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Radiation Modality Utilization and Cardiopulmonary Mortality Risk in the Elderly with Esophageal Cancer

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Abstract

BACKGROUND—It is currently unclear if the superior normal organ sparing effect of Intensity Modulated Radiation Therapy (IMRT) as compared to three-dimensional radiation therapy (3D) has clinical impact on survival and cardiopulmonary mortality in esophageal cancer (EC) patients.

METHODS—We identified 2,553 patients older than age 65 years from the SEER/Texas Cancer Registry-Medicare databases who had non-metastatic EC diagnosed between 2002 and 2009 and were treated with either 3D (n=2,240) or IMRT (n=313) within 6 months of diagnosis. The outcomes of the two cohorts were compared using Inverse Probability of Treatment Weighting (IPTW) adjustment.

RESULTS—Except for marital status, year of diagnosis, and SEER region, both radiation cohorts were well balanced for various patient, tumor, and treatment characteristics, including the use of IMRT vs. 3D in urban/metro or rural areas. IMRT use increased from 2.6% in 2002 to 30% in 2009, while 3D use decreased from 97.4% in 2002 to 70% in 2009. On propensity score IPTW-adjusted multivariate analysis, IMRT was not associated with EC-specific mortality (HR 0.93, 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

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associations were seen after adjusting for the type of chemotherapy, physician experience, and sensitivity analysis removing hybrid radiation claims.

CONCLUSIONS—In this population-based analysis, IMRT use was significantly associated with lower all-cause mortality, cardiac mortality, and other-cause mortality in EC patients.

CONDENSED ABSTRACT

It is currently unclear if the dosimetric advantages of organ sparing by Intensity Modulated Radiation Therapy (IMRT) compared to three dimensional conformal radiation therapy (3D) can translate to survival and cardiopulmonary mortality benefit in esophageal cancer patients. This SEER/Texas Cancer Registry-Medicare population-based study found that while there were no differences in cancer or pulmonary-specific mortality, all-cause and cardiac-specific mortality were significantly reduced in IMRT-treated patients under a propensity score adjusted multivariate analysis.

Keywords

Esophageal cancer; IMRT; 3D conformal radiation therapy; SEER; propensity score; cardiopulmonary mortality

INTRODUCTION

Radiation technologies have evolved substantially over time, from 2-dimensional (2D) planning on plain x-ray films to 3-Dimensional (3D) computerized tomography (CT)-based treatment planning. Intensity Modulated Radiation Therapy (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 showing toxicity reduction compared to conventional radiotherapy methods, including 3D conformal radiotherapy[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 newly diagnosed EC, chemoradiation, either preoperative or definitive, is done as a standard of care[4]. However, given the location of most tumors, the heart dose can be substantial, particularly when standard 3D technique is used. Planning studies have shown that IMRT preferentially spares the heart over the lungs[5–7]. How this dosimetric advantage translates to clinical benefit for patients is still not convincingly proven, since there are no large randomized trials comparing IMRT to 3D in EC. Previously, a propensity matched analysis of single institution data comparing the long term outcomes of patients treated with either IMRT or 3D radiotherapy from 1998 to 2010 was reported[8]. The authors found significantly improved overall survival and cardiac-specific mortality for IMRT, but no differences in distant recurrence rate, cancer-specific survival, or pulmonary-related deaths. However, another single institution data 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 this study, we evaluated the Surveillance, Epidemiology, and End Results (SEER)-Medicare and the Texas Cancer Registry-Medicare-linked databases to assess the overall and cause-specific mortality rates of EC patients 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 EC patients treated with radiotherapy.

PATIENTS AND METHODS

Data source

Patients older than age 65 years were identified from the National Cancer Institute (NCI)-supported SEER-Medicare database and the Texas Cancer Registry (TCR), Medicare-linked database. The SEER 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 and Health Services in 1979, is the fourth largest state population-based registry. Data on 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 that 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 supplement table 1. This research was reviewed by the Institutional Review Board and granted an exemption.

Cohort selection

A multistep process (supplement table 2) was used to select the patients from the two databases based on their first diagnosis of EC (31,101: SEER 1973-2009, 6,856: TCR 1995-2007), with the histologically and microscopically confirmed diagnosis of squamous or adenocarcinoma but not diagnosed at the time of autopsy. Our patients were aged > 65 with stage I-III EC, had enrolled in Medicare parts A and B for 12 months prior to 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 must also not have had a second cancer within 1 year of diagnosis.

