative immunotherapy is more likely to be given in high-volume esophagectomy centers and research and academic hospitals, which is an unsurprising yet important factor to note in current practices. The use of neoadjuvant immunotherapy did not cause clinically significant delays in surgery and was not associated with worse perioperative outcomes. Immunotherapy use was associated with more nodes examined, higher rates of complete pathologic response, and more nodal downstaging. Immunotherapy use was associated with improved survival in univariate and multivariate analyses, and this improvement in

TABLE 2. Multivariable analysis of potential predictors of neoadjuvant immunotherapy use

	Odds ratio (95% CI Lower-95% CI higher)	*P* value
Age (per decade)	0.659 (0.534-0.813)	<.001
Female (vs male)	0.923 (0.529-1.609)	.776
Race (vs White)		
Black	0.328 (0.044-2.421)	.274
Other	1.401 (0.496-3.963)	.524
Insured (vs not insured)	0.761 (0.236-2.458)	.648
Charlson comorbidity index (vs 0)		
1	0.834 (0.514-1.352)	.461
≥2	1.157 (0.611-2.19)	.655
Income above median	1.016 (0.649-1.593)	.943
Education above median	1.457 (0.914-2.324)	.114
Distance to facility (per 50 miles)	1.03 (0.999-1.063)	.056
Squamous cell carcinoma histology (vs adenocarcinoma)	0.396 (0.167-0.938)	.035
Clinical T stage (vs T1)		
T2	100 (0-100)	.976
T3	100 (0-100)	.976
Clinical N positive (vs N negative)	1.298 (0.842-2.001)	.237
Mid esophagus tumor location (vs distal location)	0.943 (0.431-2.067)	.884
Facility type (vs community program)		
Integrated network program	1.55 (0.878-2.738)	.131
Research/academic	1.803 (1.148-2.832)	.011

CI, Confidence interval.

survival held true in propensity-matched analysis. These findings all support the continued investigation into the use of immunotherapy before surgery for esophageal cancer.

The use of immunotherapy in the treatment of esophageal cancer began with the subgroup of patients with unresectable or metastatic disease. Several randomized controlled trials such as ATTRACTION-3, ESCORT, and KEYNOTE-181 have shown effectiveness with the use of nivolumab, camrelizumab and pembrolizumab, respectively.[20-22] Although this was a big step forward in the treatment of esophageal cancer, the results from these

TABLE 3. Perioperative outcomes (unadjusted) stratified by whether neoadjuvant immunotherapy was used in the neoadjuvant setting in esophageal cancer

	Preoperative immunotherapy (n = 165)	Chemoradiotherapy only (n = 10,183)	*P* value
Days to definitive surgery	148 (128, 177)	138 (120, 162)	<.001
30-d mortality	2 (1.4%)	260 (2.9%)	.443
90-d mortality	5 (3.6%)	624 (6.9%)	.173
Major morbidity	24 (14.5%)	1584 (15.6%)	.805
Hospital LOS, days, median [IQR]	9 (7-13)	9 (7-13)	.389
Unplanned readmission	11 (6.7%)	537 (5.3%)	.542
Nodes examined	17 (11, 24.8)	15 (10, 21)	.018
Complete response	48 (29.1%)	2156 (21.2%)	.018
T downstaging	96 (58.2%)	5576 (54.8%)	.425
N downstaging	82 (49.7%)	4092 (40.2%)	.017
Positive surgical margins	8 (4.9%)	541 (5.5%)	.901
Adjuvant radiation	3 (1.8%)	50 (0.5%)	.052
Adjuvant systemic therapy	52 (31.5%)	600 (5.9%)	<.001

LOS, Length of stay; *IQR*, interquartile range.

