Impact of intensity modulated radiation therapy on survival in anal cancer

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Background: This study was designed to investigate the impact of intensity modulated radiation therapy (IMRT) on overall survival (OS) in patients treated with chemoradiation (CRT) for anal cancer (AC).

Methods: We performed a case-control, propensity score (PS) matched analysis of the National Cancer Data Base (NCDB) of patients diagnosed with non-metastatic AC from 2004 to 2013. Only patients receiving concurrent CRT were included. Patients were stratified into two groups based on the RT technique: IMRT *vs.* non-IMRT. Multivariate analysis (MVA) and Kaplan-Meier (KM) plots for OS were obtained for the matched and unmatched groups.

Results: A total of 8,108 patients diagnosed between 2004 and 2013 were eligible for the study, of which 3,307 (40.8%) and 4,801 (59.2%) were in the IMRT and non-IMRT groups, respectively. Median follow-up for all patients was 54.4 months. After PS matching, MVA for OS showed that IMRT was associated with improved OS compared to non-IMRT (HR 0.83, 95% CI: 0.74–0.94; P=0.002). Adjusted KM analysis showed that the 5-year OS for patients treated with IMRT was 74.6% *vs.* 70.5% (P=0.0022).

Conclusions: To our knowledge, this is the largest study to date that evaluates the impact of IMRT on OS for patients with AC. Our investigation shows that IMRT based concurrent CRT for non-metastatic AC is associated with improved survival when compared to similar patients treated with non-IMRT based therapy. In the absence of randomized evidence, our analysis might provide additional support for increasing the use of IMRT for patients with AC receiving concurrent CRT.

Keywords: Intensity modulated radiation therapy (IMRT); radiotherapy technique; anal cancer (AC); overall survival (OS); National Cancer Data Base (NCDB)

Introduction

The incidence of anal cancer (AC) has been rising at an average annual rate of 2.2% over the last 10 years. Concomitantly, death rates have also been increasing, on average, at 3.2% each year between 2004–2013 (1). Historically, the management of this disease was abdominoperineal resection (APR). However, in 1974, Nigro *et al.* introduced sphincter preserving chemoradiation (CRT) as a new treatment paradigm (2). Subsequent

studies have since confirmed the efficacy of this treatment approach, which has led to the establishment of CRT as the first line treatment for AC (3-7). This paradigm shift from surgical management to CRT has yielded excellent clinical outcomes with 5-year colostomy rate and overall survival (OS) of 12% and 78%, respectively, as reported in the long-term update of RTOG 98-11 (8).

Although CRT for AC has demonstrated excellent response rates, this treatment option is associated with significant toxicities. Patients can experience painful moist skin desquamation, diarrhea, and a significant decline in bone marrow reserve. In the initial report of RTOG 98-11, the rate of acute non-hematologic grade 3 or 4 toxicity was 74% in both mitomycin/5-fluorouracil (5-FU) and cisplatin/5-FU groups (9). More recently, the ACT II trial found similar grades 3–4 adverse events of 71% and 72%, in the mitomycin/5-FU and cisplatin/5-FU groups, respectively (10).

One potential method to reduce radiotherapy (RT) related toxicity, is to utilize intensity modulated radiation therapy (IMRT) since it affords the opportunity to deliver highly conformal doses to the tumor while minimizing dose to adjacent organs. IMRT is particularly suited for the treatment of AC because of the abundance of adjacent organs at risk such as small intestine, rectosigmoid colon, bladder, skin, bone marrow, and external genitalia. RTOG 0529, the first multi-institutional trial examining the role of IMRT in AC, found that IMRT was associated with significant sparing of acute grade 2+ hematologic, grade 3+ dermatologic and gastrointestinal toxicity (11). However, whether such reductions in toxicity can potentially translate into an improvement in survival, remains to be seen.

The present study was designed to evaluate the difference in survival of patients with AC treated with IMRT versus non-IMRT based CRT. We utilized the National Cancer Data Base (NCDB), a large, prospectively acquired database that includes approximately 70% of newly diagnosed cancer patients treated at over 1,500 facilities in the United States.

Methods

Patient selection

The NCDB 2014 Participant User File (PUF) for AC was obtained for this analysis. This included patients with AC diagnosed between 2004 and 2013. The database was queried for patients with non-metastatic AC patients. In order to be eligible, patients were required to have histologic confirmation of malignancy. We excluded patients that had *in-situ* disease, non-squamous histology, metastatic disease at diagnosis, and patients with history of prior malignancy. We further excluded patients who did not receive definitive concurrent CRT, who received inappropriate RT doses or volumes, and cases with missing outcomes. Patients were excluded if they were treated with radiosurgery, Gamma Knife, brachytherapy, radium, and radioisotopes. Patient demographics, socioeconomic status, disease characteristics, treatment details, and treatment outcomes were available for analysis. Patients were stratified into two groups: patients receiving IMRT based CRT and patients who received non-IMRT based CRT (*Figure 1*).

