Trends in intensity modulated radiation therapy use for locally advanced rectal cancer at National Comprehensive Cancer Network centers

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Abstract

Purpose: Intensity modulated radiation therapy (IMRT) has been rapidly incorporated into clinical practice because of its technological advantages over 3-dimensional conformal radiation therapy (CRT). We characterized trends in IMRT utilization in trimodality treatment of locally advanced rectal cancer at National Comprehensive Cancer Network cancer centers between 2005 and 2011.

Methods and materials: Using the prospective National Comprehensive Cancer Network Colorectal Cancer Database, we determined treatment patterns for 976 patients with stage II-III rectal cancer who received pelvic radiation therapy at contributing centers between 2005 and 2011. Multivariable logistic regression was used to identify factors associated with IMRT versus 3-dimensional CRT. Radiation therapy compliance and time to completion were used to compare acute toxicity.

Sources of support: This work had no specific funding.
Conflicts of interest: The authors have no conflicts of interest to disclose.

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https://doi.org/10.1016/j.adro.2017.10.001
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Results: A total of 947 patients (97%) received 3-dimensional CRT (80%) or IMRT (17%). Ninety-eight percent of these patients received radiation therapy preoperatively, and 81% underwent definitive resection. IMRT use increased from <13% pre-2009 to >30% in 2010 and thereafter, with significant variability among institutions (range, 0%-43%). Other factors associated with IMRT use included age ≥65 years, dose >50.4 Gy, African-American race, and no transabdominal surgery. Rates of and time to radiation therapy completion were similar between the groups.

Conclusions: Although most patients with stage II–III rectal cancer at queried National Cancer Institute–designated cancer centers between 2005 and 2011 received 3-dimensional CRT, significant and increasing numbers received IMRT. IMRT utilization is highly variable among institutions and not uniform among sociodemographic groups but may be more consistently embraced in specific clinical settings. Given this trend, comparative-effectiveness research is needed to evaluate the benefits of IMRT for rectal cancer.

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Introduction

On the basis of randomized evidence, neoadjuvant chemoradiation therapy followed by surgery is the preferred treatment approach for locally advanced rectal cancer and is endorsed by the National Comprehensive Cancer Network (NCCN).

This therapy is commonly delivered with 3-dimensional conformal radiation therapy (CRT), but novel technologies such as intensity modulated radiation therapy (IMRT) present an attractive alternative. IMRT improves multiple dosimetric parameters that correlate with toxicity and offers an opportunity for dose escalation, which may improve rates of pathologic complete response and outcomes.

Over the past decade, IMRT has become a widely accepted alternative to 3-dimensional CRT for many cancers, including anal carcinoma. Although prospective clinical data on its efficacy for rectal cancer are limited, other considerations may be driving its adoption. The extent of current IMRT use for rectal cancer and factors that may promote it are unknown. Using the NCCN Colorectal Cancer Outcomes Database, we evaluated trends in its use at dedicated cancer centers between 2005 and 2011 and analyzed the patient factors associated with its use. We also sought to evaluate acute toxicity associated with IMRT versus 3-dimensional CRT using surrogate measures in the NCCN database.

Methods and materials

Data source

Data were acquired from the NCCN Colorectal Cancer Outcomes Project, a prospective database of abstracted medical records from 8 participating NCCN institutions, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH; Memorial Sloan-Kettering Cancer Center, New York, NY; The University of Texas M.D. Anderson Cancer Center, Houston, TX; Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Roswell Park Cancer Institute, Buffalo, NY; City of Hope Comprehensive Cancer Center, Duarte, CA; and the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL. These 8 institutions were selected for participation in the colorectal database project on the basis of participation in prior database collection efforts. The selected institutions include the 2 largest specialty cancer centers in the United States, encompass geographic diversity, and resemble the composition of patients seen at all 21 NCCN institutions.