TABLE 4. Multivariable analysis of potential predictors of a complicated perioperative course (defined as a composite index of the occurrence of 30-day death, a hospital stay after surgery more than 20 days, or readmission) for patients treated with preoperative immunotherapy to evaluate if preoperative immunotherapy increases operative risk

	Odds ratio (95% CI Lower-95% CI higher)	*P* value
Age (per decade)	1.23 (1.144-1.322)	<.001
Female (vs male)	1.071 (0.907-1.264)	.417
Race (vs White)		
Black	1.098 (0.801-1.506)	.56
Other	1.36 (0.973-1.902)	.072
Insured (vs not insured)	0.655 (0.428-1.002)	.051
Charlson comorbidity index (vs 0)		
1	1.131 (0.977-1.309)	.099
≥2	1.342 (1.098-1.64)	.004
Income above median	0.834 (0.722-0.963)	.013
Education above median	0.873 (0.756-1.008)	.064
Distance to facility (per 50 miles)	0.979 (0.955-1.005)	.109
Squamous cell carcinoma tumor histology (vs adenocarcinoma)	1.124 (0.917-1.377)	.259
Clinical T stage (vs T1)		
T2	1.778 (1.071-2.95)	.026
T3	1.501 (0.923-2.443)	.102
Clinical N positive (vs N negative)	0.995 (0.868-1.14)	.939
Mid esophagus tumor location (vs distal location)	1.11 (0.898-1.372)	.335
Facility type (vs community program)		
Integrated network program	1.187 (0.996-1.415)	.055
Research/academic	1.281 (1.115-1.472)	<.001
Immunotherapy	0.921 (0.54-1.571)	.762

CI, Confidence interval.

trials did not provide any information on the intraoperative and postoperative effect of immunotherapy that could impact patients having esophagectomy. However, findings from treatment of other malignancies such as non–small cell lung cancer have raised potential concern over the impact of neoadjuvant immunotherapy use on short-term surgical outcomes, which may be particularly important given that esophagectomy is already known to be associated with significant potential morbidity.[15,23] Known side effects of PD-1 and PD-L1 specific inhibitors such as pneumonitis and other autoimmune toxicities are a source of concern because they have been shown to increase surgical difficulty. A case series by Chaft and colleagues[24] showed feasibility and success of lung resection after neoadjuvant immunotherapy but observed the presence of dense mediastinal and hilar fibrosis, particularly in patients who were strong responders to the immunotherapy drug studied. Likewise, a phase 1 trial by Bott and colleagues[25] demonstrated a conversion rate of 54% from minimally invasive approaches to open thoracotomies due to hilar inflammation and fibrosis presumably secondary to immunotherapy. Nevertheless, ongoing trials in lung cancer continue to show high rates of R0 resection and major pathologic response with subsequent high rates of progression-free survival with the use of neoadjuvant immunotherapy. Of note, our current study does not suggest that neoadjuvant immunotherapy use delays surgery or worsens short-term outcomes, supporting the continued use and investigation of immunotherapy before esophagectomy for esophageal cancer.[26]

Although there is a lack of randomized clinical trials investigating the effect of neoadjuvant immunotherapy on long-term esophageal cancer outcomes due to its novelty, there have been some publications purporting its benefit. A meta-analysis by Wang and colleagues[27] reviewed 20 articles and found that the rates of pathologic complete response and R0 resection were higher in patients who had neoadjuvant immunotherapy and chemotherapy as opposed to standard chemoradiotherapy. They also found less treatment-related adverse events and no increase in surgical delay or intraoperative complications in the immunotherapy group, showing that immunotherapy is safe as a neoadjuvant treatment in esophageal cancer. Sihag and colleagues[28] retrospectively analyzed the use of neoadjuvant immunotherapy in addition to chemoradiotherapy in a modern cohort from a large American cancer center and found

