Original Article

Utilization of neoadjuvant intensity-modulated radiation therapy and proton beam therapy for esophageal cancer in the United States

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Background: Randomized esophageal cancer (EC) trials have utilized two- or three-dimensional conformal radiotherapy (3DCRT). Advanced radiotherapy (RT) techniques [(ARTs): intensity-modulated radiotherapy (IMRT) and proton beam therapy (PBT)] may have benefits, but are relatively unproven. This is the first study to date evaluating utilization of ARTs versus 3DCRT in the trimodality setting in the United States.

Methods: The National Cancer Data Base (NCDB) was queried (2004–2013) for newly-diagnosed cT1b-T4bN0/N+M0 EC receiving neoadjuvant CRT followed by esophagectomy. The primary objective was to assess temporal trends, with multivariable logistic regression analysis assessing factors predictive of receiving ARTs. Secondarily, Kaplan-Meier analysis evaluated overall survival (OS), Cox proportional hazards modeling determined variables associated with OS, and postoperative complications were compared between cohorts.

Results: Altogether, 3,138 patients met criteria; 1,398 (45%) received 3DCRT, and 1,740 (55%) received ARTs (99% IMRT, 1% PBT). Temporally, utilization of ARTs is steadily rising in the United States, from 20% in 2004 to 69% in 2013, corresponding with a progressive decrease in utilization of 3DCRT. ARTs were more often delivered with advancing age, squamous cell histology, N2+ disease, and at academic centers ($P<0.05$ for all). Centers in the Southwest were more likely to use ARTs, and those in the Midwest least likely ($P<0.05$ for both). As expected, there were no OS differences ($P=0.8477$); there were also no differences in postoperative events ($P>0.05$ for all). Treatment at an academic center independently correlated with improved OS ($P<0.001$).

Conclusions: Utilization of ARTs (IMRT in the vast majority) is steadily rising in the United States; 3DCRT is now used in a minority of patients. This has implications for payers and insurance coverage. ART use is impacted by not only age and disease factors, but also regional and facility differences. Treatment at an academic facility independently correlated with higher survival, which has implications for patient counseling.

Keywords: Esophageal cancer (EC); radiation therapy; chemotherapy; esophagectomy; intensity-modulated radiation therapy; proton beam therapy (PBT)

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Introduction

Esophageal cancer (EC) is a major cause of not only oncologic mortality, but also treatment-related morbidity. This is especially apparent following trimodality therapy, which is now the standard of care for locally advanced EC (1). In continual efforts to reduce therapy-related toxicities, use of advanced radiotherapy (RT) techniques (ARTs), namely intensity-modulated RT (IMRT) and proton beam therapy (PBT), have come to the forefront of management of EC—often without level I evidence supporting their utility (2-9).

However, virtually all randomized EC trials have utilized either two- or three-dimensional conformal RT (3DCRT) techniques (1,10); in the absence of a randomized comparison, the role of ARTs in EC is uncertain. The National Comprehensive Cancer Network (11) recently revised a statement on RT technique by eliminating the phrase "3-D treatment planning is strongly encouraged" and replaced it with "IMRT or PBT is appropriate in clinical settings where reduction in dose to organs at risk… is required that cannot be achieved by 3-D techniques."

Although there are substantial drawbacks with ARTs, including the often prohibitive cost and subsequent lack of insurance coverage, there are multiple theoretical (yet unproven) benefits that may be noteworthy in EC. First, treatment in the neoadjuvant setting poses intra- and post-procedural risks; extensive data from MD Anderson Cancer Center have observed fewer postoperative complications following neoadjuvant ART-based therapy (12-15). Next, as survivorship following therapy for EC rises, RT-induced toxicities (e.g., cardiopulmonary) may become significant, as shown for multiple neoplasms (16-18); thus, utilizing ARTs to protect against these late complications may be of benefit (19-24).