Rigorous data quality assurance processes are maintained for the NCCN Outcomes Database Project, including initial and follow-up data management training for study personnel, online edit checks during Web-based data entry, programmed logic checks against the pooled data repository, routine quality assurance reports to each institution for rectification by data managers, and onsite audits of a random sample of source documents against the submitted data within the first few months of data collection (repeated annually). Each NCCN institution was audited for data completeness and quality at least twice during the study period. Data-collection processes, data-transmission methods, and data-storage protocols were approved by the institutions’ institutional review boards.

Data were abstracted by NCCN-trained research assistants as previously described. Comorbidity was assigned using the Charlson Comorbidity Index, based on chart review. The zip codes of patients’ residences were used to derive median household income by linking the codes to the 2000 census data.

Cohort definition

We identified all registered patients in the database with clinical stage II–III rectal cancer who underwent pelvic radiation therapy (RT) at the participating institutions between September 1, 2005 and May 31, 2011 and were alive with follow-up of at least 120 days from diagnosis (n = 1461). We excluded patients with rectosigmoid junction or synchronous colon and rectal tumors (n = 485) and patients who...
received intraoperative radiation (n = 6), brachytherapy (n = 2), proton therapy (n = 2), or incompletely categorized techniques (n = 1).

**Evaluation of predictors of treatment-planning method**

The demographic characteristics analyzed included age at diagnosis, sex, racial/ethnic background, insurance (private, Medicare, Medicaid), household income, NCCN institution, distance to the nearest RT facility, and year of diagnosis. Age was analyzed by decade. Median household income and distance to the nearest RT facility were divided into quartiles. The clinical patient characteristics analyzed included body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, Charlson Comorbidity Index score, history of inflammatory bowel disease, and history of pelvic RT for prior cancer. Tumor characteristics included clinical TNM stage, preoperative tumor fixation, and tumor distance from the anal verge. For patients whose operative report noted the distance from the dentate line, 2 cm were added to the measurement.

**Indirect measures of toxicity**

In the absence of more detailed data on side effects, we used completion of RT within 6 weeks and receipt of at least 45 Gy, a minimum acceptable dose of conventionally fractionated RT, as surrogate measures of toxicity.

**Statistical analysis**

The association between IMRT use and patient characteristics was characterized using descriptive statistics. A simple χ² test for association compared proportions between 3-dimensional CRT and IMRT. The association between IMRT use and each variable was assessed independently in a univariate logistic regression model. Parameters found to be potentially associated with no preoperative RT on the basis of a P value ≤.20 were included in the initial multivariable model.

The final multivariable model included those predictors with 2-sided P <.05. Point estimates of the final multivariable model were reported as odds ratios (ORs) and 95% confidence intervals with the 2-sided P value for each OR. Fisher’s exact test was used to compare rates of inadequate dose receipt (<4500 cGy) or duration of RT >6 weeks between patients treated with IMRT versus 3-dimensional CRT. All statistical analyses were conducted using SAS software (SAS Institute, Cary, NC).

**Results**

Among 965 patients with stage II–III rectal cancer who were diagnosed between September 1, 2005 and May 31, 2011 and treated with external beam RT at a participating NCCN institution, 778 patients (80%) were treated with 3-dimensional CRT, 169 (17%) with IMRT, 16 (2%) with 2-dimensional CRT, and 2 (<1%) with a combination of techniques.

To accurately evaluate the trends and factors associated with IMRT, we compared IMRT to the predominant RT technique, 3-dimensional CRT. Among 947 3D-CRT or IMRT patients, the median age was 57 years; 116 patients (10%) were ≥75 years of age (Table 1). The majority was Caucasian (83%), male (58%), with an ECOG performance status of 0 (82%), no comorbidities (74%), and stage III rectal cancer (71%). Seven patients had a history of inflammatory bowel disease and 5 of connective tissue disease.

