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ORIGINAL RESEARCH—CLINICAL

Immunotherapy Plus Chemoradiation Improves Overall Survival in Stage IV Esophageal Cancer: A Cohort Study

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BACKGROUND AND AIMS: The association of immunotherapy in combination with radiation therapy (RT) or chemoradiation with the overall survival (OS) of patients diagnosed with stage IV esophageal cancer (EC) is unknown. The aim of the current study is to explore the association of immunotherapy with OS in patients with advanced stage EC who received chemotherapy, RT, or chemoradiation. **METHODS:** We conducted a cohort study using the National Cancer Database and included patients diagnosed between 2013 and 2020 with stage IV esophageal adenocarcinoma or squamous cell carcinoma. The association of immunotherapy with OS was assessed with Cox proportional hazards regression, adjusted for age at diagnosis, race, sex, stage, histology, Charlson score, education, income, insurance, hospital type, place of living, region, distance to facility, year of diagnosis, and treatment modality. **RESULTS:** Of 18,260 patients, 2946 (17%) received immunotherapy. In the multivariable COX analysis, patients who received immunotherapy had significantly improved OS compared with no immunotherapy (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.67–0.75; $P < .001$). Chemotherapy plus immunotherapy was associated with improved OS compared to chemotherapy alone (HR: 0.69; 95% CI: 0.64–0.75; $P < .001$). RT plus immunotherapy was associated with improved OS compared to RT alone (HR: 0.60; 95% CI: 0.46–0.78; $P < .001$). Treatment with chemoradiation plus immunotherapy was associated with significantly improved OS compared with chemoradiation alone (HR 0.78; 95% CI: 0.71–0.86; $P < .001$). **CONCLUSION:** The addition of immunotherapy to chemotherapy, RT, and chemoradiation was associated with improved OS compared with chemotherapy alone, RT alone, or chemoradiation alone in patients with stage IV EC.

Keywords: Immunotherapy; Esophageal Cancer; Chemotherapy; Chemoradiation

Introduction

Each year in the United States, more than 19,000 people are diagnosed with esophageal cancer (EC), and more than 15,000 people die from it.[1] Survival of patients diagnosed with stage IV EC is poor, with only 5% surviving 5 years.[2] Esophageal squamous cell carcinoma (ESCC) is the predominant type worldwide, while esophageal adenocarcinoma (EAC) is more common in the United States and other Western countries.[3] Systemic chemotherapy is a standard of care treatment for metastatic EC with preferred first-line regimens being fluoropyrimidine (fluorouracil or capecitabine) combined with oxaliplatin or cisplatin.[4] Trastuzumab is added to the first-line chemotherapy regimens in human epidermal growth factor receptor 2-positive metastatic adenocarcinoma patients.[4,5] The role of surgery and radiation therapy (RT) remains controversial in these patients.[6–8] In principle, all treatments in these patients are considered palliative.[2,4,9] Some of the stage IV patients who are medically fit and have oligometastases may receive definitive concurrent chemoradiation or sequential chemoradiation.[4] However, the overall survival (OS) with chemotherapy is still disappointing with a median OS of 6–10 months and the majority of the patients succumb to the disease.[10–12] Therefore, novel treatment strategy such as immunotherapy is desperately needed to improve the OS outcomes of the patients.

Immunotherapy first made inroads in cancer in the setting of metastatic melanoma with ipilimumab (an anti-cytotoxic T-lymphocyte-associated antigen 4) in 2011 and pembrolizumab (anti-programmed death-1) in 2014.[13,14] Since this time, the role of immunotherapy has expanded to include various malignancies, including EC.[15,16] In 2021, the U.S. Food and Drug Administration approved nivolumab in combination with chemotherapy for the initial treatment of patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and EAC.[17] In CHECKMATE-649, a clinical trial of nivolumab plus chemotherapy was associated with improved OS compared to chemotherapy (hazard ratio [HR]: 0.80; confidence interval [CI]: 0.71, 0.90).[17] In CHECKMATE-648, a clinical trial of nivolumab plus chemotherapy and nivolumab plus ipilimumab were associated with higher OS compared to chemotherapy alone in advanced ESCC (HR: 0.74; CI: 0.58–0.96; $P = .002$ and HR: 0.78; CI: 0.62–0.98; $P = .01$).[18]

Abbreviations used in this paper: **CI, confidence interval; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; NCDB, National Cancer Database; OS, overall survival; RT, radiation therapy.**

