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Scientific Article

Utilization of short-course radiation therapy for patients with nonmetastatic rectal adenocarcinoma in the United States

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Abstract

Purpose: Preoperative short-course radiation therapy (SCRT) for patients with nonmetastatic rectal adenocarcinoma has been studied in European trials, but is not often used in the United States. We aim to describe the utilization of preoperative SCRT among patients with nonmetastatic rectal cancer in the National Cancer Database and describe factors associated with its use.

Methods and materials: The National Cancer Database was queried for patients treated with preoperative radiation therapy followed by surgery for nonmetastatic rectal adenocarcinoma between 2004 and 2014. Patient, tumor, and treatment-related characteristics were compared between patients treated with SCRT (20-25 Gy in <7 fractions) and patients treated with long-course radiation therapy (45-70 Gy in $\geq$ 25 fractions). Univariate and multivariate Cox regression analyses were used to evaluate factors associated with overall survival. Survival rates were compared using an inverse-probability-weighted regression adjustment method.

Results: A total of 42,336 patients were included for analysis of which 41,867 patients (98.9%) were treated with long-course radiation therapy and 469 patients (1.1%) with SCRT. Patients treated with SCRT were older, had more comorbidities, had earlier T-stage, and were more likely to be clinically node-negative. Patients treated with SCRT were more likely to be treated at an academic center, have Medicare insurance, and be treated without chemotherapy. Patients treated with SCRT had lower pathological complete response rates (4.3% vs 6.9%; $P < .001$) and higher rates of positive circumferential resection margins (8.3% vs 5.2%; $P = .001$). On multivariate analysis, radiation fractionation was not significantly associated with overall survival.

Conclusions: SCRT is used for only approximately 1% of patients treated preoperatively for nonmetastatic rectal cancer in the United States. The results of recently completed randomized trials may further inform patterns of practice in the United States and abroad.

Conflicts of interest: None.

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Introduction

Approximately 39,910 new cases of rectal cancer were estimated to be diagnosed in the United States in 2017.[1] Although frequently combined with colon cancer (as colorectal cancer), rectal cancer is particularly challenging with regard to treatment strategies and oncologic outcomes.[2] The management of nonmetastatic rectal cancer represents a prime example of the evolution of multidisciplinary management of patients with cancer.[3] Although surgery alone is a standard approach for patients with stage I disease, neoadjuvant (chemo)radiation therapy has proved particularly useful for patients with stage II/III disease[4] and is currently considered the standard of care.[5]

Preoperative radiation therapy protocols for rectal cancer have evolved during the past 2 decades along 2 distinct lines. Preoperative short-course radiation therapy (SCRT) was developed primarily in Northern European countries, and preoperative long-course (chemo) radiation therapy (LCRT) was developed primarily in the United States as well as some European countries, such as Germany. A number of landmark trials including Swedish and Dutch trials compared surgery alone with preoperative SCRT followed by surgery, and found decreased local recurrence (LC) rates with SCRT.[6,7] The landmark German Rectal Cancer Trial evaluated the LCRT + concurrent chemotherapy approach in both preoperative and postoperative settings and found preoperative LCRT to be superior in terms of LC and colostomy-free survival.[8]

The preferred preoperative treatment regimen differed by geographic region. However, recent studies have compared the SCRT and LCRT regimens. A Polish study found no differences in LC or overall survival (OS),[9] and a study from Australia/New Zealand also found no difference in LC rates or OS. In addition, rates of late toxicity, distant recurrence, and relapse-free survival were no different between SCRT and LCRT. Patients in the LCRT arm were more likely to have serious radiation dermatitis, and patients in the SCRT arm were more likely to have a permanent stoma.[10,11] The Stockholm III study showed noninferior oncologic outcomes with 2 SCRT regimens (immediate surgery and delayed interval to surgery) compared with LCRT.[12] Another trial comparing SCRT and LCRT, both with a delayed interval to surgery, showed greater tumor downstaging and downsizing with LCRT. However, margin-negative resection (R0) and postopertative morbidity rates were equivalent.[13] Overall, SCRT is widely considered equivalent in terms of LC and OS compared with LCRT, and is therefore considered a standard option for patients with T3N0 or T1-3N1-2 rectal adenocarcinoma. SCRT is currently not recommended for patients with T4 disease because of its apparent inferior downsizing and downstaging potential.[5]

Despite mounting evidence, ongoing controversy remains in the United States with regard to the optimal preoperative radiation therapy approach for patients with rectal cancer.[14] Given the historical predominance of the LCRT approach among U.S. oncologists, we sought to evaluate the utilization rates of preoperative SCRT in the United States among academic and community hospitals using the American College of Surgeons Commission on Cancer's National Cancer Database (NCDB).