Radiation use selection

All patients must have started radiotherapy within 6 months after diagnosis based on radiation claims. Patients who had 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 codes 77290, 76370, 77014, 77295. We excluded any 2D patients (77280, 77285) and patients who had radiation but were not categorized using these codes. There were 173 patients that 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 two types of radiation

treatment claims, and the first treatment delivery dates (supplement table 3). Using this stepwise approach, we further were able to define 138 patients into either IMRT or 3D. Sensitivity analysis was performed to evaluate if inclusion of these patients affected the multivariable analysis. The rest of 35 Patients who couldn't be stratified using this approach were considered inevaluable and excluded from this study.

Baseline patient, tumor, and treatment characteristics

Demographic information included age, gender, race/ethnicity, marital status (not available in TCR), SEER regions, urban/rural setting, educational attainment, and income level. Tumor characteristics included stage (localized vs regional (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 radiation treatment. Comorbidities were recorded as either the Klabunde adaptation of the Charlson comorbidity index, or as individual comorbid illnesses existing within 12 months prior to EC diagnosis, such as congestive heart failure, hypertension, other heart diseases (CAD, MI), diabetes, or pulmonary diseases (COPD).

Physician experience

To document physician demographics and experience in the utilization 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 UPIN and NPI numbers, redundancy was eliminated by crosslinking the NPI to the UPIN numbers. We collected information regarding the physicians' age (by 2010), gender, 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 the said physician.

Statistical analysis

We used χ^2 analysis to compare the proportion of 3D vs IMRT use among the baseline characteristics. Propensity score (PS) was calculated to predict the conditional probability of patients receiving IMRT vs. 3D based on their pre-treatment 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 (KM) survival curves were generated for overall, EC-specific, cardiac, pulmonary, or other non-cancer, non-cardiopulmonary cause deaths ("other deaths"). Statistical analysis was carried out using SAS software program version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patients, treatment, and physician characteristics

We initially identified 3,403 patients aged 66 years or older diagnosed with non-metastatic EC from 1997 to 2009 who met our inclusion criteria. We further confined our analysis to the patients treated between 2002-2009, with 2,240 treated with 3D and 313 with IMRT. IMRT use increased from a rate of 2.6% in 2002 to 31.2% in 2009 (Figure 1). Table 1 summarizes the baseline characteristics of the study cohort. For the most part the two groups were well balanced excepted for the marital status, the SEER region, and the year of diagnosis. The use of IMRT was only slightly higher in metro vs. rural areas, but the difference was not significant. There were no differences in the income or education levels of the two cohorts. The median number of radiation treatment fractions is 26 for 3D and 28 for IMRT, but the difference is not statistically significant.

Physician experience or hospital volume have been shown to be influential factors in the clinical outcomes of surgical patients[10, 11]. We therefore included physician characteristics in the context of the radiation technologies utilized (Table 2). While board certification, gender, and the type of medical degree (MD vs DO) did not differ among physicians using the two radiation modalities, younger physicians (which correlated with being more recent graduates from medical schools, having fewer years in practice and having 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 two 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, IPTW-adjusted baseline patient, tumor, and physician characteristics are listed in supplemental 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 KM 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 to 3D, but not for EC-specific or pulmonary mortality. We found no relationship between the board certification of the physicians, graduation years, physicians' gender, US vs. non-US training, or physician type, on any of the mortality outcomes of patients.

The most common chemotherapy doublets used were cisplatin/5FU (37.2%), carboplatin/paclitaxel (22.6%), and Docetaxel/5FU (5.9%) (supplemental table 6). For the patients who had chemotherapy, 52% were treated with a 5FU-based regimen. We evaluated if the chemotherapy regimen influenced survival and cause-specific mortality. Under multivariable analysis, the use of any chemotherapy was significantly associated with an improved overall survival and EC-specific and other cause mortality, but not for pulmonary and cardiac mortality (Table 3). We performed a separate multivariable analysis to determine if there was influence of 5FU-based regimen on any of the clinical outcomes. We found 5FU-based regimen to exert similar protective effects on overall and EC-specific survival, including cardiac mortality, compared to either no-chemotherapy use or non-5FU based regimen. 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 that the cardiac mortality rate may decrease over time for the 3D patients. We evaluated this possibility by examining the cardiac mortality rate in the 3D group between 2002 and 2008, but not in 2009 since the treatment claims data and death record is not mature. The overall cardiac mortality rate for the entire cohort of 3D patients is 5.5%. The average yearly cardiac mortality for the 3D group is 5.7% (± 1.4%), and did not change over the years (Chisq p=0.391). This rate is nearly 5 fold higher in comparison to the rate for IMRT (data not shown).

