Original Article

Utilization of intensity modulated radiation therapy for anal cancer in the United States

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Background: Chemoradiotherapy for anal cancer (AC) can incur substantial treatment-related toxicities. Whereas radiotherapy (RT) for AC has historically been delivered with two- or three-dimensional conformal RT (2D/3DCRT) techniques, intensity-modulated RT (IMRT) is associated with improved target conformality and lower doses to organs-at-risk (OARs). This is the first investigation to date evaluating trends of IMRT utilization in the United States.

Methods: The National Cancer Data Base (NCDB) was queried [2004–2015] for AC patients receiving definitive chemoradiotherapy with a defined RT technique (3DCRT versus IMRT). Following analysis based on temporal trends, multivariate logistic regression determined factors associated with receipt of IMRT. Secondarily, Kaplan-Meier analysis compared OS between the 3DCRT and IMRT groups, and Cox proportional hazards modeling determined variables associated with OS.

Results: Altogether, 11,396 patients met study criteria; 1,288 (11%) were treated with 3DCRT and 10,108 (89%) with IMRT. Temporally, utilization of IMRT rose significantly, from 28% in 2004 to 96% in 2015, corresponding with a progressive decrease in 3DCRT usage. IMRT was more likely delivered in node-positive disease, at academic centers, and in southern/western regions (P<0.05 for all). T3–4 disease was less likely to receive IMRT (P<0.05). As expected, there were no OS differences based on RT technique (P=0.402). Predictors of worse OS included advancing age, male gender, increasing comorbidities, advanced T-stage, and nodal positivity (P<0.05 for all). In addition to racial- and insurance-related factors, receipt of therapy at academic centers independently predicted for improved OS (P<0.05 for all).

Conclusions: Based on findings from this large, contemporary dataset, IMRT is now the most widely utilized RT technique for AC, and 3DCRT is used in a very small minority of patients. IMRT utilization is impacted by multiple characteristics, such as disease- and regional-related factors. These observations have implications for payers and insurance coverage; improved survival at academic centers has ramifications for patient counseling.

Keywords: Anal cancer (AC); radiotherapy (RT); chemotherapy; chemoradiotherapy; intensity modulated radiation therapy; 3D conformal radiation therapy (3DCRT)

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Introduction

Combined chemoradiotherapy (CRT) for anal cancer (AC) is an efficacious measure which provides high rates of disease control and survival; it is thus the consensus paradigm to treat most cases of AC (1). However, concurrent CRT can also incur high rates of treatment-related toxicities, including perianal symptoms, which can be severely debilitating and substantially impair tolerance of full-dose CRT as well as quality of life. To this extent, radiation therapy (RT) has markedly advanced from the historical use of two- or three-dimensional conformal RT (2D/3DCRT) to inverse-planned intensity-modulated RT (IMRT), which creates highly conformal dose distributions and minimizes toxicities to several organs-at-risk (OARs).

IMRT for AC has proven to reduce doses to multiple RT-sensitive OARs (e.g., external genitalia and bowel) as compared to 3DCRT (2-4). As such, multiple retrospective reports have shown IMRT to be safe and effective as part of a CRT regimen (5-11). However, prospective evidence for this is lacking, as just one trial has evaluated concurrent IMRT-based CRT to date; toxicity profiles were encouraging but did not meet its primary endpoint (12). As a result, both IMRT and 3DCRT are listed as recommended RT techniques in this circumstance (1).

In this study, the first of its kind to date, we sought to evaluate national trends of IMRT utilization as part of concurrent CRT for AC. We specifically evaluated temporal trends, along with factors associated with greater likelihood of IMRT delivery. Given the lack of prospective evidence and relatively low volume of retrospective data, this analysis of a large, contemporary national database has implications on payers and insurance coverage along with patient counseling.

