



# The Financial Impact of Fractionation Scheme and Treatment Planning Method for Rectal Cancer in the United States

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## Abstract

**We performed a population-based analysis of the total annual cost of various radiotherapy regimens for rectal cancer in the United States. The target population was estimated using the Surveillance, Epidemiology, and End Results database and radiotherapy costs by the Hospital Outpatient Prospective Payment System. Short-course radiotherapy may have the potential to save US \$106 to 232 million annually compared with long-course chemoradiotherapy, likely without impacting outcomes. Intensity-modulated radiotherapy increases the cost of treatment by 34% and 50% for short-course and long-course chemoradiotherapy, respectively.**

**Background:** Preoperative long-course chemoradiotherapy (CRT) and short-course radiotherapy (SCR) for locally advanced rectal cancer (LARC) were found to have equivalent outcomes in 3 randomized trials. SCR has not been widely adopted in the United States (US). Three-dimensional (3D) treatment planning is standard, whereas intensity-modulated radiotherapy (IMRT) is controversial. In this study, we assessed the economic impact of fractionation scheme and planning method for payers in the US. **Materials and Methods:** We performed a population-based analysis of the total cost of radiotherapy for LARC in the US annually. The national annual target population was calculated using the Surveillance, Epidemiology, and End Results database. Radiotherapy costs were based on billing codes and 2018 pricing by Medicare's Hospital Outpatient Prospective Payment System. **Results:** We estimate that 12,945 patients with LARC are treated with radiotherapy annually in the US. The cost of CRT with 3D or IMRT is US \$15,882 and \$23,745 per patient, respectively. With SCR, the cost with 3D or IMRT is \$5,458 and \$7,323 per patient, respectively. The use of SCR would lead to 53% to 77% annual savings of \$106,168,871 to \$232,105,727 compared with CRT. IMRT increases the total cost of treatment by 34% to 50%, and if adopted widely, would lead to an excess cost of \$24,152,134 and \$101,784,723 annually with SCR and CRT, respectively. **Conclusions:** SCR may have the potential to save approximately US \$106 to t232 million annually in the US, likely without impacting outcomes. Lack of evidence showing benefit with costly IMRT should limit its use to clinical trials. It would be reasonable for public and private payers to consider which type of radiation is most suited to reimbursement.

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**Keywords:** Chemoradiation, Hypofractionation, Intensity-modulated radiotherapy, Radiotherapy, Short-course radiotherapy

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## Introduction

Colorectal cancer is the third most common cancer diagnosed in the United States (US) and the third leading cause of cancer death.<sup>1</sup> Of newly diagnosed patients with colorectal cancer, 30.7% are rectal cancers.<sup>1</sup> Of rectal cancer cases, 38% and 36% are diagnosed with localized and regional disease, respectively.<sup>2</sup>

The benefit of combined modality treatment for rectal cancer was demonstrated in multiple trials. In a Dutch trial, local recurrence was 5% in the group randomized to short course preoperative radiotherapy (SCR) and surgery and 11% in the surgery-alone

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group ( $P < .0001$ ). Although overall survival did not differ between groups, there was a significant difference in 10-year cancer-specific deaths with radiotherapy (RT).<sup>3</sup>

The sequence of treatment modalities has also been a subject of research. In a German trial, preoperative chemoradiation (CRT) demonstrated a significant decrease in local failure over postoperative CRT (6% vs. 13%;  $P = .006$ ) with no significant effect on disease-free survival, overall survival, or sphincter preservation. There was significantly less acute and late toxicity with preoperative CRT.<sup>4</sup> This study established preoperative treatment as the standard of care. National Surgical Adjuvant Breast and Bowel Project R-03 (NSABP R-03) compared pre- and postoperative CRT in T3 to 4 or node-positive patients. There was a significant advantage in 5-year disease-free survival with preoperative CRT.<sup>5</sup>