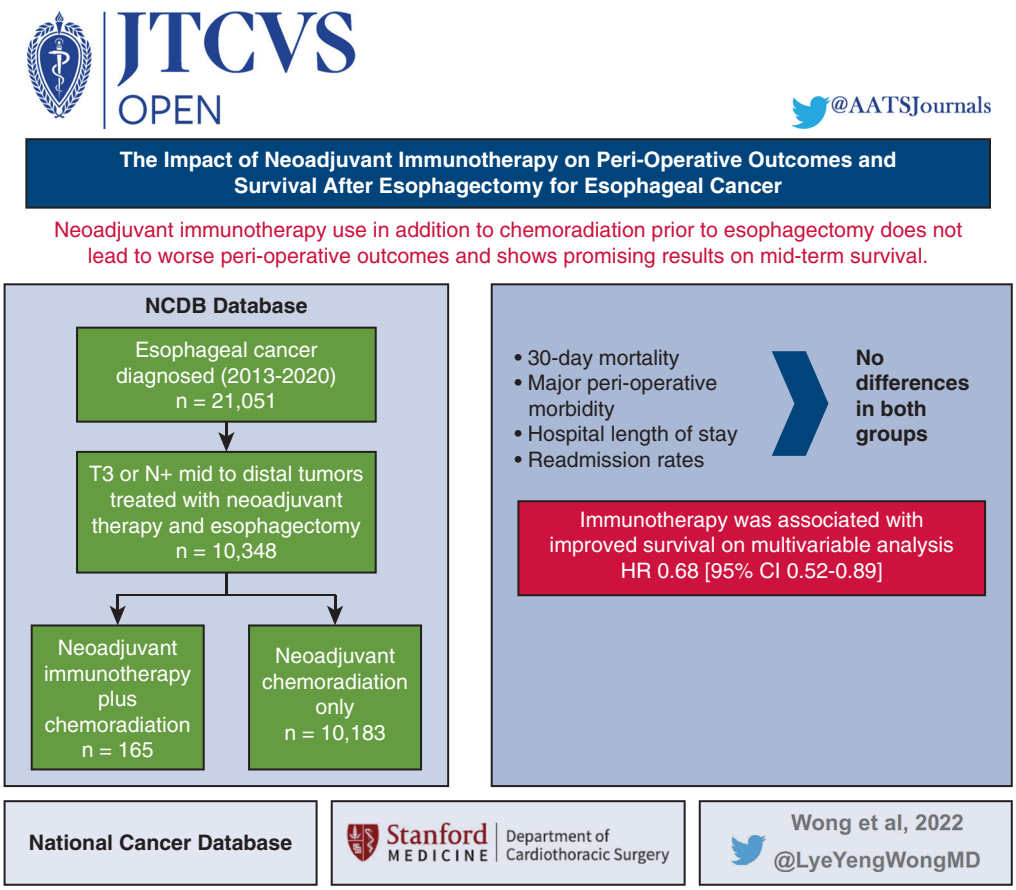

FIGURE 1. Visual abstract.

that 30-day perioperative outcomes were not statistically significant between groups, which aligns with our results from this study.

Stepping stones such as the aforementioned trials have paved the way for ongoing esophageal cancer studies that will provide us key principles and guidelines for the use

TABLE 5. Cox proportional hazards model (adjusted for clustering) for overall survival in patients treated with induction chemoradiation with or without immunotherapy and surgery for locally advanced esophageal cancer

	Odds ratio (95% CI lower-95% CI higher)	*P* value
Age (per decade)	1.15 (1.11-1.19)	<.001
Female (vs male)	0.80 (0.74-0.87)	<.001
Squamous cell carcinoma (vs adenocarcinoma)	0.86 (0.78-0.95)	.003
Clinical T stage (vs T1)		
T2	1.12 (0.90-1.42)	.31
T3	1.44 (1.16-1.79)	<.001
Clinical N positive	1.28 (1.20-1.37)	<.001
Charlson comorbidity index (vs 0)		
1	1.12 (1.04-1.20)	.001
2+	1.30 (1.17-1.43)	<.001
Mid esophagus location (vs distal location)	1.23 (1.11-1.36)	<.001
Neoadjuvant immunotherapy	0.68 (0.52-0.89)	.006
Adjuvant systemic therapy	1.17 (1.04-1.31)	.008

CI, Confidence interval.