Methods and materials

We first obtained the necessary ethical and regulatory approvals from the University of Texas MD Anderson Cancer Center institutional review board as well as a waiver of informed consent because the information in the Commission on Cancer's NCDB is de-identified. Subsequently, we extracted the data of this analysis from the NCDB registry.

Selection of study cohort

The initial cohort from the NCDB 2014 release included 243,466 patients with rectal cancer (International Classification of Diseases for Oncology 3rd edition disease topography code C209) who were diagnosed between 2004 and 2014. We first restricted our analysis to the subset of patients who received radiation therapy to the pelvis (n = 102,959), and then excluded patients who received miscellaneous forms of radiation such as Gamma Knife, LINAC-based radiation surgery or therapy with radioisotopes (n = 1265). Next, we excluded patients with stage 4 disease (n = 12,320). Subsequently, we excluded patients who received no (n = 15,343) or unknown (n = 163) rectal surgery, adjuvant radiation after surgery (n = 18,082), intraoperative radiation therapy (n = 65), or had unknown/incomplete radiation records in the NCDB (n = 5843).

We also excluded patients who received either <20 Gy (n = 521) or >70 Gy (n = 265) and those who received brachytherapy or radioisotope boosts (n = 696). This left us with a cohort of 48,396 patients. We excluded patients who did not have any follow-up or survival data available in the NCDB (n = 5804). We divided the remaining 42,592 patients into short course (SC; 20-25 Gy in <7 fractions) and long course (LC; 45-70 Gy in ≥25 fractions) cohorts. Patients who received dose/fractionation regimens outside of the above-specified groups were excluded (n = 256), leaving 42,336 patients for analysis. The final SC cohort for analysis included 469 patients, and the final LC cohort included the remaining 41,867 patients (Fig 1).

Data collection

Patient-specific variables extracted from the NCDB for each case included age at the time of diagnosis, sex (male or female), race (White, Black, Asian/Pacific Islander, and

