ORIGINAL ARTICLE

Utilization and Outcomes of Radiation in Stage IV Esophageal Cancer

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ABSTRACT

Introduction: For patients with stage IV esophageal cancer, esophageal radiation may be used selectively for local control and palliation. We aimed to understand patterns of radiation administration among patients with stage IV esophageal cancer and any potential survival associations.

Methods: In this retrospective cohort study, the National Cancer Database was queried for patients with metastatic stage IV esophageal cancer diagnosed between 2016 and 2019. Patterns of radiation use were identified. Survival was determined through Kaplan-Meier analysis of propensity score-matched pairs of patients who did and did not receive radiotherapy and time-to-event models.

Results: Overall, 12,088 patients with stage IV esophageal cancer were identified, including 32.7% who received esophageal radiation. The median age was 65 (interquartile range [IQR]: 58–73) years, and 82.6% were male. Among the irradiated patients, the median total radiation dose was 35 (IQR: 30–50) Gy administered in a median of 14 (IQR: 10–25) fractions given in 22 (IQR: 14–39) days. Overall, esophageal radiation was not associated with better survival (log-rank $p = 0.41$). When stratified by radiation dose, a survival advantage (over no radiation) was found in the 1144 patients (29% of the irradiated patients) who received 45 to 59.9 Gy (time ratio = 1.28, 95% confidence interval: 1.20–1.37, $p < 0.001$) and the 88 patients (2.2%) who received 60 to 80 Gy (time ratio = 1.37, 95% confidence interval: 1.11–1.69, $p = 0.003$).

Conclusions: One-third of the patients with metastatic stage IV esophageal cancer in the National Cancer Database received esophageal radiation. Most received a radiation dose that, although consistent with palliative regimens, was not associated with a survival advantage. Further study is warranted to understand the indications for radiation in stage IV esophageal cancer and potentially reevaluate the most appropriate radiation dose for palliation.

Keywords: Stage IV esophageal cancer; Radiation; Prognosis; Palliative radiation

Introduction

Stage IV esophageal cancer can be a particularly difficult scenario to manage, with less than 5% of patients living 5 years.[1,2] Given the tendency for stage IV patients to have esophageal cancer throughout the body, systemic therapy has served as the primary treatment modality in the past several decades.[3]

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Esophageal radiation may alleviate obstructive symptoms (dysphagia, odynophagia) and bleeding from esophageal tumors and has been used selectively in patients with stage IV esophageal cancer.[4] The National Comprehensive Cancer Network treatment guidelines have identified several scenarios in which esophageal radiation is listed as a palliative option in stage IV esophageal cancer.[3]

Similar to other forms of cancer treatment, the benefits of radiation treatment must be considered in the context of potential risks and alternative treatments. Esophageal radiation exposes patients to risks of side effects, complications, and transient declines in quality of life. For example, esophagitis, pneumonitis, myocarditis, and hematologic complications are common sequelae of radiation.[5] Furthermore, alternate treatments are available to palliate symptoms from primary esophageal cancers. Esophageal stents, cryotherapy, photodynamic therapy, or even cytotoxic chemotherapy may accomplish many of the goals of palliative radiation.[3,6–9] As a result, patient selection must balance possible adverse effects, possible symptomatic improvement, and potential survivorship gains. Better understanding of the current relationship between radiotherapy of the esophagus in newly diagnosed stage IV esophageal cancer and survival may facilitate informed decision making.

The National Cancer Database (NCDB) is one of the largest and most comprehensive cancer registries and captures detailed treatment information, which includes the administration of radiation in esophageal cancer.[10,11] We evaluated patterns of radiation administration among patients with esophageal cancer with distant metastases in the NCDB and survival in hopes of increasing the understanding of the current role of radiation in stage IV esophageal cancer.

Materials and Methods

Data Source

The NCDB is a prospective registry of cancer care taking place at Commission on Cancer–accredited hospitals and captures 72% of all newly diagnosed cancers in the United States.[10,11] The NCDB 2019 Participant User File,[12] which contains deidentified patient information, was used for this retrospective cohort study, which was performed in accordance with our institutional review board-approved protocol, with consent waived. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed.

Study Population

Patients aged 18 years or older who were diagnosed with having metastatic stage IV esophageal cancer from 2016 to 2019 without a prior history of malignancy were eligible for inclusion. Patients were excluded if data on whether they received radiation were missing (n = 291) or if the primary site of radiation was not to the esophagus (n = 1450). A sensitivity analysis comparing the attributes of included and excluded patients did not identify any clinically relevant differences (data available on request).

