Original Article

Radiation Modality Use and Cardiopulmonary Mortality Risk in Elderly Patients With Esophageal Cancer

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BACKGROUND: It is currently unclear whether the superior normal organ-sparing effect of intensity-modulated radiotherapy (IMRT) compared with 3-dimensional radiotherapy (3D) has a clinical impact on survival and cardiopulmonary mortality in patients with esophageal cancer (EC). **METHODS:** The authors identified 2553 patients aged > 65 years from the Surveillance, Epidemiology, and End Results (SEER)-Medicare and Texas Cancer Registry-Medicare databases who had nonmetastatic EC diagnosed between 2002 and 2009 and were treated with either 3D (2240 patients) or IMRT (313 patients) within 6 months of diagnosis. The outcomes of the 2 cohorts were compared using inverse probability of treatment weighting adjustment. **RESULTS:** Except for marital status, year of diagnosis, and SEER region, both radiation cohorts were well balanced with regard to various patient, tumor, and treatment characteristics, including the use of IMRT versus 3D in urban/metropolitan or rural areas. IMRT use increased from 2.6% in 2002 to 30% in 2009, whereas the use of 3D decreased from 97.4% in 2002 to 70% in 2009. On propensity score inverse probability of treatment weighting-adjusted multivariate analysis, IMRT was not found to be associated with EC-specific mortality (hazard ratio [HR], 0.93; 95% confidence interval [95% CI], 0.80-1.10) or pulmonary mortality (HR, 1.11; 95% CI, 0.37-3.36), but was significantly associated with lower all-cause mortality (HR, 0.83; 95% CI, 0.72-0.95), cardiac mortality (HR, 0.18; 95% CI, 0.06-0.54), and other-cause mortality (HR, 0.54; 95% CI, 0.35-0.84). Similar associations were noted after adjusting for the type of chemotherapy, physician experience, and sensitivity analysis removing hybrid radiation claims. **CONCLUSIONS:** In this population-based analysis, the use of IMRT was found to be significantly associated with lower all-cause mortality, cardiac mortality, and other-cause mortality in patients with EC. ***Cancer* 2016;122:917-28.** © *2015 American Cancer Society.*

KEYWORDS: 3-dimensional conformal radiotherapy, cardiopulmonary mortality, esophageal cancer, intensity-modulated radiotherapy (IMRT), propensity score, Surveillance, Epidemiology, and End Results (SEER).

INTRODUCTION

Radiation technologies have evolved substantially over time, from 2-dimensional (2D) planning on plain x-ray films to 3-dimensional (3D) computerized tomography-based treatment planning. Intensity-modulated radiotherapy (IMRT) is the next level of advancement that delivers better prescription dose conformality to the tumor but increases the low-dose spread to surrounding tissues. For some sites of disease, IMRT is an accepted standard based on evidence demonstrating toxicity reduction compared with conventional radiotherapy methods, including 3D conformal radiotherapy (hereafter referred to as 3D).[1-3] However for many sites of disease, including esophageal cancer (EC), 3D remains the standard approach due to the uncertain benefits of the more expensive and technically demanding IMRT.

For patients with newly diagnosed EC, chemoradiation, either preoperative or definitive, is performed as a standard of care.[4] However, given the location of the majority of tumors, the dose to the heart can be substantial, particularly when standard 3D techniques are used. Planning studies have shown that IMRT preferentially spares the heart over the lungs.[5-7] How this dosimetric advantage translates into clinical benefit for patients is still not convincingly proven, because to our knowledge there are no large randomized trials comparing IMRT with 3D in patients with EC. Previously, a propensity-matched analysis of single-institution data comparing the long-term outcomes of patients treated with either IMRT or 3D

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radiotherapy from 1998 to 2010 was reported.[8] The authors found significantly improved overall survival and cardiac-specific mortality for patients treated with IMRT, but no differences in distant disease recurrence rate, cancer-specific survival, or pulmonary-related deaths. However, another single-institution data analysis found no difference in overall survival but only reduced short-term toxicity for patients treated with IMRT.[9] The benefit of IMRT, particularly in improving long-term clinical outcomes, remains unclear.

For the current study, we evaluated the Surveillance, Epidemiology, and End Results (SEER)-Medicare and the Texas Cancer Registry (TCR)-Medicare-linked databases to assess the overall and cause-specific mortality rates of patients with EC who were treated with radiotherapy. On the basis of the dosimetric advantages of IMRT, we hypothesized that IMRT may produce clinical benefit by reducing cardiopulmonary mortality in patients with EC who are treated with radiotherapy.

MATERIALS AND METHODS

Data Source

Patients aged > 65 years were identified from the National Cancer Institute-supported SEER-Medicare database and the TCR-Medicare-linked database. The SEER database provided information from 17 geographic locations in the United States, representing approximately 25% of the nation's incident cancers linked to Medicare claims. The TCR, as a legislative mandate of the Texas Department of State Health Services in 1979, is the fourth largest state population-based registry. Data regarding vital statistics and cause-specific deaths are obtained through linkage with the Texas vital statistics and mortality data, the Social Security Death Index, and the National Death Index. Data collection follows standard registry rules, and core data items are similar to those collected on the SEER-Medicare database. The TCR data have been linked to Medicare claims using the same algorithm as the SEER-Medicare linkage. The files from the cancer registries were used to identify patients diagnosed with EC and the vital status of these patients. Subsequent treatment was identified from Medicare claims using billing codes. The relevant codes used are summarized in Supporting Information Table 1. This research was reviewed by the Institutional Review Board and granted an exemption.

Cohort Selection

A multistep process (see Supporting Information Table 2) was used to select the patients from the 2 databases based on their first diagnosis of EC (31,101 from SEER for 1973-2009 and 6856 from TCR for 1995-2007), with the histologically and microscopically confirmed diagnosis of squamous cell carcinoma or adenocarcinoma but who were not diagnosed at the time of autopsy. Our patients were aged >65 years with non-metastatic EC, had enrolled in Medicare parts A and B for 12 months before diagnosis without health maintenance organization insurance, and stayed enrolled until 12 months after diagnosis or death if the patient died within 12 months of diagnosis. Patients also must not have been diagnosed with a second cancer within 1 year of diagnosis.