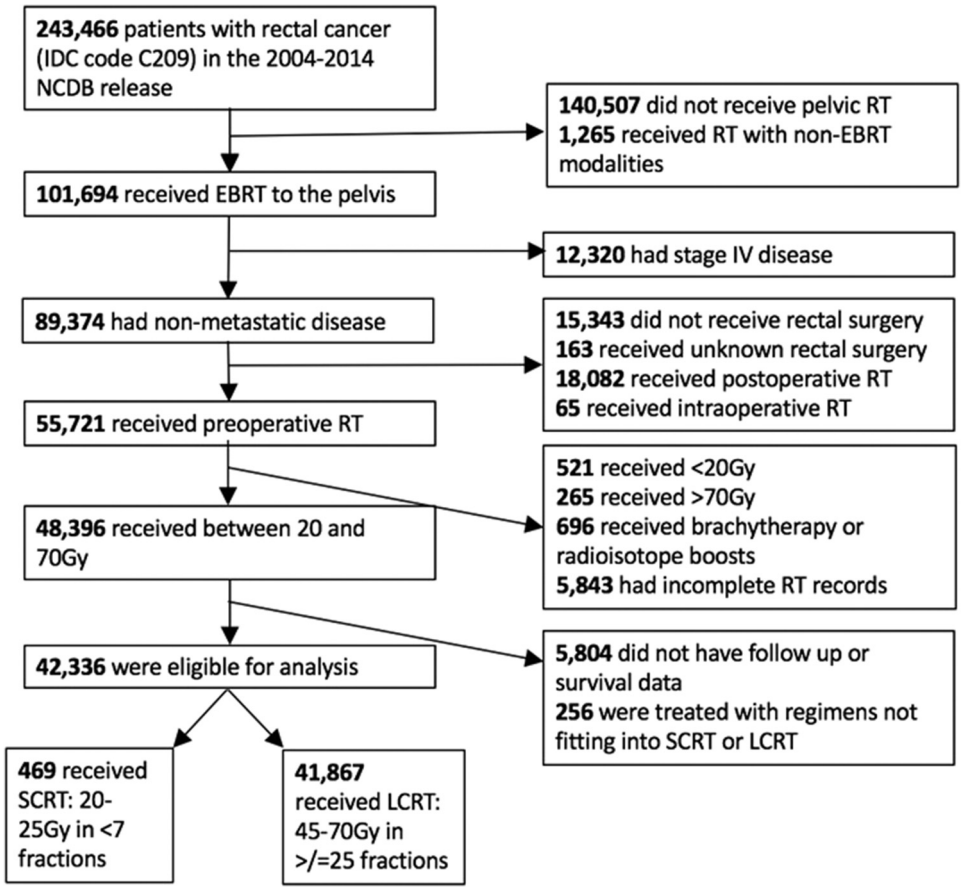

Figure 1 Flow diagram of patients with nonmetastatic rectal cancer treated with preoperative pelvic external beam radiation included in this analysis.

Other), and the Charlson-Deyo Comorbidity score (0, 1, or 2 +). Year of diagnosis was also recorded as $\leq$2009 or >2009. Per the NCDB methodology, patients diagnosed between 2004 and 2009, and between 2010 and 2014, were staged using the 6th and 7th editions of the American Joint Committee on Cancer staging criteria, respectively. Changes between the 6th and 7th editions included the subdivision of T4 into T4a and T4b in the 7th edition, but T-staging data in our analysis were simplified to T1, T2, T3, or T4. In addition, N-staging changed in the 7th edition to subdivide N1 into N1a, N1b, and N1c and N2 into N2a and N2b, but the N-staging data in our analysis were simplified to N0, N1, or N2.

All recorded clinical staging information was obtained preoperatively. Tumor size was recorded in centimeters. When available, surgical pathology variables were collected including the circumferential resection margin (CRM) status (positive or negative) as well as the pathologic tumor response (complete, moderate, minimal, or poor). Pathologic tumor response is defined in the NCDB as complete response (tumor regression grade 0) = no viable cancer cells, moderate response (tumor regression grade 1) = single cells or small groups of cancer cells, minimal response (tumor regression grade 2) = residual cancer outgrown by fibrosis, and poor response (tumor regression grade 3) = minimal or no tumor kill (ie, extensive residual cancer).[15] Finally, each patient was coded as having Medicaid, Medicare, other government insurance, private insurance, or no insurance.

Center-specific variables that were extracted from the NCDB for each case included facility type (community or academic). Community centers included community cancer programs and comprehensive community cancer programs; academic centers included academic/research programs and integrated network cancer programs. Treatment-specific variables that were extracted for each case included the days from diagnosis to initiation of radiation therapy, radiation modality (3-dimensional conformal radiation or intensity modulated radiation therapy), and the total dose of radiation in Gy. The total dose/fractionation groups were subdivided into SC (20-25 Gy in $\leq$7 fractions) and LC (45-70 Gy in $\geq$25 fractions). Chemotherapy data were also collected including whether patients received no chemotherapy, single-agent chemotherapy, or combination chemotherapy either concurrently or sequentially with radiation.

The recorded vital status was either deceased or alive. Median OS was calculated as months from the time of diagnosis to the last contact or death. Patients who were lost to follow up after treatment were censored at the date of the last recorded follow up.

Statistical considerations

The Pearson χ^2 test to evaluate the frequency of various characteristics by treatment group (SC vs LC) and Kaplan-Meier survival estimates were used to estimate OS. Kaplan-Meier survival curves were adjusted for significant variables as identified in the multivariate analysis, and Log-rank testing was used for between-group survival comparisons.

Cox regression analyses were used to perform univariate and multivariate analyses to identify factors associated with improved OS, and hazard ratios with corresponding 95% confidence intervals were generated accordingly. After a Bonferroni correction was applied to account for the 15 variables tested in the univariate analysis, statistical significance was considered if the 2-tailed P-value $< .003$ was achieved. Factors with $P < .003$ on univariate analysis were subsequently retained in the multivariate model.

OS was adjusted for the significant factors found on multivariable analysis using a robust inverse-probability-weighted regression adjustment (IPWRA) method with nearest-neighbor matching. Nearest-neighbor matching estimators impute the missing potential outcome for each subject by using an average of the outcomes of similar subjects in the other treatment group. Similarity between subjects is based on a weighted function of the covariates for each observation. Treatment effects adjusted for in this analysis included sex, age, race, N-stage, Charlson-Deyo score, insurance status, facility type, CRM status, tumor response, and chemotherapy type. This IPWRA method was carried out with a nearest neighbor match of up to 100 cases given the disparity in numbers of patients treated with SCRT compared with LCRT, although a minimum of 1 match is required for this technique. All statistical analyses were performed using the STATA statistical software, version 14 (College Station, TX).