Independent Variables

Variables included esophageal radiotherapy as a categorical variable (none, 0.1–29.9 Gy, 30–44.9 Gy, 45–59.9 Gy, and 60–80 Gy). These categories were chosen to represent ranges for palliative and definitive dosing of external beam radiation therapy.[3–5,13–16] In a manner consistent with previous studies,[17,18] age was included as a categorical variable (18–34, 35–49, 50–64, 65–79, ≥80 y). Survival models with age as a continuous variable were created as sensitivity analyses, yielding similar results (data available on request). Other independent variables included sex (female, male), race (White, Black, Other), ethnicity (Hispanic, non-Hispanic), median household income of the patient's ZIP code of residence (categorized as quartiles: <$40,227, $40,227–$50,353, $50,354–$63,332, ≥$63,333), insurance status (private, uninsured, Medicaid, Medicare, other government), modified Charlson-Deyo Comorbidity Index (CCI) (0, 1, 2, 3+), U.S. Census region (Midwest, Northeast, South, West), facility type (nonacademic, academic), area of residence (metropolitan, urban, rural), year of diagnosis, histology (adenocarcinoma, squamous cell carcinoma [SCC], other), tumor location (cervical esophagus, upper esophagus, mid-esophagus, lower esophagus, overlapping lesion, unspecified), surgery (no surgery, local destruction, local excision, esophagectomy), chemotherapy (yes, no), and immunotherapy (yes, no). Extent of stage IV disease (nonregional lymph nodes only, single-organ involvement, multiorgan involvement) was also included as a covariate owing to an increasing understanding that, across multiple cancer types, the pattern of metastatic organ involvement at the time of diagnosis of stage IV cancer is a prognostic factor.[19–21] A comprehensive definition of NCDB variables is available online.[22]

Characteristics and Predictors of Radiotherapy

Basic characteristics of the radiotherapy that was administered to the esophagus (dosage, number of fractions, length of treatment) were elucidated. A logistic regression model incorporating age, sex, race, ethnicity, median income, insurance status, modified CCI, U.S. Census region, facility type, area of residence, year of diagnosis, histology, tumor location, and metastatic extent was created to identify characteristics that were associated with receiving any esophageal radiotherapy.

Patients diagnosed in 2019 were excluded from the analysis in case their radiation regimens had not been completed or updated in the NCDB.

Survival Analyses

To evaluate the overall association between prognosis and receipt of esophageal radiation, an unadjusted Kaplan-Meier (KM) curve comparing the survival of patients who received radiotherapy (any dose between 0.1 and 80 Gy) and who did not receive radiotherapy was created and the log-rank test was used. Adjusted survival analyses were also conducted as KM curves among patients who were propensity score matched for age, sex, race, ethnicity, income, insurance status, modified CCI, U.S. Census region, facility type, area of residence, year of diagnosis, histology, extent of metastasis, surgery, chemotherapy, and immunotherapy.

Survival analyses in which radiation dose was stratified into 0.1 to 29.9, 30 to 44.9, 45 to 59.9, and 60 to 80 Gy were also performed. This was done with unadjusted KM curves (now stratified by radiation dose) and the log-rank test. Furthermore, multivariable time-to-event models were created because our initial approach of using Cox proportional hazard models violated the proportional hazards assumption (by Schoenfeld residual assessment[23]). The time-to-event model incorporated radiation dose and the same covariates as the propensity score matching procedure. A time ratio (TR) of greater than one signifies that the factor is associated with longer survival (accelerates survival time). A hypothetical TR of 0.5 can be interpreted as the median time to death in patients with a certain characteristic being half the median time to death in the reference group.

Only patients with adenocarcinoma and SCC were included in the survival analysis. Survival data were only available for patients diagnosed between 2016 and 2018. Patients who were coded as receiving more than 80 Gy were excluded (n = 7), as this would be well outside the reference range of the suggested dosages. For the propensity-matched KM analysis, patients receiving less than 30 Gy (n = 318) were also excluded, as these patients may have had their treatment stopped early or received less radiation than is common at our institution and a number of previously reported palliative dosage schemes.[14,24,25]

In an attempt to minimize potential bias from particularly unhealthy patients being disproportionately represented in the no radiation arm, patients were excluded if they were coded in the NCDB as not receiving radiation because it was not recommended because of advanced age, poor health, or tumor attributes (n = 166). Patients were also excluded if they died before the planned or recommended therapy (n = 168). Furthermore, because of the potential for immortal time bias, all survival analysis was landmarked at 64 days, the median time from diagnosis to the end of radiotherapy. Patients who were excluded owing to landmarking were more likely to be above or equal to 80 years old, be uninsured or with Medicare, have a CCI score greater than or equal to 3, be treated at a nonacademic facility, and to have received no radiation or 0.1 to 29.9 Gy of esophageal radiation, no chemotherapy, or no immunotherapy (Supplementary Table 1).

As a sensitivity analysis, survival analysis was performed including only patients who received chemotherapy (with or without radiation). This was done because chemotherapy was a standard of care during the studied time frame and to mitigate (1) the bias against patients who were too unhealthy for any treatment and (2) to account for survival benefits attributable to chemotherapy. As another sensitivity analysis, the survival analyses were stratified by histology.

Missing Data Strategy

The median percentage of missing data across all variables was 1.4%, and 22.4% (n = 2708) of the patients had at least one piece of missing sociodemographic covariate data. The data seemed to be missing at random. A multiple imputation strategy was used to account for missing sociodemographic data (Supplementary Methods).

Statistical Analysis

Significance was set at two-sided p value less than 0.05. Data were analyzed with SAS statistical software version 9.4 (SAS Institute).