In this cohort, radiation was delivered preoperatively in 849 patients (98%), and 865 patients (91%) underwent definitive transabdominal resection. The median RT dose was 5040 cGy (range, 1080-7640 cGy), with no significant difference in median doses for 3-dimensional CRT versus IMRT. Chemotherapy was administered to 99% of patients receiving neoadjuvant RT and 85% receiving adjuvant RT.

As expected, IMRT use increased substantially over time, from under 13% in 2005 to 2008 to 23% in 2009, 32% in 2010, and 38% in 2011 (Fig 1). Interestingly, significant variability was noted among different NCCN centers, ranging from 0% to 43% of all patients with stage II–III rectal cancer who were receiving pelvic RT (Fig 2). There was no correlation between center volume and rate of IMRT use. The 2 highest-volume centers, responsible for 320 and 294 of 947 eligible patients, used IMRT in 26% and 7% of their respective treatments, respectively, but even greater variability was noted for centers registering 40 to 70 patients each.

Demographic and clinical characteristics that were significantly associated with the use of IMRT over 3-dimensional CRT after controlling for year of diagnosis are presented in Table 2. Center effect could not be included in the final multivariable model due to the 0% IMRT use at 1 center. However, a multivariable analysis on a limited cohort excluding this center showed the same results (data not shown).

Intriguingly, after year of diagnosis, the strongest predictors for IMRT use were treatment parameters, including dose >50.4 Gy (adjusted OR [aOR], 3.12, P = .0002) and no transabdominal surgery (aOR: 1.96: P = .03). The patient characteristics that were significantly associated with IMRT in the multivariable model included age and African-American race. The extremes of age, including age at diagnosis of 65 to 74 years and ≥75 years or <45 years, were associated with a higher likelihood of receiving IMRT.
Table 1  Characteristics of patients with stage II-III rectal cancer treated with pelvic radiation therapy between 2005 and 2011 at National Comprehensive Cancer Network centers by radiation therapy modality