Methods

This study analyzed the National Cancer Data Base (NCDB), which is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. The NCDB consists of de-identified information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population (13-29). The NCDB contains information not included in the Surveillance, Epidemiology, and End Results (SEER) database, including details regarding use of systemic therapy. The data used in the study were derived from a de-identified NCDB file. The ACS 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 2004–2015. The inclusion criteria for this study involved patients age ≥18 with newly-diagnosed cT1–4 N0–3M0 anal comprising histologic codes of squamous cell carcinoma [International Classification of Disease for Oncology (ICD-O-3) codes 8051, 852, 8053, 8070-78, 8081, 8083-84, 8094, 8560, 8570]. For inclusion, patients required histological diagnostic confirmation and receipt of definitive concurrent CRT, defined as initiation of chemotherapy within 15 days of commencing RT. Since the purpose of the study was to compare the effect of radiation technique, inclusion criteria specifically involved the presence of a record of RT technique. Additionally, since our study sought to determine factors associated with use of IMRT, patients with unknown facility type or location were excluded. 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 (30). 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 included demographic data, comorbidity information, clinicopathologic tumor parameters, and treatment facility characteristics. All statistical tests were two-sided, with $P<0.05$ denoting statistical significance, and performed with STATA (version 14, College Station, TX, USA) software. The primary goal herein was to evaluate temporal trends and predictors of IMRT use. After baseline characteristics were compared between the IMRT and 3DCRT groups using χ^2 or Fisher's exact tests (non-parametric and parametric settings, respectively), multivariable logistic regression modeling was utilized to determine characteristics predictive for IMRT delivery. Overall survival (OS, defined as the interval between diagnosis and death, or censored at

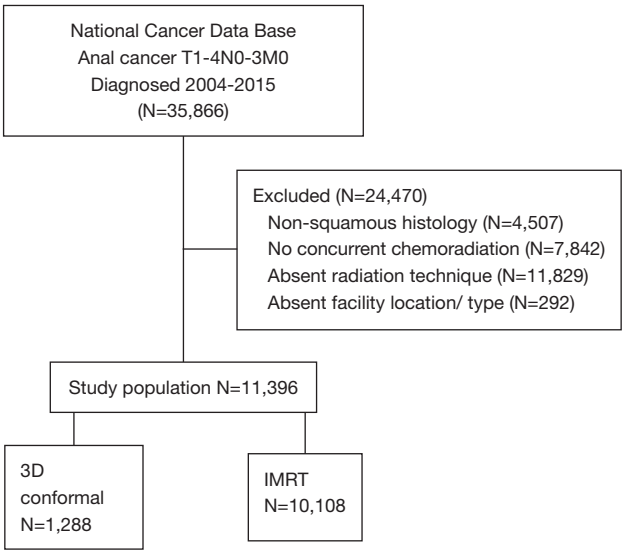

Figure 1 Patient selection diagram. IMRT, intensity-modulated radiotherapy.

last contact) was not expected be different between groups and was thus investigated secondarily. The Kaplan-Meier method was used for survival analysis, and comparisons between IMRT and 3DCRT groups were performed with the log-rank test. Endpoints such as local control and cancer specific survival are not recorded in the NCDB. Patients with an unknown vital status were excluded from survival analysis. Univariate Cox proportional hazards modeling was additionally used to identify variables associated with OS, followed by multivariate analysis that included variables that were either significant or with a strong trend towards significance on univariate analysis.

Results

A complete flow diagram of patient selection is given in *Figure 1*. In total, 11,396 patients met study criteria (*Table 1*). Of these, 1,288 (11%) were treated with 3DCRT and 10,108 (89%) with IMRT. Analysis of temporal trends revealed a sharp rise in IMRT from 28% in 2004 to 96% in 2015 (*Figure 2*). This rise seemed to largely occur between 2004 and 2010; in the current decade, IMRT was delivered to >90% of patients without appreciable increase.

On multivariable logistic regression analysis (*Table 2*), patients treated with IMRT were more likely to be older (P=0.011) and Hispanic (P=0.021). IMRT was also more commonly delivered at academic centers (P<0.001). There were also regional differences; IMRT was more frequent in the South Atlantic (DC, DE, FL, GA, MD, NC, SC, VA, WV), West South Central (AR, LA, OK, TX), Mountain (AZ, CO, ID, MT, NM, NV, UT, WY), and Pacific (AK, CA, HI, OR, WA) regions (P<0.05 for all). Although IMRT was less likely administered for T3–4 disease (P<0.05 for both), it was more likely in node-positive cases (P<0.001). Of note, RT technique was not significantly impacted by patient insurance or income (P>0.05 for both).