Owing to the high controversy surrounding these technologies, evaluating national practice patterns and trends is essential. This is the first study to date evaluating utilization of ARTs versus 3DCRT as part of neoadjuvant CRT for locally advanced EC in the United States. These results have implications for ART utilization going forward as well as insurance coverage by payers.

Methods

This investigation analyzed the National Cancer Data Base (NCDB), which is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, which consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population (25-32). The NCDB contains information not included in the Surveillance, Epidemiology, and End Results database, including details regarding use of systemic therapy and radiation dose. The data used in the study were derived from a de-identified NCDB file. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

The most recently released NCDB dataset corresponded to the years 2004–2013. Inclusion criteria for this study involved patients age ≥18 with newly-diagnosed cT1b-T4a N0/N+ M0 EC comprising histologic codes of adenocarcinoma (International Classification of Disease for Oncology (ICD-O-3) codes 8140, 8141, 8143, 8144, 8145, 8147, 8255, 8260, 8310, 8340, 8480, 8481) or squamous cell carcinoma (ICD-O-3 codes 8052, 8053, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8078, 8083, 8084, 8560). For inclusion, patients required histological diagnostic confirmation and receipt of neoadjuvant CRT followed by partial or complete esophagectomy (surgical procedure of the primary site codes 30, 40, 50–55, 80). Since the purpose of the study was to compare the effect of radiation technique, inclusion criteria included the presence of a record of RT technique. Patients receiving either IMRT or PBT were included in the ART cohort, and were compared to patients receiving 3DCRT. In order for inclusion in the study, patients required a radiation dose of at least 35 Gy per published trials (33). The use of concurrent therapy was defined as receipt of chemotherapy within 21 days of RT. Using a classification scheme from other published studies utilizing the NCDB, an academic facility was an institution with both an accession of more than 500 newly diagnosed cancer cases per year and one that provided postgraduate medical education in at least four program areas, including internal medicine and general surgery (34). All other facilities, including Comprehensive Community Cancer Programs, Community Cancer Programs, and Integrated Network Programs, were categorized as non-academic, as none of these institutions require graduate medical education.

Information collected on each patient broadly

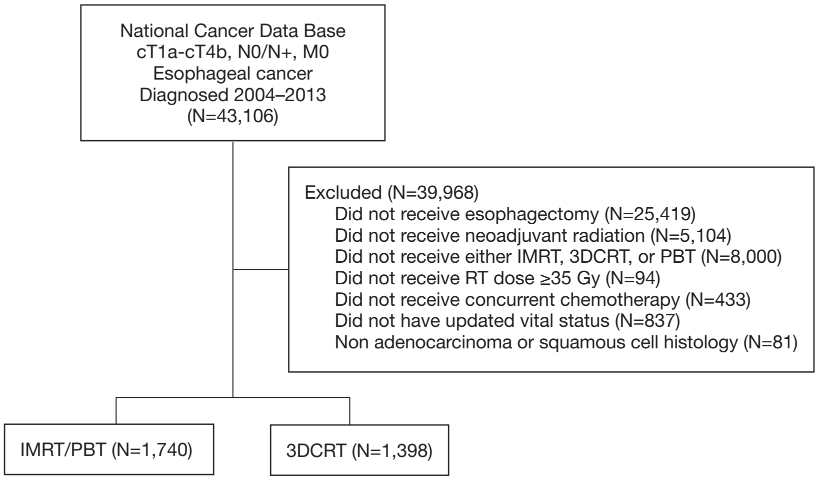

Figure 1 Patient selection diagram. IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy; 3DCRT, three-dimensional conformal radiotherapy.

