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Use of Neoadjuvant Short-Course Radiotherapy for Rectal Adenocarcinoma in the United States: Insights into Patterns of Practice and Outcomes

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Abstract

Aim: European data demonstrated the safety of short-course radiation (SC-RT) for Locally Advanced Rectal Adenocarcinoma (LARC); however, use of SC-RT in the US remains unknown. This study characterized patterns of use of SC-RT in the US and its short-term and oncologic outcomes compared to long-course radiation (LC-RT).

Methods: Patients with clinical stage II and III rectal adenocarcinoma undergoing neoadjuvant therapy followed by resection were included. Descriptive statistics, propensity matching, and survival analysis used to compare SC-RT *vs*. LC-RT.

Results: Of 28,968 patients identified: 326 received SC-RT and 28,642 LC-RT. SC-RT slightly increased in use from 0.3% of cases in 2004 to 2.3% in 2015. Patients undergoing the SC-RT were older, had more comorbidities, and had Medicare (all p<0.0001). SC-RT was offered more at academic centers, and with regional variation (p<0.05). After propensity matching, rate of complete pathologic response was less in the SC-RT *vs*. LC-RT cohort (12% *vs*. 21%, p<0.0001). Hospital lengths of stay and readmission rates were similar. Sphincter preservation, completeness of surgical resection, and circumferential margins were similar between groups. Among all patients, 5-year overall survival was significantly less for SC-RT (51% *vs*. 47%, p=0.005); however, survival tended towards significance when the cohort limited to patients <80 years without significant comorbidities (65% *vs*. 73%, p=0.058).

Conclusion: Use of short-course radiotherapy for LARC in the US is slowly increasing but remains significantly low. While surgical and short-term oncologic outcomes appear to be comparable to LC-RT, this study argues for level 1 evidence from the US examining long-term survival.

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Introduction

Neoadjuvant chemoradiation therapy is associated with improved survival for locally advanced rectal cancer [1-6]. Continuous improvements in chemotherapy and radiation therapy have led to increased sphincter preservation and decreased complications. Conventional neoadjuvant radiation therapy is the delivery of 40.5-50.4 Gy administered in 28 fractions. Chemotherapy can be added to this regimen for improved tumor response. As delivered dose of the chemoradiotherapy increases, there is an associated increase in local toxicities and adverse events such that short-course radiation therapy (SC-RT) has been explored as a way to mitigate these adverse events and reduced compliance while providing equivalent oncologic benefit.

Randomized control trials mainly from Northern Europe demonstrated non-inferiority of SC-RT compared to conventional long course (LC-RT) radiation therapy have been performed. These trials demonstrate equivalent oncologic outcomes, with the potential for decreased postoperative complications, decreased duration of therapy, increased compliance and decreased cost [7-9]. Despite the growing evidence from these trials there is a paucity of data from the US, with an overall low adoption of SC-RT in contemporary practice [2,10]. Our aims were to characterize patterns of use of SC-RT in the US and its outcomes compared to LC-RT.

Methods

The National Cancer Database (NCDB) is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide,

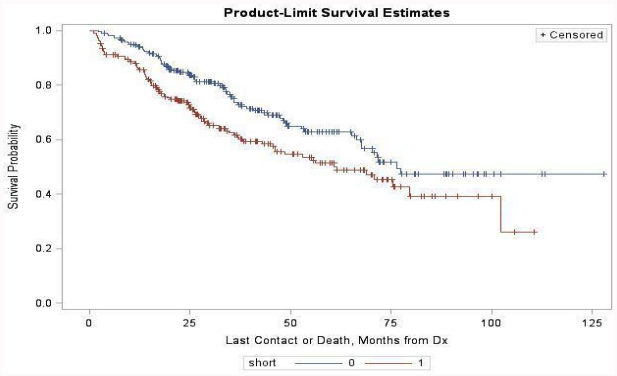

Figure 1: Overall survival of matched patients undergoing short- *vs.* long-course neoadjuvant therapy. Blue Line=0=Long Course, Red Line=1=Short Course.