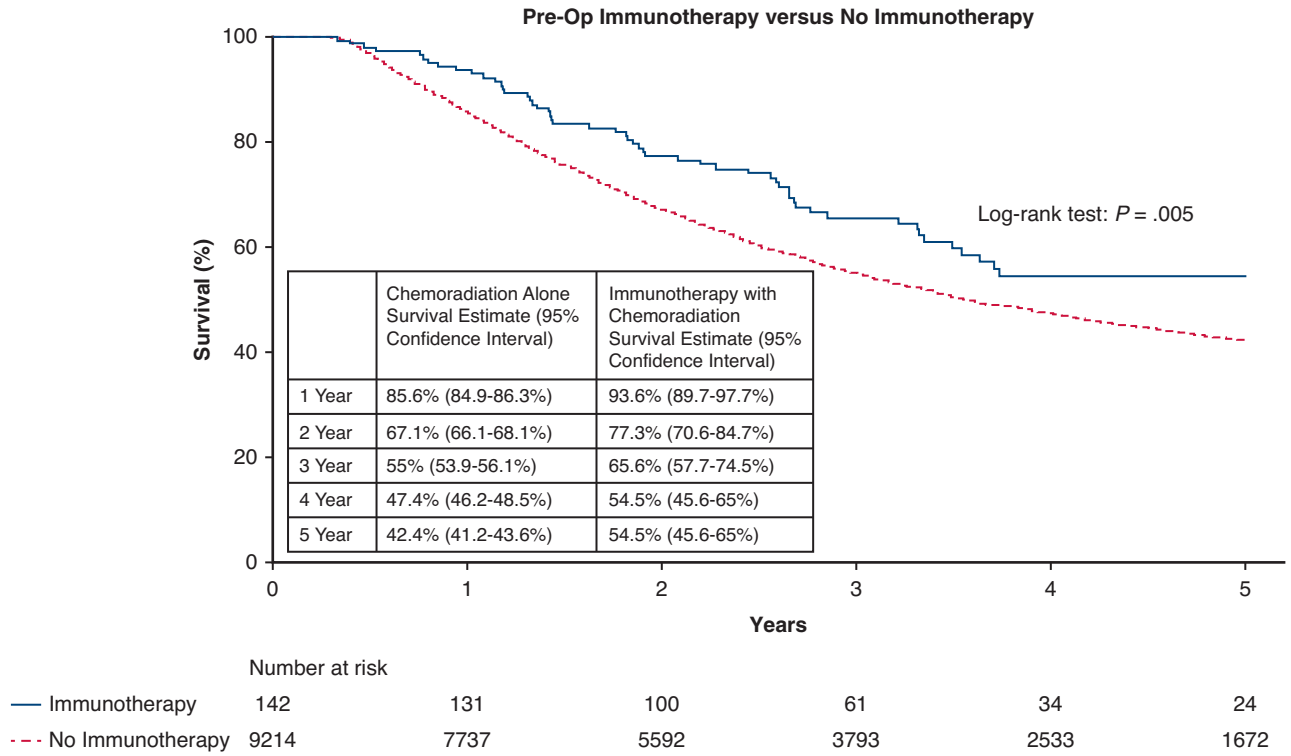

FIGURE 2. Kaplan–Meier survival curves stratified by whether neoadjuvant immunotherapy was given in addition to just chemoradiotherapy alone.

of neoadjuvant immunotherapy. The PERFECT trial published in 2021 was a phase II feasibility trial that used 5 cycles of atezolizumab in addition to standard neoadjuvant chemoradiation for resectable esophageal cancer.[29] The number of treatment-related adverse effects from immunotherapy was comparable to rates reported in the CROSS trial demonstrating its safety and efficacy. Although the addition of atezolizumab did not seem to affect the number of responders as measured through pathologic complete response and preoperative and intraoperative progression rates, those who did respond derived long-term benefits as seen in OS and disease-free survival on long-term follow up.

Although immunotherapy seems well tolerated by the average patient on large analyses such as ours, its use is still not risk free. According to our results, younger patients are more likely to receive immunotherapy; thus, its use must also be studied in the elderly population to fully understand the side effect profile on perioperative outcomes. It will be imperative to distinguish patients who have unique clinical and tumor characteristics that predict strong responsiveness to immunotherapy so that physicians can triage neoadjuvant treatment accordingly. Prognostic biomarkers in adenocarcinoma and squamous cell carcinoma, and the correlation of PD-L1 expression and compete pathologic response rates are not well defined, but large retrospective studies will hopefully be able to elucidate trends and patterns that result in preliminary findings to inform the running of larger clinical trials.[30-32] Moreover, our results showed that patients with education above the median were more likely to receive immunotherapy, which highlights the potential disparity in esophageal cancer care. This finding highlights the important responsibility physicians hold during the shared decision-making process, ensuring that patients of various medical literacy and socioeconomic status understand their available treatment options. Our results interestingly showed that adjuvant systemic therapy was associated with worse survival. We speculate that giving additional postresection therapy may have been a marker of a patient being perceived to have worse disease or a higher chance or recurrence, in a way that may not be determinable from the NCDB dataset. In addition, we speculate that perhaps giving additional systemic therapy could perhaps be related to life-threatening treatment related complications that worsened survival. Finally, patients who received preoperative immunotherapy may have been more likely to also received postoperative immunotherapy, and thus would have been recorded as receiving additional systemic therapy.