Patient demographics

Patient's age at diagnosis, gender, race, type of health insurance, geographic location, education, median income quartile, treatment facility type were available for analysis. Geographic location was determined by the zip code of the patient's residence recorded at the time of diagnosis. This was then classified and compared as metropolitan, urban, or rural location. Level of education for each patient was inferred by using the patient's zip code at the time of diagnosis and with the aid of US census data, determined the number of adults in the patient's zip code who did not graduate from high school. Patient level of income was estimated by matching the patient's zip code to the median household income for the area of residence derived from US Census data. Treatment facility was categorized as academic/research center (post-graduate medical education training program and participation in cancer clinical research), which includes National Cancer Institute (NCI) designated comprehensive cancer center, or non-academic which includes community cancer program (more than 100 but ≤500 of new annual cancer cases) and comprehensive community cancer program (more than 500 new annual cancer cases). Charlson-Deyo score was used as a surrogate marker for patient co-morbidities. Charlson-Deyo score was categorized as 0, 1, or 2, and above to indicate increasing levels of comorbid conditions (12).

Disease characteristics

The following disease related variables were evaluated: diagnosis year, American Joint Cancer Committee (AJCC) clinical tumor and nodal stage, lymphovascular space invasion and tumor grade. Patients were staged based on

620

Jhaveri et al. Impact of IMRT on survival in AC
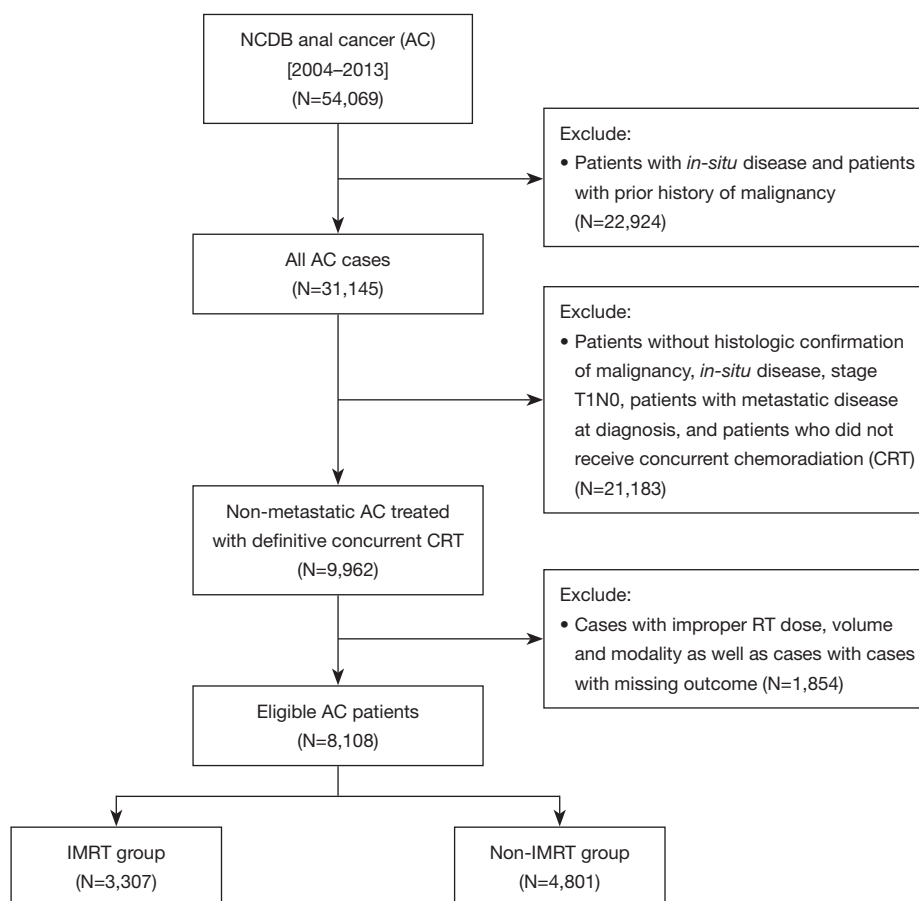
Figure 1 CONSORT diagram for patient selection. NCDB, National Cancer Data Base; IMRT, intensity modulated radiation therapy.

the AJCC staging edition in use during the year in which the case was diagnosed.

Treatment details

Patients were eligible if they were treated with concurrent CRT. Chemotherapy agent (multi-agent versus single-agent), RT dose, and RT modality (IMRT *vs.* other) were also evaluated. Patients were excluded if they received inappropriate RT volume (outside the pelvis), non-standard RT dose (<44 or >70 Gy), or if they were unable to complete the prescribed course of RT. Patients were stratified in the IMRT group if their RT modality was IMRT, an external beam technique that was required to be clearly stated in the patient record. The remaining patients were stratified into the non-IMRT group. The non-IMRT group included patients that received 3D conformal RT (3D-CRT) and RT not otherwise specified (RT-NOS). 3D-CRT was defined as an external beam technique using multiple, fixed portals

shaped to conform to a target volume. Again, 3D-CRT was required to be clearly stated in the patient record in order to be categorized as 3D-CRT. RT-NOS was categorized as patients who received RT using an external beam therapy machine with mixed energy photons and/or electrons.

Outcome

The primary outcome of this study was OS—defined as time from diagnosis to time of death or last follow-up.