There were about 5% of patients who 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 (supplemental 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). Interestingly, when we evaluated the cardiac mortality risk for 3D, IMRT, and hybrid treatment, the risk for the hybrid treatment was intermediate between 3D and IMRT patients (Fisher's exact test, p=0.0016).

Discussion

In this population-based analysis of non-metastatic EC patients 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 is seen regardless of the experience of the physicians, either based on the number of years in practice or the patient volume, factors known to be critical for surgical outcomes[10, 11], or by the type of chemotherapy used.

These results are in line with a previously reported single-institution retrospective analysis of the long-term outcomes of EC patients treated with chemoradiation[8]. In that report, the authors found overall survival to be significantly better in IMRT-treated patients compared to 3D. However, there was no difference in cancer-specific or pulmonary-related deaths, but 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 present study. Previously, the "other deaths" were all unknown deaths due to lost follow up. The "other-cause deaths" for the current study were all other causes reported in the claims data that were not cancer, pulmonary, or cardiac-related. Interestingly, we still saw 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 people can greatly increase the risk to the development of future myocardial infarction[12, 13]. In one SEER analysis in 558,871 women treated for breast cancer, left sided breast cancer had a

higher cardiac mortality ratio that was evident within 10 years, and the ratio increases over time[14]. A more detailed population-based case-control study in 2,168 women 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 heart dose 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. Interestingly, when compared to case-matched controls, the greatest increase in the rate of major coronary events was actually seen in the first 9 years, at 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's likely that most of the dose is concentrated at the anterior portion of the heart, 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 EC, IMRT reduces heart dose without a difference in the lung dose compared to 3D, with volumes of heart getting 30 Gy (or V30) to be ~60% for 3D and ~20% for IMRT[7, 17] and V45 to be 35% for 3D and 0% for IMRT[7]. Since V45 significantly predicts for radiation-induced ischemic changes in the heart[18, 19], patients treated with 3D likely had heart doses that were substantially above this clinically relevant level compared to IMRT. Tumor location may also be an important factor, since mid to distal esophageal tumors (which accounts for most of the cases in the US) traverse the entire segment of the heart, compared to more proximal tumors. However, the billing coding for tumor location was not precise enough to allow us explore this aspect.

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

Our study is limited by Medicare claims data, which are largely dependent on the reliability of the billing practices. A number of patients (about 5%) had treatment with both 3D and IMRT within the same time frame and therefore it was difficult to decipher the modality to assign these patients to. We managed to place the majority of these hybrid patients into different treatment bins based on an algorithm we developed. However, using sensitivity analysis, we found that the effect seen for IMRT was the same regardless of these hybrid patients. There is also the limitation of determining precisely if 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 either be scored as being cancer-related or cardiac-related. The definition could be vague and difficult to determine.

In conclusion, our findings 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 to clinically meaningful improvements in the outcomes of patients. In the absence of high quality prospective randomized trial comparing IMRT to 3D, these data provide the evidence that IMRT should be the preferred choice for the treatment of esophageal cancer, and that the current standard-of-care approach using 3D-CRT should be re-evaluated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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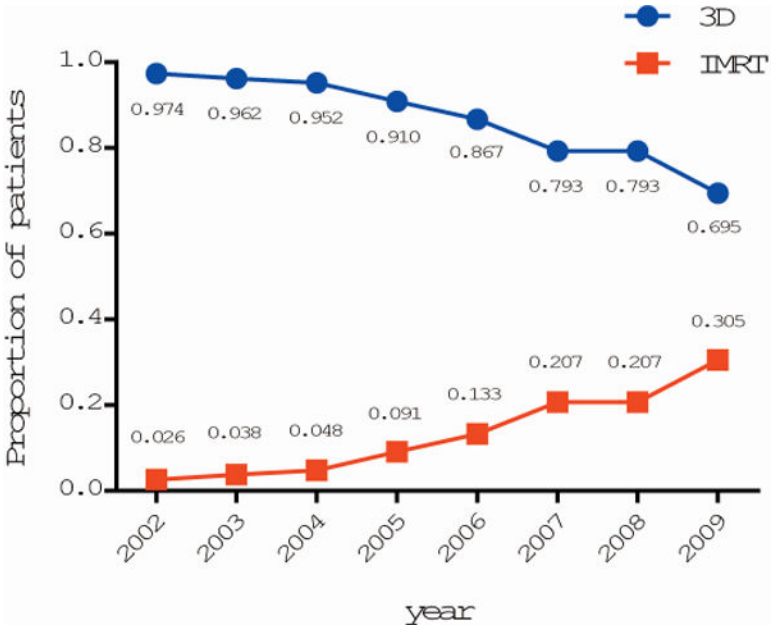