Study Strengths and Limitations

A strength of this study is using a national dataset that allows assessment of longer-term outcomes. The study's results are likely more generalizable than small studies from highly specialized centers, although the still small sample size in this early immunotherapy experience is still a

considerable limitation on the power of the study to make definitive comments on several clinical issues related to immunotherapy use in this way. Our study has several limitations, mainly with respect to the retrospective nature and lack of specific perioperative data in regards to both specific esophagectomy surgical approach as well as specific complications, which led to our inferred definition for major morbidity. There was a lack of detail regarding pretreatment programmed death-ligand 1 status and the immunotherapy agents/doses given to patients, which potentially reflects uncontrolled heterogeneity in the immunotherapy group. The rationale for using immunotherapy in a setting where it is not yet considered standard therapy can also lead to uncontrolled selection bias, both in cases where patients may have been perceived to have more advanced or unresectable disease, or where patients are more fit to tolerate novel aggressive therapy and be enrolled in clinical trials. It is also possible that patients who sought treatment at more specialized centers may have had better support overall that allowed better tolerance of therapies. Education level, possibly a marker of socioeconomic status, was statistically significant between the 2 groups with higher rates of patients with education above the median in the immunotherapy group. We did try to control for that possible selection bias with both multivariable analysis and propensity matching using available metrics, but the possibility of unmeasured confounding associated with immunotherapy remain. Finally, we only evaluated patients who received chemoradiation and not chemotherapy alone and who completed both neoadjuvant therapy and surgery. Therefore, our study cannot comment on immunotherapy use when induction chemotherapy alone is used, which may be the preferred practice pattern at some centers for distal esophageal or gastroesophageal junction adenocarcinomas. Patients also may have been started on treatment with immunotherapy and plans for subsequent surgery, but then not able to have proceeded with surgery due to complications from immunotherapy; this study design and the used dataset do not allow for assessment of this important clinical scenario that obviously can impact a patient's treatment and outcomes.

CONCLUSIONS

The CROSS trial published a decade ago was revolutionary in changing the landscape of esophageal cancer treatment. More recent data with longer-term follow-up results continue to confirm the benefits of neoadjuvant chemoradiation for resectable esophageal cancer.[33] Immunotherapy is currently in the beginning stages but may become a practice change of a similar magnitude. With more randomized control trials and continued integration into standard practice, neoadjuvant immunotherapy could create a dynamic shift in improving morbidity and mortality in one of the most common yet deadly malignancies worldwide. Within the constraints of our study design, the results show neoadjuvant immunotherapy with chemoradiation can be safe for esophageal cancer and support continued study into its use.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: chemoradiation, esophageal cancer, immunotherapy, neoadjuvant, survival