Results

Patients' characteristics

A total of 42,336 patients were included in the current analysis of which 41,867 patients (98.9%) were treated with LCRT and 469 patients (1.1%) with SCRT. Compared with patients who were treated with LCRT, patients treated with SCRT were older (median age: 68 vs. 60 years; $P < .001$), more often female (44.1% vs. 37.5%; $P = .003$), more often White (89.6% vs. 86.7%; $P = .018$), had more comorbidities (Charlson comorbidity index >1: 8.2% vs. 3.9%; $P < .001$), had earlier clinical T-stage (T1/2 disease: 28.8% vs. 12%; $P < .001$), and were often clinically node-negative ($P < .001$).

Patients treated with SCRT were also more likely to be treated at an academic center (59.1% vs 41.9%; $P < .001$), have Medicare insurance (54.4% vs. 36.2%; $P < .001$), and be treated without chemotherapy (no chemotherapy: 55% vs 2.1%; $P < .001$). Patients treated with SCRT had lower pathological complete response rates (4.3% vs 6.9%; $P < .001$), higher rates of positive CRM (8.3% vs 5.2%; $P = .001$), and lower rates of pathological complete response (4.3% vs 7.9%; $P < .001$). There was a longer interval from the beginning of radiation therapy to the date of surgery for patients in the LCRT group compared with the SCRT group (median interquartile range, 93 [81-104] vs 13 [5-28], respectively; $P < .001$). There was no difference between both groups in terms of tumor size ($P = .960$), radiation therapy modality (intensity modulated radiation therapy vs 3-dimensional conformal radiation; $P = .769$), or diagnosis period ($P = .062$; Table 1).

Survival outcomes

Univariate and multivariate analyses were conducted to analyze factors potentially associated with worse OS in the studied cohort. On multivariate analysis, radiation fractionation was not significantly associated with OS ($P = .08$); but factors associated with worse OS included male sex ($P < .001$), age >60 years ($P < .001$), Charlson-Deyo comorbidity score of 1 +($P < .001$), increasing tumor size in cm ($P < .001$), N2 stage ($P < .001$), treatment at a community center ($P < .001$), nonprivate health insurance ($P < .001$), less than a complete pathological response to neoadjuvant treatment ($P < .001$), positive CRM ($P < .001$), and not receiving chemotherapy ($P < .001$; Table 2).

Subsequently, OS was assessed for matched cases using an inverse-probability weight regression adjustment using nearest neighbor matching. Median OS was higher in patients receiving LCRT compared with SCRT (126 vs 103 months), and 2- and 5-year OS rates were higher as well (91% vs 86%, and 74% vs 65%, respectively; log rank $P < .001$; Table 3; Fig 2).

Postoperative hospital stay and readmission days

Patients who received SCRT had a median interquartile range hospital stay of 7 days (2-13 days) compared with 6 days (2-10 days) for patients who received LCRT ($P < .001$). The median (range) for readmission hospital days, however, was no different between the SCRT and LCRT groups (0 [0-9] vs 0 [0-9], respectively; $P = .518$).

Table 1 Baseline characteristics of patients with nonmetastatic rectal adenocarcinoma treated with either short- or long-course neoadjuvant radiation therapy (National Cancer Database; 2004 and 2014)

