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Utilization of Neoadjuvant Intensity-modulated Radiation Therapy for Rectal Cancer in the United States

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Abstract. *Background/Aim: Advances in technology have expanded the use of intensity-modulated radiotherapy (IMRT). The goal of this study was to investigate trends in the utilization of IMRT for rectal cancer (RC) in USA. Materials and Methods: The National Cancer Database was queried for RC patients receiving neoadjuvant chemoradiotherapy with either IMRT or three-dimensional conformal radiation therapy (3DCRT). Differences in factors associated with receipt of 3DCRT versus IMRT were determined and temporal trends were analyzed. Results: From 2005 to 2009, IMRT utilization increased, but remained constant and roughly equivalent to 3DCRT from 2010 to 2014. Patients who received IMRT were more likely to have T4 disease (p=0.014), while patients diagnosed in 2004-2006 (p<0.0001) and 2007-2008 (p=0.015) were less likely to receive IMRT. There were no significant differences in postoperative outcomes between patients receiving 3DCRT and IMRT. Conclusion: IMRT utilization initially increased, but is now used at similar frequencies to 3DCRT and offers similar short-term postoperative outcomes.*

The current standard-of-care for locally advanced rectal cancer (RC) is neoadjuvant chemoradiotherapy (CRT) followed by surgery, with or without adjuvant chemotherapy (CT) (1). Although optimal timing of chemotherapy is still controversial, neoadjuvant radiotherapy (RT) is preferred over adjuvant RT (2, 3).

Gastrointestinal and genitourinary toxicities may occur as a result of RT use, with ample data describing this in the context of three-dimensional conformal radiation therapy (3DCRT) (2-4). However, advancements in modern technology have led to the emergence of intensity-modulated radiation therapy (IMRT), which offers more conformal treatment and may result in fewer toxicities (5-8). Comparative retrospective data have shown significantly decreased toxicities with IMRT (7, 9). Furthermore, multiple prospective non-randomized trials using IMRT for RC have reported encouraging survival and toxicity outcomes (10-12).

Despite this positive evidence, the use of IMRT remains controversial. Consensus American Society for Radiation Oncology (ASTRO) guidelines recommend that IMRT "May Be Appropriate" in the neoadjuvant and adjuvant settings for RC (13). Given the controversy regarding its role in treatment of RC, national patterns of utilization of IMRT are unclear. Thus, the goal of this study was to evaluate the utilization of neoadjuvant IMRT for RC in the United States.

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Key Words: Rectal cancer, radiation therapy, intensity modulated radiotherapy.

Materials and Methods

This retrospective study analyzed the National Cancer Data Base (NCDB), which is a jointly sponsored database by the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. Data includes de-identified information regarding first-course treatments and outcomes from approximately 70% of all malignant cancers diagnosed at CoC-accredited facilities within the United States. All patient data in the NCDB are de-identified and therefore were exempt from review by an institutional review board.

The NCDB dataset used for analysis corresponded to the years 2004-2015. Inclusion criteria for this study were patients ≥18 years with T1-T4 N0-3 M0 RC with histologically confirmed adenocarcinoma (International Classification of Disease for Oncology [ICD-O-3] histologic codes: 8140, 8211, 8213, 8240, 8244, 8261, 8263, 8480, 8510, and 8560) treated with neoadjuvant radiation therapy followed by surgery. As we intended to compare use of neoadjuvant IMRT *versus* 3DCRT, patients without a documented RT technique were excluded. Demographic, clinico-pathologic, and treatment facility characteristics were collected for each patient. The overall cohort was divided into two study cohorts: 1) those who received 3DCRT prior to surgery, and 2) those who received IMRT prior to surgery.