| Variable                        | Category | All (n = 947) | 3D-CRT (n = 778) | IMRT (n = 169) |
|---------------------------------|----------|--------------|------------------|---------------|
| Median age at diagnosis (range) |          | 57 (19-93)   | 57 (19-91)       | 58 (22-93)    |
| Age at diagnosis (y)            | <45      | 157 (17%)    | 120 (15%)        | 37 (22%)      |
|                                 | 45-54    | 258 (27%)    | 220 (28%)        | 38 (22%)      |
|                                 | 55-64    | 257 (27%)    | 224 (29%)        | 33 (20%)      |
|                                 | 65-74    | 183 (19%)    | 144 (19%)        | 39 (23%)      |
|                                 | 75+      | 92 (10%)     | 70 (9%)          | 22 (13%)      |
| N (column %)                    |          |              |                  |               |
| Sex                             | Male     | 549 (58%)    | 462 (59%)        | 87 (51%)      |
|                                 | Female   | 398 (42%)    | 316 (41%)        | 82 (49%)      |
| Race                            | Caucasian| 783 (83%)    | 652 (84%)        | 131 (78%)     |
|                                 | African-American | 80 (8%) | 56 (7%) | 24 (14%) |
|                                 | Asian, Pacific Islander | 60 (6%) | 53 (7%) | 7 (4%) |
|                                 | Other    | 24 (3%)      | 17 (2%)          | 7 (4%)        |
| Insurance                       | Private  | 585 (62%)    | 496 (64%)        | 89 (53%)      |
|                                 | Medicare | 258 (27%)    | 199 (26%)        | 59 (35%)      |
|                                 | Medicaid | 66 (7%)      | 53 (7%)          | 13 (8%)       |
|                                 | Other    | 38 (4%)      | 30 (4%)          | 8 (5%)        |
| Center                          |          |              |                  |               |
|                                 | 8        | 40 (4%)      | 38 (5%)          | 2 (1%)        |
|                                 | 1        | 65 (7%)      | 59 (8%)          | 6 (4%)        |
|                                 | 2        | 53 (6%)      | 37 (5%)          | 16 (9%)       |
|                                 | 7        | 294 (31%)    | 274 (35%)        | 20 (12%)      |
|                                 | 4        | 56 (6%)      | 56 (7%)          | 0 (0%)        |
|                                 | 6        | 49 (5%)      | 28 (4%)          | 21 (12%)      |
|                                 | 3        | 320 (34%)    | 237 (30%)        | 83 (49%)      |
|                                 | 5        | 70 (7%)      | 49 (6%)          | 21 (12%)      |
| Diagnosis year                  |          |              |                  |               |
|                                 | 2005     | 56 (6%)      | 50 (6%)          | 6 (4%)        |
|                                 | 2006     | 153 (16%)    | 146 (19%)        | 7 (4%)        |
|                                 | 2007     | 178 (19%)    | 166 (21%)        | 12 (7%)       |
|                                 | 2008     | 145 (15%)    | 124 (16%)        | 21 (12%)      |
|                                 | 2009     | 179 (19%)    | 134 (17%)        | 45 (27%)      |
|                                 | 2010     | 182 (19%)    | 121 (16%)        | 61 (36%)      |
|                                 | 2011     | 54 (6%)      | 37 (5%)          | 17 (10%)      |
| Body mass index                 | <25      | 294 (31%)    | 235 (30%)        | 59 (35%)      |
|                                 | 25-30    | 360 (38%)    | 297 (38%)        | 63 (37%)      |
|                                 | ≥30      | 269 (28%)    | 231 (27%)        | 38 (22%)      |
|                                 | Unknown  | 24 (3%)      | 15 (2%)          | 9 (5%)        |
| ECOG performance status         | 0        | 775 (82%)    | 646 (83%)        | 129 (76%)     |
|                                 | 1        | 94 (10%)     | 70 (9%)          | 24 (14%)      |
|                                 | 2+       | 26 (3%)      | 22 (3%)          | 4 (2%)        |
|                                 | Unknown  | 52 (5%)      | 40 (5%)          | 12 (7%)       |
| Charlson Comorbidity Index      | 0        | 698 (74%)    | 564 (72%)        | 134 (79%)     |
| Score                           | 1        | 165 (17%)    | 146 (19%)        | 19 (11%)      |
|                                 | 2+       | 84 (9%)      | 68 (9%)          | 16 (9%)       |
| Clinical TNM stage              | II       | 272 (29%)    | 221 (28%)        | 51 (30%)      |
|                                 | III      | 675 (71%)    | 557 (72%)        | 118 (70%)     |
| Preoperative tumor              | No       | 709 (75%)    | 574 (74%)        | 135 (80%)     |
|                                | Yes      | 109 (12%)    | 91 (12%)         | 18 (11%)      |
| Fixation                        | Unknown  | 129 (14%)    | 113 (15%)        | 16 (9%)       |
| Tumor distance                  | <5 cm    | 356 (38%)    | 286 (37%)        | 70 (41%)      |
| From anal verge                 | 5-10 cm  | 289 (31%)    | 242 (31%)        | 47 (28%)      |
|                                | >10 cm   | 267 (28%)    | 223 (29%)        | 44 (26%)      |
| History of connective tissue disease | No    | 942 (99%)    | 774 (99%)        | 168 (99%)     |
|                                | Yes      | 5 (1%)       | 4 (1%)           | 1 (1%)        |
| History of inflammatory bowel disease | No    | 940 (99%)    | 773 (99%)        | 167 (99%)     |
|                                | Yes      | 7 (1%)       | 5 (1%)           | 2 (1%)        |
| Transabdominal                  | No       | 82 (9%)      | 56 (7%)          | 26 (15%)      |
| Surgery                        | Yes      | 865 (91%)    | 722 (93%)        | 143 (85%)     |
| Radiation therapy dose          | ≤5040 cGy | 874 (92%)    | 733 (94%)        | 141 (83%)     |