Parameter	All cases (n = 42,336)	Long course (n = 41,867)	Short course (n = 469)	*P*-value (test)*
Diagnosis year; n (%)				.062 (Pearson χ^2)
≤2009	23,112 (54.6%)	22,876 (54.6%)	236 (50.3%)	
>2009	19,224 (45.4%)	18,991 (45.4%)	233 (49.7%)	
Sex; n (%)				.003 (Pearson χ^2)
Male	26,434 (62.4%)	26,172 (62.5%)	262 (55.9%)	
Female	15,902 (37.6%)	15,695 (37.5%)	207 (44.1%)	
Age; median [IQR]	60 [51.5-68.5]	60 [51.5-68.5]	68 [58-78]	<.001 (Wilcoxon rank-sum)
Race; n (%)				.018 (Pearson χ^2)
White	36,736 (86.8%)	36,316 (86.7%)	420 (89.6%)	
Black	3352 (7.9%)	3324 (7.9%)	28 (6.0%)	
Asian	1415 (3.3%)	1408 (3.4%)	7 (1.5%)	
Other	833 (2.0%)	819 (2.0%)	14 (3.0%)	
Charlson-Deyo comorbidity score; n (%)				<.001 (Pearson χ^2)
0	33,804 (79.8%)	33,473 (80.0%)	331 (70.6%)	
1	6880 (16.3%)	6782 (16.2%)	98 (20.9%)	
2+	1652 (3.9%)	1612 (3.9%)	40 (8.2%)	
Tumor size in cm; median [IQR]	4.0 [2.8-5.3]	4.0 [2.8-5.3]	3.8 [2.8-4.8]	.960 (Wilcoxon rank-sum)
cT Stage†; n (%)				<.001 (Pearson χ^2)
Tx	6527 (15.4%)	6,434 (15.4%)	93 (19.8%)	
T1	1216 (2.9%)	1185 (2.8%)	31 (6.6%)	
T2	3960 (9.4%)	3856 (9.2%)	104 (22.2%)	
T3	28,141 (66.5%)	27,914 (66.7%)	227 (48.4%)	
T4	2492 (5.9%)	2478 (5.9%)	14 (3.0%)	
cN Stage†; n (%)				<.001 (Pearson χ^2)
Nx	5668 (13.4%)	5605 (13.4%)	63 (13.4%)	
N0	19,954 (47.1%)	19,657 (47.0%)	297 (63.3%)	
N1	14,588 (34.5%)	14,500 (34.6%)	88 (18.8%)	
N2	2126 (5.0%)	2105 (5.0%)	21 (4.5%)	
Facility type†; n (%)				<.001 (Pearson χ^2)
Community center	22,579 (53.3%)	22,397 (53.5%)	182 (38.8%)	
Academic center	17,837 (42.1%)	17,560 (41.9%)	277 (59.1%)	
Other/unknown	1920 (4.5%)	1910 (4.6%)	10 (2.1%)	
Insurance; n (%)				<.001 (Pearson χ^2)
Private	21,223 (50.1%)	21,061 (50.3%)	162 (34.5%)	
Medicare	15,400 (36.4%)	15,145 (36.2%)	255 (54.4%)	
Medicaid	543 (2,552 (6.0%)	2526 (6.0%)	26 (5.5%)	
Other government	543 (1.3%)	537 (1.3%)	6 (1.3%)	
Uninsured	2099 (5.0%)	2084 (5.0%)	15 (3.4%)	
Unknown	519 (1.2%)	514 (1.2%)	5 (1.1%)	
Pathologic tumor response; n (%)				<.001 (Pearson χ^2)
Complete	3342 (7.9%)	3322 (7.9%)	20 (4.3%)	
Moderate	3645 (8.6%)	3634 (8.7%)	11 (2.3%)	
Minimal	2068 (4.9%)	2049 (4.9%)	19 (4.1%)	
Poor	966 (2.3%)	929 (2.2%)	37 (7.9%)	
Unknown	32,315 (76.3%)	31,933 (76.3%)	382 (81.4%)	
CRM; n (%)				.001 (Pearson χ^2)
Negative	36,287 (85.7%)	35,912 (85.8%)	375 (80.0%)	
Positive	2219 (5.2%)	2180 (5.2%)	39 (8.3%)	
Unknown	3830 (9.0%)	3775 (9.0%)	55 (11.7%)	

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Table 1 (*continued*)

Parameter	All cases (n = 42,336)	Long course (n = 41,867)	Short course (n = 469)	*P*-value (test)*
Duration from the beginning of radiation to surgery in days; median [IQR]	93 [81-104]	93 [81-104]	13 [5-28]	<.001 (Pearson χ^2)
Radiation therapy modality; n (%)				.769 (Pearson χ^2)
IMRT	5243 (12.4%)	5187 (12.4%)	56 (11.9%)	
3DCRT	37,093 (87.6%)	36,680 (87.6%)	413 (88.1%)	
Total radiation therapy dose in Gy; median [IQR]	50.4 [50.1-50.7]	25 [25-25]	50.4 [50.4-50.4]	<.001 (Wilcoxon rank-sum)
Chemotherapy; n (%)				<.001 (Pearson χ^2)
No chemotherapy	1122 (2.7%)	864 (2.1%)	258 (55.0%)	
Single agent	23,052 (54.5%)	22,993 (54.9%)	59 (12.6%)	
Combination	14,914 (35.2%)	14,772 (35.3%)	142 (30.3%)	
Unspecified chemotherapy	3155 (7.5%)	3147 (7.5%)	8 (1.7%)	
Unknown	93 (0.2%)	91 (0.2%)	2 (0.4%)	

3DCRT, 3-dimensional conformal radiation therapy; CRM, circumferential resection margin; IMRT, intensity modulated radiation therapy; IQR, interquartile range

* Patients diagnosed between 2004 and 2009 were staged according to the 6th edition of the TNM system, and patients diagnosed between 2010 and 2014 according to the 7th edition. Patients with distant metastatic disease were excluded.