Radiation Use Selection

All patients must have initiated radiotherapy within 6 months after diagnosis based on radiation claims. Patients who underwent brachytherapy within 12 months of diagnosis were excluded. For IMRT, we used the Healthcare Common Procedure Coding System (HCPCS) codes 77418 and G0174, and for 3D we used HCPCS codes 77290, 76370, 77014, and 77295. We excluded any patients treated with 2D radiotherapy (HCPCS codes 77280 and 77285) and patients who received radiotherapy but were not categorized using these codes. There were 173 patients who were hybrids, having both IMRT and 3D delivery claims in their Medicare records. To categorize these into either IMRT or 3D, we formulated a stepwise approach to segregate these patients using criteria involving radiation course delivery time, the number of fractions between the 2 types of radiotherapy claims, and the first treatment delivery dates (see Supporting Information Table 3). Using this stepwise approach, we were able to further define 138 patients into either IMRT or 3D. Sensitivity analysis was performed to evaluate whether the inclusion of these patients affected the multivariable analysis. The remaining 35 patients who could not be stratified using this approach were considered unevaluable and were excluded from the current study.

Baseline Patient, Tumor, and Treatment Characteristics

Demographic information included age, sex, race/ethnicity, marital status (not available in the TCR), SEER regions, urban/rural setting, educational attainment, and income level. Tumor characteristics included stage (localized vs regional [lymph node positive]), grade, and year of diagnosis. Treatment characteristics included the use of chemotherapy within 6 months of diagnosis and the performance of esophagectomy after radiotherapy. Comorbidities were recorded as either the Klabunde adaptation of the Charlson comorbidity index or as individual

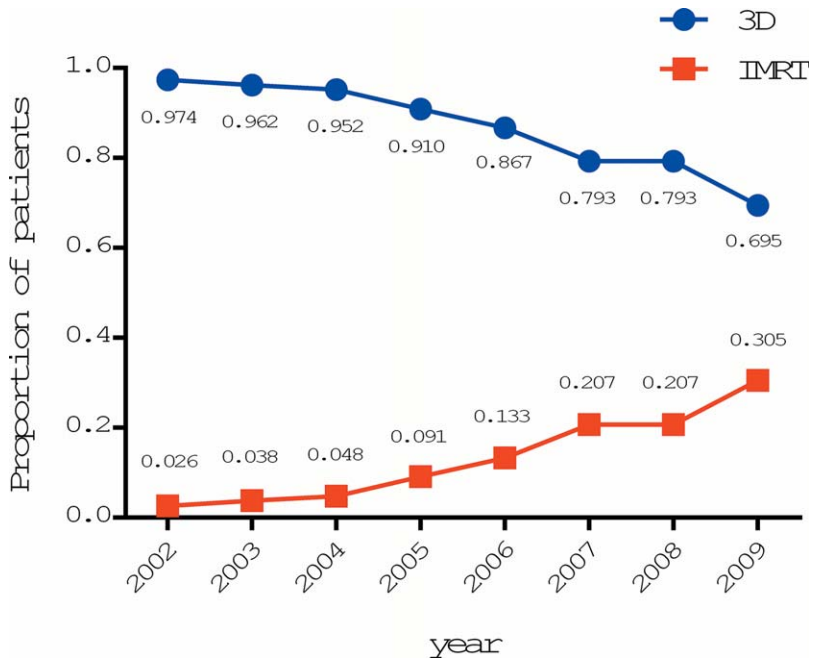

Figure 1. The use of 3-dimensional conformal radiotherapy (3D) and intensity-modulated radiotherapy (IMRT) for the treatment of esophageal cancer from 2002 to 2009.

comorbid illnesses existing within 12 months before the diagnosis of EC, such as congestive heart failure, hypertension, other heart diseases (coronary artery disease or myocardial infarction), diabetes, or pulmonary diseases.

Physician Experience

To document physician demographics and experience in the use of the radiation technologies, we collected information from physicians who performed the radiation claims using the Unique Physician Identification Number (UPIN) or the National Provider Identifier (NPI) (for claims made after June 2007). For physicians having both UPINs and NPI numbers, redundancy was eliminated by crosslinking the NPI numbers to the UPINs. We collected information regarding the physicians' age (by 2010), sex, primary and secondary specialties, board certification status, US trained (yes/no), number of years in practice after training, and EC case load based on the number of yearly claims by said physician.

Statistical Analysis

We used chi-square analysis to compare the percentage of 3D versus IMRT use among the baseline characteristics. The propensity score was calculated to predict the conditional probability of patients receiving IMRT versus 3D based on their pretreatment variables. We calculated the propensity score as a continuous covariate using logistic regression to predict the patients' possibility of receiving IMRT or 3D. The covariates adjusted in the logistic regression include the patients' demographics, comorbidities, tumor characteristics, physician characteristics, the type of chemotherapy, and the type of radiation technology used. We also calculated the inverse probability of treatment weights (IPTW) using the propensity score obtained from the logistic regression. The IPTW-adjusted Kaplan-Meier survival curves were generated for overall; EC-specific; cardiac; pulmonary; or other noncancer, noncardiopulmonary cause deaths ("other deaths"). Statistical analysis was performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC).