Statistical analysis

All statistical analyses were conducted using SAS 9.4 (Cary, NC, USA). Univariate associations between each variable and the two study cohorts (IMRT *vs.* non-IMRT) were calculated using the χ^2 test for categorical covariates and ANOVA for numerical covariates. The univariate analysis (UVA) between each covariate of interest and OS was

assessed using Cox proportional hazard model and log-rank test. A multivariable Cox proportional hazard model for OS was fit using the backward selection method and a removal criterion of 0.20. Hazard ratios (HR) with associated 95% confidence interval (CI) were generated for each covariate and the outcome. Kaplan-Meier (KM) survival analysis was performed to generate OS curves comparing the outcomes of the two cohorts.

Propensity score (PS) analysis was implemented to account for the differences in patient demographics, tumor characteristics, and treatment details between both groups (13). A multinomial logistic regression model was created to estimate the propensity of a patient being in the IMRT or non-IMRT cohort. Variables included in the PS model were those hypothesized to be associated with OS (14). IMRT patients were matched 1:1 with non-IMRT patients using a greedy matching algorithm. Effectiveness of matching was evaluated by calculating the standardized differences of the covariates between treatment groups (15,16). After PS matching was applied, the effect of RT modality in the matched sample was recalculated using a Cox proportional hazard model. Adjusted KM curves were then regenerated to compare the outcomes of the two groups.

Results

The initial query of the NCDB 2014 anal cancer database resulted in 54,069 cases. After applying the aforementioned inclusion and exclusion criteria, there were a total of 8,108 eligible patients as depicted in *Figure 1*. Patients were then stratified based on the radiation modality: IMRT (n=3,307; 40.8%) and non-IMRT (n=4,801; 59.2%).

Patient characteristics

There were 5,368 (66.2%) female and 2,740 (33.8%) male patients. There were 4,545 (56.0%) of patients with stage II disease, and 3,563 (44%) with stage III disease. The majority of patients (n=6,879, 84.8%) were treated with multi-agent chemotherapy. The median and mean age at diagnosis was 57 and 58.29 years, respectively. The median and mean RT dose were 54 and 54.01 Gy, respectively. The median and mean duration of RT was 47.0 and 49.5 days, respectively. The median follow-up time for all patients was 54.4 months.

IMRT usage

Between 2004 and 2007, there were 2,246 patients

diagnosed with AC who received concurrent CRT. In that time period, 86.6% (n=1,944) of patients received non-IMRT and 13.4% (n=302) received IMRT. For the 2,528 AC cases diagnosed between 2008 and 2010, 60.9% (n=1,539) and 39.1% (n=989) received non-IMRT and IMRT, respectively. Next, for the 3,334 patients diagnosed with AC between 2011–2013, 39.5% (n=1,318) and 60.5% (n=2,016) of patients were treated with non-IMRT and IMRT, respectively. *Figure S1* plots the annual IMRT usage trend nationwide. This shows an increasing use of IMRT from 2004 to 2013. For the year 2013, 61% of patients received IMRT based CRT.

UVA

Table 1 demonstrates the baseline demographic, disease characteristics, and treatment details between the two patient groups. The two groups were well balanced except for patients in the IMRT group were statistically (all P<0.05) more likely to be older at diagnosis (age ≥50 years 79.3% *vs.* 75.7%), have Medicare or other government insurance (34.6% *vs.* 32.6%), reside in areas with median annual household income of $36,000–$45,999 (30.7% *vs.* 29.0%) and in areas with <14% no high school degree (36.3% *vs.* 32.4%), be treated at an Academic/Research Program (37.7% *vs.* 31.1%), diagnosed with clinical N2 disease (17.9% *vs.* 14.8%) and overall stage III (46.9% *vs.* 41.9%), have no evidence of lymphovascular space invasion (14.9% *vs.* 7.9%), treated with multi-agent chemotherapy (87.8% *vs.* 82.8%), diagnosed in 2011–2012 (38.2% *vs.* 17.4%), and complete RT in a shorter duration (median 45 *vs.* 48 days).

Multivariate analysis (MVA)

Unadjusted MVA for OS showed that IMRT (HR 0.84, 95% CI: 0.75–0.93; P<0.001), male gender (HR 1.65, 95% CI: 1.50–1.81; P<0.005), presence of lymphovascular space invasion (HR 2.07, 95% CI: 1.49–2.88; P<0.001), academic/ research treatment facility (HR 0.86, 95% CI: 0.75–0.98; P=0.021), Medicare insurance (HR 1.40, 95% CI: 1.18–1.66; P<0.001), rural patient location (HR 1.44, 95% CI:1.05– 1.98; P=0.023), receipt of single agent chemotherapy (HR 1.39, CI: 1.11–1.73; P=0.004), age ≥50 years (HR 1.19, 95% CI: 1.05–1.34; P=0.006), Charlson-Deyo score ≥1 (HR 1.50, 95% CI: 1.35–1.67; P<0.001), advanced AJCC clinical nodal stage (HR 1.63, 95% CI: 1.41–1.89; P<0.001), clinical tumor stage (HR 3.26, 95% CI: 2.36–4.51; P<0.001), and

Table 1 Baseline patient demographic, disease, and treatment related characteristics stratified by treatment group