Figure 1.
The utilization of 3D and IMRT for the treatment of EC from 2002 to 2009.

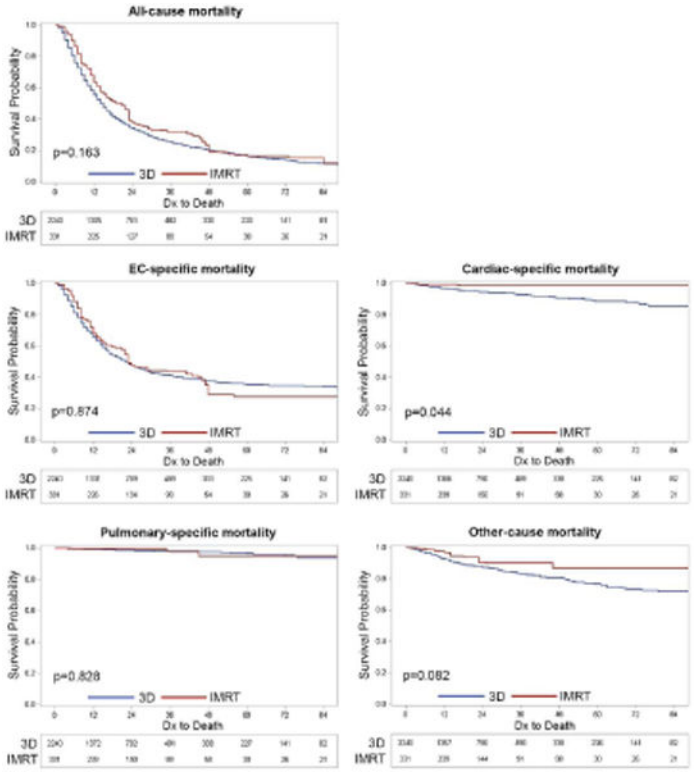

Figure 2.

IPTW-adjusted overall survival and cause-specific survival of patients treated with 3D versus IMRT. P value is by log-rank testing.

Table 1

Patient demographic, clinical and tumor characteristics

	Overall Cohort N = 2553 (100%)	3D N=2240(100%)	IMRT N=313 (100%)	Chi-sq *P*
Age				
66-70	729(28.6)	634(28.3)	95(30.4)	0.7698
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)	0.0403
Not married	771(30.2)	674(30.1)	97(31.0)	
Unknown *	552(21.6)	469(20.9)	83(26.5)	
Histology				
Adeno	1423(55.7)	1255(56.0)	168(53.7)	0.4325
SCCA	1130(44.3)	985(44.0)	145(46.3)	
Race/Ethnicity				
White	2095(82.1)	1834(81.9)	261(83.4)	0.0619
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)	0.3529
Regional	1562(61.2)	1378(61.5)	184(58.8)	
Gender				
Female	744(29.1)	657(29.3)	87(27.8)	0.5757
Male	1809(70.9)	1583(70.7)	226(72.2)	
Patients receiving Surgery After Radiation Treatment				
No	2107(82.5)	1855(82.81)	252(80.5)	0.3152
Yes	446(17.5)	385(17.19)	61(19.5)	
Tumor Grade				
Well differentiated	123(4.8)	108(4.8)	15(4.8)	0.9662
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)	