3D-CRT, 3-dimensional conformal radiation therapy; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity modulated radiation therapy.
(aOR: 1.94, 1.95, and 1.71 respectively; \( P = .03 \)). African-American patients were more likely than Caucasian patients to receive IMRT (aOR: 1.91; \( P = .04 \)). There was no association between IMRT and sex, stage, BMI, ECOG performance status, comorbidity burden, tumor fixation, tumor distance from anal verge, presence of connective tissue disease, or history of inflammatory bowel disease.

Toxicity associated with treatment was assessed indirectly using treatment duration and total dose as surrogates. Overall, 93 patients (9.8%) required >6 weeks to complete RT, and 21 patients (2.2%) received <45 Gy. There were no significant differences between IMRT and 3-dimensional CRT in these parameters (8.9% vs 10% and 3.6 vs 1.9%, respectively).

**Discussion**

Dramatic increases in IMRT use have been noted for several malignancies over the past decade, often preceding mature clinical evidence of its benefits over other techniques.\(^\text{15-17}\) In keeping with this trend, we show the rapid adoption of IMRT for locally advanced rectal cancer at 8 NCCN institutions that were designated to be a part of the outcomes project. Interestingly, although an increase in use of IMRT was also noted in a study that examined this trend using the NCDB database over a similar time period (2004-2013), our findings show several important differences that complement existing literature.\(^\text{18}\) Although Coffman et al noted that IMRT use in the sampled cohort increased to represent the majority of all rectal RT between 2010 and 2013, IMRT use in our cohort continued to represent a minority of all rectal treatments. Furthermore, the NCDB data suggest that academic/research centers are more likely than all other hospitals to use IMRT for neoadjuvant therapy, but our data show that in a sampling of National Cancer Institute–designated cancer centers, IMRT use is significantly below that reported in the population-based NCDB study. The discrepancy may be due to the limited number of centers included in our study compared with the NCDB; however,
### Table 2  Variables associated with IMRT use versus 3-dimensional conformal radiation therapy on multivariate analysis