Covariate	Level	Statistics	Treatment modality		P value
			Non-IMRT (n=4,801)	IMRT (n=3,307)	
Age at diagnosis	Age <50 years	N (Col %)	1,169 (24.35)	684 (20.68)	<0.001
	Age ≥50 years	N (Col %)	3,632 (75.65)	2,623 (79.32)	
Gender	Male	N (Col %)	1,608 (33.49)	1,132 (34.23)	0.49
	Female	N (Col %)	3,193 (66.51)	2,175 (65.77)	
Race	White	N (Col %)	4,151 (86.46)	2,880 (87.09)	0.414
	Other	N (Col %)	650 (13.54)	427 (12.91)	
Geographic location	Metropolitan	N (Col %)	3,848 (82.29)	2,718 (83.94)	0.109
	Urban	N (Col %)	742 (15.87)	458 (14.14)	
	Rural	N (Col %)	86 (1.84)	62 (1.91)	
Median income	<$30,000	N (Col %)	705 (15.12)	423 (13.19)	0.032
	$30,000–$35,999	N (Col %)	894 (19.18)	581 (18.12)	
	$36,000–$45,999	N (Col %)	1,351 (28.98)	985 (30.72)	
	$46,000+	N (Col %)	1,712 (36.72)	1,217 (37.96)	
Percent no high school degree	≥29%	N (Col %)	845 (18.13)	511 (15.94)	0.002
	20–28.9%	N (Col %)	1,158 (24.84)	755 (23.55)	
	14–19.9%	N (Col %)	1,148 (24.62)	776 (24.2)	
	<14%	N (Col %)	1,511 (32.41)	1,164 (36.31)	
Facility type	Community/Integrated Network Cancer Program	N (Col %)	956 (20.8)	655 (20.36)	<0.001
	Comprehensive Community Cancer Program	N (Col %)	2,213 (48.14)	1,350 (41.96)	
	Academic/Research Program	N (Col %)	1,428 (31.06)	1,212 (37.67)	
Insurance status	Not insured/unknown	N (Col %)	459 (9.56)	263 (7.95)	0.046
	Private	N (Col %)	2,304 (47.99)	1,573 (47.57)	
	Medicaid	N (Col %)	470 (9.79)	326 (9.86)	
	Medicare/other government	N (Col %)	1,568 (32.66)	1,145 (34.62)	
Charlson-Deyo score	0	N (Col %)	3,953 (82.34)	2,687 (81.25)	0.212
	1+	N (Col %)	848 (17.66)	620 (18.75)	
Diagnosis year	2004–2007	N (Col %)	1,944 (40.49)	302 (9.13)	<0.001
	2008–2010	N (Col %)	1,539 (32.06)	989 (29.91)	
	2011–2012	N (Col %)	837 (17.43)	1,262 (38.16)	
	2013	N (Col %)	481 (10.02)	754 (22.8)	

Table 1 (*continued*)

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Covariate	Level	Statistics	Treatment modality		P value
			Non-IMRT (n=4,801)	IMRT (n=3,307)	
AJCC clinical T stage	T1	N (Col %)	156 (3.25)	134 (4.06)	0.112
	T2	N (Col %)	2,844 (59.3)	1,931 (58.52)	
	T3	N (Col %)	1,261 (26.29)	901 (27.3)	
	T4	N (Col %)	450 (9.38)	272 (8.24)	
	Tx	N (Col %)	85 (1.77)	62 (1.88)	
AJCC clinical N stage	N0	N (Col %)	2,932 (61.15)	1,857 (56.24)	<0.001
	N1	N (Col %)	586 (12.22)	441 (13.36)	
	N2	N (Col %)	711 (14.83)	592 (17.93)	
	N3	N (Col %)	466 (9.72)	381 (11.54)	
	Nx	N (Col %)	100 (2.09)	31 (0.94)	
AJCC clinical stage group	Stage II	N (Col %)	2,789 (58.09)	1,756 (53.1)	<0.001
	Stage III	N (Col %)	2,012 (41.91)	1,551 (46.9)	
Tumor grade	Well/moderately differentiated	N (Col %)	2,287 (47.64)	1,550 (46.87)	0.697
	Poorly differentiated/ undifferentiated	N (Col %)	1,302 (27.12)	896 (27.09)	
	Cell type not determined	N (Col %)	1,212 (25.24)	861 (26.04)	
Lymphovascular space invasion	Not present	N (Col %)	379 (7.89)	492 (14.88)	<0.001
	Present	N (Col %)	80 (1.67)	91 (2.75)	
	Not applicable/unknown	N (Col %)	4,342 (90.44)	2,724 (82.37)	
Agent of chemotherapy	Agent not documented	N (Col %)	318 (6.62)	119 (3.6)	<0.001
	Single-agent	N (Col %)	506 (10.54)	286 (8.65)	
	Multi-agent	N (Col %)	3,977 (82.84)	2,902 (87.75)	
Radiotherapy dose (Gy)	–	Mean	53.97	54.1	0.361
	–	Median	54	54	
	–	Min	44	44	
	–	Max	69.8	69.4	
	–	Std Dev	5.2	4.1	
Duration of radiotherapy (days)	–	Mean	50.7	47.71	<0.001
	–	Median	48	45	
	–	Std Dev	16.14	10.54	