Results

Patient Characteristics

Overall, 12,088 stage IV patients were identified (Supplementary Fig. 1), including 32.7% (n = 3951) who received radiation to the esophagus (Table 1 and Supplementary Table 2). The median age was 65 (interquartile range [IQR]: 58–73) years, with 82.6% (n = 9981) male, 8.3% (n = 1006) black, and 87.9% (n = 10,622) white patients. Adenocarcinoma represented 69.9% (n = 8448) of the patients and SCC 19.1% (n = 2303). In total, 63.3% (n = 7647) received chemotherapy and 13.8% (n = 1664) received immunotherapy.

Patterns of Radiation Administration

Overall, 32.7% (n = 3951) of the patients received radiation to the esophagus. The median total radiation dose administered was 35 (IQR: 30–50) Gy (Supplementary Fig. 2). The median number of fractions was 14 (IQR: 10–25) given in 22 (IQR: 14–38) days. The

Table 1. Basic Characteristics of the Patients With Stage IV Esophageal Cancer

Characteristic		No Radiation, No. (col %[a]) n = 8137	Radiation, No. (col %[a]) n = 3951	Chi-Square *p* Value
Radiation dose (Gy)	0	8137 (100)	0 (0)	<0.001
	0.1-29.9	0 (0)	710 (18)	
	30-44.9	0 (0)	1850 (46.8)	
	45-59.9	0 (0)	1144 (29)	
	60-80	0 (0)	88 (2.2)	
	Missing	0 (0)	159 (4)	
Age (y)	18-34	55 (0.7)	25 (0.6)	0.11
	35-49	576 (7.1)	252 (6.4)	
	50-64	3242 (39.8)	1662 (42.1)	
	65-79	3446 (42.4)	1603 (40.6)	
	≥80	818 (10.1)	409 (10.4)	
Sex	Male	6703 (82.4)	3278 (83)	0.42
	Female	1434 (17.6)	673 (17)	
Race[b]	White	7180 (88.2)	3442 (87.1)	0.3
	Black	651 (8)	355 (9)	
	Other	251 (3.1)	125 (3.2)	
Ethnicity	Non-Hispanic	7593 (93.3)	3728 (94.4)	0.07
	Hispanic[c]	389 (4.8)	154 (3.9)	
Year of diagnosis	2016	1858 (22.8)	983 (24.9)	0.04
	2017	2035 (25)	926 (23.4)	
	2018	2112 (26)	1038 (26.3)	
	2019	2132 (26.2)	1004 (25.4)	
Histology[d]	Adenocarcinoma	5799 (68.6)	2649 (31.4)	<0.001
	Squamous cell carcinoma	1339 (58.1)	964 (41.9)	
	Other	999 (74.7)	338 (25.3)	
Tumor location[d]	Cervical esophagus	40 (47.6)	44 (52.4)	<0.001
	Upper esophagus	197 (53.4)	172 (46.6)	
	Mid-esophagus	750 (60.7)	485 (39.3)	
	Lower esophagus	5416 (67.7)	2584 (32.3)	
	Overlapping lesion	533 (66.3)	271 (33.7)	
	Unspecified	1201 (75.3)	395 (24.8)	
Surgery	No surgery	8049 (98.9)	3829 (96.9)	<0.001
	Local destruction	29 (0.4)	7 (0.2)	
	Local excision	17 (0.2)	8 (0.2)	
	Esophagectomy	33 (0.4)	100 (2.5)	
Chemotherapy	No chemotherapy	3350 (41.2)	984 (24.9)	<0.001
	Any chemotherapy	4699 (57.8)	2948 (74.6)	
Immunotherapy	No immunotherapy	6986 (85.9)	3423 (86.6)	0.049
	Any immunotherapy	1140 (14)	524 (13.3)	

[a]Column percentages are provided, with the exception of histology and tumor location, for which row percentages are provided for ease of interpretation.
[b]"Other" race includes the following categories defined by the NCDB (see also: https://www.facs.org/quality-programs/cancer/ncdb/puf): American Indian, Aleutian, or Eskimo; Chinese; Japanese; Filipino; Hawaiian; Korean; Vietnamese; Laotian; Hmong; Kampuchean (including Khmer and Cambodian); Thai; Asian Indian or Pakistani, no other specification; Asian Indian; Pakistani; Micronesian, no other specification; Chamorran; Guamanian, no other specification; Polynesian, no other specification; Tahitian; Samoan; Tongan; Melanesian, no other specification; Fiji Islander; New Guinean; Other Asian, including Asian, no other specification and Oriental, no other specification; Pacific Islander, no other specification; Other.
[c]Includes the following categories defined by the NCDB (see previous reference): Mexican (includes Chicano); Puerto Rican; Cuban; South or Central American (except Brazil); Other specified Spanish/Hispanic origin (includes European; excludes Dominican Republic); Spanish, NOS; Hispanic, NOS; Latino, NOS; Spanish surname only; Dominican Republic.
[d]For these variables, row percentages are provided instead of column percentages.
col, column; NCDB, National Cancer Database; No., number; NOS, not otherwise specified.

median time from diagnosis to start of esophageal radiotherapy was 34 (IQR: 21–57) days.