Median follow-up was 39.4 months (interquartile range, 23.2–62.5 months). Recognizing that OS was not expected to be different between groups, this analysis was performed secondarily. The 5- and 10-year OS for patients treated in the 3DCRT and IMRT groups were 72.0%/58.8% and 73.8%/59.7%, respectively (P=0.402) (*Figure 3*). In the overall cohort, there were several predictors of OS on Cox multivariate analysis (*Table 3*). These included advancing age, male gender, increasing comorbidities, advanced T stage, and node positivity (P<0.05 for all). Improved OS was observed in Hispanic patients, those treated at academic centers, and those with private/other governmental insurance (P<0.05 for all).

Discussion

Combined CRT for AC is difficult for patients to tolerate; to this extent, IMRT has proved to be a radiation technique associated with toxicity reduction. In this investigation, we demonstrate the sharp rise of IMRT from the mid-2000s to the mid-2010s. The large majority of patients are now treated with IMRT, with just a small minority still treated with 3DCRT. There were regional and disease-related factors associated with IMRT administration. Although RT technique did not impact OS as expected, academic centers were more likely to deliver IMRT, and OS was independently higher at these institutions.

The time course corresponding to the most rapid increase in IMRT utilization was between 2004 and 2010, with time points in the current decade showing consistently high (>90%) IMRT use. Although several pivotal papers (5,6) were published [and the RTOG 0529 trial commenced (12)] detailing the benefits of IMRT in this neoplasm between that time period, the findings herein likely correspond to a general increase in IMRT use during similar time periods owing to the adoption of new technology.

Table 1 Demographic characteristics of all patients

Characteristic	3DCRT, n=1,288 (%)	IMRT, n=10,108 (%)	P value
Age (years)			
<55	435 (33.8)	3,196 (31.6)	0.081
55–64	410 (31.8)	3,526 (34.9)	
65+	443 (34.4)	3,386 (33.5)	
Sex			
Male	359 (27.9)	3,072 (30.4)	0.063
Female	929 (72.1)	7,036 (69.6)	
Race			
White	1,150 (89.3)	8,574 (84.8)	<0.001
African American	85 (6.6)	876 (8.7)	
Hispanic	35 (2.7)	452 (4.5)	
Other/not recorded	18 (1.4)	206 (2.0)	
T stage			
T1	243 (18.9)	1,986 (19.7)	0.324
T2	621 (48.2)	5,023 (49.7)	
T3	306 (23.8)	2,295 (22.7)	
T4	118 (9.2)	804 (8.0)	
N stage			
N0	922 (71.6)	6,552 (64.8)	<0.001
N+	366 (28.4)	3,556 (35.2)	
Charlson Deyo score			
0	1,044 (81.1)	8,178 (80.9)	0.196
1	169 (13.1)	1,259 (12.5)	
2	42 (3.3)	300 (3.0)	
≥3	33 (2.6)	371 (3.7)	
Facility type			
Non-academic	1,010 (78.4)	6,609 (65.4)	<0.001
Academic	278 (21.6)	3,499 (34.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	3DCRT, n=1,288 (%)	IMRT, n=10,108 (%)	P value
Facility location			
New England	89 (6.9)	597 (5.9)	<0.001
Middle Atlantic	191 (14.8)	1,370 (13.6)	
South Atlantic	279 (21.7)	2,315 (22.9)	
East North Central	277 (21.5)	1,893 (18.7)	
East South Central	83 (6.4)	589 (5.8)	
West North Central	136 (10.6)	888 (8.8)	
West South Central	51 (4.0)	536 (5.3)	
Mountain	35 (2.7)	581 (5.7)	
Pacific	147 (11.4)	1,339 (13.2)	
Income			
≤$62,999	927 (72.0)	6,981 (69.1)	0.005
$63,000+	350 (27.2)	3,086 (30.5)	
Not recorded	11 (0.9)	41 (0.4)	
Residence			
Urban	1,015 (78.8)	8,376 (82.9)	<0.001
Metropolitan	220 (17.1)	1,349 (13.3)	
Rural	29 (2.3)	154 (1.5)	
Other/not recorded	24 (1.9)	229 (2.3)	
Insurance			
Medicaid	112 (8.7)	908 (9.0)	0.486
Medicare	479 (37.2)	3,698 (36.6)	
Private	588 (45.7)	4,717 (46.7)	
Uninsured	74 (5.7)	476 (4.7)	
Government/other	35 (2.7)	309 (3.1)	
Colectomy			
Yes	23 (1.8)	60 (0.6)	0.873
No	1,256 (97.5)	9,877 (97.7)	
Not recorded	9 (0.7)	171 (1.7)	