RESULTS

Patients, Treatment, and Physician Characteristics

We initially identified 3403 patients aged $\geq$ 66 years who were diagnosed with nonmetastatic EC from 1997 to 2009 and who met our inclusion criteria. We further confined our analysis to the patients treated between 2002 and 2009, with 2240 patients treated with 3D and 313 patients treated with IMRT. IMRT use increased from a rate of 2.6% in 2002 to 31.2% in 2009 (Fig. 1). Table 1 summarizes the baseline characteristics of the study cohort. For the most part, the 2 groups were well balanced

TABLE 1. Patient Demographic, Clinical, and Tumor Characteristics

	Overall Cohort N = 2553 (%)	3D N=2240 (%)	IMRT N=313 (%)	Chi-square *P*
Age, y				
66-70	729 (28.6)	634 (28.3)	95 (30.4)	.7698
71-75	669 (26.2)	584 (26.1)	85 (27.2)	
76-80	560 (21.9)	496 (22.1)	64 (20.5)	
>80	595 (23.3)	526 (23.5)	69 (22.0)	
Years of diagnosis				
2002-2003	695 (27.2)	672 (30)	23 (7.4)	<.0001
2004	369 (14.5)	351 (15.7)	18 (5.8)	
2005	313 (12.3)	284 (12.7)	29 (9.3)	
2006	349 (13.7)	302 (13.5)	47 (15.0)	
2007	362 (14.2)	287 (12.8)	75 (24.0)	
2008	216 (8.7)	171 (7.6)	45 (14.4)	
2009	249 (9.8)	173 (7.7)	76 (24.3)	
Marital status				
Married	1230 (48.2)	1097 (49.0)	133 (42.5)	.0403
Not married	771 (30.2)	674 (30.1)	97 (31.0)	
Unknown[a]	552 (21.6)	469 (20.9)	83 (26.5)	
Histology				
Adenocarcinoma	1423 (55.7)	1255 (56.0)	168 (53.7)	.4325
SCCA	1130 (44.3)	985 (44.0)	145 (46.3)	
Race/ethnicity				
White	2095 (82.1)	1834 (81.9)	261 (83.4)	.0619
Hispanic	144 (5.6)	120 (5.4)	24 (7.7)	
Black/other	314 (12.3)	286 (12.8)	28 (9.0)	
Stage				
Localized	991 (38.8)	862 (38.5)	129 (41.2)	.3529
Regional	1562 (61.2)	1378 (61.5)	184 (58.8)	
Sex				
Female	744 (29.1)	657 (29.3)	87 (27.8)	.5757
Male	1809 (70.9)	1583 (70.7)	226 (72.2)	
Patients undergoing surgery after radiotherapy				
No	2107 (82.5)	1855 (82.81)	252 (80.5)	.3152
Yes	446 (17.5)	385 (17.19)	61 (19.5)	
Tumor grade				
Well differentiated	123 (4.8)	108 (4.8)	15 (4.8)	.9662
Moderately differentiated	957 (37.5)	839 (37.5)	118 (37.7)	
Poorly differentiated	1033 (40.5)	910 (40.6)	123 (39.3)	
Unknown	440 (17.2)	383 (17.1)	57 (18.2)	
Charlson comorbidity index				
0	1510 (59.2)	1313 (58.6)	197 (62.9)	.2957
1	664 (26.0)	593 (26.5)	71 (22.7)	
≥2	379 (14.9)	334 (14.9)	45 (14.34)	
Regions (SEER plus Texas)				
California plus Hawaii	563 (22.1)	484 (21.6)	79 (25.2)	.0632
6 SEER regions combined[b]	636 (24.9)	576 (25.7)	60 (19.2)	
Greater Georgia	256 (10.0)	232 (10.4)	24 (7.7)	
Kentucky	161 (6.3)	141 (6.3)	20 (6.4)	
Louisiana	134 (5.3)	116 (5.2)	18 (5.8)	
New Jersey	324 (12.7)	284 (12.7)	40 (12.8)	
Texas	479 (18.8)	407 (18.2)	72 (23)	
Use of chemotherapy				.0881
No	411 (16.1)	371 (16.6)	40 (12.8)	
Yes	2142 (83.9)	1869 (83.4)	273 (87.2)	
Urban/rural				
Big metropolitan	1285 (50.3)	1124 (50.2)	161 (51.4)	.5954
Less urban/rural	411 (16.1)	369 (16.5)	42 (13.4)	
Metropolitan	805 (31.5)	701 (31.3)	104 (33.2)	
Urban	168 (6.6)	148 (6.6)	20 (6.4)	
Percentage of adults with <12 y of education				
Lowest quartile	625 (24.5)	544 (24.3)	81 (25.9)	.627
2nd quartile	607 (23.8)	529 (23.6)	78 (24.9)	
3rd quartile	640 (25.1)	560 (25.0)	80 (25.6)	
Highest quartile	681 (26.7)	607 (27.1)	74 (23.6)	
Percentage of family living below poverty line				
Lowest quartile	629 (24.6)	548 (24.5)	81 (25.9)	.5019

TABLE 1. *Continued*

	Overall Cohort N = 2553 (%)	3D N=2240 (%)	IMRT N=313 (%)	Chi-square *P*
2nd quartile	627 (24.6)	561 (25.0)	66 (21.1)	
3rd quartile	641 (25.1)	560 (25.0)	81 (25.9)	
Highest quartile	656 (25.7)	571 (25.5)	85 (27.2)	
Pre-CHF[c]				
No	2048 (80.2)	1798 (80.27)	250 (79.87)	.8693
Yes	505 (19.8)	442 (19.73)	63 (20.13)	
Pre-other heart disease[c]				
No	2038 (79.8)	1786 (79.73)	252 (80.51)	.7477
Yes	515 (20.2)	454 (20.27)	61 (19.49)	
Pre-hypertension[c]				
No	1313 (51.4)	1161 (51.83)	152 (48.56)	.2785
Yes	1240 (48.6)	1079 (48.17)	161 (51.44)	
Pre-diabetes[c]				
No	2100 (82.3)	1845 (82.37)	255 (81.47)	.6974
Yes	453 (17.7)	395 (17.63)	58 (18.53)	
Pre-respiratory disease[c]				
No	2031 (79.6)	1780 (79.46)	251 (80.19)	.765
Yes	522 (20.5)	460 (20.54)	62 (19.81)	
No. of radiation fractions				
Mean ± SD	24 ± 8.5	24 ± 8.5	25 ± 8.1	.1433
Median	26	26	28	

Abbreviations: 3D, three-dimensional conformal radiotherapy; CHF, congestive heart failure; IMRT, intensity-modulated radiotherapy; SCCA, squamous cell carcinoma; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.
[a] Marital status was unknown for allTexas Cancer Registry patients.
[b] The 6 SEER regions include Connecticut, Detroit, Iowa, New Mexico, Seattle, and Utah.
[c] Pre-disease within 1 year before diagnosis of esophageal cancer, and except for hypertension, are parts of Charlson comorbidity index and therefore were not included into Cox modeling that was adjusted for Charlson comorbidityindex.

except with regard to marital status, the SEER region, and the year of diagnosis. The use of IMRT was only slightly higher in patients residing in metropolitan versus rural areas, but the difference was not significant. There were no differences noted with regard to the income or education levels of the 2 cohorts. The median number of radiotherapy fractions was 26 for patients receiving 3D and 28 for patients undergoing IMRT, but the difference was not statistically significant.