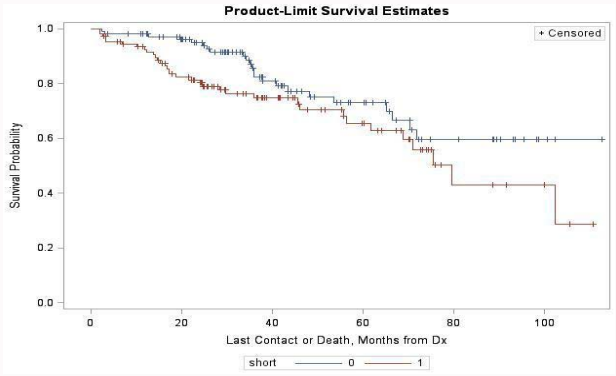

Figure 2: Overall survival of healthy younger patients undergoing short- *vs.* long-course neoadjuvant therapy. Blue Line=0=Long Course, Red Line=1= Short Course.

facility-based, comprehensive clinical surveillance data set that currently captures 70% of all newly diagnosed malignancies in the United States. It was established in 1989 and currently contains more than 29 million cancer cases from more than 1500 CoC-accredited cancer programs from all 50 states, Puerto Rico, and the District of Columbia.

Data were coded according to the CoC Registry Operations and Data Standards Manual, the American Joint Committee for Cancer (AJCC) Manual for Staging of Cancer and the International Classification of Disease for Oncology. To reduce data errors and maintain the integrity of the database, all data were extracted from medical records by trained and certified tumor registrars. Data were validated locally and at the NCDB level. Data were de-identified and submitted to the NCDB in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The Duke University Institutional Review Board granted this study an exemption status.

The NCDB participant user file was used to identify all stage II or III rectal adenocarcinoma patients who underwent neoadjuvant radiation followed by surgery between 2004 and 2015. The following International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 8140/3, 8141/3, 8143/3, 8144/3, 8145/3, 8147/3, 8150/3, 8210/3, 8211/3, and 8220/3 were used to identify patients with rectal adenocarcinoma. Patients <18 years and those who did not undergo surgery were excluded. Patient variables including age at diagnosis, gender, race, level of education, insurance status, type of insurance, year of diagnosis, and comorbidity were extracted from the database. Comorbidity was represented by the modified Charlson/Deyo scoring system with a score of ≥ 1 indicating presence of comorbidity. Hospital type and location were provided in the dataset. Clinical and pathologic AJCC stages and were provided. Pathologic tumor responses were documented in the dataset as complete, moderate, and no response. Data about extent of surgery, sphincter preservation, and lymph node harvest, and margin positivity, hospital length of stay, 30-readmissions, and mortality with 90-days from surgery were obtained.

The cohort was categorized based on type of neoadjuvant RT received into two groups: patients who underwent SC-RT and patients who underwent LC-RT. SC-T was defined as receipt of a total preoperative radiation dose of 25 Gy delivered in 5 fractions within a week, while LC-RT was defined as receipt of a total preoperative radiation dose of 40.5-50.4 Gy delivered in 28 fractions.

Statistical Analysis

Baseline characteristics were reported using frequencies and proportions for categorical variables. Descriptive data were compared across groups using the Wilcoxon Rank Sum test for continuous variables and Pearson chi-square or Fisher's exact tests for categorical variables.

Multivariable logistic regression was used to predict factors that were associated with use of SC-RT versus LC-RT. We then developed propensity scores, which were defined as the conditional probability of undergoing SC-RT versus LC-RT. Patients were then matched on these propensity scores, using a 1:1 nearest neighbor algorithm. The following variables were used on our propensity match: patient age at diagnosis, gender, race, insurance type, comorbidity score, hospital type, clinical T stage, clinical N stage, and year of diagnosis.

Overall survival was defined from the time of diagnosis to time of death or last follow-up. Survival time was censored for patients alive at the end of the study period. Estimates of overall survival proportions were computed using the Kaplan-Meier method, and survival distributions were compared across groups using the log-rank test.

Sensitivity Analysis

Before propensity matching, patients undergoing SC-RT were more likely older with multiple comorbidities. This could potentially influence outcomes and overall survival between the SC-RT and LC-RT groups. Therefore, a subset survival analysis of patients younger <80 year and a comorbidity score of ≤ 1 was performed.

Results

Baseline characteristics

A total of 28968 patients with clinical stage II or III rectal adenocarcinoma were identified from the NCDB (2004-2015). The vast majority of patients underwent long-course neoadjuvant radiation (N=28642) while only 326 patients underwent neoadjuvant SC-RT. Patients undergoing SC-RT were significantly older (median 69 *vs.* 60 years, p<0.0001) and more often had Medicare insurance (54% *vs.* 36%, p<0.0001) and comorbid conditions (30% *vs.* 20%, p<0.0001). Patients receiving SC-RT *vs.* LC-RT tended to have clinical stage II *vs.* stage III cancer (51% *vs.* 46%, p=0.08). Compared with LC-RT, SC-RT was more likely to be offered at academic centers (68% *vs.* 35%, p<0.0001) and in the Midwestern US region (42% *vs.*

Table 1: Demographic, clinical, and pathologic characteristics of patients with stage II/III rectal cancer undergoing short *vs*. long course neoadjuvant radiation.