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

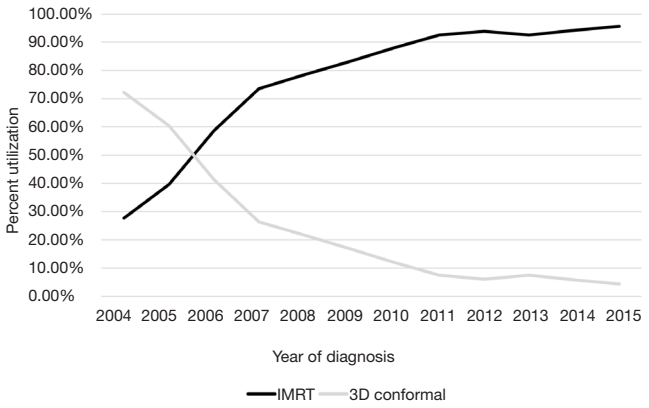

Figure 2 Temporal trends in IMRT and 3DCRT utilization. IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy.

It is important to document that IMRT use was not independently linked with socioeconomic or insurance status, which would signal the necessity to address health disparities. Additionally, it is rather intuitive that IMRT was more often delivered for node-positive disease, given the clear need to treat pelvic and/or inguinal lymphatics (thus maximizing the therapeutic ratio for IMRT over 3DCRT). Although T3–4 disease was less likely treated with IMRT, which may seem counterintuitive, it is possible that these high-risk cases necessitated more urgent therapy (an advantage of forward-planned 3DCRT given the "effort" needed to generate a treatment plan), It is also possible that more of these patients were treated palliatively with lower doses, thus diminishing the value of IMRT over 3DCRT. To this extent, it is important to consider that the

Table 2 Multivariate logistic regression for factors predictive of IMRT utilization

Characteristic	Odds ratio	95% confidence interval	P value
Age (years)			
<55	1 (reference)	–	–
55–64	1.209	1.045–1.399	0.011
65+	1.108	0.915–1.341	0.292
Sex			
Male	1 (reference)	–	–
Female	0.914	0.800-1.044	0.186
Race			
White	1 (reference)	–	–
African American	1.232	0.969–1.568	0.089
Hispanic	1.521	1.065–2.172	0.021
Other/not recorded	1.306	0.798–2.136	0.288
T stage			
T1	1 (reference)	–	–
T2	0.946	0.806–1.110	0.495
T3	0.816	0.677–0.984	0.034
T4	0.727	0.569–0.929	0.011
N stage			
N0	1 (reference)	–	–
N+	1.404	1.226–1.608	<0.001