Physician experience or hospital volume have been shown to be influential factors in the clinical outcomes of patients treated with surgery.[10,11] Therefore, we included physician characteristics in the context of the radiation technologies used (Table 2). Although board certification, sex, and the type of medical degree (Doctor of Medicine [MD] vs Doctor of Osteopathic Medicine [DO]) did not differ among physicians using the 2 radiation modalities, younger physicians (which was correlated with being a more recent graduate from medical school, having fewer years in practice, and having a lower clinical volumes) used IMRT significantly more frequently than older, more seasoned physicians. US-trained physicians also used IMRT less often than non-US-trained physicians.

To compare the outcomes of the 2 groups, we applied the IPTW Cox model analysis, in which each patient is weighted to create a pseudopopulation that mimics what would be attained in a randomized trial. The propensity score and IPTW-adjusted baseline patient, tumor, and physician characteristics are listed in Supporting Information Tables 4 and 5. This was applied to generate the fitted multivariate IPTW-adjusted Cox model for survival analysis comparing 3D and IMRT (Table 3). The IPTW-adjusted Kaplan-Meier survival analysis for all-cause, EC-specific, cardiac-specific, pulmonary-specific, or other-cause mortality is shown in Figure 2. IMRT was significantly associated with lower all-cause mortality, cardiac-specific mortality, and other-cause mortality compared with 3D, but not for EC-specific or pulmonary mortality. We found no relation between the board certification of the physicians, years since graduation, physicians' sex, US training versus non-US training, or physician type on any of the mortality outcomes of the patients.

The most common chemotherapy doublets used were cisplatin and 5-fluorouracil (5-FU) (37.2%), carboplatin and paclitaxel (22.6%), and docetaxel and 5-FU (5.9%) (see Supporting Information Table 6). Of those patients who underwent chemotherapy, 52% were treated with a 5-FU-based regimen. We evaluated whether the chemotherapy regimen influenced survival and cause-

TABLE 2. Characteristics of the Physicians Associated With the Treated Patients[a]

	Overall Cohort N = 2553 (%)	3D N=2240 (%)	IMRT N=313 (%)	Chi-square*P*
Board certified				
Yes	2190 (85.8)	1928 (86.1)	262 (83.7)	.5293
No/unknown	363 (14.2)	312 (13.9)	51 (16.3)	
Year of graduation				
Prior to 1980	657 (25.7)	594 (26.5)	63 (20.1)	.0421
1980-1989	947 (37.1)	833 (37.2)	114 (36.4)	
After 1990	652 (25.5)	558 (24.9)	94 (30.0)	
Unknown	297 (11.6)	255 (11.4)	42 (13.4)	
Physician sex				
Female	393 (15.4)	343 (15.3)	50 (16.0)	.5145
Male	1863 (73.0)	1642 (73.3)	221 (70.6)	
Unknown	297 (11.6)	255 (11.4)	42 (13.4)	
US trained				
No	376 (14.7)	313 (14.0)	63 (20.1)	.0111
Yes	1901 (74.5)	1687 (75.3)	214 (68.4)	
Unknown	276 (10.8)	240 (10.7)	36 (11.5)	
Physician type				
MD	2244 (87.9)	1969 (87.9)	275 (87.9)	.5126
DO/unknown	309 (12.1)	271 (12.1)	38 (12.1)	
Physician age, y				
34-46	407 (15.9)	341 (15.2)	66 (21.1)	.0099
46-52	619 (24.3)	537 (24.0)	82 (26.2)	
52-60	673 (26.4)	606 (27.1)	67 (21.4)	
60-85	557 (21.8)	501 (22.4)	56 (17.9)	
Unknown	297 (11.6)	255 (11.4)	42 (13.4)	
Physician years in training				
3-13	470 (18.4)	388 (17.3)	82 (26.2)	.0017
13-19	563 (22.1)	503 (22.5)	60 (19.2)	
19-28	652 (25.5)	579 (25.9)	73 (23.3)	
28-61	521 (20.4)	470 (21.0)	51 (16.3)	
Unknown	347 (13.6)	300 (13.4)	47 (15.0)	

Abbreviations: 3D, three-dimensional conformal radiotherapy; DO, Doctor of Osteopathic Medicine; IMRT, intensity-modulated radiotherapy; MD, Doctor of Medicine.

[a] A total of 1124 physicians by Unique Physician Identification Number had seen the cohort of 2553 patients. Among these, information was missing for 136 physicians, resulting in the demographic information for up to 297 patients' physicians not being identified.

specific mortality. On multivariable analysis, the use of any chemotherapy was found to be significantly associated with an improved overall survival and EC-specific and other-cause mortality, but not with pulmonary and cardiac mortality (Table 3). We performed a separate multivariable analysis to determine whether the use of an 5-FU-based regimen had any influence on any of the clinical outcomes. We found 5-FU-based regimens to exert similar protective effects on overall and EC-specific survival, including cardiac mortality, compared with either the use of no chemotherapy or non-5-FU-based regimens. Even after adjusting for the type of chemotherapy used, IMRT remained significantly associated with better overall survival, lower cardiac-specific mortality, and other-cause mortality, but was not associated with EC-specific and pulmonary-specific mortality (data not shown).

There is the possibility that with better understanding of radiation planning dose constraints, the cardiac mortality rate may decrease over time for patients treated with 3D. We evaluated this possibility by examining the crude cardiac mortality rate in the 3D group between 2002 and 2008, but not in 2009 because the treatment claims data and death record were not mature. The overall cardiac mortality rate for the entire cohort of 3D patients was 5.5%. The average yearly cardiac mortality rate for the patients treated with 3D was 5.7% (±1.4%), and did not change over the years (chi-square $P = .391$). This rate is nearly 5-fold higher in comparison with the rate for IMRT (data not shown).