Most current article

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Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy for patients with metastatic or locally advanced esophageal carcinoma who are not candidates for surgical resection or definitive chemoradiation was approved based on the findings from KEYNOTE-590, a multicenter randomized trial.[19] Patients who received pembrolizumab plus chemotherapy had better OS compared to the placebo plus chemotherapy arm (HR: 0.73; 95% CI: 0.62, 0.86; $P < .0001$).[19] Pembrolizumab has also been approved based on the findings from KEYNOTE-180 and KEYNOTE-181 for locally advanced or metastatic ESCC patients who progressed on one or more lines of standard treatments and have a programmed death ligand 1 expression combined positive score of ≥ 10.[18,19] Patients who received pembrolizumab had better OS compared to chemotherapy (HR: 0.64; 95% CI: 0.46–0.90; $P < .001$).[20]

The improvement in patient outcomes with immunotherapy in metastatic EC seen in the clinical trial setting is difficult to generalize to other patients as clinical trials are universally based on a small number of specifically defined patients who are treated in prestigious medical centers with optimal support services and follow-up. Patients participating in clinical trials have unique characteristics that are different from regular cancer patients. Studies investigating the role of immunotherapy in combination with current standard of care treatments using real-world data are lacking. The objectives of the current study are to investigate the association of immunotherapy combined with chemotherapy, RT, and chemoradiation with the OS of ESCC and EAC patients using the National Cancer Database (NCDB). We also want to report treatment patterns and trends in the use of immunotherapy in stage IV EC patients.

Methods

Data Source

The data for the current study were extracted from the NCDB, the largest hospital-based cancer registry in the United States, a consortium of 1500 commission on accredited cancer hospitals. It captures more than 70% of cancer cases diagnosed in the United States annually and as of 2022, it contains information about approximately 34 million cancer cases.

Study Population

Patients aged 18 years and older diagnosed with stage IV invasive primary adenocarcinoma or squamous cell carcinoma of the esophagus between 2013 and 2020 were identified from the NCDB. Patients who had >1 cancer, histology type other than adenocarcinoma or squamous cell carcinoma, patients who were missing information about surgery, chemotherapy, RT, or immunotherapy, patients who had definitive surgery, and patients who did not receive any treatment were excluded. If chemotherapy and immunotherapy or RT and immunotherapy or chemotherapy and RT were started > 180 days of each other, those patients were excluded because the six-month therapy duration aligns with the standard first-line chemotherapy regimen typically employed for stage IV EC. For the subset analysis of the chemotherapy cohort, patients who started immunotherapy>30 days before chemotherapy were excluded due to a small number. In the subset analysis of the RT cohort, patients who received RT > 90 days before immunotherapy and patients who started immunotherapy >30 days before RT were also excluded due to a small number. For the chemoradiation cohort, patients who started chemotherapy >30 days before immunotherapy were excluded due to a small number. The histology codes of 8140, 8141, 8143, 8145, 8147, 8260, 8261, 8263, 8255, 8480, 8481, 8570, 8571, 8572, 8573, and 8574 were used to identify adenocarcinoma, while tumors with 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8078 codes were identified as squamous cell carcinoma. The primary outcome of the study was OS, which was measured in months and calculated from the time of diagnosis to the time of death or last follow-up. Those alive or lost to follow-up were censored.

Covariates

The main predictors for OS were immunotherapy, chemotherapy plus immunotherapy, RT plus immunotherapy, and chemoradiation plus immunotherapy. Other covariates included age at diagnosis, sex, race, income, education, insurance status, treatment facility type, location of the facility, distance from the facility, comorbidity type, histology type, RT, chemotherapy, surgery, and year of diagnosis. Multivariable analyses were adjusted for the above factors.

Statistical Analysis

Baseline characteristics of the patients were reported by immunotherapy. Median and ranges were reported for age at diagnosis, while frequency and proportions were reported for categorical variables. The predictors of using immunotherapy were reported using multivariable logistic regression analysis. The odds ratio was reported as the measure of association between the factors of interest and the likelihood of receiving immunotherapy. The OS and median survival times were reported using the Kaplan-Meier method. The difference in the OS between the groups was investigated by log-rank test. Cox proportion analysis was conducted to estimate the HR and its 95% CI. A P value $< .05$ was considered significant. All tests were two-tailed tests. We used SAS 9.4 (SAS Institute Inc.) for the analysis.

Results

The final analysis included 18,260 patients. Of these, 15,317 (83.9%) were men, 15,976 (88.2%) were White individuals, 1546 (8.5%) were Black individuals, 584 (3.3%) belonged to other racial and ethnic groups, 17,409 (98.1%) were living in urban areas, 17,318 (96.4%) had health insurance, 11,909 (66.3%) were treated in community cancer hospitals, and 13,201 (73.3%) had a comorbidity score of zero. Overall, 2946 (17.1%) received immunotherapy. Among the 18,205 patients used for the subset analyses, 25.2% (6402/18,205) received only chemotherapy, 9.5% (1724/18,205) received chemotherapy plus immunotherapy, 13.1% (2388/18,205) received only RT, 0.5% (97/18,205) received RT plus immunotherapy, 35.8%