IMRT, intensity modulated radiation therapy; AJCC, American Joint Cancer Committee.
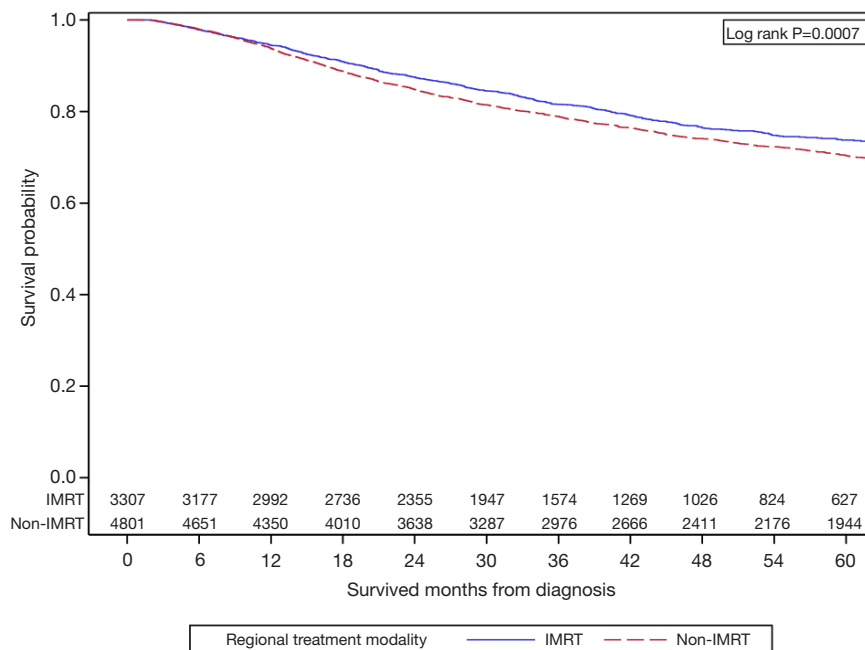
Figure 2 Unadjusted Kaplan-Meier survival analysis stratified by treatment group. IMRT, intensity modulated radiation therapy.

total RT dose (HR 1.00, 95% CI: 1.00–1.00; P=0.01) were also statistically significant.

Treatment outcome

Figure 2 shows the unadjusted KM survival analysis stratified by treatment group. The 5-year OS of the IMRT group was 73.8% *vs.* 70.4% in the non-IMRT group (P=0.0007).

PS analysis

All variables that were statistically significant on UVA between the two groups and MVA for OS were incorporated into the PS matching. Age, gender, race, education, median income quartile, geographic location, treatment facility type, health insurance status, diagnosis year, Charlson-Deyo score, tumor grade, lymphovascular space invasion, agent of chemotherapy, AJCC clinical tumor and nodal stage, and RT dose were all included in the balancing. This resulted in 2,334 IMRT patients being matched to similar 2,334 non-IMRT patients with standardized differences across all variables <0.1 (*Table 2*). After application of PS matching, Cox-proportional model for OS showed that the IMRT group had superior survival with HR 0.83 (95% CI:

0.74–0.94, P=0.002). The adjusted KM survival analysis comparing the two cohorts is shown in *Figure 3*. This shows that IMRT is associated with improved OS at 2 years 87.6% *vs.* 84.5%, and at 5 years 74.6% *vs.* 70.5%, P=0.0022. Median OS was not reached in both groups.

Discussion

The use of advanced RT techniques to minimize inadvertent dose to adjacent organs has been proven to have a dosimetric advantage in AC (17,18), however, whether such dosimetric advantages translate into clinical gains in survival remains largely unknown. The large, prospectively acquired, multi-institutional database such as the NCDB potentially allows for large statistical power needed to detect a small survival difference when evaluating the impact of RT technique on clinical outcomes. Our investigation of 8,108 non-metastatic AC patients shows that treatment with IMRT has statistically significant superior OS when compared to similar patients treated with non-IMRT based CRT. This survival advantage persisted despite the implementation of statistical techniques to eliminate selection bias. To our knowledge, this is the first study with the primary end point of OS that evaluates the impact

Table 2 Propensity Score matched patient characteristics stratified by treatment group