Approximately 5% of patients had billing claims in which both 3D and IMRT were used. We used a multistep process to segregate these patients into either the 3D or IMRT groups (see Supporting Information Table 3). We also performed sensitivity analysis to exclude these patients from the Cox multivariate analysis and found no influence in the multivariate model even after excluding these patients (data not shown). It is interesting to note that when we evaluated the cardiac mortality risk for 3D,

TABLE 3. Fitted Cox Model Using Inverse Probability of Treatment Weights

Parameter	All-Cause Deaths				EC-Specific Deaths				Cardiac-Specific Deaths				Pulmonary-Specific Deaths				Deaths from Other Causes			
	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*
Radiotherapy																				
3D	Ref				Ref				Ref				Ref				Ref			
IMRT	0.831	0.725	0.952	0.0075	0.934	0.795	1.097	0.4063	0.183	0.062	0.544	0.0022	1.111	0.367	3.363	0.8525	0.543	0.351	0.842	0.0064
Age, y																				
66-70	Ref				Ref				Ref				Ref				Ref			
71-75	1.026	0.907	1.16	0.6871	0.952	0.816	1.11	0.5276	0.893	0.512	1.558	0.6893	0.674	0.245	1.853	0.4442	1.292	0.935	1.784	0.1202
76-80	1.201	1.056	1.366	0.0054	1.18	1.008	1.382	0.04	0.935	0.512	1.709	0.8279	1.043	0.393	2.768	0.9318	1.383	0.976	1.959	0.0679
>80	1.324	1.158	1.514	<.0001	1.208	1.024	1.426	0.025	1.939	1.11	3.386	0.02	0.917	0.286	2.941	0.8835	1.285	0.877	1.881	0.1983
Year of diagnosis																				
2002	Ref				Ref				Ref				Ref				Ref			
2003	0.962	0.818	1.13	0.6348	0.952	0.79	1.148	0.6053	0.761	0.412	1.405	0.382	0.163	0.029	0.909	0.0386	1.151	0.751	1.765	0.5189
2004	1.033	0.876	1.219	0.6974	0.921	0.76	1.117	0.4037	1.109	0.599	2.053	0.7416	0.863	0.279	2.668	0.7982	1.257	0.812	1.945	0.3057
2005	0.981	0.826	1.166	0.8311	0.918	0.751	1.122	0.4043	0.473	0.218	1.026	0.0582	1.276	0.436	3.735	0.6563	1.162	0.736	1.832	0.5197
2006	0.982	0.826	1.167	0.8338	0.878	0.717	1.074	0.206	0.685	0.339	1.386	0.2933	0.99	0.318	3.078	0.9856	0.869	0.536	1.408	0.568
2007	1.123	0.945	1.333	0.1877	0.877	0.713	1.078	0.2113	0.827	0.42	1.628	0.583	0.437	0.1	1.904	0.2705	1.37	0.876	2.142	0.1679
2008	1.165	0.955	1.421	0.1312	0.793	0.621	1.013	0.0634	0.494	0.198	1.236	0.1317	0.787	0.157	3.931	0.77	1.4	0.801	2.448	0.2376
2009	1.046	0.859	1.273	0.6545	0.255	0.181	0.359	<.0001	0.085	0.013	0.536	0.0087	-	-	-	-	0.575	0.28	1.179	0.1307
Marital status																				
Married	Ref				Ref				Ref				Ref				Ref			
Not married	1.155	1.037	1.287	0.0088	1.139	0.998	1.301	0.0538	1.338	0.844	2.122	0.216	1.656	0.723	3.794	0.2333	0.904	0.653	1.251	0.5421
Unknown	1.076	0.833	1.389	0.5747	0.925	0.653	1.311	0.6617	0.965	0.321	2.905	0.9498	-	-	-	-	0.986	0.476	2.042	0.9706
Race/ethnicity																				
White	Ref				Ref				Ref				Ref				Ref			
Hispanic	0.766	0.622	0.944	0.0122	0.733	0.562	0.955	0.0215	0.964	0.441	2.107	0.9269	0.634	0.123	3.256	0.5849	0.702	0.412	1.197	0.194
Black	0.999	0.848	1.178	0.9931	1.015	0.831	1.241	0.8814	1.263	0.637	2.502	0.5038	0.659	0.158	2.757	0.5683	0.845	0.537	1.33	0.4674
Other	1.088	0.826	1.432	0.5485	1.029	0.742	1.427	0.8641	0.775	0.176	3.425	0.7372	2.988	0.684	13.045	0.1455	1.012	0.419	2.443	0.979
Histology																				
Adenocarcinoma	Ref				Ref				Ref				Ref				Ref			
SCCA	1.064	0.963	1.176	0.2238	1.086	0.96	1.229	0.1911	0.952	0.613	1.479	0.8262	1.48	0.668	3.275	0.3339	0.944	0.717	1.242	0.6815
Stage																				
Localized	Ref				Ref				Ref				Ref				Ref			
Regional	1.261	1.149	1.383	<.0001	1.258	1.122	1.411	<.0001	0.855	0.581	1.257	0.4248	1.285	0.62	2.662	0.5003	1.235	0.961	1.586	0.099
Sex																				
Female	Ref				Ref				Ref				Ref				Ref			
Male	1.094	0.984	1.216	0.0972	1.112	0.975	1.268	0.1124	0.988	0.636	1.533	0.9558	0.956	0.417	2.193	0.9152	0.938	0.704	1.251	0.6633