Table 1. Baseline Characteristics and Logistic Regression Analysis of the Factors Associated With Receiving Immunotherapy of Patients Diagnosed With Stage IV Esophageal Cancer Between 2013 and 2020 (N = 18,260)

Variable	Immunotherapy 2946 (17.1%)	No immunotherapy 15,314 (83.9%)	Total 18,260	OR (95% CI)	*P*
Age at diagnosis continuous, median with range	63 (22–90)	64 (20–90)	64 (20–90)	0.99 (0.98–0.99)	.001
Sex					
Female	366 (16.8)	2577 (19.52)	2943 (16.1)	0.94 (0.82–1.08)	.40
Male	2580 (83.2)	12,737 (80.48)	15,317 (83.9)	Ref	
Race					
White	2733 (93.8)	13,243 (87.2)	15,976 (88.2)	Ref	
Black	104 (2.7)	1442 (9.10)	1546 (8.5)	0.82 (0.64–1.05)	.11
Non White/Non Black	78 (3.6)	506 (3.3)	584 (3.3)	1.05 (0.78–1.42)	.74
Unknown	29	126	154		
Histology					
Adenocarcinoma	2778 (94.3)	11,713 (76.5)	14,491 (79.4)	3.97 (3.29–4.79)	.001
Squamous cell carcinoma	168 (5.7)	3601 (23.5)	3769 (20.6)	Ref	
Charlson/Deyo score					
0	2186 (74.2)	11,015 (71.9)	13,201 (73.3)	Ref	
1	502 (17.0)	1512 (18.2)	3289(18.0)	0.93 (0.83–1.06)	.28
≥2	258 (8.8)	1512 (9.9)	1770 (9.7)	0.95 (0.80–1.12)	.51
Education					
≥10.9% NHD	1028 (41.9)	6279 (48.0)	7307 (47.1)	0.89 (0.79–0.99)	.04
<10.9% NHD	1423 (58.1)	6789 (52.0)	8212 (52.9)	Ref	
Unknown	495	2246	2741		
Income					
<$50,353	911 (37.20)	5651 (43.3)	6562 (42.4)	0.92 (0.82–1.04)	.17
≥$50,353	1538 (62.80)	7391 (56.7)	8929 (57.6)	Ref	
Unknown	452	2317	2769		
Insurance					
Yes	2819 (97.0)	14,499 (96.3)	17,318 (96.4)	Ref	.39
No	86 (3.0)	560 (3.7)	646 (3.6)	0.89 (0.68–1.16)	
Unknown	41	255	296		
Hospital type					
Community	1882 (65.7)	10,027 (66.4)	11,909 (66.3)	0.97 (0.88–1.08)	.61
Academic	983 (34.3)	5080 (33.6)	6063 (33.7)	Ref	
Unknown	81	207	288		
Place of living					
Urban	2791 (98.2)	14,618 (98.1)	17,409 (98.1)	Ref	.98
Rural	50 (1.8)	285 (1.9)	335 (1.9)	0.99 (0.70–1.43)	
Unknown	105	411	516		
Region					
Northeast	641 (22.4)	3302 (21.9)	3943 (21.9)	0.89 (0.76–1.05)	.16
Midwest	872 (30.4)	4372 (28.9)	5244 (29.2)	1.02 (0.88–1.17)	.83
South	895 (31.2)	5169 (34.2)	6064 (33.7)	0.93 (0.80–1.08)	.33
West	457 (16.0)	2264 (15.0)	2721 (15.2)	Ref	
Unknown	81	207	288		
Distance to facility					
<5.8	1135 (38.5)	6288 (41.1)	7423 (40.7)	Ref	
5.8–13.4	696 (23.6)	3491 (22.80)	4187(22.9)	1.14 (1.01–1.29)	.04
13.5–38.6	739 (25.1)	37,24 (24.3)	4463 (24.4)	1.05 (0.92–1.18)	.48
≥38.7	376 (12.8)	3811 (11.8)	2187 (12.0)	1.04 (0.88–1.22)	.69
Chemotherapy					
No	109 (3.7)	2399 (15.6)	2497 (13.7)	0.30 (0.24–0.38)	.001
Yes	2873 (96.3)	12,926 (84.4)	15,763 (86.3)	Ref	
RT					
No	1757 (59.6)	6402 (41.8)	8159 (44.7)	1.50 (1.36–1.65)	.001
Yes	1189 (40.4)	8912 (58.2)	10,101 (55.3)	Ref	
Year of diagnosis					
2013–2017	1344 (45.6)	8589 (56.1)	9933 (54.4)	0.62 (0.57–0.69)	.001
2018–2020	1602 (54.4)	6725 (43.9)	8327 (45.6)	Ref	

NHD, no high school degree.