Predictors of Radiation Administration

A multivariable logistic regression model was created to evaluate characteristics associated with receipt of esophageal radiotherapy (Table 2). A number of patient attributes were associated with lower likelihood of receiving esophageal radiation, such as female sex (OR = 0.87, 95% confidence interval [CI]: 0.78–0.96, p = 0.009), uninsured status (OR = 0.69, 95% CI: 0.55–0.86, p = 0.001), and Hispanic ethnicity (OR = 0.81, 95% CI:

Table 2. Predictors of Receiving Esophageal Radiation in Stage IV Esophageal Cancer

Characteristic		OR (95% CI)	*p* Value
Age (Y)	18-34	1.12 (0.56-2.23)	0.75
	35-49	0.91 (0.76-1.08)	0.27
	50-64	Ref	.
	65-79	0.96 (0.85-1.08)	0.46
	≥80	1.05 (0.89-1.24)	0.58
Sex	Male	Ref	.
	Female	0.87 (0.78-0.96)	0.009
Race	White	Ref	.
	Black	0.91 (0.77-1.07)	0.25
	Other	0.93 (0.73-1.18)	0.54
Ethnicity	Non-Hispanic	Ref	.
	Hispanic	0.81 (0.66-0.99)	0.04
Median income	<$40,227	Ref	.
	$40,227-$50,353	1.12 (0.99-1.28)	0.08
	$50,354-$63,332	1.01 (0.89-1.16)	0.83
	≥$63,333	1.01 (0.88-1.16)	0.88
Insurance status	Private	Ref	.
	Uninsured	0.69 (0.55-0.86)	0.001
	Medicaid	1.06 (0.92-1.22)	0.43
	Medicare	0.94 (0.83-1.06)	0.28
	Other government	1.64 (1.25-2.16)	<0.001
CCI	0	Ref	.
	1	0.96 (0.86-1.06)	0.4
	2	0.89 (0.75-1.05)	0.16
	3+	0.85 (0.71-1.02)	0.08
Region	Midwest	Ref	.
	Northeast	0.78 (0.69-0.88)	<0.001
	South	0.94 (0.85-1.04)	0.21
	West	1.02 (0.9-1.16)	0.74
Facility type	Nonacademic[a]	Ref	.
	Academic	0.86 (0.79-0.94)	<0.001
Area of residence	Metropolitan	0.91 (0.81-1.02)	0.11
	Urban	Ref	.
	Rural	1.1 (0.83-1.47)	0.5
Year of diagnosis	2016	Ref	.
	2017	0.86 (0.77-0.97)	0.01
	2018	0.93 (0.83-1.04)	0.19
	2019	0.91 (0.81-1.01)	0.09
Histology	Adenocarcinoma	Ref	.
	Squamous cell carcinoma	1.55 (1.37-1.75)	<0.001
	Other	0.76 (0.66-0.87)	<0.001
Tumor location	Cervical esophagus	1.54 (0.97-2.44)	0.07
	Upper esophagus	1.3 (1.02-1.67)	0.04
	Mid-esophagus	Ref	.
	Lower esophagus	0.88 (0.76-1.01)	0.07
	Overlapping lesion	0.91 (0.75-1.11)	0.37
	Unspecified	0.6 (0.5-0.71)	<0.001
Metastatic extent[b]	Distant LN only	1.66 (1.47-1.88)	<0.001
	Single organ	Ref	.
	Multiorgan	0.78 (0.71-0.85)	<0.001

Note: The outcome variable was receipt of any radiation directed primarily to the esophagus, regardless of dose (≥0.1 Gy).
[a]Includes community cancer program, comprehensive cancer program, integrated network cancer program, and other specified types of cancer programs.
[b]"Distant LN Only" signifies metastatic disease limited to nonregional lymph nodes only. The "Single Organ" group signifies metastatic disease limited to a single systemic organ (excluding distant, nonregional lymph nodes), and "Multi-Organ" signifies metastatic disease that has spread to multiple organs. Patients who were documented as having both nonregional lymph node metastases and single systemic organ metastases were included in the "Multi-Organ" group.
CCI, Charlson-Deyo Comorbidity Index; CI, confidence interval; LN, lymph node; Ref, reference.