included demographic data, comorbidity information, clinicopathological tumor parameters, and treatment facility characteristics. All statistical tests were two-sided, with a threshold of P<0.05 for statistical significance, and were performed using Stata (version 14, College Station, TX, USA). Fisher's exact or χ^2 test analyzed categorical proportions between groups in the non-parametric and parametric settings, respectively. The primary goal herein was to evaluate temporal trends and predictors of ART use. Multivariable logistic regression modeling was utilized to determine characteristics that were predictive for receipt of ART. Survival was not expected to show differences between groups and thus was performed only secondarily. The Kaplan-Meier method was used for survival analysis, and comparisons between the ART and 3DCRT groups were performed with the log-rank test. Overall survival (OS) was defined as the interval between the date of diagnosis and the date of death or last contact. Univariate analysis was performed to determine which factors were associated with OS, and subsequently Cox multivariate analysis was performed including variables that were either significant or showed a strong trend to statistical significance on univariate analysis. The proportional hazards assumption was checked graphically using log-log plots. Patients with unknown or not recorded values for income, insurance status, and treatment facility type were excluded from the multivariate logistic regression modeling and the Cox proportional hazards analysis due to their low absolute numbers and lack clinical significance.

Results

A complete flow diagram of patient selection is provided in *Figure 1*; 3,138 patients met study criteria. Of these, 1,398 (45%) were treated with 3DCRT, and 1,740 (55%) with ARTs. In the ART cohort, 18 (1%) received PBT and 1,722 (99%) IMRT. *Table 1* displays clinical characteristics of the analyzed patients. Of note, most patients had adenocarcinomas located in the distal esophagus and locally advanced disease.

The primary objective of this study was to evaluate temporal trends and predictors of ART delivery. *Figure 2* displays that utilization of ARTs is steadily rising in the United States, from 20% in 2004 to 69% in 2013, which corresponds with a progressive drop in 3DCRT. Multivariable logistic regression analysis was performed to evaluate factors independently associated with receiving ARTs (*Table 2*). ARTs were more often delivered to patients with advancing age, squamous cell histology, N2+ disease, and at academic centers (P<0.05 for all). There were also regional differences: as compared to the Northeast US, Southwestern (P=0.001) and Western (trend, P=0.088) regions were more likely to deliver ART; the Midwest was less likely to do so (P<0.001). Corroborating the results of *Figure 2*, there was a powerful and independent influence of time period on ART administration, with more recent years associated with over a threefold higher likelihood of ART delivery (odds ratio 3.41, 95% confidence interval 2.80–4.15, P<0.001).

Secondary analyses of the dataset included OS analysis

Table 1 Baseline characteristics of patients with esophageal cancer receiving neoadjuvant chemoradiation