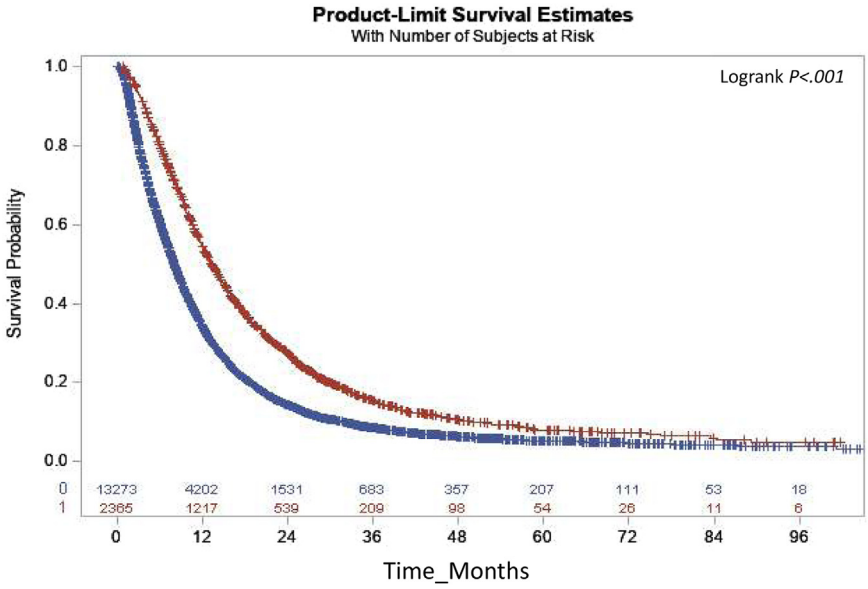

Figure 1. Overall survival of the entire cohort, (blue) patients who received no immunotherapy and (red) patients who received immunotherapy.

(6524/18,205) received chemoradiation alone, and 5.9% (1070/18,205) received chemoradiation plus immunotherapy. The median age at diagnosis for the entire cohort was 64 (20–90) years. In the multivariable logistic analysis, younger age, adenocarcinoma, higher education level, receiving chemotherapy, not receiving RT, distance of 5.8–13.4 miles from treatment facility compared to <5.8 miles, and diagnosis between 2018 and 2020 compared to 2013 and 2017 were positively associated with receiving immunotherapy. The OR of the factors associated with receiving immunotherapy is provided in Table 1.

Patients who received immunotherapy had better median OS compared to patients who did not receive immunotherapy (13.2; 95% CI: 12.7–13.9 months vs 8.0; 95% CI: 7.8–8.2 months; $P < .001$) (Figure 1). Chemotherapy plus immunotherapy was associated with improved OS compared to chemotherapy alone (14.6; 95% CI: 13.4–15.5 months vs 9.2; 95% CI: 8.9–9.5 months; $P < .001$) (Figure 2). RT plus immunotherapy was associated with improved OS compared to RT alone (6.2; 95% CI: 4.4–8.3 months vs 2.7; 95% CI: 2.6–2.9 months; $P < .001$) (Figure 3). Chemoradiation plus immunotherapy was associated with improved OS compared to chemoradiation alone (12.4; 95% CI: 11.7–13.3 months vs 9.3; 95% CI: 9.0–9.5 months; $P < .001$) (Figure 4).

In the multivariable Cox regression analysis, patients who received immunotherapy had better OS compared to patients who did not receive immunotherapy (HR: 0.71; 95% CI: 0.67–0.75; $P < .001$) (Table 2).

In the subset analyses, chemotherapy plus immunotherapy was associated with improved OS compared to chemotherapy alone (HR: 0.69; 95% CI: 0.64–0.75; $P < .001$) (Table 3). Patients who started chemotherapy and immunotherapy within 30 days of each other (concurrent) or chemotherapy >90 days before immunotherapy had better OS compared to patients who received chemotherapy

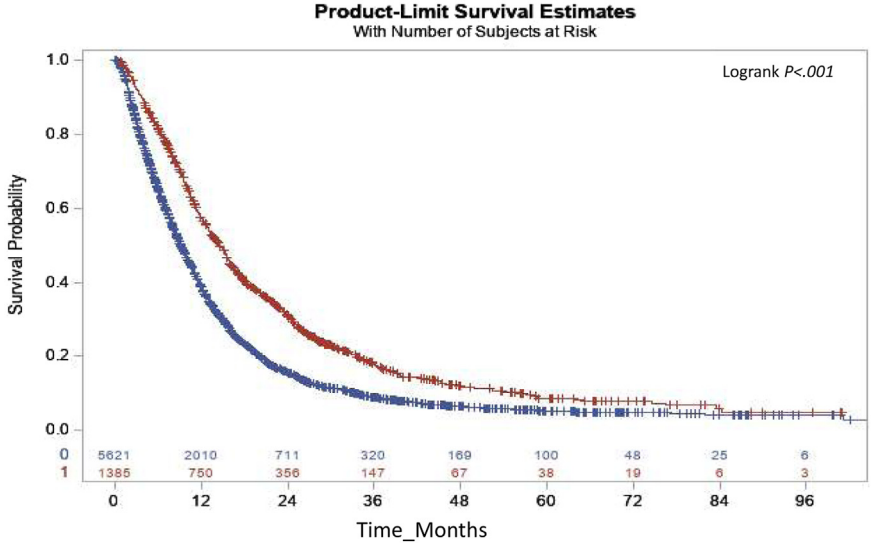

Figure 2. Overall survival of the chemotherapy cohort, (blue) chemotherapy without immunotherapy and (red) chemotherapy with immunotherapy.