† Community centers include community cancer programs and comprehensive community cancer programs, and academic centers include academic/research programs and integrated network cancer programs.

Discussion

The current analysis summarizes the baseline characteristics as well as outcomes of patients with non-metastatic rectal adenocarcinoma who were treated with SCRT compared with LCRT before definitive surgery. According to the current analysis of the NCDB, SCRT is quite uncommonly used in the United States (only 1% of all neoadjuvant cases). Patients who received neoadjuvant treatment with SCRT rather than LCRT were older, had more medical comorbidities, and tended to have earlier stage disease or more favorable disease. This is in line with previous retrospective studies,[16] and may be due to the logistical convenience of SCRT compared with LCRT among groups of patients with compromised general conditions.

A recent survey study of U.S. radiation oncologists revealed the general lack of enthusiasm for SCRT, despite the preponderance of high-quality data suggesting SCRT is safe and effective.[16–19] The most often cited reasons include concerns of insufficient downstaging, sphincter preservation, and a desire for longer follow-up of the existing randomized trials. Interestingly, 20% of respondents reported that future changes to oncology reimbursement may cause them to reconsider their use of SCRT.[20] In our NCDB cohort, patients with private insurance were less likely to be offered SCRT compared with patients with governmental insurance. Whether this is related to the payment procedures in both insurance systems is not yet known with certainty.

Likewise, countries with single-payer health care system have been noted to historically be more likely to investigate and adopt SCRT. This might be related to the perceived higher cost-effectiveness of SCRT.[20] Furthermore, the reasons survey respondents listed as reasons to choose SCRT for patients closely mirrored the factors that were found in our own analysis: Patients who could not receive chemotherapy or patients with high comorbidities. Responding radiation oncologists who practice at academic centers also reported being more likely to offer SCRT to their patients, which agrees with our finding of patients receiving SCRT more often at academic centers.[20]

There were some observed differences in surgical pathology variables between patients who received SCRT and LCRT in the current analysis. LCRT was associated with higher rates of polymerase chain reaction (pCR; 7.9% vs 4.3%) and lower rates of positive CRM (5.2% vs 8.3%) compared with SCRT. The decreased pCR rate with SCRT is consistent with a previously published systematic review[17] and randomized comparisons between SCRT and LCR.[9,10] Although the correlation between pathological complete response and better survival outcomes has been shown,[18,19,21] randomized studies have shown no differences in survival between patients receiving SCRT and LCRT. The Trans-Tasman Radiation Oncology Group Trial suggested that LCRT may lead to better LC rates for distal rectal tumors,[10] but because the NCDB does not provide data on the location of tumors, we were unable to explore this point with our data set.

The typical duration between end of SCRT and surgery has historically been approximately 1 week. A recently reported randomized study (Stockholm III) evaluated whether the prolongation of this duration might affect the outcomes of these patients, particularly with regard to

Table 2 Univariate and multivariate analysis for factors affecting overall survival in the entire cohort