Covariate	Level	Statistics	Treatment modality		P value	Standardized difference
			Non-IMRT (n=2,334)	IMRT (n=2,334)		
Age at diagnosis	<50 years	N (Col %)	457 (19.58)	458 (19.62)	0.971	0.001
	≥50 years	N (Col %)	1,877 (80.42)	1,876 (80.38)		0.001
Gender	Male	N (Col %)	769 (32.95)	777 (33.29)	0.804	0.007
	Female	N (Col %)	1,565 (67.05)	1,557 (66.71)		0.007
Race	White	N (Col %)	2,024 (86.72)	2,028 (86.89)	0.863	0.005
	Other	N (Col %)	310 (13.28)	306 (13.11)		0.005
Geographic location	Metropolitan	N (Col %)	1,929 (82.65)	1,948 (83.46)	0.428	0.022
	Urban	N (Col %)	352 (15.08)	345 (14.78)		0.008
	Rural	N (Col %)	53 (2.27)	41 (1.76)		0.037
Median income	<$30,000	N (Col %)	329 (14.1)	312 (13.37)	0.774	0.021
	$30,000–$35,999	N (Col %)	449 (19.24)	434 (18.59)		0.016
	$36,000–$45,999	N (Col %)	685 (29.35)	691 (29.61)		0.006
	$46,000+	N (Col %)	871 (37.32)	897 (38.43)		0.023
Percent no high school degree	≥29%	N (Col %)	401 (17.18)	386 (16.54)	0.905	0.017
	20–28.9%	N (Col %)	547 (23.44)	563 (24.12)		0.016
	14–19.9%	N (Col %)	573 (24.55)	567 (24.29)		0.006
	<14%	N (Col %)	813 (34.83)	818 (35.05)		0.004
Facility type	Community/Integrated Network Cancer Program	N (Col %)	457 (19.58)	484 (20.74)	0.6	0.029
	Comprehensive Community Cancer Program	N (Col %)	1034 (44.3)	1,026 (43.96)		0.007
	Academic/Research Program	N (Col %)	843 (36.12)	824 (35.3)		0.017
Insurance type	Not insured/unknown	N (Col %)	195 (8.35)	199 (8.53)	0.996	0.006
	Private	N (Col %)	1,114 (47.73)	1,113 (47.69)		0.001
	Medicaid	N (Col %)	218 (9.34)	220 (9.43)		0.003
	Medicare/other government	N (Col %)	807 (34.58)	802 (34.36)		0.005
Charlson-Deyo score	0	N (Col %)	1,892 (81.06)	1,894 (81.15)	0.94	0.002
	1+	N (Col %)	442 (18.94)	440 (18.85)		0.002
Diagnosis year	2004–2007	N (Col %)	284 (12.17)	285 (12.21)	0.708	0.001
	2008–2010	N (Col %)	856 (36.68)	870 (37.28)		0.012
	2011–2012	N (Col %)	753 (32.26)	718 (30.76)		0.032
	2013	N (Col %)	441 (18.89)	461 (19.75)		0.022

Table 2 (*continued*)

626

Jhaveri et al. Impact of IMRT on survival in AC

Table 2 (*continued*)

Covariate	Level	Statistics	Treatment modality		P value	Standardized difference
			Non-IMRT (n=2,334)	IMRT (n=2,334)		
AJCC clinical T stage	T1	N (Col %)	94 (4.03)	93 (3.98)	0.997	0.002
	T2	N (Col %)	1,382 (59.21)	1,384 (59.3)		0.002
	T3	N (Col %)	603 (25.84)	597 (25.58)		0.006
	T4	N (Col %)	211 (9.04)	213 (9.13)		0.003
	Tx	N (Col %)	44 (1.89)	47 (2.01)		0.009
AJCC clinical N stage	N0	N (Col %)	1,343 (57.54)	1,336 (57.24)	0.98	0.006
	N1	N (Col %)	321 (13.75)	312 (13.37)		0.011
	N2	N (Col %)	401 (17.18)	408 (17.48)		0.008
	N3	N (Col %)	243 (10.41)	253 (10.84)		0.014
	Nx	N (Col %)	26 (1.11)	25 (1.07)		0.004
Grade	Well/moderately differentiated	N (Col %)	1,104 (47.3)	1,092 (46.79)	0.918	0.01
	Poorly differentiated/ undifferentiated	N (Col %)	655 (28.06)	656 (28.11)		0.001
	Cell type not determined	N (Col %)	575 (24.64)	586 (25.11)		0.011
Lymph vascular invasion	Not present	N (Col %)	304 (13.02)	306 (13.11)	0.982	0.003
	Present	N (Col %)	66 (2.83)	64 (2.74)		0.005
	Not applicable/unknown	N (Col %)	1,964 (84.15)	1,964 (84.15)		0
Agent of chemotherapy	Agent not documented	N (Col %)	116 (4.97)	101 (4.33)	0.566	0.031
	Single-agent	N (Col %)	217 (9.3)	214 (9.17)		0.004
	Multi-agent	N (Col %)	2,001 (85.73)	2,019 (86.5)		0.022
Total radiation dose (Gy)	44–50.4	N (Col %)	278 (11.91)	279 (11.95)	0.986	0.001
	50.4–54	N (Col %)	407 (17.44)	411 (17.61)		0.005
	>54	N (Col %)	1,649 (70.65)	1,644 (70.44)		0.005

of IMRT in AC. Moreover, our analysis provides insight into the nationwide practice patterns and usage of IMRT (*Figure S1*). We observed that for new cases diagnosed in 2013, 61% of patients were treated with IMRT.

The results of our study are directly comparable to phase III, randomized, multi-institutional clinical trials including: ACCORD-03 (19), RTOG 98-11 (8), and ACT II (10) where patients were treated with non-IMRT based CRT. In the present study, the 5-year of 70.5% in the non-IMRT group is similar to the 71% 5-year OS of the non-induction, standard RT dose group in the ACCORD-03 trial (19). Next,