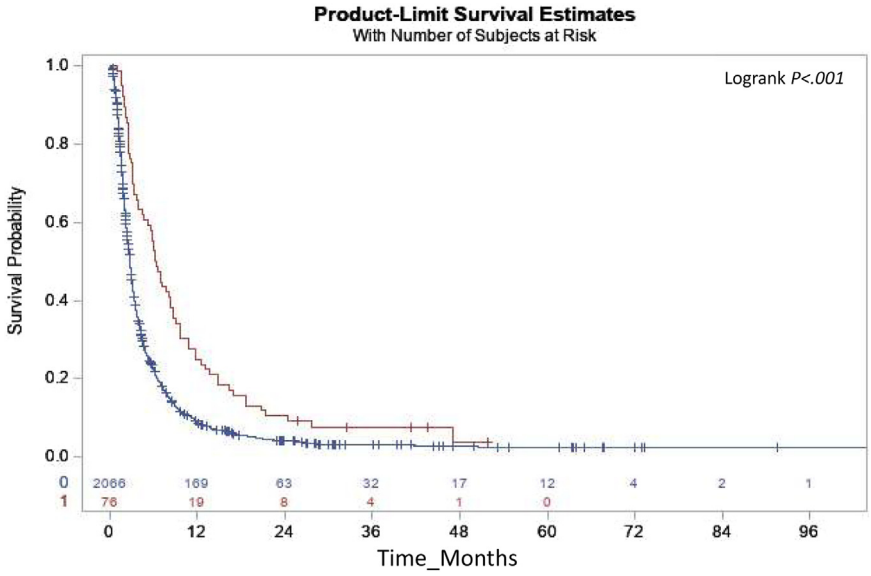

Figure 3. Overall survival of the radiation therapy (RT) cohort, (blue) RT without immunotherapy and (red) RT with immunotherapy.

alone (HR: 0.69; 95% CI: 0.64–0.75; $P < .001$; and HR: 0.56; 95% CI: 0.41–0.76; $P < .001$, respectively), while there was no difference in the OS of patients who started chemotherapy 31–90 days before immunotherapy and patients who received chemotherapy alone (HR: 0.82; 95% CI: 0.65–1.03; $P = .08$) (Table A1). There was no difference in the OS of patients who started chemotherapy 31–90 or >90 days before immunotherapy and patients who started chemotherapy and immunotherapy concurrently (HR: 1.19; 95% CI: 0.94–1.50; $P = .15$ and HR: 0.81; 95% CI: 0.59–1.11; $P = .18$, respectively) (Table A2). However, patients who started chemotherapy >90 days before immunotherapy had better OS compared to patients who started chemotherapy 31–90 days before immunotherapy (HR: 0.68; 95% CI: 0.47–0.99; $P = .04$) (Table A2). Interestingly, when we used the 90 days point of starting immunotherapy after chemotherapy as a starting cutoff point for the survival analysis, patients with concurrent chemotherapy and immunotherapy and patients who started chemotherapy 31–90 days before immunotherapy had worse OS compared to starting chemotherapy >90 days before immunotherapy (HR: 1.42; 95% CI: 1.04–1.95; $P = .03$ and HR: 1.83; 95% CI: 1.25–2.69; $P = .002$).

RT plus immunotherapy was associated with improved OS compared to RT alone (HR: 0.60; 95% CI: 0.46–0.78; $P < .001$) (Table 3). Concurrent RT and immunotherapy and starting RT 31–90 days before starting immunotherapy were both associated with improved OS compared to RT alone (HR: 0.66; 95% CI: 0.48–0.91; $P = .01$ and HR: 0.50; 95% CI: 0.32–0.79; $P = .003$) (Table A1). There was no difference in the OS of patients who started RT 31–90 days before starting immunotherapy and patients who received concurrent RT plus immunotherapy (HR: 0.76; 95% CI: 0.44–1.32; $P = .32$).