Different fractionation schemes have been explored. SCR was initially associated with a higher rate of toxicities.<sup>6</sup> However, later trials comparing it with standard CRT have generally found similar outcomes.<sup>7,8</sup> Notably, although there were significantly more acute serious adverse events with CRT, rates of late toxicity were not significantly different.<sup>8</sup> Initial results from a study comparing pathologic downstaging with delayed surgery after CRT or SCR found a trend to more pathologic downstaging with CRT; however, there was no difference in R0 resection or sphincter preservation rates.<sup>9</sup>

Intensity-modulated radiotherapy (IMRT) was studied in rectal cancer with the intention to minimize toxicity to normal tissues and improve the therapeutic ratio by the more conformal treatment delivery. However, lack of prospective data demonstrating benefit from this costly time-consuming method makes it controversial.<sup>10</sup>

The most recent clinical practice statement by the American Society of Radiation Oncology (ASTRO) rates SCR as “appropriate” for intermediate risk disease (T1-2N1 or T3N0)  $\leq 10$  cm from the anal verge and  $\geq 2$  mm from the edge of the mesorectal fascia and for moderate- to high-risk disease (T1-2N2, T3N1, or T4N0)  $< 5$  cm from the anal verge or  $\geq 5$  cm from the anal verge and  $\geq 2$  mm from the mesorectal fascia. For alternative indications, it was defined as “may be appropriate.”<sup>11</sup> However, the most recent Clinical Practice Guidelines from the European Society of Medical Oncology (ESMO) have determined that there is no clear definition of which T and N sub-stages require CRT over SCR. These guidelines suggest that selection of the preoperative approach is based more on the risk of a positive circumferential resection margin at total mesorectal excision surgery. If either circumferential resection margin and/or R0 resection status are predicted at risk, CRT is advised.<sup>12</sup> However, a more recent trial found no difference in local efficacy between SCR and consolidation chemotherapy compared with CRT in cT4 or advanced cT3 rectal cancer.<sup>13</sup>

Regarding the treatment planning method, the ASTRO clinical practice statement states that IMRT-based CRT (CRT-IMRT) or SCR “may be appropriate,”<sup>11</sup> whereas The National Comprehensive Cancer Network (NCCN) clearly states that IMRT should only be used in the setting of a clinical trial or unique situations such as recurrent disease or re-irradiation.<sup>14</sup>

In recent years, there has been an increasing focus placed on understanding the cost and value of cancer care. This has led to the development of various frameworks that aim to understand value.<sup>15,16</sup> Although the focus has been on pharmaceutical

interventions, there are widespread opportunities for improving value in other fields such as surgery, radiation, and end-of-life care.

The objective of this study was to assess the difference in cost between CRT (traditional three-dimensional [3D] based [CRT-3D] and CRT-IMRT) and SCR (SCR-3D and SCR-IMRT) from the payers' perspective of the US.

## Materials and Methods

### Methodological Overview

We performed a population-based budget impact analysis according to the guidelines set forth by the International Society of Pharmacoeconomics and Outcomes Research.<sup>17</sup> We performed the analysis from the payer's perspective in the US. The budget impact model was developed using Matlab version R2018b (The Mathworks, Inc).

### Target Population

We used the Surveillance, Epidemiology, and End Results (SEER) database to estimate the target population of patients treated annually with external beam radiotherapy (EBRT) for rectal cancer. We performed a frequency analysis on treatment with EBRT for localized and regional rectal cancer in the latest year summarized in the SEER cancer statistics, 2014.<sup>18</sup> We excluded all patients who refused EBRT and cases in which it is unknown whether EBRT was eventually administered. We then estimated the total number of patients treated in the US by extrapolation, based on the fact that the SEER database covers approximately 28% of the US population. We therefore multiplied the results by 3.57.

### Radiation Treatment Cost Estimates

In order to estimate treatment costs for various fractionation schemes, we used billing codes by the Outpatient Prospective Payment System (OPPS) 2018 pricing.<sup>18</sup> We performed multiple analyses to assess the societal cost when different fractionation regimens are used nationwide. The billing codes included and price of various fractionation schemes (28 fractions of CRT and 5 fractions of SCR by planning method) are presented in Tables 1-4. To calculate annual costs, we regarded all patients treated annually with EBRT as if all were treated with the same fractionation scheme and planning method. We then calculated the total annual cost of treatment, and then the annual saving for various fractionation schedules and techniques. As tolerability was generally equal, we included the EBRT-associated cost only with no consideration of adverse event management.