the 5-year OS of the mitomycin group in RTOG 98-11 and the no maintenance mitomycin group of ACT II study were 78.3% and 79%, respectively. This difference in survival is likely due to tumor and treatment heterogeneity amongst the studies. Only 30% of patients in the mitomycin group of RTOG 98-11 and 31% of patients in maintenance mitomycin group of ACT II trial had nodal metastases, compared to the non-IMRT group of the present study which included 41% of patients with N1–N3 disease. Furthermore, 100% of patients in the aforementioned randomized trials received multi-agent chemotherapy,
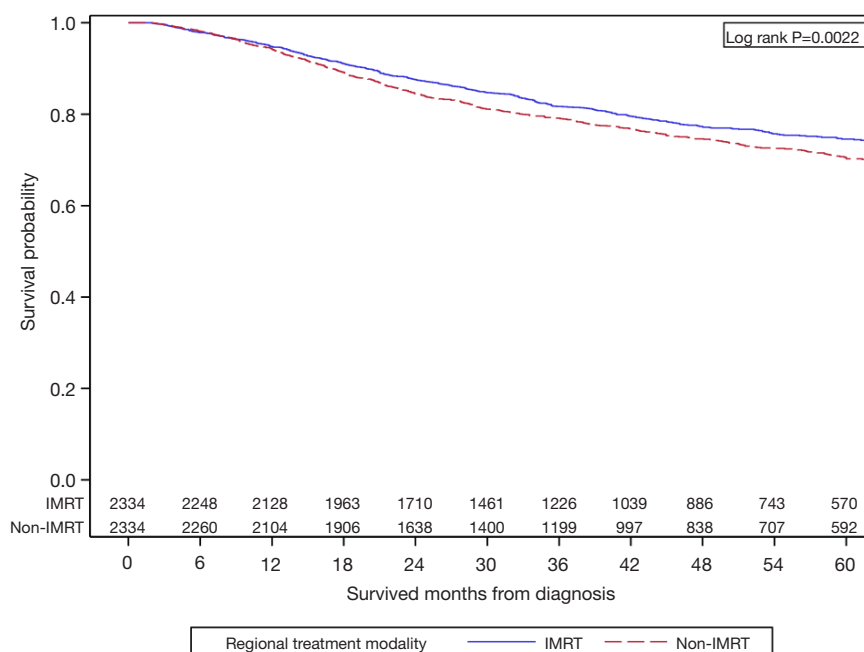
Figure 3 Adjusted Kaplan-Meier survival analysis stratified by treatment group. IMRT, intensity modulated radiation therapy.

whereas, 86% of patients in the non-IMRT group received multi-agent chemotherapy. In the present analysis, the type of chemotherapy (mitomycin *vs.* cisplatin) could not be included in the analysis since this information is not captured in the NCDB. Additionally, our series reflects a broader, non-clinical trial, patient population representing approximately 70% of cancer diagnoses annually.

The rationale for using IMRT for AC was proposed after the publication of RTOG 98-11, where dose escalation to 59.4 Gy for T2–T4 lesions was suggested in order to improve local control. This led to grades 3–4 non-hematologic toxicity rates of 73% in the mitomycin group. Similarly, in the ACT II trial, 71% of patients in the no maintenance mitomycin group, despite using a lower RT dose of 50.4 Gy, suffered from grade 3 or 4 adverse events. Since patients in both of these trials were treated with non-IMRT, it is possible that their clinical outcomes are hampered by treatment related toxicities. In an effort to reduce chemotherapy related toxicities, there have been randomized clinical trials attempting to substitute mitomycin for cisplatin, however, at the time of publication, mitomycin with 5-FU used concurrently with RT, still remains the standard of care. While mitomycin and 5-FU have remained as the standard first line systemic agents, the dose, volume, and technique of RT utilized in AC has

evolved over time. Since chemotherapy related toxicities could not be mitigated any further, attention was turned towards minimizing the side effects related to RT in order to maximize the therapeutic ratio. To that end, RTOG 0529, a phase II multi-institutional trial evaluating the role of IMRT in AC, showed that IMRT was associated with significant sparing of acute grade 2+ hematologic, grade 3+ dermatologic and gastrointestinal toxicity (11). Notably, the adoption of IMRT amongst radiation oncologists was associated with a learning curve: 81% of patients in RTOG 0529 required planning revisions and 46% required multiple resubmissions. In order to avoid reduction in local control by so called "marginal miss", IMRT requires understanding the complexities associated with target and nodal basin delineation. Due to the challenges associated with adopting IMRT into practice, one could postulate that IMRT could potentially lead to inferior outcomes. However, the results of this study, even after PS matching, directly contradict this hypothesis and align with previously published single institutional data (20).

The survival gains from using IMRT are hypothesis generating and this could be due to a combination of multiple factors: decreased treatment related acute side effects resulting in fewer treatment breaks, reduction in myelosuppression, and decreased long-term events. Due to