TABLE 3. *Continued*

Parameter	All-Cause Deaths				EC-Specific Deaths				Cardiac-Specific Deaths				Pulmonary-Specific Deaths				Deaths from Other Causes			
	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*
Surgery after radiotherapy																				
No	Ref				Ref				Ref				Ref				Ref			
Yes	0.581	0.509	0.663	<.0001	0.494	0.416	0.588	<.0001	0.543	0.276	1.068	0.0769	0.507	0.167	1.54	0.2309	0.872	0.635	1.197	0.3957
Grade																				
Well differentiated	Ref				Ref				Ref				Ref				Ref			
Moderately differentiated	0.97	0.788	1.194	0.7716	1.051	0.811	1.363	0.7063	0.764	0.337	1.731	0.5189	0.715	0.162	3.151	0.6581	0.844	0.508	1.401	0.5111
Poorly differentiated	1.114	0.841	1.476	0.4522	1.157	0.815	1.643	0.4133	0.804	0.248	2.601	0.7154	0.716	0.092	5.555	0.7495	0.952	0.511	1.772	0.8757
Undifferentiated	1.146	0.927	1.416	0.2074	1.254	0.964	1.633	0.0922	0.902	0.395	2.058	0.8056	1.434	0.331	6.209	0.6297	0.733	0.427	1.259	0.2608
Unknown	0.999	0.799	1.249	0.9931	1.014	0.767	1.342	0.9211	1.104	0.464	2.628	0.8223	0.25	0.034	1.845	0.1739	0.892	0.514	1.547	0.6834
Charlson comorbidity index																				
0	Ref				Ref				Ref				Ref				Ref			
1	1.136	1.024	1.259	0.0157	1.025	0.901	1.166	0.7061	1.777	1.113	2.838	0.0161	3.887	1.732	8.723	0.001	1.333	1.021	1.739	0.0345
≥2	1.451	1.279	1.646	<.0001	1.253	1.069	1.47	0.0055	4.288	2.716	6.769	<.0001	4.534	1.748	11.76	0.0019	1.311	0.912	1.885	0.1441
SEER region																				
California plus Hawaii	Ref				Ref				Ref				Ref				Ref			
6 SEER regions combined[a]	0.94	0.822	1.076	0.3697	0.846	0.719	0.996	0.044	1.159	0.651	2.065	0.6152	1.075	0.344	3.363	0.9006	1.462	0.95	2.249	0.0842
Greater Georgia	1.269	1.069	1.506	0.0065	1.156	0.938	1.424	0.1731	1.254	0.577	2.726	0.5672	1.17	0.247	5.548	0.843	2.175	1.312	3.607	0.0026
Kentucky	1.273	1.04	1.558	0.0192	1.244	0.975	1.588	0.0787	1.355	0.562	3.269	0.4988	1.744	0.366	8.302	0.4846	1.546	0.81	2.952	0.1863
Louisiana	1.029	0.834	1.27	0.7883	0.872	0.668	1.139	0.3144	1.042	0.407	2.665	0.9315	1.699	0.299	9.645	0.5496	1.813	0.984	3.341	0.0563
New Jersey	0.833	0.706	0.984	0.0312	0.709	0.576	0.874	0.0012	1.091	0.53	2.247	0.8135	0.533	0.14	2.033	0.3569	1.449	0.881	2.383	0.1442
Texas	0.99	0.73	1.343	0.9502	0.941	0.629	1.406	0.7649	0.968	0.257	3.65	0.9616	-	-	-	-	2.657	1.147	6.155	0.0226
Chemotherapy																				
No	Ref				Ref				Ref				Ref				Ref			
Yes	0.631	0.558	0.713	<.0001	0.625	0.539	0.724	<.0001	0.663	0.399	1.103	0.1138	1.113	0.322	3.852	0.8654	0.54	0.384	0.76	0.0004
Rural/urban																				
Big metropolitan	Ref				Ref				Ref				Ref				Ref			
Less urban	0.953	0.804	1.13	0.5803	0.987	0.801	1.217	0.905	0.607	0.266	1.389	0.2374	0.499	0.107	2.334	0.3769	0.824	0.527	1.286	0.3936
Metropolitan	1.175	1.06	1.302	0.0021	1.174	1.035	1.331	0.0127	1.025	0.659	1.596	0.9116	0.361	0.136	0.958	0.0408	1.116	0.84	1.483	0.4487
Rural	1.202	0.874	1.653	0.2586	1.022	0.668	1.565	0.9197	0.343	0.042	2.774	0.3159	3.051	0.59	15.775	0.1832	1.82	0.909	3.646	0.0909
Urban	1.066	0.883	1.287	0.508	1.066	0.845	1.346	0.5895	1.891	0.971	3.683	0.0612	0.799	0.193	3.303	0.7565	0.828	0.485	1.415	0.49