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Odds ratio	95% confidence interval	P value
Charlson Deyo score			
0	1 (reference)	–	–
1	0.988	0.828–1.179	0.893
2	0.952	0.681–1.330	0.772
≥3	1.198	0.824–1.742	0.343
Facility type			
Non-academic	1 (reference)	–	–
Academic	1.931	1.672–2.229	<0.001
Facility location			
New England	1 (reference)	–	–
Middle Atlantic	0.989	0.751–1.303	0.938
South Atlantic	1.357	1.045–1.762	0.022
East North Central	1.099	0.846–1.427	0.481
East South Central	1.294	0.932–1.796	0.124
West North Central	1.079	0.805–1.447	0.611
West South Central	1.712	1.182–2.481	0.004
Mountain	2.951	1.955–4.455	<0.001
Pacific	1.486	1.117–1.977	0.007
Income			
≤$62,999	1 (reference)	–	–
$63,000+	1.100	0.956–1.266	0.182
Not recorded	0.336	0.155–0.726	0.006
Residence			
Urban	1 (reference)	–	
Metropolitan	0.851	0.721–1.005	0.058
Rural	0.774	0.512–1.171	0.226
Other/not recorded	1.526	0.931–2.502	0.093
Insurance			
Medicaid	1 (reference)	–	–
Medicare	1.012	0.784–1.305	0.930
Private	1.018	0.816–1.272	0.872
Uninsured	0.795	0.577–1.100	0.160
Government/other	1.016	0.675–1.530	0.939

3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

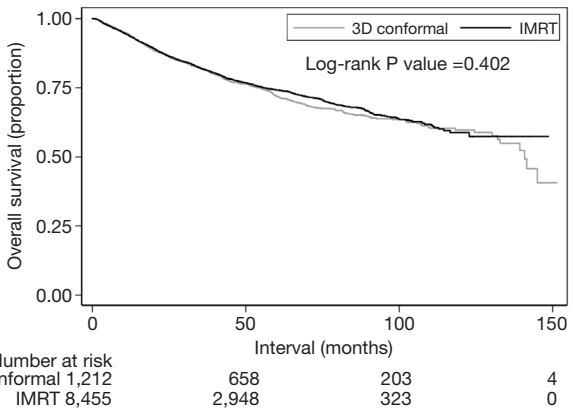

Figure 3 Kaplan-Meier overall survival curves comparing those receiving IMRT-based versus 3DCRT-based chemoradiation for anal cancer. IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy.

NCDB does not record information on whether a patient's treatment plan was initially commenced with one technique and subsequently switched to another.

Regional differences were also appreciated between IMRT and 3DCRT usage, along with therapy at academic centers. Although it is clear that academic institutions are more at the forefront of newer therapies, modalities, and techniques, the independently finding of improved OS at these facilities has far-reaching implications on patient counseling and management by both oncologists and referring providers. These findings are in accord with data from other neoplasms demonstrating improved outcomes at academic and/or high-volume facilities (31,32). There are several potential reasons for this, not limited to greater multimodality coordination, streamlined and thorough diagnostic processes, technical expertise, ancillary support staff for close clinical monitoring, and potentially the availability of salvage therapies (or clinical trials). Nevertheless, this finding may impact any case of nonmetastatic AC and could warrant revisions in patterns of patient education.

In light of these data together with the aforementioned lack of further prospective work regarding this topic, it is important to appraise the cost-effectiveness of IMRT in this clinical circumstance. Two studies of cost have been performed using the SEER-Medicare database, demonstrating higher base costs for IMRT but decreased hospitalization-related costs (33,34). Presently, however, because neither of these "cost" studies were comparative "cost-effectiveness" studies, this question remains unresolved to date with respect to formal medico-economic analyses. Nevertheless, this work demonstrates the high rate of IMRT utilization across the nation, which also was not impacted by insurance or socioeconomic status; this may assist in indirectly speaking to this issue.

Although the NCDB provides a unique platform with which to study this important clinical question, limitations cannot go unacknowledged. First, NCDB investigations are inherently retrospective and can never eliminate selection biases, including referral patterns, judgment by individual providers, and nature of follow-up management. Second, although the NCDB encompasses roughly 70% of the US population, only CoC-accredited centers contribute data. Thus, the findings may not necessarily be representative of the entire US and international population, including countries without access to advanced technologies. Third, there was no specific dose-based cutoff in this study, which as mentioned above may have resulted in the inclusion of some palliatively-treated 3DCRT patients and skew the data accordingly (however, there were no statistical differences in OS). Fourth, the inclusion of T1N0 patients (albeit a very small percentage) may also skew the aforementioned figures as well. Lastly, the NCDB does not keep track of several noteworthy variables, such as HIV status, RT field design/volumes, specific chemotherapy type, or other endpoints such as tolerance of therapy (including premature cessation of chemotherapy and/or RT).