Chemoradiation plus immunotherapy was associated with improved OS compared to chemoradiation alone (HR:

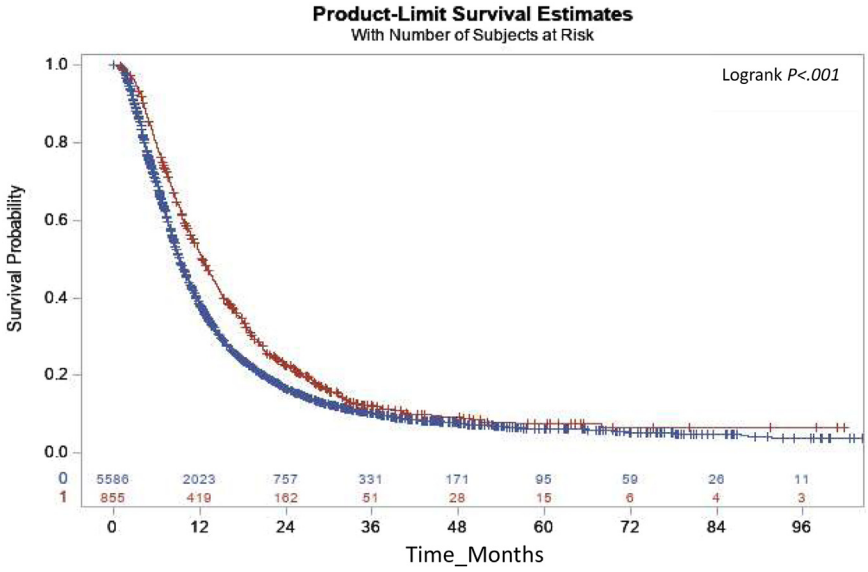

Figure 4. Overall survival of the chemoradiation cohort, (blue) chemoradiation without immunotherapy and (red) chemoradiation with immunotherapy.

Table 2. Multivariable Cox Regression Analysis of the Factors Associated With OS Including Immunotherapy

Variable	HR (95% CI)	*P*
Age at diagnosis continuous	1.00 (1.00–1.01)	.001
Immunotherapy		
Yes	0.71 (0.67–0.75)	.001
No	Ref	
Sex		
Male	Ref	.001
Female	0.85 (0.80–0.89)	
Race		
White	Ref	
Black	0.99 (0.92–1.07)	.81
Non White/Non Black	0.91 (0.81–1.03)	.12
Histology		
Adenocarcinoma	0.95 (0.90–0.99)	.04
Squamous cell carcinoma	Ref	
Charlson/Deyo score		
0	Ref	
1	1.10 (1.04–1.15)	.001
≥2	1.22 (1.14–1.30)	.001
Education		
≥10.9% NHD	0.99 (0.95–1.04)	.77
<10.9% NHD	Ref	
Income		
<$50,353	1.04 (0.99–1.09)	.10
≥$50,353	Ref	
Insurance		
No	1.36 (1.23–1.51)	.001
Yes	Ref	
Hospital type		
Academic	Ref	
Community	1.13 (1.08–1.18)	.001
Place of living		
Urban	Ref	.27
Rural	1.08 (0.94–1.25)	
Region		
Northeast	1.05 (0.98–1.12)	.15
Midwest	1.12 (1.05–1.19)	.001
South	1.07 (1.01–1.14)	.02
West	Ref	
Distance to facility		
<5.8	Ref	
5.8–13.4 (22.88)	1.02 (0.97–1.07)	.53
13.5–38.6	0.99 (0.94–1.04)	.60
≥38.7	1.02 (0.96–1.09)	.54
Chemotherapy		
Yes	0.34 (0.32–0.36)	.001
No	Ref	
RT		
Yes	0.96 (0.92–0.99)	0.03
No	Ref	
Year of diagnosis		
2013–2017	1.145 (1.10–1.19)	.001
2018–2020	Ref	

NHD, no high school degree.

Table 3. Multivariable Cox Regression Analysis of Combining Immunotherapy With Chemotherapy, RT, and Chemoradiation

Variable	N	HR (95% CI)	*P*
Chemotherapy and immunotherapy			
Chemotherapy alone	6402	Ref	.001
Chemotherapy plus immunotherapy	1724	0.69 (0.64–0.75)	
RT and immunotherapy			
RT alone	2388	Ref	.001
RT plus immunotherapy	97	0.60 (0.46–0.78)	
Chemoradiation and immunotherapy			
Chemoradiation alone	6524	Ref	.001
Chemoradiation plus immunotherapy	1070	0.78 (0.71–0.86)	