TABLE 3. *Continued*

Parameter	All-Cause Deaths				EC-Specific Deaths				Cardiac-Specific Deaths				Pulmonary-Specific Deaths				Deaths from Other Causes			
	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*	HR	95% CI		Probability> chi-square *P*
Education																				
Lowest quartile	Ref				Ref				Ref				Ref				Ref			
2nd quartile	1.17	1.022	1.34	0.0228	1.164	0.985	1.375	0.0754	1.749	0.921	3.32	0.0876	2.132	0.72	6.316	0.1718	1.003	0.676	1.486	0.99
3rd quartile	1.063	0.913	1.238	0.4319	1.088	0.903	1.311	0.3777	1.384	0.68	2.82	0.3702	2.522	0.747	8.521	0.1363	1.174	0.761	1.813	0.4679
Highest quartile	1.096	0.913	1.315	0.3264	0.971	0.775	1.218	0.8004	1.124	0.495	2.551	0.7792	2.028	0.441	9.314	0.3634	1.659	1.003	2.743	0.0486
Poverty																				
Lowest quartile	Ref				Ref				Ref				Ref				Ref			
2nd quartile	0.9	0.788	1.027	0.1188	0.874	0.742	1.029	0.1065	0.567	0.295	1.089	0.0882	1.059	0.396	2.829	0.9089	0.853	0.585	1.244	0.409
3rd quartile	1.048	0.897	1.223	0.5572	0.979	0.808	1.187	0.8319	1.605	0.83	3.102	0.1595	0.322	0.079	1.309	0.1133	0.828	0.528	1.301	0.4135
Highest quartile	0.998	0.824	1.208	0.9816	0.954	0.754	1.208	0.6984	1.135	0.506	2.548	0.7589	0.728	0.168	3.158	0.672	0.927	0.546	1.575	0.7801
Physicians board certified																				
No	Ref				Ref				Ref				Ref				Ref			
Unknown	1.213	0.6	2.453	0.5914	0.858	0.356	2.068	0.7338	19.84	1.717	229.262	0.0167	-	-	-	-	0.667	0.099	4.504	0.6773
Yes	1.072	0.814	1.413	0.6209	1.003	0.722	1.392	0.986	2.788	0.641	12.122	0.1714	0.608	0.092	4.02	0.6053	0.982	0.436	2.214	0.9655
Year of graduation																				
Prior to 1980	Ref				Ref				Ref				Ref				Ref			
1980-1989	1.031	0.823	1.292	0.7904	1.072	0.809	1.421	0.6299	1.011	0.424	2.409	0.9807	11.87	0.529	266.14	0.119	0.98	0.501	1.918	0.9526
After 1990	1.097	0.825	1.458	0.5253	1.135	0.798	1.614	0.4825	1.5	0.45	5.002	0.5091	12.59	0.359	442.04	0.163	0.766	0.333	1.764	0.5315
Physician sex																				
Female	Ref				Ref				Ref				Ref				Ref			
Male	1.007	0.886	1.145	0.9119	0.934	0.799	1.092	0.3915	1.609	0.881	2.939	0.1219	0.987	0.346	2.815	0.9802	1.169	0.793	1.722	0.4308
Physician US-trained																				
No	Ref				Ref				Ref				Ref				Ref			
Unknown	1.602	0.794	3.229	0.1879	1.634	0.685	3.896	0.268	0.045	0.005	0.385	0.0047	-	-	-	-	11.651	0.891	152.4	0.0612
Yes	0.981	0.854	1.127	0.7826	0.984	0.83	1.165	0.8477	0.648	0.375	1.121	0.1209	1.383	0.372	5.149	0.6286	1.196	0.809	1.769	0.3685
Physician type																				
DO	Ref				Ref				Ref				Ref				Ref			
MD	1.352	0.874	2.092	0.1756	1.212	0.736	1.995	0.4505	0.402	0.088	1.831	0.2386	0.149	0.025	0.91	0.0391	5.734	0.65	50.54	0.1158
Years of physician training																				
3-13	Ref				Ref				Ref				Ref				Ref			
13-19	1.028	0.857	1.233	0.7661	0.983	0.789	1.225	0.8788	1.293	0.529	3.163	0.5732	0.753	0.141	4.034	0.7409	1.199	0.714	2.014	0.4918
19-28	1.158	0.925	1.451	0.2001	1.185	0.902	1.556	0.2226	1.925	0.664	5.579	0.2275	0.711	0.094	5.379	0.7416	1.091	0.586	2.03	0.7845
28-61	0.959	0.699	1.315	0.7944	0.902	0.613	1.328	0.6026	1.457	0.396	5.363	0.5716	8.283	0.183	375.59	0.2773	1.104	0.456	2.669	0.8268
Unknown	0.915	0.627	1.336	0.6469	0.945	0.602	1.483	0.8054	1.518	0.434	5.306	0.5132	-	-	-	-	1.42	0.473	4.265	0.5318
No. of fractions																				
	0.971	0.965	0.976	<.0001	0.964	0.958	0.97	<.0001	0.983	0.96	1.006	0.1519	0.997	0.95	1.047	0.9131	0.985	0.97	1	0.0538

Abbreviations: 95% CI, 95% confidence interval; 3D, three-dimensional conformal radiotherapy; DO, Doctor of Osteopathic Medicine; EC, esophageal cancer; HR, hazard ratio; IMRT, intensity-modulated radiotherapy; MD, Doctor of Medicine; Ref, referent; SCCA, squamous cell carcinoma; SEER, Surveillance, Epidemiology, and End Results.

[a] The 6 SEER regions are Connecticut, Detroit, Iowa, New Mexico, Seattle, and Utah.

Figure 2.

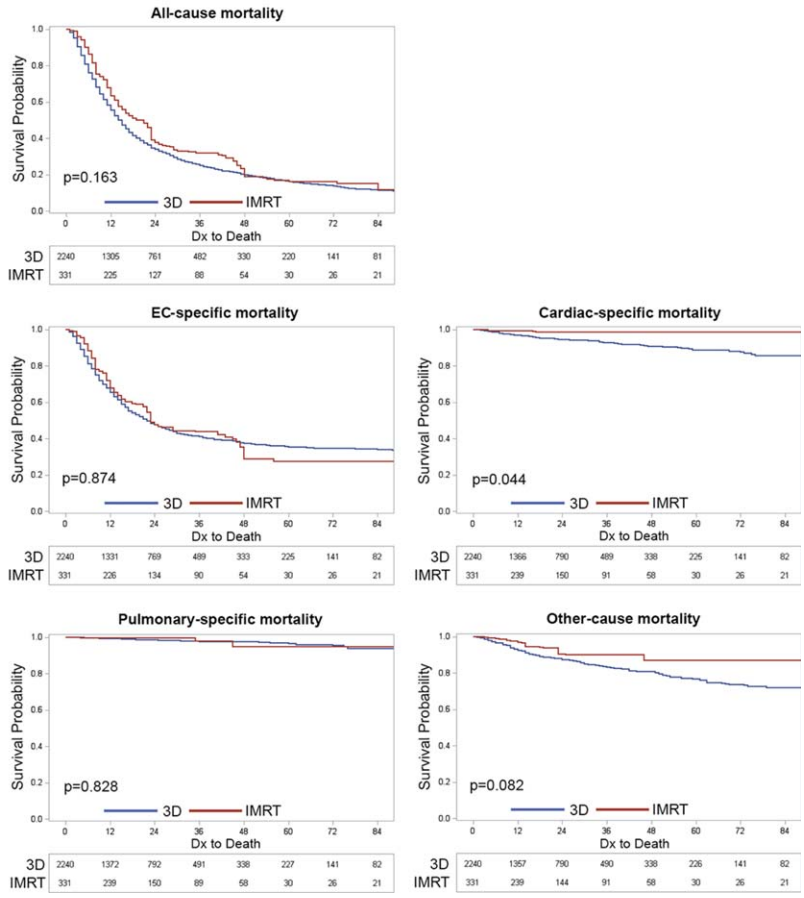

Figure 2. Inverse probability of treatment weighting-adjusted overall survival and cause-specific survival of patients treated with 3-dimensional conformal radiotherapy (3D) versus intensity-modulated radiotherapy (IMRT). The *P* value was derived from log-rank testing. Dx indicates diagnosis; EC, esophageal cancer.