Characteristic	Advanced radiation n=1,740; (%)	3D conformal n=1,398; (%)	P value
Age			
<60	617 (35.5)	559 (40.0)	0.018
60–70	788 (45.3)	608 (43.5)	
>70	335 (19.3)	231 (16.5)	
Sex			
Male	1,451 (83.4)	1,188 (85.0)	0.227
Female	289 (16.6)	210 (15.0)	
Race			
White	1,593 (91.6)	1,295 (92.6)	0.688
African American	66 (3.8)	43 (3.1)	
Hispanic	39 (2.2)	29 (2.1)	
Other/not recorded	42 (2.4)	31 (2.2)	
Histology			
Adenocarcinoma	1,387 (79.7)	1,185 (84.8)	<0.0001
Squamous cell	353 (20.3)	213 (15.2)	
cT stage			
T1b	28 (1.6)	10 (0.7)	<0.0001
T2	293 (16.8)	327 (23.4)	
T3	1,291 (74.2)	1,057 (75.6)	
T4a	29 (1.7)	4 (0.3)	
pN stage			
N0	589 (33.9)	519 (37.1)	<0.0001
N1	949 (54.5)	785 (56.2)	
N2–3	202 (11.6)	94 (6.7)	
Charlson Deyo score			
0	1,299 (74.7)	1,063 (76.0)	0.455
1	355 (20.4)	278 (19.9)	
2	86 (4.9)	57 (4.1)	
Tumor location			
Cervical/upper	25 (1.4)	13 (0.9)	0.159
Thoracic/middle	202 (11.6)	134 (9.6)	
Abdominal/lower	1,377 (79.1)	1,136 (81.3)	
Overlapping	81 (4.7)	60 (4.3)	
Not recorded	55 (3.2)	55 (3.9)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristic	Advanced radiation n=1,740; (%)	3D conformal n=1,398; (%)	P value
Facility type			
Non academic	804 (46.2)	801 (57.3)	<0.0001
Academic	907 (52.1)	573 (41.0)	
Not recorded	29 (1.7)	24 (1.7)	
Insurance			
Medicaid	87 (5.0)	77 (5.5)	0.246
Private	869 (49.9)	721 (51.6)	
Medicare	693 (39.8)	542 (38.8)	
Not insured	41 (2.4)	34 (2.4)	
Other/not recorded	50 (2.9)	24 (1.7)	
Income			
<$46,000	972 (55.9)	778 (55.7)	0.044
$46,000+	705 (40.5)	590 (42.2)	
Not recorded	63 (3.6)	30 (2.1)	
Year of diagnosis			
2004–2008	215 (12.4)	462 (33.0)	<0.0001
2009–2013	1,525 (87.6)	936 (67.0)	
Distance from facility			
≤20 miles	1,022 (58.7)	841 (60.2)	0.455
>20 miles	703 (40.4)	550 (39.3)	
Not recorded	14 (0.8)	7 (0.5)	
Region			
Northeast	432 (24.8)	325 (23.2)	<0.0001
Southeast	471 (27.1)	330 (23.6)	
Southwest	69 (4.0)	15 (1.1)	
Midwest	483 (27.8)	534 (38.2)	
West	256 (14.7)	169 (12.1)	
Not recorded	29 (1.7)	25 (1.8)	
Post-operative statistics			
30-day mortality	65 (3.74)	47 (3.4)	0.575
90-day mortality	135 (7.8)	95 (6.8)	0.303
Length of postoperative hospital stay	12.2 days	12.2 days	0.955
30-day readmission	104 (6.0)	83 (5.9)	0.963

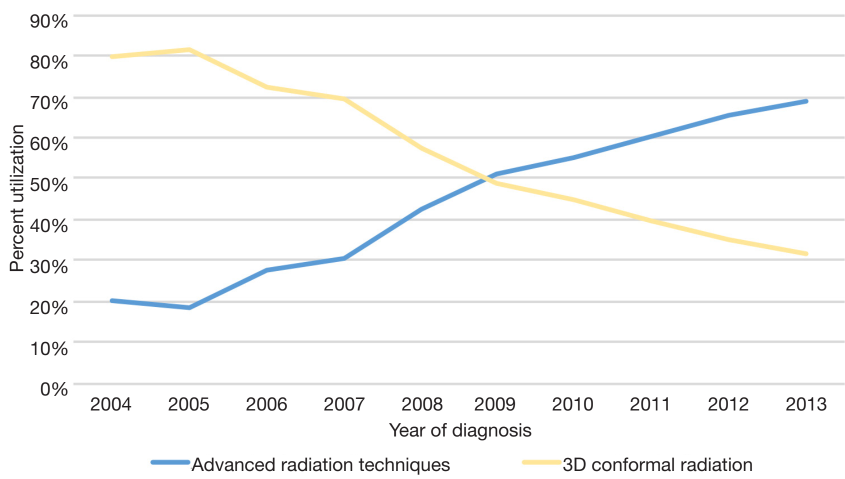

Figure 2 Temporal trends in delivery of radiotherapy technique.