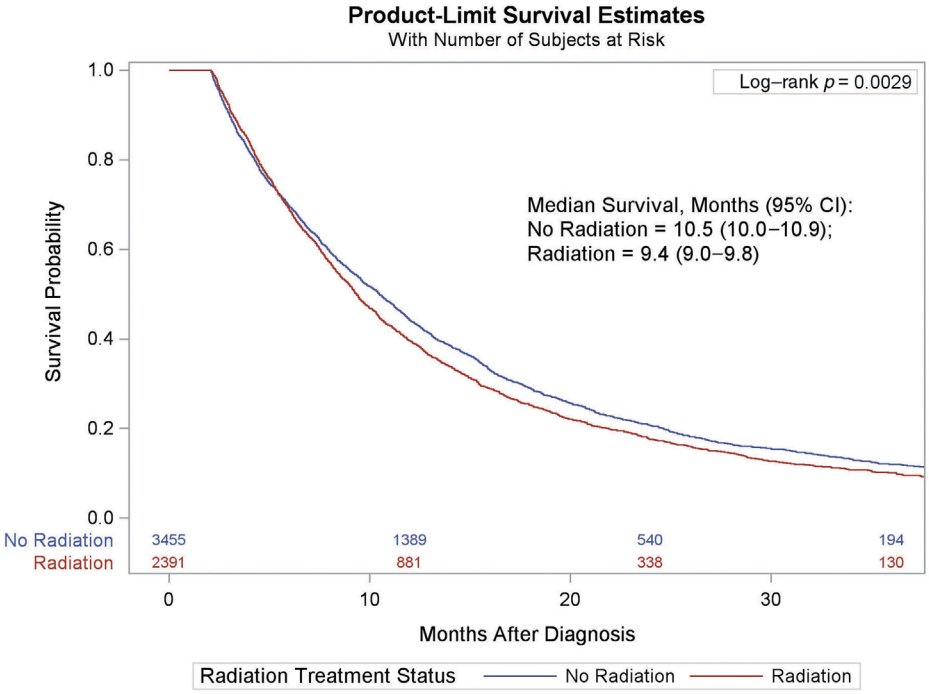

Figure 1. Kaplan-Meier curves of radiation versus no radiation for all patients with stage IV esophageal cancer, unadjusted model. The "radiation" group included patients receiving 0.1 to 80 Gy of esophageal radiation. CI, confidence interval.

0.66–0.99, $p = 0.04$). Tumor attributes were also associated with radiation administration. For example, patients with SCC (compared with those with adenocarcinoma) were more likely to receive esophageal radiotherapy (OR = 1.55, 95% CI: 1.37–1.75, $p < 0.001$), as were patients with tumors in the upper esophagus (compared with those whose tumors were in the mid-esophagus) (OR = 1.30, 95% CI: 1.02–1.67, $p = 0.04$). Patients whose systemic disease involved multiple organs were less likely to receive radiation (OR = 0.78, 95% CI: 0.71–0.85, $p < 0.001$) than those with single-organ metastatic involvement. Facility characteristics were also identified as predictors. Patients in the Northeast were less likely to receive radiation than those in the Midwest (OR = 0.78, 95% CI: 0.69–0.88, $p < 0.001$), as were patients treated at academic institutions (OR = 0.86, 95% CI: 0.79–0.94, $p < 0.001$) than those at nonacademic institutions.

Overall Association of Esophageal Radiation With Survival—Unadjusted and Adjusted Analyses

Overall, with a median follow-up of 18.2 (IQR: 5.8–33.7) months among the surviving patients, the unadjusted KM curve revealed a slightly worse prognosis for patients receiving radiation (median survival = 9.4 mo, 95% CI: 9.0–9.8, log-rank $p = 0.003$) compared with no radiation (10.5, 95% CI: 10.0–10.9) (Fig. 1). Adjusted analysis was performed using KM analysis among propensity score-matched patients. This model revealed no significant difference in survival between patients who received esophageal radiation (median survival = 9.9 mo, 95% CI: 9.4–10.4, $p = 0.41$) and those who did not (10.3, 95% CI: 9.7–10.8) (Fig. 2).

Survival Stratified by Radiation Dose—Unadjusted and Adjusted Analyses

In the unadjusted KM curve stratified by radiation dose, patients receiving 45 to 59.9 Gy (median survival = 13.0 mo, 95% CI: 12.1–13.8, log-rank $p < 0.001$) and 60 to 80 Gy (15.4, 95% CI: 10.0–20.9) had a better prognosis than patients who received no esophageal radiotherapy (10.5, 95% CI: 10.0–10.9) (Fig. 3). Adjusted survival analysis stratified by radiation dose was performed using a multivariable time-to-event model (Fig. 4[26]). The model revealed worse survival for patients who received 0.1 to 29.9 Gy to the esophagus compared with no radiotherapy (TR = 0.79, 95% CI: 0.71–0.87, $p < 0.001$] but a better survival for patients who received 45 to 59.9 Gy (TR = 1.28, 95% CI: 1.20–1.37, $p < 0.001$) and 60 to 80 Gy (TR = 1.37, 95% CI: 1.11–1.69, $p = 0.003$). As a sensitivity analysis, relandmarking at 83 days (the median time from diagnosis to end of radiation treatment for patients receiving ≥45 Gy) was performed with no change in the directionality, magnitude, or significance of the results.