### Chemotherapy Cost Estimates

We have included the 2 well-established standard-of-care concurrent chemotherapy regimens in our analysis: capecitabine at 825 mg/m<sup>2</sup> twice daily and continuous infusion fluorouracil at 200 mg/m<sup>2</sup>, both 5 days a week during CRT. The cost of chemotherapy was based on the Payment Allowance Limits for Medicare Part B Drugs by Centers for Medicare and Medicaid Services (CMS).<sup>19</sup> The price for 500 mg of fluorouracil and capecitabine is US \$1.79 and \$3.51, respectively. The mean dose was calculated based on mean US values for body-surface area of 1.86 m<sup>2</sup> and body weight of 82 kg.<sup>20</sup> The cost of intravenous (IV) catheter insertion and IV treatment handling should be taken into account for continuous infusion fluorouracil-based CRT. The cost of catheter insertion and

**Table 1** CPT Codes and Prices for Short-course Radiotherapy

CPT Code	Description	Number of Units	Cost per Unit, <sup>a</sup> \$	Total Cost, \$
<b>Treatment planning codes</b>				
77290	Simulation: complex	1	426.56	426.56
77280	Simulation: simple	1	170.75	170.75
77295	3D plan	1	1484.60	1,484.60
77263	Treatment planning complex	1	179.91	179.91
77300	Basic dose calculation	3	166.26	498.78
<b>Treatment delivery codes</b>				
77334	Treatment device: complex	3	403.52	1,210.56
77427	Weekly treatment management	1	201.63	201.63
77336	Physics consult hour	1	131.52	131.52
77412	Treatment delivery; complex	5	230.66	1,153.30
Total cost per patient - \$5,457.61				

Abbreviations: CPT = Current Procedural Terminology; 3D = 3-dimensional.

<sup>a</sup>The total cost per code includes the professional component and technical charge when applicable.

prolonged chemotherapy infusion initiation with a pump by the Current Procedural Terminology, 4th Edition (CPT) 2018 pricing by the CMS (codes 36561 and 96416) are \$382.31 and \$147.24, respectively. We have excluded neoadjuvant (non-concurrent) and adjuvant chemotherapy from this analysis as there is no clear consensus of their use.

### Sensitivity Analysis

A 10% range was applied for all parameters of the model. We performed a univariate sensitivity analysis to assess which parameters had the greatest impact on cost savings. A probabilistic sensitivity analysis was performed using a Monte Carlo simulation. The model was run 100,000 times, using the parameters included.

### Results

Our frequency analysis of the SEER database for patients with rectal cancer referred for radiotherapy in 2014 found that a

total of 3626 patients were treated with EBRT. One thousand sixty-six of these patients had localized disease, whereas 2560 had regional disease. A total of 4663 patients were either not treated with EBRT or it is unknown whether it was administered (Figure 1). As the SEER database covers 28% of the population, we estimate that approximately 12,945 patients with rectal cancer would be treated annually with radiation in the US.

The cost of chemotherapy is drug-dependent. Assuming normal renal function, the mean daily dose of capecitabine is 3069 mg — rounded down to 3000 mg for simplification, which is \$21.05 per day and \$589.51 per treatment course. With continuous infusion fluorouracil, the mean daily dose is 372 mg, which is \$1.33 per day and \$37.38 per treatment course. The treatment course includes 6 prolonged chemotherapy infusion initiations with a pump, thus the total cost of IV treatment handling with continuous infusion fluorouracil is \$883.44.