Table 2 Characteristics predictive for ART delivery on multivariable logistic regression analysis

Characteristic	Odds ratio	95% confidence interval	P value
Age			
<60	1 (reference)	–	–
60–70	1.260	1.038–1.531	0.019
>70	1.569	1.184–2.079	0.002
Sex			
Male	1 (reference)	–	–
Female	0.969	0.773–1.214	0.783
Race			
White	1 (reference)	–	–
African American	0.897	0.568–1.417	0.641
Hispanic	0.988	0.553–1.765	0.967
Other/not recorded	0.773	0.443–1.348	0.364
Histology			
Adenocarcinoma	1 (reference)	–	–
Squamous cell	1.496	1.162–1.927	0.002
cT stage			
T1b	1 (reference)	–	–
T2	0.660	0.304–1.432	0.293
T3	0.647	0.302–1.389	0.262
T4a	2.823	0.763–10.437	0.120

Table 2 *(continued)*

Table 2 *(continued)*

Characteristic	Odds ratio	95% confidence interval	P value
pN stage			
N 0	1 (reference)	–	–
N1	1.080	0.911–1.281	0.377
N2–3	1.736	1.281–2.351	<0.0001
Charlson Deyo score			
0	1 (reference)	–	–
1	1.000	0.822–1.218	0.997
2	1.166	0.801–1.696	0.423
Tumor location			
Cervical/upper	1 (reference)	–	–
Thoracic/middle	0.610	0.279–1.333	0.215
Abdominal/lower	0.603	0.280–1.298	0.196
Overlapping	0.673	0.290–1.563	0.358
Facility type			
Non academic	1 (reference)	–	–
Academic	1.639	1.383–1.942	<0.0001
Insurance			
Medicaid	1 (reference)	–	–
Private	1.355	0.928–1.977	0.115
Medicare	1.090	0.726–1.636	0.678
Not insured	0.968	0.518–1.807	0.917
Income			
<$46,000	1 (reference)	–	–
$46,000+	0.932	0.788–1.101	0.407
Year of diagnosis			
2004–2008	1 (reference)	–	–
2009–2013	3.406	2.797–4.147	<0.0001
Distance from facility			
≤20 miles	1 (reference)	–	–
>20 miles	0.894	0.749–1.067	0.214
Region			
Northeast	1 (reference)	–	–
Southeast	1.157	0.922–1.452	0.208
Southwest	3.067	1.628–5.775	0.001
Midwest	0.686	0.557–0.845	<0.0001
West	1.263	0.965–1.652	0.088

ART, advanced radiotherapy technique.

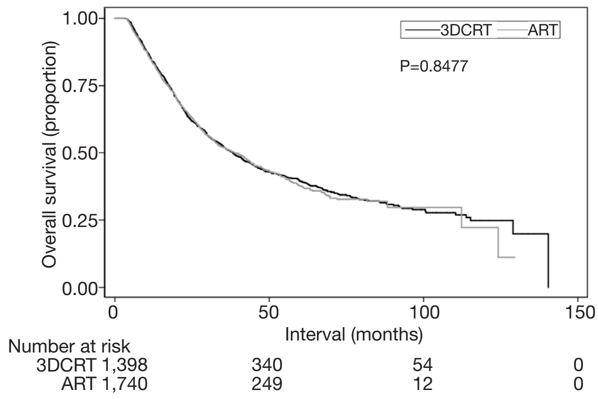

Figure 3 Kaplan-Meier overall survival curve comparing those receiving ARTs versus 3DCRT. ARTs, advanced radiotherapy techniques; 3DCRT, three-dimensional conformal radiotherapy.

and evaluation of postoperative events. Median follow-up was 25.4 months (interquartile range (IQR), 15.3–42.3 months). Kaplan-Meier estimates of OS between groups are illustrated in *Figure 3*; as expected, there were no differences in OS between the ART and 3DCRT cohorts (38.8 *vs.* 38.2 months, P=0.8477). Multivariate Cox proportional hazards modeling examining independent predictors of OS is displayed in *Table 3*. There were several factors associated with poorer OS: age >70, male gender, node-positive disease, Charlson Deyo comorbidity index of 2, lower income, and treatment at a community facility (P<0.05 for all). Lastly, as coded by the NCDB, there were no differences between the respective groups in terms of 30-day mortality (3.7% *vs.* 3.4%, P=0.575), 90-day mortality (7.8% *vs.* 6.8%, P=0.303), average postoperative hospitalization (12.2 *vs.* 12.2 days, P=0.955), or 30-day readmission rates (6.0% *vs.* 5.9%, P=0.963).