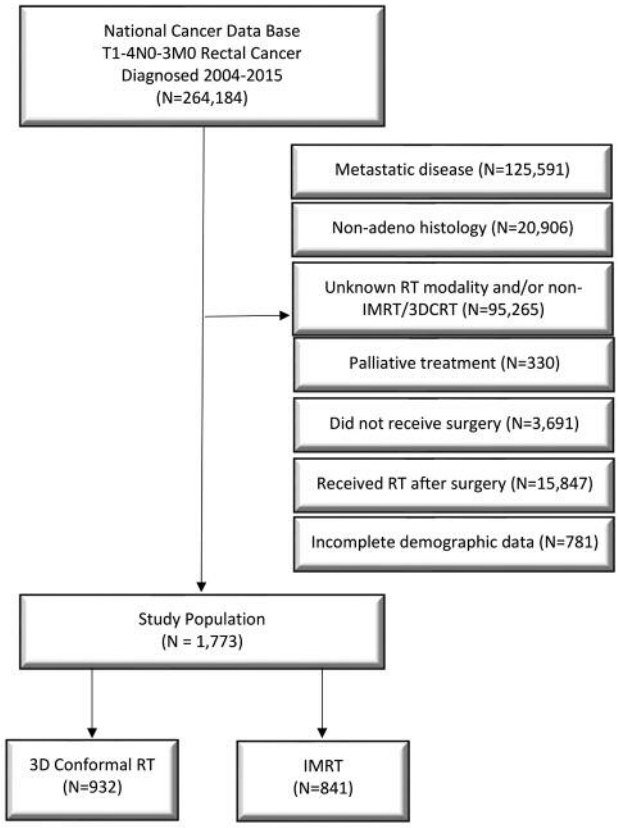

Figure 1. *Patient selection diagram.*

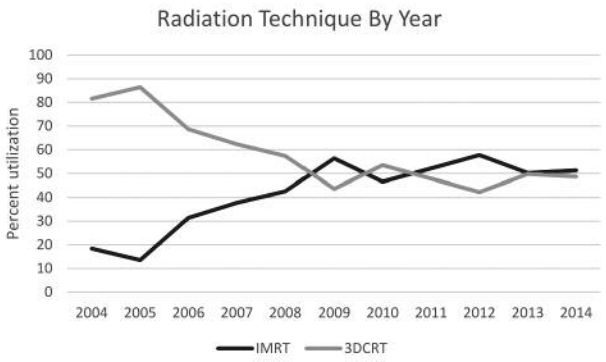

Figure 2. *Temporal trends in IMRT and 3DCRT utilization.*

The primary goal was to evaluate temporal trends and predictors of IMRT use.

Baseline characteristics were compared between IMRT and 3DCRT cohorts 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 receipt. Thirty-day readmission and 30-day/90-day post-operative mortality rates were compared using Fisher's exact test, and length of post-operative hospital stay was compared with the Mann-Whitney *U*-test. All statistical tests were two-sided, with a threshold of $p<0.05$ for statistical significance and were performed using IBM SPSS Statistics (version 24).

Results

A total of 1,773 patients were identified per study inclusion criteria (Figure 1). Use of 3DCRT and IMRT were 81% and 19%, respectively, in 2004. There was an increase in IMRT use from 2005-2009 from 12% to 58% along with a corresponding decrease in 3DCRT from 88% to 42% (Figure 2). From 2010-2014, both RT techniques were utilized at similar rates.

Table I displays baseline characteristics of the study cohorts. On multivariable analysis, patients treated with 3DCRT *versus* IMRT were less likely to have T4 disease relative to T1 disease (Odds ratio (OR), 0.53; 95% confidence interval (CI), 0.32-0.88; $p=0.014$) and receive treatment in the West South-Central USA (Texas, Oklahoma, Arkansas, and Louisiana) relative to New England (OR=0.33; 95%CI=0.19-0.63; $p=0.001$). Patients were more likely to receive 3DCRT compared to IMRT if diagnosed in 2004-2006 (OR=3.40; 95%CI=2.27-5.08; $p<0.001$) or 2007-2008 (OR=1.46; 95%CI=1.08-1.99; $p=0.015$). Of note, there were no differences between groups with regard to socioeconomic or insurance-related parameters ($p>0.05$ for all).

Because the NCDB records post-operative 30-day readmission, 30-day mortality, 90-day mortality, and length of hospital stay, these data were compared between the IMRT and 3DCRT cohorts. Comparing 3DCRT to IMRT, there were no significant differences in median post-operative days to discharge (5 days for both, $p=0.136$), 30-day readmission rate (8% for both, $p=0.76$), or 30/90-day mortality rate (1% for all, $p=0.928$ and 0.839, respectively).