Variables	Short Course (N=326)	Long Course (N=28642)	p-value
Patient age (Yrs, median, IQR)			
N	326	28642	<0.0001
Median	69	60	
Q1, Q3	57.0, 79.0	52.0, 69.0	
Patient age group			
<65 yrs	135(42.6%)	17720(62.7%)	<0.0001
65-79 yrs	101(31.9%)	8575(30.4%)	
≥ 80 yrs	81(25.6%)	1945(6.9%)	
Female gender	132(40.5%)	1049 (36.6%)	0.1653
Race			
Black	21(6.4%)	2351(8.2%)	0.1695
Other	14(4.3%)	1764(6.2%)	
White	291(89.3%)	24527(85.6%)	
Insurance status			
No	12(3.7%)	1295(4.6%)	0.5063
Yes	314(96.3%)	26964(95.4%)	
Insurance type			
Private	97(29.8%)	14305(50.6%)	<0.0001
Medicare	176(54.0%)	10153(35.9%)	
Medicaid	30(9.2%)	2019(7.1%)	
Other	11(3.4%)	487(1.7%)	
None	12(3.7%)	1295(4.6%)	
Charlson-Deyo Score			
0	229(70.2%)	22922(80.0%)	<0.0001
1	67(20.6%)	4559(15.9%)	
2	19(5.8%)	880(3.1%)	
3	11(3.4%)	281(1.0%)	
Hospital location			
Midwest	134(42.4%)	8579(31.3%)	0.0003
South	72(22.8%)	8232(30.1%)	
Northeast	60(19.0%)	5947(21.7%)	
West	50(15.8%)	4612(16.9%)	
Hospital type-grouped			
Academic	216(68.4%)	9542(34.9%)	<0.0001
Community	11(3.5%)	2553(9.3%)	
Comprehensive community	89(28.2%)	15275(55.8%)	
Year of diagnosis			
2004	3(0.9%)	1005(3.5%)	<0.0001
2005	3(0.9%)	1195(4.2%)	
2006	2(0.6%)	1478(5.2%)	
2007	5(1.5%)	1670(5.8%)	
2008	9(2.8%)	2015(7.0%)	
2009	19(5.8%)	2255(7.9%)	
2010	28(8.6%)	2490(8.7%)	
2011	31(9.5%)	2735(9.5%)	
2012	25(7.7%)	3094(10.8%)	
2013	49(15.0%)	3356(11.7%)	
2014	68(20.9%)	3728(13.0%)	
2015	84(25.8%)	3621(12.6%)	
Tumor size (cm, median, IQR)			
N	286	21678	0.2303
Median	41.5	40	
Q1, Q3	30.0, 55.0	29.0, 55.0	
Clinical T stage			
1	5(1.5%)	248(0.9%)	0.1797
2	24(7.4%)	1475(5.2%)	
3	271(83.9%)	24515(86.9%)	
4	23(7.1%)	1988(7.0%)	
Clinical stage			
II	166(50.9%)	13176(46.0%)	0.0765
III	160(49.1%)	15466(54.0%)	

31%, p=0.0003), (Table 1). Use of SC-RT slightly increased from <1% of rectal cancer patients in 2004 to 2.3% in 2015 (p<0.0001).

Propensity matching

A total of 307 patients who underwent SC-RT were matched to 307 patients who underwent LC-RT. Following propensity matching, no significant differences were observed in patient demographics, clinical presentation, or hospital characteristics between the SC-RT *vs*. LC-RT treatment groups (Table 2).

Time from completion of RT to surgery was significantly shorter in the SC-RT group (median 14 *vs*. 99 days, p<0.0001). Pathologic tumor stage was not different between groups. However, patients undergoing SC-RT were less likely to achieve complete pathologic response (12% *vs*. 21%, p<0.0001) (Table 3). The rates of sphincter preservation, negative radial and/or circumferential margins were similar between groups. The percentage of adequate lymph node harvest of at least 12 nodes was greater in the SC-RT *vs*. LC-RT group (90% *vs*. 67%, p<0.0001). Hospital length of stay and 30-day readmissions was not different between treatment groups. Mortality within 90 days from surgery was significantly higher in the SC-RT versus LC-CRT group (8% *vs*. 1%, p=0.002).