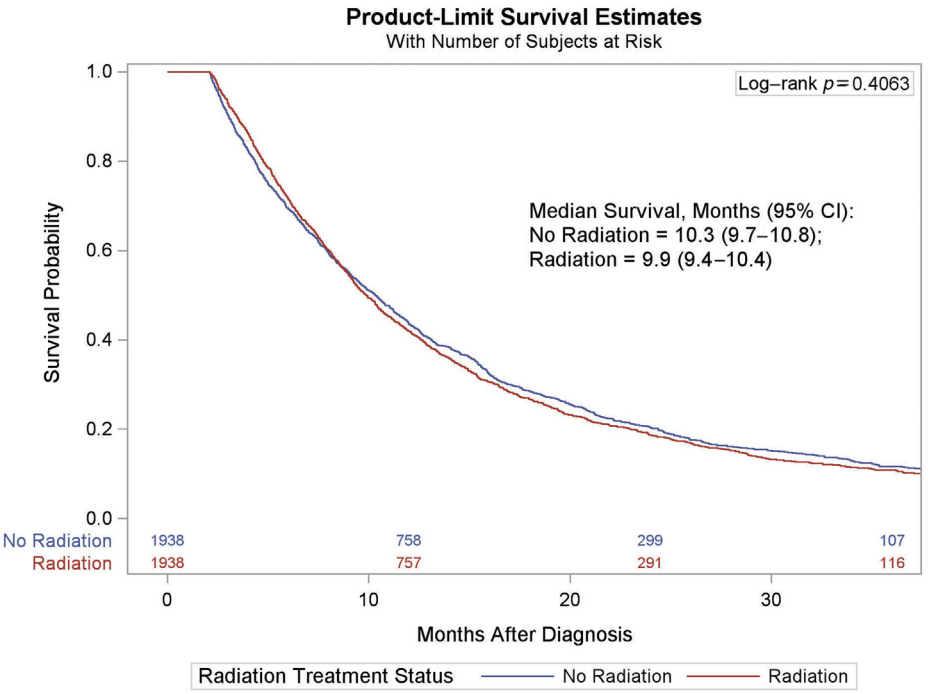

Figure 2. Kaplan-Meier curves of radiation versus no radiation for all patients with stage IV esophageal cancer (propensity-matched cohorts). For this propensity-matched analysis, patients receiving 0.1 to 29.9 Gy were excluded; thus, the "radiation" group received between 30 and 80 Gy of esophageal radiation. CI, confidence interval.

Sensitivity Analyses

Several sensitivity analyses were performed. Recognizing the potential impact of chemotherapy on survival, the survival analyses were performed including only those patients who received chemotherapy (with or without radiation). Similar patterns to those noted in the

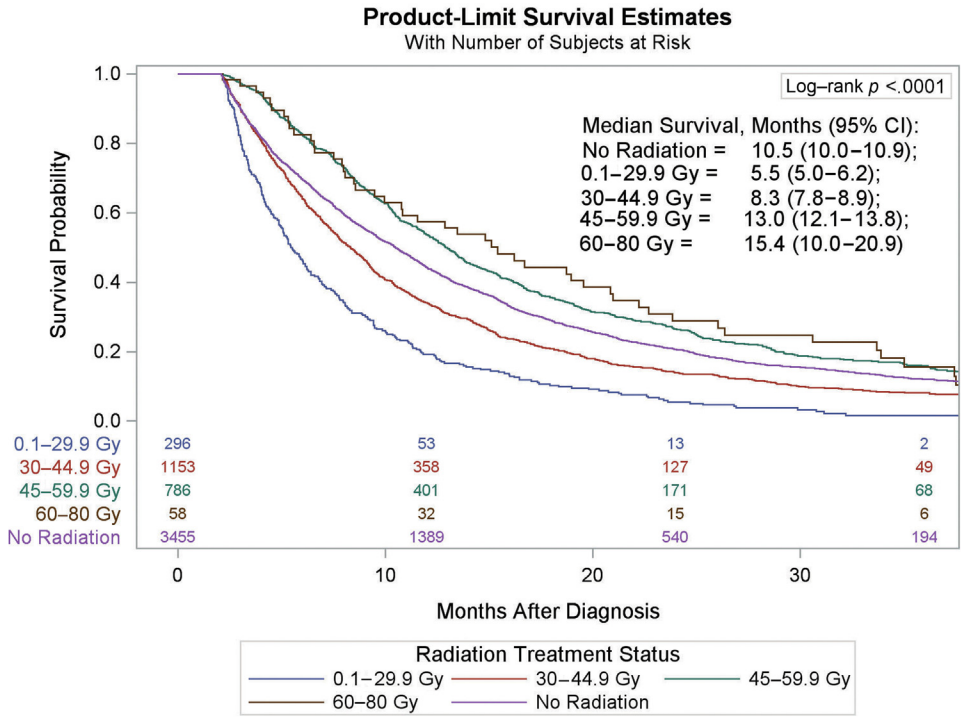

Figure 3. Unadjusted Kaplan-Meier curves stratified by radiation dose. CI, confidence interval.