Discussion

The use of pre-operative 3DCRT remains the standard-of-care for treatment of non-metastatic RC, owing to the vast majority of available prospective trials having utilized this technique. However, modern series have utilized IMRT and have noted favorable toxicity data as compared to those of historical 3DCRT studies. In this investigation, we observed a dramatic increase in the use of IMRT from the 2004-2009, with roughly equal use of IMRT and 3DCRT thereafter. Along with regional differences, patients with T4 disease were more likely to receive IMRT. Readmission rates, mortality, and length of post-operative hospital stay were comparable between study cohorts.

The increased likelihood of receiving IMRT in patients with T4 disease may be explained by the need to treat the external iliac lymph nodes given the advanced extent of

Table I. *Characteristics of the patients within each treatment group and multivariable logistic regression analysis evaluating predictors of receiving 3DCRT.*

Parameter	IMRT (N=841)	3DCRT (N=932)	Multivariable	
			OR (95%CI)	*p*-Value
Age (years)				
Median (range)	64 (40-90)	62 (40-90)	1.01 (0.99-1.02)	0.426
Gender				
Male	507 (60%)	553 (59%)	REF	REF
Female	334 (40%)	379 (41%)	0.99 (0.81-1.21)	0.934
Race				
White	736 (88%)	825 (88%)	REF	REF
Black	70 (8%)	74 (8%)	1.11 (0.76-1.61)	0.606
Other	35 (4%)	33 (4%)	0.89 (0.53-1.49)	0.650
T stage				
T1	215 (26%)	264 (28%)	REF	REF
T2	244 (29%)	269 (29%)	0.90 (0.69-1.17)	0.411
T3	330 (39%)	367 (39%)	0.88 (0.68-1.13)	0.306
T4	52 (6%)	32 (4%)	0.53 (0.32-0.88)	**0.014**
N stage				
N0	609 (72%)	680 (73%)	REF	REF
N+	232 (28%)	252 (27%)	0.96 (0.76-1.21)	0.727
Charlson Deyo score				
0	630 (75%)	708 (76%)	REF	REF
1	160 (19%)	175 (19%)	1.05 (0.81-1.35)	0.725
≥2	51 (6%)	49 (5%)	0.97 (0.63-1.49)	0.873
Insurance type				
Uninsured	20 (2%)	36 (4%)	0.92 (0.67-1.25)	0.577
Private	360 (43%)	471 (51%)	0.91 (0.66-1.25)	0.555
Medicaid/other government	75 (9%)	47 (5%)	1.07 (0.77-1.49)	0.673
Medicare	386 (46%)	378 (40%)	REF	REF
Income (US dollars/year)				
<$30,000	146 (17%)	157 (17%)	REF	REF
$30,000-$34,999	226 (27%)	234 (25%)	0.92 (0.68-1.27)	0.622
$35,000-$45,999	238 (28%)	253 (27%)	0.90 (0.65-1.24)	0.518
≥$46,000	231 (28%)	288 (31%)	1.04 (0.75-1.45)	0.807
Patient residence				
Metro	701 (83%)	757 (81%)	REF	REF
Rural	123 (15%)	148 (16%)	1.05 (0.77-1.41)	0.775
Urban	17 (2%)	27 (3%)	1.31 (0.67-2.56)	0.437
Facility location				
New England	36 (4.3%)	48 (5%)	REF	REF
Middle Atlantic	143 (17%)	114 (12%)	0.62 (0.37-1.04)	0.071
South Atlantic	191 (23%)	184 (20%)	0.77 (0.46-1.27)	0.297
East North Central	138 (16%)	251 (27%)	1.45 (0.88-2.40)	0.143
East South Central	40 (5%)	62 (7%)	1.26 (0.68-2.34)	0.465
West North Central	88 (11%)	100 (11%)	0.87 (0.50-1.49)	0.603
West South Central	63 (8%)	26 (3%)	0.33 (0.17-0.63)	**0.001**
Mountain	49 (6%)	49 (5%)	0.84 (0.46-1.55)	0.579
Pacific	93 (11%)	98 (10%)	0.89 (0.52-1.53)	0.699
Facility type				
Academic	231 (28%)	243 (26%)	REF	REF
Community	610 (62%)	689 (64%)	0.99 (0.78-1.24)	0.908
Distance to treating facility (mi)				
Median (IQR)	9.4 (4.0-23.4)	9.8 (4.4-21.8)	1.00 (0.99-1.00)	0.623
Year of Diagnosis				
2004-2006	42 (5%)	141 (15%)	3.40 (2.27-5.08)	**<0.001**
2007-2008	118 (14%)	172 (18%)	1.46 (1.08-1.99)	**0.015**
2009-2010	214 (25%)	201 (22%)	0.97 (0.74-1.28)	0.829
2011-2012	234 (28%)	192 (21%)	0.89 (0.67-1.16)	0.381
2013-2014	233 (28%)	226 (24%)	REF	REF