**Table 2** CPT Codes and Prices for IMRT-based Short-course

CPT Code	Description	Number of Units	Cost per Unit, <sup>a</sup> \$	Total Cost, \$
<b>Treatment planning codes</b>				
77301	IMRT treatment plan	1	1,690.42	1,690.42
77263	Treatment planning complex	1	179.71	179.71
77338	Multileaf collimator for IMRT	1	578.47	578.47
77300	Basic dose calculation	3	166.26	498.78
<b>Treatment delivery codes</b>				
77332	Treatment device: complex	1	403.61	403.61
77386	IMRT treatment delivery; complex	5	548.04	2,740.2
77014	Cone beam	5	47.56	237.8
77470	Special treatment procedure	1	661.22	661.22
77336	Physics consult hour	1	131.52	131.52
77427	Weekly treatment management	1	201.63	201.63
Total cost of radiotherapy per patient - \$7,323.36				

Abbreviations: CPT = Current Procedural Terminology; IMRT = intensity-modulated radiotherapy.

<sup>a</sup>The total cost per code includes the professional component and technical charge when applicable.

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**Table 3** CPT Codes and Prices for Long-course 3D-based Chemoradiotherapy

CPT Code	Description	Number of Units	Cost per Unit, <sup>a</sup> \$	Total Cost, \$
<b>Treatment planning codes</b>				
77290	Simulation: complex	1	426.56	426.56
77280	Simulation: simple	1	170.75	170.75
77295	3D plan	1	1,484.60	1,484.60
77263	Treatment planning complex	1	179.91	179.91
77300	Basic dose calculation	3	166.26	498.78
<b>Treatment delivery codes</b>				
77332	Treatment device: simple	1	157.19	157.19
77334	Treatment device: complex	3	403.52	1,210.56
77412	Treatment delivery: complex	28	230.66	6,458.48
77014	Cone beam	28	47.56	1,331.68
77470	Special treatment procedure	1	661.22	661.22
77336	Physics consult hour	6	131.52	789.12
77427	Weekly treatment management	6	201.63	1,209.78
Total cost of radiotherapy per patient - \$14,578.63				
• With fluorouracil \$15,881.76				
• With capecitabine - \$15,168.03				

Abbreviation: CPT = Current Procedural Terminology; 3D = 3-dimensional.  
<sup>a</sup>The total cost per code includes the professional component and technical charge when applicable.

The cost of various radiotherapy fractionation schemes is summarized in Tables 1-4 and ranges between \$5,457 for SCR-3D and \$22,441 for CRT-IMRT.

The total cost per treatment course includes radiotherapy and chemotherapy when applicable. Thus, CRT-3D with capecitabine or continuous infusion of fluorouracil costs \$15,168.03 or \$15,881.76. CRT-IMRT with capecitabine or continuous infusion fluorouracil, costs \$23,030.89 or \$23,744.62. The saving per

patient with SCR compared with CRT ranges between 52.8% (when comparing CRT-3D and SCR-IMRT) and up to 76.7% (when comparing CRT-IMRT and SCR-3D).