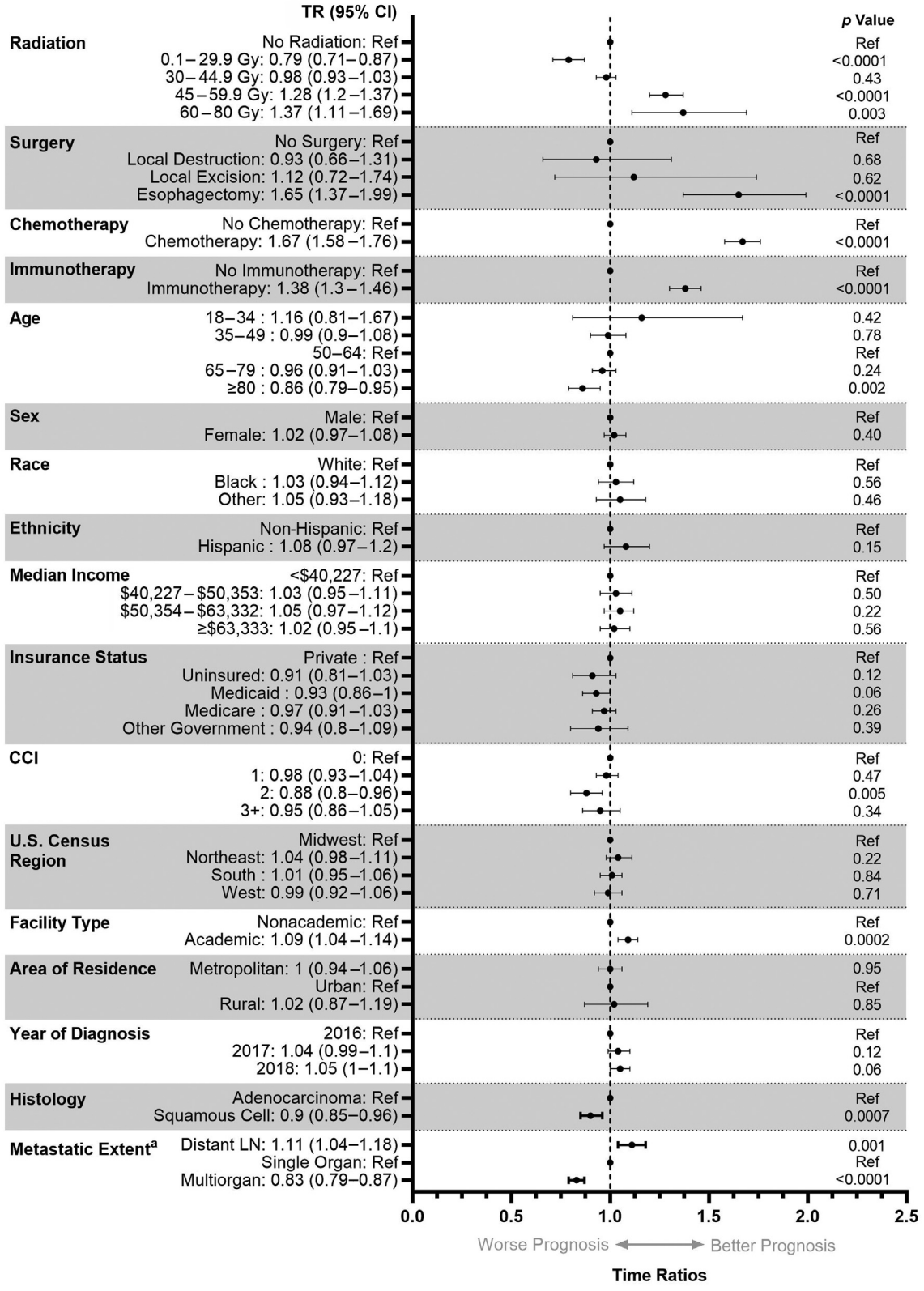

Figure 4. Forest plot of TRs from multivariable time-to-event model. Parametric time-to-event models were evaluated using Akaike Information Criteria, identifying the γ distribution as providing the best fit.[26] A TR of greater than one means that the factor is associated with longer survival (accelerates survival time). A hypothetical TR of 0.5 can be interpreted as the median time to death in patients with a certain characteristic being half the median time to death in the Ref group. CI indicated graphically with error bars. "Distant LN" signifies metastatic disease limited to nonregional lymph nodes only. CCI, Charlson-Deyo Comorbidity Index; CI, confidence interval; Ref, reference; TR, time ratio.

primary models were observed (Supplementary Fig. 3*A* and *B*). Recognizing potentially different radiosensitivities across tumor types, the models were performed stratified by histology (Supplementary Fig. 4*A*-*D*). Again, similar patterns were observed.

Discussion

In the United States, approximately one-third (32.7%) of the patients with metastatic stage IV esophageal cancer receive esophageal radiotherapy. This is consistent with a previous Surveillance, Epidemiology, and End Results–based study which found this rate to be 39.9%.[27] The practice patterns were variable, with differences noted across different sociodemographic cohorts and different types of hospitals and regions of the country. It is possible that academic institutions have greater access to advanced endoscopic procedures[28] to palliate symptoms and therefore use radiation less often, although the regional differences could represent different levels of clinician and patient enthusiasm for radiation as a palliative approach in different parts of the country. Alternatively, this could reflect differences in prevalence of obstructive symptoms at presentation or nutritional reserve.

Among the patients who received radiation, there was considerable variability in the dose that was administered. The recommended dose for palliation is itself a bit variable, with a range of 20 to 40 Gy across the guidelines.[3–5,8,13–16] In the current study, 64.8% of the patients who received radiation received less than 45 Gy, 29% received between 45 and 59.9 Gy, and 2.2% received considerably more radiation (60–80 Gy).