Parameter	Univariate			Multivariate		
	HR	*P*-value	95% CI	HR	*P*-value*	95% CI
Diagnosis year						
≤ 2009	Reference			N/A		
>2009	1.00	.968	0.96-1.05			
Sex						
Female	Reference			Reference		
Male	1.14	<.001	1.10-1.19	1.17	<.001	1.12-1.22
Age						
≤60	Reference			Reference		
>60	1.92	<.001	1.85-1.99	1.38	<.001	1.30-1.46
Race				N/A		
White	Reference					
Non-White	1.07	.009	1.02-1.13			
Charlson-Deyo comorbidity score						
0	Reference			Reference		
1	1.49	<.001	1.42-1.56	1.32	<.001	1.25-1.39
2 +	2.35	<.001	2.18-2.53	1.97	<.001	1.81-2.16
Tumor size in cm (Unit HR)	1.02	<.001	1.01-1.02	1.02	<.001	1.01-1.02
T Stage†				N/A		
Tx	Reference					
T1	1.15	.640	0.63-2.10			
T2	1.03	.923	0.57-1.87			
T3	1.20	.542	0.67-2.17			
T4	2.10	.015	1.16-3.80			
N Stage†						
N0	Reference			Reference		
N1	1.24	.416	0.94-1.03	1.06	.022	1.01-1.11
N2	0.98	<.001	1.47-1.47	1.45	<.001	1.31-1.60
Facility type‡						
Community center	Reference			Reference		
Academic center	0.87	<.001	0.84-0.91	0.91	<.001	0.87-0.95
Insurance						
Private	Reference			Reference		
Medicare	2.18	<.001	2.10-2.27	1.64	<.001	1.55-1.74
Medicaid/Other government	1.59	<.001	1.47-1.71	1.58	<.001	1.44-1.74
Uninsured	1.52	<.001	1.40-1.65	1.45	<.001	1.30-1.61
Tumor response						
Complete	Reference			Reference		
Moderate	1.38	<.001	1.20-1.58	1.26	.005	1.07-1.47
Minimal	2.01	<.001	1.74-2.32	1.62	<.001	1.37-1.91
Poor	2.94	<.001	2.51-3.45	2.04	<.001	1.70-2.45
CRM						
Negative	Reference			Reference		
Positive	1.92	<.001	1.77-2.08	1.74	<.001	1.58-1.92
Radiation therapy modality						
IMRT	Reference					
3DCRT	0.92	.006	0.86-0.97	N/A		
Radiation therapy dose group; N (%)						
Short course	Reference			Reference		
Long course	0.72	<.001	0.61-0.84	1.18	.083	0.98-1.42
Chemotherapy; n (%)						
No chemotherapy	Reference			Reference		

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Table 2 (*continued*)

Parameter	Univariate			Multivariate		
	HR	*P*-value	95% CI	HR	*P*-value*	95% CI
Single agent	0.62	<.001	0.56-0.68	0.65	<.001	0.58-0.73
Combination	0.47	<.001	0.43-0.52	0.56	<.001	0.50-0.63
Unspecified chemotherapy	0.62	<.001	0.56-0.70	0.65	<.001	0.57-0.75

3DCRT, 3-dimensional conformal radiation therapy; CI, confidence interval; CRM, circumferential resection margin; HR, hazard ratio; IMRT, intensity modulated radiation therapy; IQR, interquartile range; N/A, not applicable

* After a Bonferroni correction was applied to account for the 15 variables tested in the univariate analysis, statistical significance was considered if the 2-tailed *P*-value < .003 was achieved. Factors with $P < .003$ on univariate analysis were retained in the multivariate model.

† Patients diagnosed between 2004 and 2009 were staged according to the 6th edition of the TNM system, and patients diagnosed between 2010 and 2014 according to the 7th edition. Patients with distant metastatic disease were excluded.

‡ Community centers include community cancer programs and comprehensive community cancer programs, and academic centers include academic/research programs and integrated network cancer programs.

pathological complete response rates as well as surgical complications. The pCR rates were much higher in the SCRT plus delayed surgery arm compared with the SCRT plus immediate surgery arm (11.8% vs 1.7%),[22] and SCRT with delay gives the same oncologic outcomes to SCRT with immediate surgery but with a lower incidence of postoperative complications.[12]

All the aforementioned randomized trials that evaluated SCRT have been conducted outside of the United States. However, Washington University is one U.S. center that has been using SCRT for patients with rectal cancer for decades. An institutional phase 2 trial evaluated whether the incorporation of induction chemotherapy after SCRT might improve the outcomes.[23] Markovina et al. published a matched-pair analysis that demonstrated that patients who were treated with this SCRT + induction chemotherapy regimen had better tumor downstaging and 3-year disease-free survival rates than a matched cohort of patients who received LCRT with concurrent chemotherapy and postoperative FOLFOX (75% vs 41%; $P < .001$ and 85% vs 68%; $P = .032$, respectively). The pCR for SCRT patients in this study was 28%, and the 3-year OS rate was 96%.[23–26]

The concept of delivering systemic chemotherapy in the interval between SCRT and surgery is currently being testing in the recently closed RAPIDO trial in which patients were randomized to either LCRT followed by surgery and adjuvant chemotherapy or SCRT followed by neoadjuvant chemotherapy followed by surgery. This trial aims to improve survival by integrating multiagent chemotherapy after SCRT in the preoperative setting with the hope of improving OS without compromising LC.[27] The results of this trial are anxiously awaited, and speculation exists that practice patterns in the United States and abroad may change if the results of the SCRT arm are favorable.