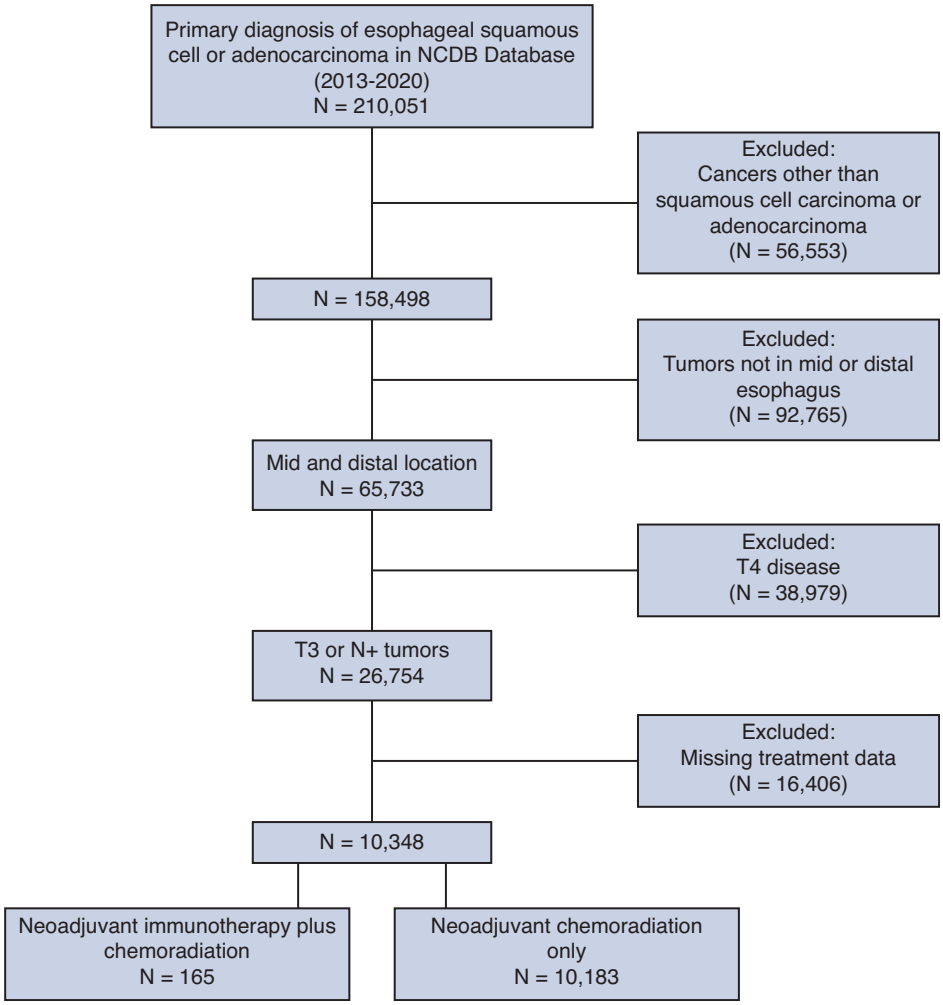

FIGURE E1. CONSORT diagram. *NCDB*, National Cancer Database.