Conclusions

From this study of a large, contemporary national database, we demonstrate that the large majority of AC patients are now treated with IMRT, with a small minority still treated with 3DCRT. Regional and disease-related factors associated with IMRT administration are described. Although RT technique did not impact OS as expected, academic centers were more likely to deliver IMRT, and OS was independently higher at these institutions. Collectively, these data have notable implications for multidisciplinary oncologic providers, payers and insurance coverage, in addition to patient counseling by both referring and treating clinicians.

Table 3 Univariate and multivariate analysis of factors predictive of overall survival

Characteristic	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Treatment group						
IMRT	1 (reference)	–	–	–	–	–
3DCRT	1.050	0.937–1.774	0.402	–	–	–
Age (years)						
<55	1 (reference)	–	–	1 (reference)	–	–
55–64	1.041	0.929–1.166	0.490	1.130	1.007–1.267	0.028
65+	1.916	1.731–2.120	<0.001	1.717	1.502–1.963	<0.001
Sex						
Male	1 (reference)	–	–	1 (reference)	–	–
Female	0.638	0.585–0.695	<0.001	0.642	0.588–0.702	<0.001
Race						
White	1 (reference)	–	–	1 (reference)	–	–
African American	1.149	0.994–1.327	0.059	0.979	0.842–1.138	0.787
Hispanic	0.641	0.499–0.824	0.001	0.567	0.440–0.731	<0.001
Other/not recorded	0.683	0.476–0.980	0.039	0.700	0.487–1.004	0.053
T stage						
T1	1 (reference)	–	–	1 (reference)	–	–
T2	1.749	1.522–2.010	<0.001	1.663	1.447–1.912	<0.001
T3	2.908	2.513–3.365	<0.001	2.374	2.044–2.758	<0.001
T4	3.410	2.869–4.052	<0.001	3.084	2.581–3.683	<0.001
N stage						
N0	1 (reference)	–	–	1 (reference)	–	–
N+	1.647	1.513–1.792	<0.001	1.501	1.373–1.640	<0.001
Charlson Deyo score						
0	1 (reference)	–	–	1 (reference)	–	–
1	1.596	1.422–1.793	<0.001	1.437	1.279–1.615	<0.001
2	2.353	1.944–2.847	<0.001	2.029	1.673–2.460	<0.001
≥3	2.053	1.712–2.461	<0.001	1.815	1.498–2.200	<0.001
Facility type						
Non-academic	1 (reference)	–	–	1 (reference)	–	–
Academic	0.898	0.820–0.983	0.020	0.868	0.791–0.953	0.003

Table 3 (*continued*)

Table 3 (*continued*)

Characteristic	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Income						
≤$62,999	1 (reference)	–	–	1 (reference)	–	–
$63,000+	0.756	0.687–0.833	<0.001	0.886	0.801–0.981	0.019
Not recorded	2.295	1.460–3.608	<0.001	2.734	1.627–4.594	<0.001
Residence						
Urban	1 (reference)	–	–	1 (reference)	–	–
Metropolitan	1.079	0.958–1.214	0.211	1.008	0.892–1.139	0.901
Rural	1.350	1.004–1.814	0.047	1.173	0.870–1.581	0.296
Other/not recorded	1.029	0.763–1.388	0.851	0.822	0.583–1.157	0.261
Insurance						
Medicaid	1 (reference)	–	–	1 (reference)	–	–
Medicare	1.179	1.019–1.364	0.027	0.914	0.772–1.083	0.300
Private	0.498	0.427–0.580	<0.001	0.583	0.498–0.682	<0.001
Uninsured	0.930	0.749–1.155	0.513	0.891	0.717–1.108	0.300
Government/other	0.666	0.503–0.884	0.005	0.640	0.481–0.852	0.002

IMRT, intensity-modulated radiotherapy; 3DCRT, three-dimensional conformal radiotherapy.

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None.

Footnote

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

Ethical statement: This study was exempt from institutional review board since study used de-identified patient information from NCDB.

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