Statistically significant *p*-Values (<0.05) are in bold. OR: Odds ratio; CI: confidence interval.

disease. Compared to 3DCRT, IMRT is able to better spare organs at risk from high dose radiation in the treatment of inguinal lymph nodes (14) and may therefore result in lower rates of bowel toxicity (7, 9). Also, as T4 RC may involve invasion of important organs such as the left kidney, prostate, colon, and cervix, IMRT may be used in efforts to spare uninvolved portions of these organs.

The temporal increase in IMRT utilization from 2005-2009, was likely due to adoption and implementation of the new technology around that time. The stabilization of IMRT usage starting after 2009 may be attributable to several obstacles, including lack of long term data, insurance reimbursement issues (although, notably, patient insurance coverage was not an independent predictor of RT technique), and increased interest in other technologies. Despite a lack of statistical significance, insurance reimbursement may have been different by region, which would also offer an explanation for regional differences in treatment. Because we analyzed groups as a whole, we were unable to rule out regionally-related insurance coverage.

In a single institution retrospective analysis comparing post-operative outcomes in RC patients who received IMRT *versus* 3DCRT, significantly fewer hospitalizations in the IMRT group were reported (15). A lack of a similar finding in our study may be partially attributable to dissimilar patient populations. The aforementioned publication excluded patients with T1 disease, while our cohort consisted of nearly 30% of patients with T1 disease; more of their patients had preoperative N+ stage and metastatic disease. Although not reported, it is possible that their cohort had a higher proportion of distal rectal tumors, which may have necessitated treatment of the inguinal lymph nodes, and thus could have increased the incidence of Gastrointestinal (GI) and Genitourinary (GU) toxicities. The NCDB does not record tumor location or toxicity endpoints, so this evaluation cannot be conclusively made in our study.

Randomized, prospective evidence is warranted to provide a definitive answer as to whether neoadjuvant IMRT is superior to 3DCRT in RC. However, phase III data assessing a similar issue in gynecologic cancers shows that IMRT was superior to 3DCRT in terms of acute GI and GU toxicity and quality of life measures (16). The study used radiation doses of 45-50.4 Gy, which is approximately equal to doses used for RC cases. Taken as a whole, it is plausible that patients with RC would experience comparable results.

Although the NCDB is a valuable resource with which to study this important clinical question, there are inherent limitations to this study. First, NCDB investigations are, by definition, retrospective and are therefore vulnerable to selection bias. Although the NCDB captures an estimated 70% of the cancer patient population in USA, only CoC-accredited institutions are able to contribute data. As a result, the data may be missing important subpopulations within USA. A large proportion of this dataset did not have proper coding of RT technique (*e.g.* missing values), which is another important shortcoming that may have biased results. Lastly, the NCDB does not collect data on several key RT variables, including radiation field design/volumes, which chemotherapeutic regimens were used, or patient-reported toxicities/quality of life measures. Hence, although the postoperative parameters given by the NCDB were similar between groups, the lack of other endpoints limits firm conclusions.

Conclusion

In this retrospective, observation study using the NCDB, a dramatic increase is demonstrated in the use of IMRT from the mid- through late 2000s, with a roughly equal use of IMRT and 3DCRT thereafter. Regional differences and T4 disease were associated with an increased likelihood of receipt of IMRT. There were no differences in readmission rates, mortality, and length of post-operative hospital stay between patients who received 3DCRT or IMRT. These results suggest that IMRT is a safe and comparable alternative to 3DCRT. Prospective data are needed to further assess long-term outcomes.

Conflicts of Interest

This study has never been presented/published before in any form. All Authors declare that conflicts of interest do not exist.

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