Overall survival

Median follow-up time was 30 months. With propensity matching, overall survival was compromised for the SC-RT *vs*. LC-RT groups at 1 year (86% *vs*. 94%), 2 years (74% *vs*. 85%), and 5 years (47% *vs*. 51%), p=0.005 (Figure 1).

Sensitivity analysis

Before propensity matching, patients undergoing SC-RT were more likely older and have multiple comorbid conditions. This could have potentially influence the compromised overall survival difference observed in the SC-RT group. Therefore, a subset analysis of patients younger than 80 years and with comorbidity score of ≤ 1 was performed. This limited the cohort to 157 patients in each group (Table 4).

Hospital length of stay and the rates of 30-day readmission and 90-day mortality were similar between groups. Complete pathologic response remained less in the SC-RT (12% *vs*. 18%, p=0.0001); the

Table 2: Demographic and clinical characteristics of patients with stage II/III rectal cancer undergoing neoadjuvant radiation after propensity matching.

Variables	Short Course (N=307)	Long Course (N=307)	p-value
Patient age (Yrs, median, IQR)			
N	307	307	0.5409
Median	69	68	
Q1, Q3	58.0, 80.0	57.0, 80.0	
Patient age group			
<65 yrs	125(40.7%)	123(40.1%)	0.9629
65-79 yrs	101(32.9%)	100(32.6%)	
≥ 80 yrs	81(26.4%)	84(27.4%)	
Female gender	125(40.7%)	118(38.4%)	0.6205
Race			
Black	20(6.5%)	18(5.9%)	0.7627
Other	13(4.2%)	10(3.3%)	
White	274(89.3%)	279(90.9%)	
Insurance status			
No	10(3.3%)	8(2.6%)	0.8118
Yes	297(96.7%)	299(97.4%)	
Insurance type			
Private	90(29.3%)	91(29.6%)	0.9722
Medicare	167(54.4%)	172(56.0%)	
Medicaid	29(9.4%)	26(8.5%)	
Other	11(3.6%)	10(3.3%)	
None	10(3.3%)	8(2.6%)	
Charlson-Deyo Score			
0	214(69.7%)	214(69.7%)	0.9331
1	63(20.5%)	67(21.8%)	
2	19(6.2%)	17(5.5%)	
3	11(3.6%)	9(2.9%)	
Hospital location			
Midwest	131(42.7%)	106(34.5%)	0.0671
South	69(22.5%)	88(28.7%)	
Northeast	58(18.9%)	72(23.5%)	
West	49(16.0%)	41(13.4%)	
Hospital type-grouped			
Academic	211(68.7%)	208(67.8%)	0.9076
Community	11(3.6%)	13(4.2%)	
Comprehensive community	85(27.7%)	86(28.0%)	
Year of diagnosis			
2004	3(1.0%)	3(1.0%)	0.9351
2005	3(1.0%)	3(1.0%)	
2006	2(0.7%)	2(0.7%)	
2007	5(1.6%)	5(1.6%)	
2008	9(2.9%)	10(3.3%)	
2009	15(4.9%)	14(4.6%)	
2010	27(8.8%)	26(8.5%)	
2011	30(9.8%)	29(9.4%)	
2012	23(7.5%)	23(7.5%)	
2013	45(14.7%)	47(15.3%)	
2014	66(21.5%)	65(21.2%)	
2015	79(25.7%)	80(26.1%)	
Tumor size (cm, median, IQR)			
N	271	248	0.5326
Median	42	40	
Q1, Q3	30.0, 55.0	30.0, 55.5	
Clinical T stage			
1	5(1.6%)	1(0.3%)	0.1885
2	21(6.9%)	14(4.6%)	
3	256(84.2%)	269(89.1%)	
4	22(7.2%)	18(6.0%)	
Clinical stage			
II	154(50.2%)	147(47.9%)	0.572
III	153(49.8%)	160(52.1%)	

rates of sphincter preservation, negative radial and/or circumferential margins were similar. Overall survival trended towards statistical significance for the SC-RT *vs.* LC-RT group at 1 year (92% *vs.* 98%), 2 years (81% *vs.* 95%), and 5 years (66% *vs.* 73%), p=0.058 (Figure 2).