0.78; 95% CI: 0.71–0.86; $P < .001$) (Table 3). Concurrent chemoradiation plus immunotherapy, chemoradiation >30 days before immunotherapy, and immunotherapy> 30 days before chemoradiation were associated with improved OS compared to chemoradiation alone (HR: 0.86; 95% CI: 0.76–0.98; $P = .03$; HR: 0.62, 95% CI: 0.50–0.76; $P = .001$; and HR: 0.72, 95% CI: 0.58–0.90; $P = .003$, respectively) (Table A1). Chemoradiation >30 days before immunotherapy was associated with improved OS compared to concurrent chemoradiation plus immunotherapy (HR: 0.71; 95% CI: 0.56–0.91; $P = .006$), while there was no difference in the OS of patients who started immunotherapy >30 before chemoradiation and patients who started concurrent chemoradiation plus immunotherapy (HR: 0.84; 95% CI: 0.65–1.07; $P = .16$) (Table A2). There was no difference in the OS of patients who started chemoradiation >30 days before the start of immunotherapy and patients who started immunotherapy> 30 days before the start of chemoradiation (HR: 1.17; 95% CI: 0.87–1.59; $P = .30$). Chemotherapy plus an RT dose of ≥ 50 Gy plus immunotherapy and chemotherapy plus an RT dose < 50 Gy plus immunotherapy were both associated with improved OS compared to chemoradiation without immunotherapy (HR: 0.82; 95% CI: 0.70–0.96; $P = .01$ and HR: 0.73; 95% CI: 0.62–0.85; $P < .001$, respectively). There was no difference in the OS of patients who received chemotherapy plus an RT dose ≥ 50 Gy plus immunotherapy and patients who received chemotherapy plus an RT dose < 50 Gy plus immunotherapy (HR: 1.13; 95% CI: 0.91–1.40; $P = .26$). In addition, the results of our analysis for immunotherapy vs no immunotherapy, chemotherapy plus immunotherapy vs chemotherapy alone, and chemoradiation plus immunotherapy vs chemoradiation alone, did not change when we included patients who started chemotherapy and immunotherapy, RT and immunotherapy, or RT and chemotherapy >180 days from each other.

Chemotherapy plus immunotherapy and chemoradiation plus immunotherapy were associated with improved OS compared to immunotherapy alone (HR: 0.62; 95% CI: 0.46–0.85; $P = .001$ and HR: 0.67; 95% CI: 0.50–0.94; $P = .02$) (Table A3). There was no difference in the OS of patients who received chemotherapy alone or chemoradiation alone or RT plus immunotherapy and patients who received

immunotherapy alone (HR: 0.92; 95% CI: 0.68–1.24; $P = .55$, HR: 0.86; 95% CI: 0.63–1.16; $P = .32$, and HR: 1.41; 95% CI: 0.95–2.09; $P = .08$, respectively). However, RT alone was associated with worse OS compared to immunotherapy alone (HR: 2.59; 95% CI: 1.91–3.52; $P < .001$) (Table A3).

Patients who received chemoradiation alone, RT alone or RT plus immunotherapy had worse OS compared to patients who received chemotherapy plus immunotherapy (HR: 1.38; 95% CI: 1.28–1.49; $P < .001$, HR: 4.17; 95% CI: 3.82–4.55; $P < .001$, and HR: 2.27; 95% CI: 1.75–2.94; $P < .001$, respectively) (Table A4). There was no difference in the OS of patients who received chemotherapy plus immunotherapy and patients who received chemoradiation plus immunotherapy (HR: 1.11; 95% CI: 0.99–1.23; $P = .07$) (Table A4).

Discussion

In this retrospective study of the NCDB, we found that for stage IV esophageal cancer, RT plus immunotherapy was associated with improved OS compared to RT alone and chemoradiation plus immunotherapy was associated with improved OS compared to chemoradiation alone, which is unique as it has not been investigated or reported previously. Chemotherapy plus immunotherapy was also associated with improved OS compared to chemotherapy alone in these patients. The current study also investigated the sequence of immunotherapy with chemotherapy, RT, and chemoradiation in stage IV esophageal cancer patients and reported some interesting findings, which have not been investigated before.

The results of our study are consistent with the findings of the clinical trials.[15–19] The median OS of (13.2, 95% CI: 12.7–13.9) months and (HR: 0.71, 95% CI: 0.67–0.75) reported for patients who received immunotherapy in our study is comparable to median OS and HR that was reported in the KEYNOTE-181 trial (10.3 95% CI: 7.0–13.5) months and (HR: 0.64, 95% CI: 0.46, 0.90).[18] The median OS of (12.4, 95% CI: 11.7–13.3) months and (HR: 0.78, 95% CI: 0.71–0.86; $P < .001$) for advanced or metastatic EC patients who received chemoradiation plus immunotherapy is comparable to what was reported for chemotherapy plus immunotherapy in previously untreated metastatic EC patients in the CHECKMATE-649 trial (13.8, 95% CI: 12.6, 14.6 months) and (HR: 0.71, 98% CI: 0.59–0.86)[16] and median OS of (12.4, 95% CI: 10.5, 14.0) months and (HR: 0.73, 95% CI: 0.62–0.86) reported for locally advanced or metastatic EC patients who were not candidates for surgical resection or definitive chemoradiation in the KEYNOTE-590 trial.[17]