| Variable                          | Category                  | Patients with IMRT N/N total (row %) | Unadjusted Odds Ratio<sup>a</sup> (95% CI) | P Value<sup>a</sup> | Adjusted Odds Ratio<sup>b</sup> (95% CI) | P Value<sup>b</sup> |
|-----------------------------------|---------------------------|--------------------------------------|------------------------------------------|---------------------|------------------------------------------|---------------------|
| Age at diagnosis (y)              | <45                       | 37/157 (24%)                         | 2.09 (1.25-3.52)                         | .01                 | 1.71 (0.97-3.02)                         | .03                 |
|                                  | 45-54                     | 38/258 (15%)                         | 1.17 (0.71-1.94)                         | .09                 | 0.98 (0.57-1.69)                         |                     |
|                                  | 55-64                     | 33/257 (13%)                         | Referent                                 | Referent            | Referent                                 | Referent            |
|                                  | 65-74                     | 39/183 (21%)                         | 1.84 (1.11-3.06)                         | .04                 | 1.94 (1.12-3.37)                         |                     |
|                                  | 75+                       | 22/92 (24%)                          | 2.13 (1.17-3.90)                         | .05                 | 1.95 (0.98-3.85)                         |                     |
| Sex                              | Male                      | 87/549 (16%)                         | Referent                                 | Referent            | Referent                                 | Referent            |
|                                  | Female                    | 82/398 (21%)                         | 1.38 (0.99-1.92)                         | .06                 | 1.16 (0.79-1.70)                         | .44                 |
| Race                             | Caucasian                 | 131/783 (17%)                        | Referent                                 | Referent            | Referent                                 | Referent            |
|                                  | African American          | 24/80 (30%)                          | 2.13 (1.28-3.57)                         | .98                 | 1.91 (1.06-3.44)                         | .04                 |
|                                  | Asian, Pacific Islander   | 7/60 (12%)                           | 0.66 (0.29-1.48)                         |                     | 0.62 (0.26-1.46)                         |                     |
|                                  | Other                     | 7/24 (29%)                           | 2.05 (0.83-5.04)                         |                     | 2.18 (0.75-6.34)                         |                     |
| Insurance                        | Private                   | 89/585 (15%)                         | Referent                                 | Referent            | Referent                                 | Referent            |
|                                  | Medicare                  | 59/258 (23%)                         | 1.65 (1.14-2.39)                         | .62                 | 1.61 (0.78-3.35)                         |                     |
|                                  | Medicaid                  | 13/66 (20%)                          | 1.37 (0.72-2.61)                         |                     | 0.91 (0.44-1.90)                         |                     |
|                                  | Other                     | 8/38 (21%)                           | 1.49 (0.66-3.35)                         |                     | 1.39 (0.56-3.43)                         |                     |
| Diagnosis year                   | 2005                      | 6/56 (11%)                           | Referent                                 | Referent            | Referent                                 | Referent            |
|                                  | 2006                      | 7/153 (5%)                           | 0.40 (0.13-1.25)                         | .44                 | 0.44 (0.14-1.43)                         |                     |
|                                  | 2007                      | 12/178 (7%)                          | 0.60 (0.22-1.69)                         | .79                 | 0.79 (0.27-2.31)                         |                     |
|                                  | 2008                      | 21/145 (14%)                         | 1.41 (0.54-3.70)                         |                     | 1.80 (0.66-4.96)                         |                     |
|                                  | 2009                      | 45/179 (25%)                         | 2.80 (1.13-6.96)                         |                     | 3.64 (1.39-9.53)                         |                     |
|                                  | 2010                      | 61/182 (34%)                         | 4.20 (1.71-10.34)                        |                     | 5.32 (2.04-13.8)                         |                     |
|                                  | 2011                      | 17/54 (31%)                          | 3.83 (1.38-10.65)                        |                     | 4.93 (1.65-14.7)                         |                     |
| Body mass index                  | <25                       | 59/294 (20%)                         | 1.53 (0.98-2.38)                         | .18                 | 1.37 (0.83-2.25)                         | .25                 |
|                                  | 25-30                     | 63/360 (18%)                         | 1.29 (0.83-1.99)                         |                     | 1.27 (0.78-2.05)                         |                     |
|                                  | ≥30                       | 38/269 (14%)                         | Referent                                 | Referent            | Referent                                 | Referent            |
| ECOG performance status          | 0                         | 129/775 (17%)                        | Referent                                 | .14                 | Referent                                 | .11                 |
|                                  | 1                         | 24/94 (26%)                          | 1.72 (1.04-2.83)                         |                     | 1.68 (0.94-2.99)                         |                     |
|                                  | 2                         | 4/26 (15%)                           | 0.91 (0.31-2.69)                         |                     | 0.39 (0.11-1.41)                         |                     |
|                                  | Unknown                   | 12/52 (23%)                          | 1.50 (0.77-2.94)                         |                     | 0.80 (0.36-1.74)                         |                     |
| Charlson Comorbidity Index score | 0                         | 134/698 (19%)                        | Referent                                 | .07                 | Referent                                 | .11                 |
|                                  | 1                         | 19/165 (12%)                         | 0.55 (0.33-0.92)                         |                     | 0.55 (0.31-0.97)                         |                     |
|                                  | 2                         | 16/84 (19%)                          | 0.99 (0.56-1.76)                         |                     | 1.04 (0.54-2.00)                         |                     |
|                                  | Unknown                   | 12/52 (23%)                          | 1.50 (0.77-2.94)                         |                     | 0.80 (0.36-1.74)                         |                     |
| Preoperative tumor fixation       | No                        | 135/709 (19%)                        | Referent                                 | .18                 | Referent                                 | .79                 |
|                                  | Yes                       | 18/109 (17%)                         | 0.60 (0.35-1.05)                         |                     | 1.13 (0.62-2.06)                         |                     |
| Tumor distance from anal verge (cm)| <5                       | 70/356 (20%)                        | Referent                                 | .53                 | Referent                                 | NA                  |
|                                  | 5-10                      | 47/289 (16%)                         | 1.26 (0.84-1.89)                         |                     | 0.85 (0.45-1.59)                         |                     |
|                                  | >10                       | 44/267 (16%)                         | 1.24 (0.82-1.88)                         |                     | 0.85 (0.45-1.59)                         |                     |
|                                  | Unknown                   | 8/35 (23%)                           | 0.83 (0.36-1.90)                         |                     | NA                                      |                     |
| History of connective tissue disease| No                      | 168/942 (18%)                        | Referent                                 | .90                 | Referent                                 | NA                  |
|                                  | Yes                       | 1/5 (20%)                            | 1.15 (0.13-10.4)                         |                     | 1.15 (0.13-10.4)                         |                     |
| History of inflammatory bowel disease/Crohn’s| No                   | 167/940 (18%)                        | Referent                                 | .46                 | Referent                                 | NA                  |
|                                  | Yes                       | 2/7 (29%)                            | 1.85 (0.36-9.6)                          |                     | 1.85 (0.36-9.6)                          |                     |
| Transabdominal surgery           | No                        | 26/82 (32%)                          | Referent                                 | .0008               | Referent                                 | .03                 |
|                                  | Yes                       | 143/865 (17%)                        | 0.43 (0.26-0.70)                         |                     | 0.51 (0.28-0.92)                         |                     |
| Radiation therapy dose (cGy)     | ≤5040                     | 141/874 (16%)                        | Referent                                 | <.0001              | Referent                                 | .002                |
|                                  | >5040                     | 28/72 (39%)                          | 3.31 (1.99-5.49)                         |                     | 3.12 (1.72-5.65)                         |                     |