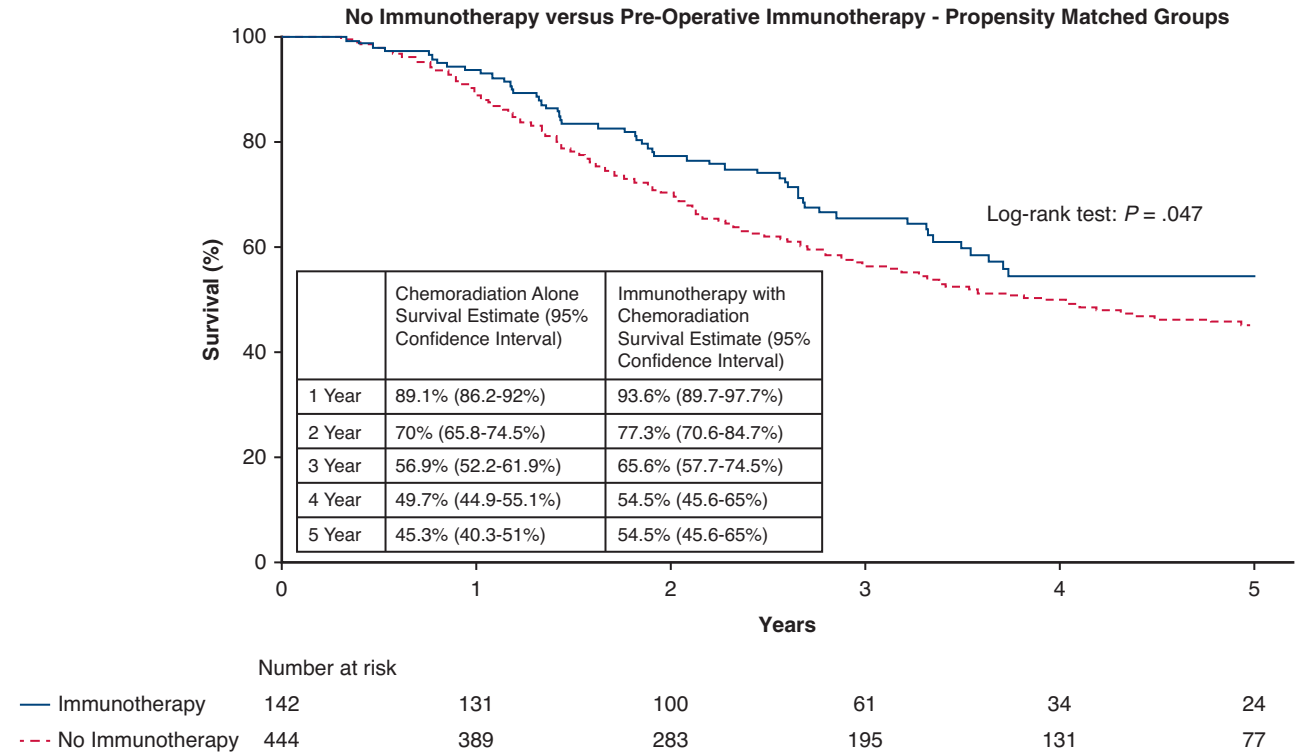

FIGURE E2. Kaplan–Meier survival curves between propensity-matched patients, stratified by whether neoadjuvant immunotherapy was given in addition to just chemoradiotherapy alone.

TABLE E1. Baseline characteristics of propensity-matched patients treated with immunotherapy and chemoradiation versus chemoradiation alone

	Preoperative immunotherapy (n = 165)	Chemoradiotherapy only (n = 495)	*P* value	Standardized mean differences
Age, median [IQR]	61 (54-67)	60 (54-67)	.812	0.0147
Female	24 (14.5%)	68 (13.7%)	.897	0.0229
Race			.945	
White	157 (95.2%)	472 (95.4%)		0.0094
Black	2 (1.2%)	8 (1.6%)		0.0369
Other	6 (3.6%)	15 (3%)		0.0324
Insured	157 (96.9%)	472 (97.1%)	.999	0.0094
Charlson comorbidity index			.932	
0	124 (75.2%)	378 (76.4%)		0.0280
1	27 (16.4%)	75 (15.2%)		0.0328
≥2	14 (8.5%)	42 (8.5%)		0.0000
Income above median	88 (68.8%)	271 (68.8%)	.999	0.0283
Education above median	93 (72.1%)	276 (69.9%)	.713	0.0538
Facility type			.541	
Community program	5 (3.1%)	14 (3%)		0.0118
Comprehensive community	34 (21.4%)	78 (16.5%)		0.1199
Integrated network program	27 (17%)	91 (19.2%)		0.0546
Research/academic	93 (58.5%)	291 (61.4%)		0.0489
Tumor histology			.517	0.3990
Adenocarcinoma	156 (94.5%)	474 (95.8%)		
Squamous cell carcinoma	9 (5.5%)	21 (4.2%)		
Tumor location			.839	0.2368
Distal esophagus	156 (94.5%)	470 (94.9%)		
Mid esophagus	9 (5.5%)	25 (5.1%)		
Clinical T stage			.439	
T1	3 (1.8%)	10 (2%)		0.0271
T2	23 (13.9%)	51 (10.3%)		0.0410
T3	139 (84.2%)	434 (87.7%)		0.0290
Clinical N stage			.038	0.0766
N negative	34 (20.6%)	143 (28.9%)		
N positive	131 (79.4%)	352 (71.1%)		

IQR, Interquartile range.

TABLE E2. Perioperative outcomes of propensity-matched patients treated with immunotherapy and chemoradiation versus chemoradiation alone

	Preoperative immunotherapy (n = 165)	Chemoradiotherapy only (n = 495)	*P* value
Days from diagnosis to surgery	148 (128-177)	140 (121-163)	.006
30-d mortality	2 (1.4%)	8 (1.8%)	.999
90-d mortality	5 (3.6%)	16 (3.7%)	.999
Major morbidity composite	24 (14.5%)	60 (12.1%)	.5
Hospital LOS, median (IQR)	9 (7-13)	8 (7-12)	.102
Unplanned readmission	11 (6.7%)	22 (4.4%)	.468
Nodes examined	17 (11-24.8)	15 (10-22)	.06
Complete response	48 (29.1%)	98 (19.8%)	.017
T downstaging	96 (58.2%)	246 (49.7%)	.072
N downstaging	82 (49.7%)	208 (42%)	.103
Positive surgical margins	8 (4.9%)	35 (7.4%)	.377
Adjuvant radiation	3 (1.8%)	13 (2.6%)	.772
Adjuvant systemic therapy	52 (31.5%)	159 (32.1%)	.962

LOS, Length of stay; *IQR*, interquartile range.