The improved OS associated with immunotherapy combined with chemotherapy, RT, or chemoradiation in the current study may be due to the synergistic interaction of immunotherapy with chemotherapy, RT, or chemoradiation. Chemotherapy and RT increase tumor-specific T cell infiltration, decrease Treg cells, and suppress myeloid-derived suppressor cells.[20–22] Studies have also shown that chemotherapy augments immune response in favor of generating immunity by inducing immunogenic cell death.[20,23] RT promotes the translocation of calreticulin from the endoplasmic reticulum to the plasma membrane. Calreticulin is a crucial signal for promoting phagocytosis, which will enable T cells to clear tumor cells.[24] RT improves the presentation of tumor-specific peptides by upregulating the expression of the major histocompatibility complex on the tumor surface, leading to enhancing the visibility of the tumor cells to cytotoxic T cells.[25] More importantly, RT induces T cell-mediated inhibition of untreated distant tumors (known as the abscopal effect), a key mechanism involving the immune system.[26] There is a direct connection between the abscopal effect and mechanisms involving the immune system.[27,28] After a tumor is irradiated, injury in the tumor leads to the release of tumor-associated antigens, which can stimulate a tumor-specific immune response, allowing the immune cells (T-cells) to recognize and attack both the primary tumor and metastatic disease in a sort of autovaccination.[29–33]

The improved OS associated with starting immunotherapy >90 days after chemotherapy compared to concurrent chemoimmunotherapy or immunotherapy 31–90 days after chemotherapy in the 90 days landmark analysis is an important finding about understanding the optimal time window for the synergistic interaction of chemotherapy and immunotherapy. Chemotherapy is associated with transient immunosuppression and starting immunotherapy during that window of systemic and local immunosuppression may minimize the synergetic effect of the interaction of immunotherapy with chemotherapy. A majority of the patients in the current study received chemotherapy and immunotherapy within 30 days of each other. The improved OS associated with receiving immunotherapy >30 days after chemoradiation compared to concurrent chemoradiation plus immunotherapy is also an indication that for the synergistic effect of immunotherapy with chemoradiation to be kicked in, immunotherapy should not be given during the transient immunosuppression period caused by chemotherapy and RT.

No difference in the OS of patients who received chemotherapy alone, RT alone, or chemoradiation alone, and immunotherapy alone is also important as immunotherapy a presumably less toxic treatment could be used in patients who refuse, cannot tolerate or are not candidates for those treatments due to poor performance status could benefit from immunotherapy. Selected patients who are not eligible for chemoradiation alone or chemoradiation plus immunotherapy due to side effects or treatment refusal could benefit equally from receiving chemotherapy plus immunotherapy as there was no difference in the OS of patients who received chemotherapy plus immunotherapy and patients who received chemoradiation plus immunotherapy, while it was associated with improved OS compared to chemoradiation alone.

To the best of our knowledge, the current study is the first to investigate the association of definitive

chemoradiation plus immunotherapy with the OS of patients diagnosed with EC. The finding provides the foundation for the future clinical trials of combining immunotherapy with chemoradiation as a first-line treatment option in locally advanced/early stage IV EC. The combination has been investigated in a current ongoing phase III randomized placebo-controlled clinical trial (KEYNOTE-975),[31] which is evaluating the role of immunotherapy plus chemoradiation vs placebo plus chemoradiation as first-line treatment of EC patients. Our results also provide an indication that the survival benefit associated with the use of immunotherapy in combination with chemotherapy could be generalized to patients who are treated with immunotherapy outside of a clinical trial setting.

The strength of the current study is the large sample size, which allowed us to adjust for various confounding and stratify by surgery status. However, the study is not without limitations. The major limitations include lack of information about cause of death, disease progression, recurrence, performance status, type of immunotherapy and if a single or combinations of immunotherapies were used, type of chemotherapy, and whether single or multi-agent chemotherapy regimens were recommended. The retrospective nature of the study and coding errors are some other limitations of the study.

Conclusion

In this comprehensive analysis of the NCDB, chemotherapy plus immunotherapy vs chemotherapy alone, RT plus immunotherapy vs RT alone, and chemoradiation plus immunotherapy vs chemoradiation alone were associated with improved OS in patients diagnosed with stage IV EC. It is the first study with a large patient population that has indicated the benefit of immunotherapy in a real-world clinical setting in patients diagnosed with stage IV EC. The study findings warrant future clinical trials of combining chemoradiation therapy or RT with immunotherapy.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.12.004.

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The data from NCDB are de-identified, therefore institutional review board approval and patient consent are not needed for the study.

Data Transparency Statement:
The NCDB data are not publicly available. Only participating institutes are eligible to apply for the data and have access to the data. The data will be made available upon reasonable request from the corresponding author if the NCDB guidelines allow data sharing.

Reporting Guidelines:
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