Discussion

Although the value of trimodality therapy in EC is now more clearly defined, there remains substantial controversy regarding optimal RT technique in this setting. There are numerous findings and reflections from this analysis of a contemporary national database, the largest of its kind to date. Utilization of ARTs (IMRT in the vast majority) is steadily rising in the United States, and 3DCRT is now used in a minority of patients. ART use is impacted by not only age and disease factors, but also regional and facility differences. As expected, there was no influence of technique on OS, and data did not display differences in postoperative events.

It is relatively clearer that ART utilization is increasing among practitioners in the United States. The results of multivariable logistic regression analysis suggest that ARTs were more often delivered for patients at higher risk of toxicities, including those that were older and with nodal positivity. Regional differences signal that advanced technologies often permeate certain areas of the United States before others. It is also very important from a medico-economic perspective that ART delivery was not impacted by socioeconomic or insurance-related factors. Although this could be a result of payers being open to ARTs for management of EC despite the lack of proven benefit in cost-effectiveness, there are many insurers who may not routinely cover ARTs, to which the results of this investigation may be substantially useful.

In addition, academic centers—largely the drivers of advancements in radiation oncology—were also more likely to deliver ARTs. The independent association between treatment at an academic facility and OS on Cox multivariate analysis has far-reaching implications on patient counseling and management by both oncologists and referring providers. These findings are in concord with data from other neoplasms demonstrating improved outcomes at academic and/or high-volume facilities (35). There are several potential reasons for this, not limited to greater multimodality coordination, streamlined diagnostic processes, technical expertise of a major surgical procedure, ancillary support staff for close clinical monitoring and clinical support such as treatments offered by speech therapy and nutrition services, greater access to rehabilitative services in academic centers, and potentially the availability of salvage therapies (or clinical trials). Nevertheless, this finding may impact any case of locally advanced EC and could warrant revisions in patterns of patient education.

The primary objective of this pattern of care study was not to evaluate OS, as it was predictable that no OS differences existed between groups. The goal of IMRT is primarily for toxicity reduction and not outcome improvement. Indeed, retrospective studies comparing outcomes for patients with EC treated with either IMRT or 3DCRT have failed to show any difference in OS, though they have demonstrated decreased rate of toxicity with the use of IMRT (36-38). However, although PBT patients comprised a minority of the ART cohort herein (and thus could not be reliably compared with the IMRT or 3DCRT cohorts), an ongoing randomized trial of PBT versus IMRT is evaluating both toxicity and progression-free (but not

Table 3 Univariate and multivariate analysis of factors predictive of overall survival for all patients

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Group						
Advanced radiation technique	1 (reference)	–	–	–	–	–
3D conformal radiation	0.972	0.877–1.079	0.597	–	–	–
Age						
<60	1 (reference)	–	–	1 (reference)		–
60–70	1.055	0.940–1.184	0.365	1.067	0.951–1.199	0.270
>70	1.233	1.066–1.425	0.005	1.242	1.074–1.436	0.004
Sex						
Male	1 (reference)	–	–	1 (reference)		–
Female	0.838	0.723–0.971	0.019	0.834	0.20–0.967	0.016
Race						
White	1 (reference)	–	–	–	–	–
African American	0.970	0.727–1.293	0.834	–	–	–
Hispanic	0.758	0.497–1.155	0.197	–	–	–
Other/not recorded	0.845	0.571–1.228	0.377	–	–	–
Histology						
Adenocarcinoma	1 (reference)	–	–	–	–	–
Squamous cell	0.956	0.834–1.096	0.523	–	–	–
cT stage						
T1b	1 (reference)	–	–	–	–	–
T2	1.026	0.589–1.789	0.927	–	–	–
T3	1.267	0.733–2.189	0.396	–	–	–
T4a	1.810	0.894–3.664	0.099	–	–	–
pN stage						
N0	1 (reference)	–	–	1 (reference)		–
N1	1.107	0.990–1.237	0.075	1.131	1.011–1.266	0.032
N2-3	1.280	1.057–1.550	0.011	1.315	1.086–1.594	0.005
Charlson Deyo score						
0	1 (reference)	–	–	1 (reference)		–
1	1.107	0.974–1.258	0.120	1.092	0.961–1.242	0.177
2	1.325	1.052–1.670	0.017	1.312	1.040–1.655	0.022