IMRT, and hybrid treatment, the risk for the hybrid treatment was intermediate between patients treated with 3D and IMRT (Fisher exact test, $P = .0016$).

DISCUSSION

In this population-based analysis of patients with nonmetastatic EC who were treated with radiotherapy, we found that the use of IMRT was associated with lower all-cause mortality, cardiac-specific mortality, and other-cause mortality, but not cancer-specific and pulmonary mortality. This effect was noted regardless of the experience of the physicians (either based on the number of years in practice or the patient volume, which are factors known to be critical for surgical outcomes)[10,11] or by the type of chemotherapy used.

These results are in keeping with a previously reported single-institution retrospective analysis of the long-term outcomes of patients with EC who were treated with chemoradiation.[8] In that report, the authors found overall survival to be significantly better in patients treated with IMRT compared with those treated with 3D. However, there was no difference in cancer-specific or pulmonary-related deaths, only in cardiac-specific deaths and "other deaths." The "other deaths" in that report were not the same as the "other-cause deaths" in the current study. Previously, the "other deaths" were all unknown deaths due to loss to follow-up. The "other-cause deaths" for the current study were all other causes reported in the claims data that were not cancer-related, pulmonary-related, or cardiac-related. It is interesting to note that we still observed a significant difference in these deaths

comparing IMRT and 3D. These studies provide consistent evidence that IMRT may influence the overall health, and importantly, cardiac health of patients who may be cured of EC.

It is widely known that radiation to the thorax can exert long-term cardiac morbidities and mortality. Low-dose radiation to the chest for the treatment of lymphoma in young patients can greatly increase the risk of developing future myocardial infarction.[12,13] In one SEER analysis of 558,871 women treated for breast cancer, patients with left-sided breast cancer had a higher cardiac mortality ratio that was evident within 10 years, and the ratio was found to increase over time.[14] A more detailed, population-based case-control study in 2168 women who were treated with radiotherapy for breast cancer was conducted in the Netherlands and Sweden.[15] The study evaluated major coronary events such as myocardial infarction, coronary revascularization, and ischemic heart disease-related deaths. The overall average of the mean dose to the heart was only 4.9 gray (Gy), yet the probability of developing a major cardiac event increased linearly with the mean heart dose, with an average increase of 7.4% per Gy within the span of 20 years with no threshold. It is interesting to note that when compared with case-matched controls, the greatest increase in the rate of major coronary events was actually observed within the first 9 years, at a rate of 16.3% per Gy from 0 to 4 years and 15.5% per Gy from 5 to 9 years. Despite the low mean heart dose, it is likely that the majority of the dose is concentrated at the anterior portion of the heart, the origin of many of the coronary vessels. The caveat is that these results are based on outdated, non-image-guided treatment approaches. Using modern techniques such as IMRT and breathhold,[16] it is expected that cardiac morbidity and mortality will be greatly reduced.

Based on some comparative planning studies for patients with EC, IMRT is reported to reduce heart dose without a difference in the lung dose compared with 3D, with volumes of heart receiving 30 Gy (V30) to be approximately 60% for 3D and approximately 20% for IMRT[7,17] and V45 reported to be 35% for 3D and 0% for IMRT.[7] Because V45 significantly predicts for radiation-induced ischemic changes in the heart,[18,19] patients treated with 3D likely received doses to the heart that were substantially above this clinically relevant level compared with IMRT. Tumor location also may be an important factor because middle to distal esophageal tumors (which account for the majority of the cases diagnosed in the United States) traverse the entire segment of the heart compared with more proximal tumors. However, the billing coding for tumor location was not precise enough to allow us to explore this.

The clinical benefit of IMRT for the treatment of cancer has been demonstrated for many sites of disease, such as reducing xerostomia risk for patients with head and neck cancers[20]; bowel toxicities for patients with cancers within the pelvis such as cervical cancer, prostate cancer, and anal cancer[21-23]; and the risk of esophagitis and pneumonitis for patients with lung cancer.[24] For patients with EC, a previously published single-institution analysis of postoperative morbidity after chemoradiation demonstrated that IMRT significantly improved postoperative pulmonary and gastrointestinal complications compared with 3D. The critical factor associated with pulmonary complications is the mean lung dose because IMRT was able to significantly reduce the mean lung dose compared with the 3D approach.[25]

The current study was limited by Medicare claims data, which are largely dependent on the reliability of the billing practices. Several patients (approximately 5%) received treatment with both 3D and IMRT within the same time frame and therefore it was difficult to decipher the modality to which these individuals should be assigned. We managed to place the majority of these hybrid patients into different treatment bins based on an algorithm that we developed. However, using sensitivity analysis, we found that the effect observed for IMRT was the same regardless of these hybrid patients. There also is the limitation of determining precisely whether the cause of death was truly cardiac or cancer in origin in a patient with a history of cancer. A patient with treated disease who dies several months later with cardiac arrest could be scored either as being a cancer-related or cardiac-related death. The definition could be vague and difficult to determine.

The findings in the current study from this population-based analysis suggest that the use of IMRT may be associated with reduced all-cause mortality, cardiac-related mortality, and other-cause mortality. Taken together, along with the previously published large single-institutional data, the theoretical dosimetric advantage of IMRT appears to translate into clinically significant improvements in the outcomes of patients. In the absence of a high-quality, prospective randomized trial comparing IMRT with 3D, the data from the current study provide evidence that IMRT should be the preferred choice for the treatment of patients with EC, and that the current standard-of-care approach using 3D should be reevaluated.

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CONFLICT OF INTEREST DISCLOSURES

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