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IMRT, intensity modulated radiation therapy.

<sup>a</sup> Univariate logistic regression.

<sup>b</sup> Multivariate logistic regression.
it may also be due to differences in the quality and type of information coded in the 2 databases used. The size difference between the databases allows for a more rigorous quality assurance process for the NCCN Colorectal Cancer database and specifically may affect the quality of RT data.

In our cohort, we excluded 1 patient with inadequate RT details, whereas Coffman et al excluded 39,072 of 62,395 patients (62%) with stage II and III rectal cancer in the NCDB database due to no RT reported, no information about the technique, or unusual RT doses, which also calls into question the quality of RT data coded for the included patients. Furthermore, the NCCN outcomes database contains more medical information that can provide context for IMRT use and which is absent from the NCDB, including BMI, performance status, distance from the ane

verge, and history of connective tissue disease or inflammatory bowel disease.

Dosimetric studies suggest advantages to IMRT in reducing total bowel dose and volume of the bowel in high-dose regions,4,6 which correlates with reduced grade ≥3 gastrointestinal toxicity.4-6 Several single-institution retrospective and prospective studies have demonstrated an improved acute toxicity profile.4,9,19-22 Analysis of a single-arm, prospective, multi-institution, phase 2 trial showed a similar trend when compared with the arm treated with the same chemotherapy and 3-dimensional CRT in a prior trial, although not when compared with all patients pooled together.20,23

We examined the clinical factors that may influence the use of IMRT in this regard, including BMI, distance from the anal verge, and history of connective tissue disease or inflammatory bowel disease, but did not observe an association. The benefits of IMRT may be more pronounced in patients who have had prior pelvic surgery and may have fixed loops of bowel due to adhesions, but this could not be examined with the NCCN outcomes database.24 Although we did not observe differences in toxicity between patients who were treated with 3-dimensional CRT and IMRT using time to completion and delivery of an appropriate dose as surrogates, these are indirect and not sensitive measures of toxicity. These surrogates may identify some patients with grade 3 and patients with grade 4 or greater toxicity, but they do not provide a comprehensive comparison of all acute toxicity experienced by patients.