The exceedingly small percentage of patients in the current cohort treated with SCRT limits our ability to reliably compare survival outcomes between the 2 regimens. Kaplan-Meier survival curves adjusted using the IPWRA method showed superior survival for patients

Table 3 OS for matched cases using an inverse-probability weight regression adjustment using nearest-neighbor matching

	Long-course RT	Short-course RT	Log rank *P*-value
Matched cases	41,866	469	
Mean OS in months [95% CI]	155.7 [152-159]	275 [142-408]	<.0001
Median OS in months	126	103	
1-year OS [95% CI]	97% [96-97%]	92% [89-94%]	
2-year OS [95% CI]	91% [91-91%]	86% [82-89%]	
3-year OS [95% CI]	85% [85-86%]	78% [74-82%]	
4-year OS [95% CI]	79% [79-80%]	74% [69-78%]	
5-year OS [95% CI]	74% [73-74%]	65% [60-70%]	
6-year OS [95% CI]	69% [68-70%]	60% [54-66%]	
12-year OS [95% CI]	51% [50-52%]	44% [36-53%]	

CI, confidence interval; OS, overall survival; RT, radiation therapy

Treatment effects that were adjusted for in this analysis included sex, age, race, N-stage, Charlson-Deyo score, insurance status, facility type, circumferential resection margin status, tumor response, and chemotherapy type. This inverse-probability weight regression adjustment method was conducted with a nearest-neighbor match of up to 100 cases, but a minimum of 1 match is required for this technique.

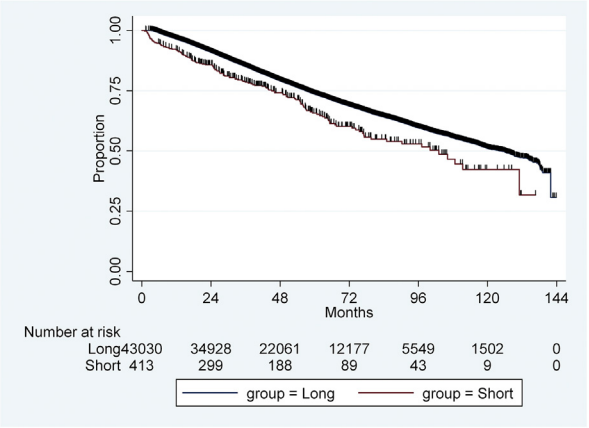

Figure 2 Inverse-probability-weighted regression-adjusted overall survival rates for matched cases for patients treated with short- and long-course radiation in the preoperative setting for nonmetastatic rectal adenocarcinoma.

who received LCRT. However, the type of fractionation was not associated with statistically significant differences in OS in the multivariate Cox regression model, which indicates that possible survival differences might be better attributable to differences in the background medical profiles of the patients in each group. This is more consistent with the aforementioned randomized studies that have found no survival differences between the SCRT and LCRT regimens.

The current analysis has several strengths that should be acknowledged. First, this study provided a relatively large number of patients for an exceedingly uncommon clinical vignette in the United States (ie, SCRT). Moreover, the NCDB in particular has additional advantages compared with other registry-based analyses (eg, based on the Surveillance, Epidemiology and End Results Database), including attention to the details of comorbidity, doses of radiation therapy, basic information about systemic therapy (single vs multiagent), and the Charlson-Deyo comorbidity index.

On the other hand, the limitations of the current analysis are similar to those reported with other large-scale retrospective analyses, including error probability within the process of data entry, the uncontrolled nature of data collection, and the heterogeneity of surgical and medical expertise as well as pathological data when collecting data from multiple institutions with variable expertise (eg, academic centers vs community hospitals). The most significant limitations of this analysis come from the variables not available within the NCDB: location of the tumor (low, mid, or high rectum), type of surgical procedure (low anterior resection vs abdominoperineal resection), local recurrence rates, need for salvage procedure, and ultimate colostomy-free survival rates, as well as short- and long-term toxicity rates.

Conclusions

Acknowledging the limitations of this study, our aims were to describe the utilization rate of SCRT in the United States as well as the population for whom SCRT is selected rather than to comment on the relative merits of either regimen. On the basis of these data, we conclude that SCRT is used for only approximately 1% of patients treated with preoperative treatment of nonmetastatic rectal cancer in the United States. The results of recently completed randomized trials may further inform patterns of practice in the United States and abroad.

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