	Overall Cohort N = 2553 (100%)	3D N=2240(100%)	IMRT N=313 (100%)	Chi-sq *P*
Charlson Score				
0	1510(59.2)	1313(58.6)	197(62.9)	0.2957
1	664(26.0)	593(26.5)	71(22.7)	
2+	379(14.9)	334(14.9)	45(14.34)	
Regions (SEER + Texas)				
California + Hawaii	563(22.1)	484(21.6)	79(25.2)	0.0632
6 SEER regions combined **	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				0.0881
No	411(16.1)	371(16.6)	40(12.8)	
Yes	2142(83.9)	1869(83.4)	273(87.2)	
Urban/Rural				
Big Metro	1285(50.3)	1124(50.2)	161(51.4)	0.5954
Less Urban/Rural	411(16.1)	369(16.5)	42(13.4)	
Metro	805(31.5)	701(31.3)	104(33.2)	
Urban	168(6.6)	148(6.6)	20(6.4)	
% of adults with <12 y of Education				
Lowest Quartile	625(24.5)	544(24.3)	81(25.9)	0.627
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)	
% of Family living below poverty line				
Lowest Quartile	629(24.6)	548(24.5)	81(25.9)	0.5019
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 ***				
No	2048(80.2)	1798(80.27)	250(79.87)	0.8693
Yes	505(19.8)	442(19.73)	63(20.13)	
Pre-Other Heart Disease ***				
No	2038(79.8)	1786(79.73)	252(80.51)	0.7477
Yes	515(20.2)	454(20.27)	61(19.49)	
Pre-Hypertension ***				
No	1313(51.4)	1161(51.83)	152(48.56)	0.2785
Yes	1240(48.6)	1079(48.17)	161(51.44)	
Pre-Diabetes ***				

	Overall Cohort N = 2553 (100%)	3D N=2240(100%)	IMRT N=313 (100%)	Chi-sq *P*
No	2100(82.3)	1845(82.37)	255(81.47)	0.6974
Yes	453(17.7)	395(17.63)	58(18.53)	
Pre-Respiratory Dz ***				
No	2031(79.6)	1780(79.46)	251(80.19)	0.765
Yes	522(20.5)	460(20.54)	62(19.81)	
Number of Fractions				
Mean ± SD	24±8.5	24±8.5	25±8.1	0.1433
Median	26	26	28	

*All TCR Patients Marital Status were Unknown

**The six SEER regions include: Conneticut, Detroit, Iowa, New Mexico, Seattle, Utah

***Pre-disease within one-year before Esophageal Cancer Diagnosis, parts of Comorbidity disease, therefore not included into Cox Modeling that has adjusted for Charlson Score.

Table 2

The Characteristics of the Physicians Associated with the Treated Patients

	Overall Cohort N = 2553 (100%)	3D N=2240(100%)	IMRT N=313 (100%)	Chi-sq *P*
Board Certified				
Yes	2190(85.8)	1928(86.1)	262(83.7)	0.5293
No/Unknown	363(14.2)	312(13.9)	51(16.3)	
Graduation Years				
Prior to 1980	657(25.7)	594(26.5)	63(20.1)	0.0421
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 Gender				
F	393(15.4)	343(15.3)	50(16.0)	0.5145
M	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)	0.0111
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)	0.5126
DO/Unknown	309(12.1)	271(12.1)	38(12.1)	
Physician Age				
34-46	407(15.9)	341(15.2)	66(21.1)	0.0099
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 Training Years				
3-13	470(18.4)	388(17.3)	82(26.2)	0.0017
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)	

*A total of 1124 physicians by Upin had seen the cohort of 2553 patients, among them, 136 physicians' information were missing, resulting up to 297 patients' physicians' demographic not identified.

Table 3

Fitted Cox Model Using Inverse Probability of Treatment Weights (IPTWs)

Parameter	All cause deaths				EC-specific deaths				Cardiac-specific deaths				Pulmonary-specific deaths				Other cause deaths			
	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq
Radiation Treatment																				
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																				
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																				

Parameter	All cause deaths				EC-specific deaths				Cardiac-specific deaths				Pulmonary-specific deaths				Other cause deaths			
	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq
Adeno	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
Gender																				
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
Surgery After Radiation																				
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 Score																				
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 + Hawaii	Ref				Ref				Ref				Ref				Ref			
6 SEER Regions Combined **	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																				

Parameter	All cause deaths				EC-specific deaths				Cardiac-specific deaths				Pulmonary-specific deaths				Other cause deaths			
	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq
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 metro	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
Metro	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
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
Graduation Years																				
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 Gender																				
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																				

Parameter	All cause deaths				EC-specific deaths				Cardiac-specific deaths				Pulmonary-specific deaths				Other cause deaths			
	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq	HR	95% CI		Pr > ChiSq
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
Physician Training Years																				
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
Number of Fractions																				
number 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

** The 6 SEER Regions are: Connecticut, Detroit, Iowa, New Mexico, Seattle, Utah.