Discussion

This nationwide study examined patterns of use and outcomes of neoadjuvant SC-RT for patients with resectable, locally advanced rectal adenocarcinoma in the US. Use of SC-RT is slowly increasing, but remains significantly low, only 2.3% of neoadjuvant radiation therapy was administered as SC-RT in 2015. In the US, there is significant regional variation, with increased adoption among academic centers compared to comprehensive and community programs. Patients undergoing SC-RT were more often older and have comorbid conditions, but they tended to have early tumor stage. SC-RT associated with a lower rate of pathologic complete response, but had equivalent rates of margins negativity and sphincter preservation. Overall, SC-RT *vs.* LC-RT associated with compromised overall survival; however, when the analysis limited to patients <80 years and have less comorbidities, overall survival tended towards being compromised in the SC-RT group (p=0.06).

Practice guidelines recommend the use of neoadjuvant radiation for patients with resectable, locally advanced rectal cancer [11], with data demonstrating significant reduction in locoregional recurrence and reported improved survival [12-15]. Traditionally, long-course chemoradiation has been the standard in the management of rectal cancer; however, use of SC-RT may have several advantages including improved patient convenience and compliance and possible lower toxicities, and decreased costs.

Several randomized clinical trials were performed to examine the oncologic effective and safety of SC-RT compared to LC-RT. However, none of these trials were done in the US [7-9]. Bujko et al. [7]. Randomized 312 rectal cancer patients in Poland to SC-RT with surgery within a week or LC-RT with surgery after 4 to 6 weeks. They reported increased surgical toxicities in the LC-RT group, but equivalent disease-free survival and 4-year overall survival [16]. In the Stockholm III trial, Erlandsson and colleagues randomized 840 Swedish patients with stage I-IV rectal adenocarcinoma to receive

Table 3: Pathologic and clinical outcomes among propensity matched stage II/III rectal cancer patients.

Variables	Short Course (N=307)	Long Course (N=307)	p-value
Pathologic stage			
I	64(26.9%)	62(31.6%)	0.742
II	74(31.1%)	55(28.1%)	
III	96(40.3%)	76(38.8%)	
IV	4(1.7%)	3(1.5%)	
Pathologic response			
Complete	14(12.0%)	33(20.8%)	<0.0001
Moderate	12(10.3%)	57(35.8%)	
Yes, NOS	21(17.9%)	29(18.2%)	
No	70(59.8%)	40(25.2%)	
Time to surgery (days)			
N	261	247	<0.0001
Median	14	99	
Q1, Q3	9.0, 30.0	90.0, 113.0	
Sphincter preservation			
No	81(32.5%)	66(27.4%)	0.2371
Yes	168(67.5%)	175(72.6%)	
Extent of surgery			
Low anterior resection	168(67.5%)	175(72.0%)	0.2884
Abdominoperineal Resection	72(28.9%)	60(24.7%)	
Exenteration	9(3.6%)	6(2.5%)	
LN harvest			
<12	26(10.1%)	75(33.5%)	<0.0001
≥ 12	231(89.9%)	149(66.5%)	
Hospital length of stay			
N	240	214	0.186
Median	7	6	
Q1, Q3	5.0, 10.0	4.0, 9.0	
Surgical margins			
Negative	248(95.4%)	234(94.7%)	0.8383
Positive	12(4.6%)	13(5.3%)	
Circumferential resection margin			
Negative	169(91.8%)	178(94.2%)	0.4204
Positive	15(8.2%)	11(5.8%)	
90-day mortality	15(7.9%)	2(1.1%)	0.0019
Adjuvant chemotherapy	86(28.7%)	77(25.6%)	0.41

neoadjuvant radiation therapy in SC-RT with immediate resection, SC-RT with delayed resection, and LC-RT with delayed resection; the primary outcome of time to local recurrence. Their findings included equivalent time to local recurrence between the three arms, equivalent local and distant recurrence, recurrence free survival, and overall survival. Patients undergoing SC-RT with delay experienced fewer postoperative complications compared to SC-RT with immediate resection; however there was an increased risk of radiation toxicity in this group [8].