In addition, IMRT may help improve sexual side effects associated with pelvic radiation as suggested for anal cancer.25,26 Despite different RT dose schedules and chemotherapy regimens, which may affect interpretation of the results, collectively, the available data suggest that IMRT is as effective as and likely associated with improved acute toxicity compared with 3-dimensional CRT. Recent retrospective data do not show an improvement in survival associated with IMRT27; however, longitudinal data including late toxicity and quality of life measures are needed to fully assess the clinical benefit. Importantly, IMRT is associated with significantly higher cost than 3-dimensional CRT; therefore, prospective trials should include economic in addition to clinical endpoints to help determine cost effectiveness.

Interestingly, increasing IMRT use was not uniform among the different institutions and continued to be selective at most. Regional differences in the use of advanced technologies have been documented in prior population-based studies and may be related to reimbursement. As experience with IMRT has grown, an increased recognition of the clinical benefits of IMRT in certain high-risk situations such as genitalia sparing and fixed small bowel in the pelvis is possible. After year of diagnosis, the most significant predictor of IMRT use in this cohort was RT dose, which is consistent with the findings reported by Coffman et al.18 Although only 8% of the overall cohort received >5040 cGy, this dose was associated with a 3-fold increased likelihood of receiving IMRT. In this setting, IMRT may facilitate the delivery of a higher dose without increasing toxicity. Not receiving surgery was the second clinical factor that was predictive of IMRT use, possibly related to the higher RT doses that are sought for poor surgical candidates. An intriguing speculation is that IMRT may have allowed for higher rates of nonoperative management. However, given the small number of patients in these groups, these associations should be interpreted with caution.

Patients at the extremes of age and African-American patients were more likely to receive IMRT. Patients at the extremes of age may be deemed more vulnerable to radiotoxicity, either due to the projected number of years the young may be affected or the frailty of the old. Although the association between race and IMRT use may be spurious and reflect the demographic composition of the centers with high IMRT use, these results are consistent with prior reports that nonwhite race predicts IMRT use in the NCDB database.18 African-American patients have been shown to present with higher-stage colorectal cancer than Caucasian patients, but stage did not predict IMRT use in this cohort. Both age >65 years and race have been shown to correlate with having nonprivate insurance, specifically Medicare and Medicaid. Reimbursement rates vary by insurance and are a significant factor in adopting advanced technologies. In this analysis, the type of insurance, whether private, Medicare, or Medicaid, did not significantly predict IMRT utilization. However, we did not have more detailed information with regard to the reimbursement policies of each carrier.

One limitation of the current study includes a limited number of included institutions. In light of the significant variability in the use of IMRT among the institutions, it is possible that the association between patient factors and use of IMRT are driven by institutions with high IMRT use. Another limitation of the NCCN database here is that predictors of IMRT use at select academic centers may not reflect factors in the community. Advantages include access to more detailed, high-quality information about RT and more clinical detail than population-based studies.
Conclusions

On the basis of a cross-sectional analysis of academic cancer centers with well-developed colorectal programs selected by the NCCN to contribute to the colorectal outcomes database, IMRT use has been rapidly increasing, albeit not uniformly among institutions. Nonetheless, the majority of NCCN centers appears to be using IMRT selectively. Given the higher costs for IMRT compared with 3-dimensional CRT, prospective longitudinal data including economic endpoints are needed to assess the clinical benefit and cost effectiveness of IMRT beyond high risk indications such as fixed small bowel and sparing the genitalia.

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