accelerated repopulation, interruption or prolongation of the prescribed RT course has been linked to inferior clinical outcomes not only in AC (21) but also in HNSCC (22), cervical cancer (23), and bladder cancer (24). Since IMRT has been shown to decrease acute side effects, it has the potential to reduce treatment breaks and in turn lead to improved tumor control. Moreover, fewer interruptions and reduction in acute toxicities can lead to completion of the prescribed chemotherapy course, as previously shown in a SEER analysis where AC patients treated with IMRT were more likely to receive ≥2 cycles of mitomycin- or cisplatin-based chemotherapy (25). In the present analysis, both groups received the same median RT dose of 54 Gy, however, the duration of RT was shorter with IMRT (mean 47.7 versus 50.7 days, median 45 versus 48 days, and standard deviation 10.5 versus 16.1 days; P<0.001). Next, combining mitomycin with RT, both of which are known to be toxic insults to the bone marrow, can collectively lead to severe hematologic toxicities and profound myelosuppression. Such levels of bone marrow toxicity, particularly in a patient population that not infrequently suffers from chronic human immunodeficiency virus (HIV) infection and possibly acquired immune deficiency syndrome (AIDS), may increase mortality from opportunistic infections. While majority of AC patients do not harbor HIV, any myelotoxic agents have the potential to attenuate the tumoricidal response emanating from the innate and adaptive immune system, which can subsequently lead to worse tumor control. Minimizing the amount of pelvic bone marrow exposed to RT has the potential to preserve the immune response both in immunocompetent and immunocompromised patients. Lastly, late toxicity including small intestinal obstructions, fistulas, ulcerations, radiation proctitis, and hip fractures, although do not directly contribute to mortality, could theoretically limit patients' ability to receive salvage treatments (including surgery, systemic therapy and re-irradiation) and in turn lead to inferior long-term survival outcomes. A potential confounder for the observation of improved survival in the IMRT group is that since patients in the IMRT group were more likely to be treated in the recent era [2010–2013], they were more likely to be staged with positron emission tomography (PET) and hence our results could be biased by stage migration. However, approximately 85–90% of AC patients present with non-metastatic disease (26) and a CT chest/abdomen/pelvis provides similar sensitivity for detecting hepatic and pulmonary metastases. Furthermore, for the non-metastatic cases, implementation of statistical tools such as PS matching, minimized the underlying patient demographic, tumor related, and treatment level heterogeneities between the two cohorts.

There are a few pertinent limitations of our analysis. Toxicity information (GI, skin, hematologic, etc.), chemotherapy agents used (mitomycin versus cisplatin), and HIV status were unavailable in the NCDB and hence could not be evaluated. Next, NCDB does not include progression free survival (PFS) or colostomy free survival (CFS) data and hence we could not compare the PFS/CFS of our patients against prior published randomized clinical trials. Majority of patients were missing the status of lymphovascular space invasion (87.2%).

Conclusions

To the best of our knowledge, this is the largest study to date that evaluates the impact of IMRT on OS in patients AC. Our investigation shows that IMRT based concurrent CRT for non-metastatic AC is associated with improved survival when compared to similar patients treated with non-IMRT based therapy. The survival benefit for IMRT persisted despite the implementation of statistical methods to minimize selection bias. Furthermore, we observed that only 61% of patients diagnosed with AC in the United States in 2013 received IMRT—likely due to lack of prospective, randomized data supporting its use. In the absence of randomized evidence, our analysis might provide additional support for increasing the use of IMRT for patients with new diagnosis AC managed with concurrent CRT.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical statement: Since this research study utilized the National Cancer Database (NCDB) which is a multi-institutional, de-identified cancer registry, informed consent or a review board approval is not necessary or applicable.

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630

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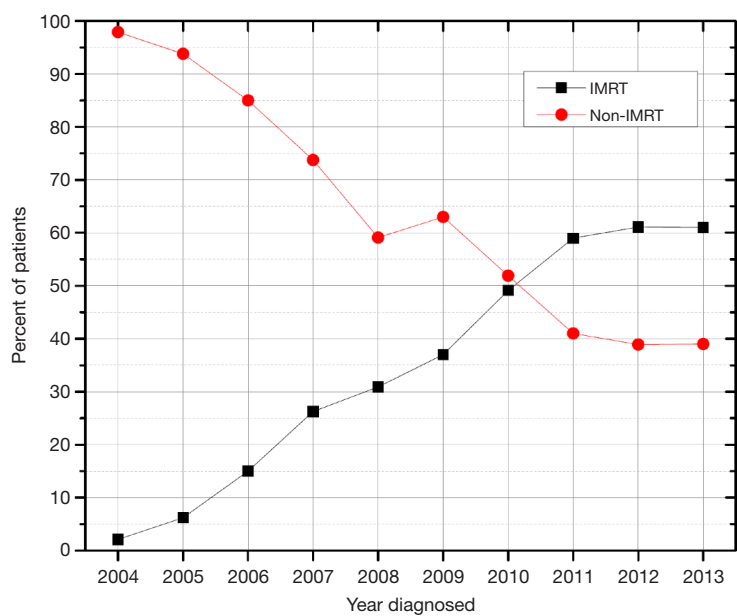
Year diagnosed	IMRT N (%)	Non-IMRT N (%)	P value
2004	11 (2.1%)	511 (97.9%)	<0.0001
2005	31 (6.2%)	469 (93.8%)	<0.0001
2006	82 (15%)	464 (85%)	<0.0001
2007	178 (26.25%)	500 (73.75%)	<0.0001
2008	233 (30.9%)	521 (59.1%)	<0.0001
2009	322 (37%)	549 (63%)	0.015
2010	434 (48.1%)	469 (51.9%)	<0.0001
2011	588 (59%)	408 (41%)	<0.0001
2012	674 (61.1%)	429 (38.9%)	<0.0001
2013	754 (61%)	481 (39%)	<0.0001

Figure S1 Nationwide IMRT usage trend. IMRT, intensity modulated radiation therapy.