Based on these published trials, the National Comprehensive Cancer Network (NCCN) amended its guidelines in 2016 to include SC-RT for patients without T4 disease. Despite this and the encouraging outcomes from these trials [7,9,17], SC-RT is only used in <3% of contemporary cases of locally advanced rectal cancer, with the overwhelming majority of patients undergoing LC-CRT. This is consistent with a previous report exploring patterns of treatment for locally advanced rectal cancer in the US from 2004-2012 [2]. Potential explanations of low adoption of this technique have been proposed including concern over limited clinical follow-up [18], late toxicity [16], and insufficient down staging [10,19]. In a survey study of 182 radiation oncologists (the majority of whom participate in multidisciplinary discussion in tumor boards settings), while the vast majority of participants expressed awareness of the SC-RT *vs.* LC-RT trials, the overwhelming majority (96%) of participants preferred the use of LC-RT *vs.* SC-RT and chose not to use SC-RT. Even among radiation oncologists who used SC-RT, many revealed that they would prescribe SC-RT not as a first line, but for selected patients with comorbidities, those who are not anticipated to receive chemotherapy, and patients with geographic barriers to attending LC-CRT [10]. The reluctance to adopt SC-RT in the US may be related to lack of data from US patients.

These trials were done in different countries that have nationalized health care system with more emphasis on cost reduction and decreasing wait times. It may be argued that these factors may result in a push to implement SC-RT more aggressively, with some potential implication on patient selection and/or outcomes. Nevertheless, these trials clearly demonstrated the oncologic safety of SC-RT. This may argue for level 1 data performed in the US.

In our study, SC-RT was more likely to be offered for older patients and patients with comorbid conditions. This may reflect attitudes of US radiation oncologists towards SC-RT, as not been seen as an equivalent neoadjuvant modality. This assumption is corroborated in Mowery et al. survey study demonstrating that for 79% of surveyed US radiation oncologist's patient comorbidities influenced preference towards SC-RT [10].

We reported that the likelihood of pathologic complete responsiveness is less with SC-RT v*s.* LC-RT. While this in contradiction to the Polish and the Stockholm trials [7,8], the Tasman Radiation Oncology Group trial showed a non-significant increased risk of local recurrence with SC-RT (7.5% *vs.* 5.7%); however, survival was not different. A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for SC-RT compared to no recurrence for LC-RT [19].

In the current study, overall survival appeared compromised among patients who underwent SC-RT compared to those who underwent LC-RT. Because of the tendency towards selecting older and sicker patients for SC-RT, we performed a sensitivity analysis by limiting the cohort to those <80 years and have a comorbid score ≤ 1. Among this younger and healthier cohort, overall survival was not different between SC-RT *vs.* LC-RT. However, there was a trend towards compromised survival among the SC-RT. Given the limitations of this retrospective review and the strong selection bias observed, we believed that it is difficult to make conclusions about the effect of SC-RT on survival just based on our study. However, these results argue for level 1 data from the US reporting on long-term survival about the safety of SC-RT perhaps in the setting of sequential chemotherapy. The recently published phase III Polish trial randomized patients with fixed clinical T3 or T4 rectal cancer

to either SC-RT with consolidated chemotherapy or LC-RT with chemotherapy. SC-RT was equivalent to LC-RT in local control; however, SC-RT associated with improved overall survival and acute toxicity [7].

The limitations of the NCDB are well characterized including the potential for coding errors, and retrospective nature of the dataset. Compared to patients in randomized control trials the included patients were subject to selection and indication bias, and incomplete characterization of the practice patterns of the participating surgeons. These confounding factors have been minimized through propensity matching in the analysis, however the small number of patients undergoing SC-RT makes definitive conclusions difficult to ascertain. Patients who underwent SC-RT were more often older and had comorbidities. This could have potentially played a factor in the observed survival difference. However, we attempted to mitigate this bias by performing sensitivity analysis of younger and healthier patients in subgroup analysis. Limitations in the granularity of the NCDB with the inability to know what agent of chemotherapy was administered, if any, during LC-RT. Additionally, while local recurrence is an important endpoint in the randomized control trials, it is not captured in the NCDB, nor is disease-free or recurrence-free survival. Compared to the recent Stockholm III trial results, patients in the US who received SC-RT underwent immediate resection of their tumors, and no conclusions can be drawn regarding the impact of delayed resection. Despite these limitations, overall survival is a clinically important end-point. This is the first characterization of contemporary use of SC-RT in the US, prompting additional studies of efficacy and implementation in this heterogeneous population.

Conclusion

Use of SC-RT for locally advanced rectal adenocarcinoma in the US is slowly increasing in frequency but remains significantly low. This may be related to skepticism about its oncologic effectiveness in the absence of data of randomized patients in the US. While surgical outcomes appear to be comparable to conventional LC-RT, the rate of complete pathologic responsiveness is lower with SC-RT compared with LC-RT. This study argues for more evidence examining the impact of SC-RT on long-term survival perhaps in the setting of sequential chemotherapy.

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