Table 3 *(continued)*

Table 3 *(continued)*

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Tumor location						
Cervical/upper	1 (reference)	–	–	–	–	–
Thoracic/middle	0.839	0.531–1.326	0.453	–	–	–
Abdominal/lower	0.857	0.556–1.321	0.485	–	–	–
Overlapping	0.916	0.563–1.490	0.724	–	–	–
Facility type						
Non academic	1 (reference)	–	–	1 (reference)		–
Academic	0.835	0.753–0.926	0.001	0.827	0.745–0.917	<0.0001
Insurance						
Medicaid	1 (reference)	–	–	–	–	–
Private	0.888	0.693–1.137	0.345	–	–	–
Medicare	1.109	0.865–1.422	0.415	–	–	–
Not insured	1.135	0.760–1.693	0.536	–	–	–
Income						
<$46,000	1 (reference)	–	–	1 (reference)		–
$46,000+	0.855	0.770–0.949	0.003	0.859	0.773-0.954	0.005
Year of diagnosis						
2004–2008	1 (reference)	–	–	–	–	–
2009–2013	1.015	0.901–1.144	0.801	–	–	–
Distance from facility						
≤20 miles	1 (reference)	–	–	–	–	–
>20 miles	1.003	0.903–1.115	0.949	–	–	–
Region						
Northeast	1 (reference)	–	–	–	–	–
Southeast	1.144	0.991–1.320	0.066	–	–	–
Southwest	0.944	0.647–1.378	0.766	–	–	–
Midwest	1.036	0.904–1.186	0.613	–	–	–
West	0.923	0.773–1.102	0.375	–	–	–

overall) survival primary endpoints (39). Next, the finding of no differences in postoperative events between ART and 3DCRT may seemingly conflict with aforementioned data (9-12), but a major area of caution from this investigation is the patients without a coded RT technique had to be excluded. This amounted to over double the patients that were included in this study. Additionally, definitions of postoperative events and complications are undoubtedly different from the NCDB and the aforementioned published work. Hence, conclusions from this paper must be tempered and do not necessarily point to the notion that 3DCRT yields equivalent postoperative events as ARTs.

There are several shortcomings of this investigation. First, in addition to retrospective selection biases, issues regarding the NCDB's lack of coding RT technique have been discussed above. Second, the NCDB does not keep track of several noteworthy variables, such as reasons for a particular treatment, elective nodal coverage, premature cessation of therapy, and salvage treatments. Although receipt of chemotherapy is recorded, specific agents are not mentioned. Although the NCDB has a record of surgical margins, this information is very frequently missing; it also does not record other endpoints such as tolerance of therapy (including specific postoperative complications or toxicities in general), cancer-specific survival, and local/regional control. Third, the inclusion of T1-2N0 patients (similar to the CROSS study) may bias towards no differences between groups, as patients more likely to benefit from ARTs may be more advanced/bulky cases. Fourth, these results were not performed in the definitive CRT setting and do not apply to this circumstance (36,40). Nevertheless, the caveats herein do not obviate the need for further investigation to corroborate these conclusions.

Conclusions

Study of a contemporary national database illustrates that utilization of ARTs (IMRT in the vast majority) is steadily rising in the United States, and 3DCRT is now used in a minority of patients. This has implications for payers and insurance coverage going forward. ART use is impacted by not only age and disease factors, but also regional and facility differences. As expected, there was no influence of technique on OS, and also did not display apparent differences in postoperative events. Trimodality therapy at academic institutions is independently associated with higher survival, which has implications for patient counseling.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

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