The risk-benefit consideration of radiation is unclear from the NCDB perspective. Radiation of the esophagus has been established as an effective approach to improve dysphagia symptoms and ultimately quality of life.[15,29] Unfortunately, the NCDB does not capture the indication for radiation treatment or symptomatic burden. In general, obstructive symptoms improve within six to eight weeks of initiation of radiation.[15,29] There are some clear drawbacks to palliative radiation in patients with esophageal cancer. One study found that patients with stage IV esophageal cancer who receive concurrent chemoradiotherapy may experience treatment-related esophagitis rate of 14.5% and treatment-related pneumonitis rate of 7.3%, when compared with chemotherapy alone.[30] Ulceration, strictures, and fistulas are also possible negative sequelae of esophageal radiation.[14,15] Radiotherapy may be inconvenient for patients, requiring daily treatment for a span of 3 to 6 weeks, depending on the administered dose. From a financial standpoint, each additional day of radiation treatment for esophageal cancer ranges between $421 and $1071.95 (from 2015 Medicare reimbursement rates).[31] These considerations are important given alternative mechanisms to palliate obstructive symptoms. More specifically, esophageal stenting can also effectively palliate obstructive symptoms and has the advantages of early symptom relief[32–34] and convenience. Systemic therapy has also been found to palliate dysphagia.[35–38] Other endoscopic approaches include tumor ablation with cryotherapy[9,39,40] or photodynamic therapy.[41–44] To be clear, every treatment carries potential complications and quality of life implications. For example, stents carry a risk of migration, perforation, and tracheoesophageal fistula.[45] Patients on photodynamic therapy have a temporary restriction to sunlight.[42–44] Given the range of different options for palliation with variable effectiveness, durability, and side effect profiles, the risk-benefit determination should be a part of shared decision making when the goal of treatment is palliation of the obstructive symptoms.

Overall, the survival analyses did not reveal a survival advantage to the administration of radiation in the NCDB, even when limited to patients who received chemotherapy and when adjusting for extent of metastatic cancer. It was only when analyzing the subset of patients who received higher doses of radiation that an association between radiotherapy and better survival was appreciated ($\geq$45 Gy), with irradiated patients living approximately 2.5 months longer than patients who did not receive radiation. This is not the first time that observational data have suggested that higher doses to the esophagus are associated with superior long-term outcomes. The survival benefit of definitive-dose radiotherapy in stage IV esophageal cancer has been suggested by several previous studies evaluating concurrent chemoradiotherapy when compared with chemotherapy alone.[30,46–48] Our study extends these findings, using a more contemporary patient population with multivariable models that adjust for metastatic pattern at presentation (nodal only, single organ, multiorgan) and exclude patients in the control arm that were felt not to be healthy enough to be irradiated.

Obviously, one interpretation of these findings is that higher doses of radiation are superior to lower doses in stage IV esophageal cancer. We caution against this interpretation of the presented data because it is unclear why patients received the different radiation doses. The higher dose patients were treated in a way that would be considered different from the standard radiation approach to palliation (mentioned previously to be 20–40 Gy). In fact, the higher dose is more consistent with the current National Comprehensive Cancer Network guidelines for definitive radiotherapy doses of 50 to 50.4 Gy (which is not recommended for stage IV esophageal cancer).[3,49] It is unclear whether these patients had some aspect of their disease that encouraged the team to

use higher doses, and this same factor correlated with a better prognosis. We attempted to adjust for this by including extent of disease but recognize that there may have been nuances that the NCDB did not capture. Therefore, we interpret the findings as a signal that more prospective studies exploring higher dose radiation in stage IV esophageal cancer are warranted, but not a justification to change the palliation approach.

The current study had a number of limitations in addition to those typically attributed to observational study.[50] There is the potential for selection bias based on characteristics that carried prognostic significance but were not adjusted for in the current study. For example, poor health that precluded radiation would also shorten survival. We attempted to adjust for this by excluding patients in the no radiation arm who were coded in the NCDB as not being eligible for radiation owing to poor health, but it is possible that differences in health persisted between the cohorts. The specific types of chemotherapy agents and number of cycles are not given in the NCDB. Finally, the NCDB does not capture tumor progression or cause of death; therefore, we cannot estimate cause-specific death rates or radiation's effects on local control of disease in the esophagus.

In summary, esophageal radiation is most often administered to patients with metastatic stage IV esophageal cancer in the United States, but there seems to be slightly less enthusiasm for radiation in this context at academic hospitals and in the Northeast. Of the patients who received esophageal radiation, two of three received a total radiation dose that was not associated with a survival advantage over no radiation. Further study of the most appropriate approach to palliating the obstructive symptoms in the setting of stage IV esophageal cancer is justified.

CRediT Authorship Contribution Statement

Peter Lee Zhan: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review and editing.

Maureen E. Canavan: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—review and editing.

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Richard C. Maduka: Investigation, Visualization, Writing—review and editing.

Michael F. Kaminski: Investigation, Validation, Visualization, Writing—review and editing.

Kimberly L. Johung: Investigation, Methodology, Writing—review and editing.

Daniel J. Boffa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—Review and editing.

Data Availability

The National Cancer Database is a nationwide clinical surveillance resource oncology data set that captures 72% of all newly diagnosed malignancies in the United States annually and is a joint project of the American Cancer Society and the American College of Surgeons. The American College of Surgeons has a data use agreement with each of its Commission on Cancer–accredited hospitals. Data access can be requested from the American College of Surgeons.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100429.

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