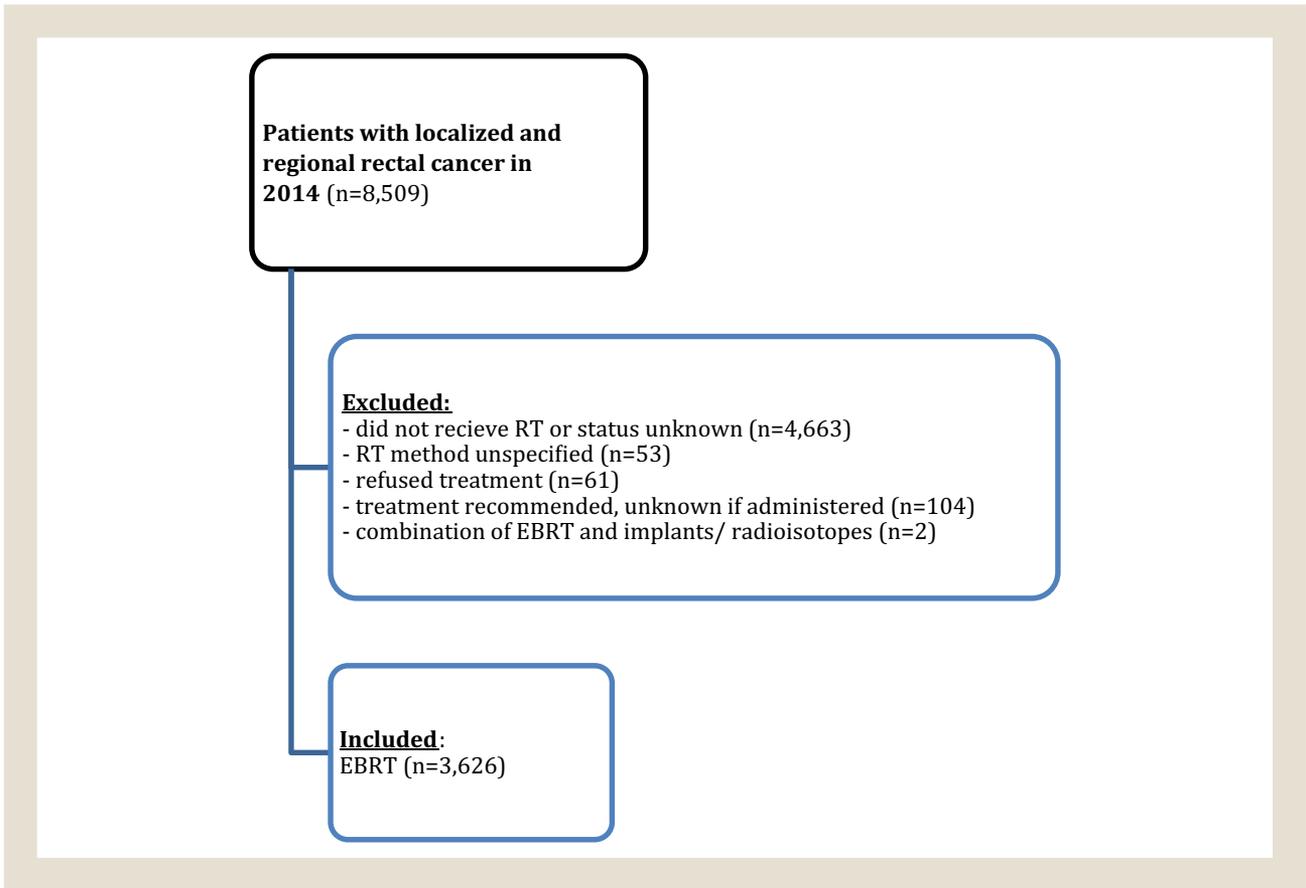
In our analysis, the annual cost to healthcare payers of standard fractionated EBRT is approximately \$200,969,766 (\$196,350,148 and \$205,589,383 for CRT-3D with capecitabine and continuous infusion fluorouracil, respectively). For CRT-IMRT, it is approximately \$302,754,488 (\$298,134,871 and \$307,374,106 with

**Table 4** CPT Codes and Prices for Long-course IMRT-based Chemoradiotherapy

CPT Code	Description	Number of Units	Cost per Unit, <sup>a</sup> \$	Total Cost, \$
<b>Treatment planning codes</b>				
77301	IMRT treatment plan	1	1,690.42	1,690.42
77263	Treatment planning complex	1	179.71	179.71
77338	Multileaf collimator for IMRT	1	578.47	578.47
77300	Basic dose calculation	3	166.26	498.78
<b>Treatment delivery codes</b>				
77332	Treatment device: simple	1	157.19	157.19
77386	IMRT treatment delivery; complex	28	548.04	15,345.12
77014	Cone beam	28	47.56	1,331.68
77470	Special treatment procedure	1	661.22	661.22
77336	Physics consult hour	6	131.52	789.12
77427	Weekly treatment management	6	201.63	1,209.78
Total cost of radiotherapy per patient - \$22,441.49				
• With fluorouracil — \$23,744.62				
• With capecitabine — \$23,030.89				

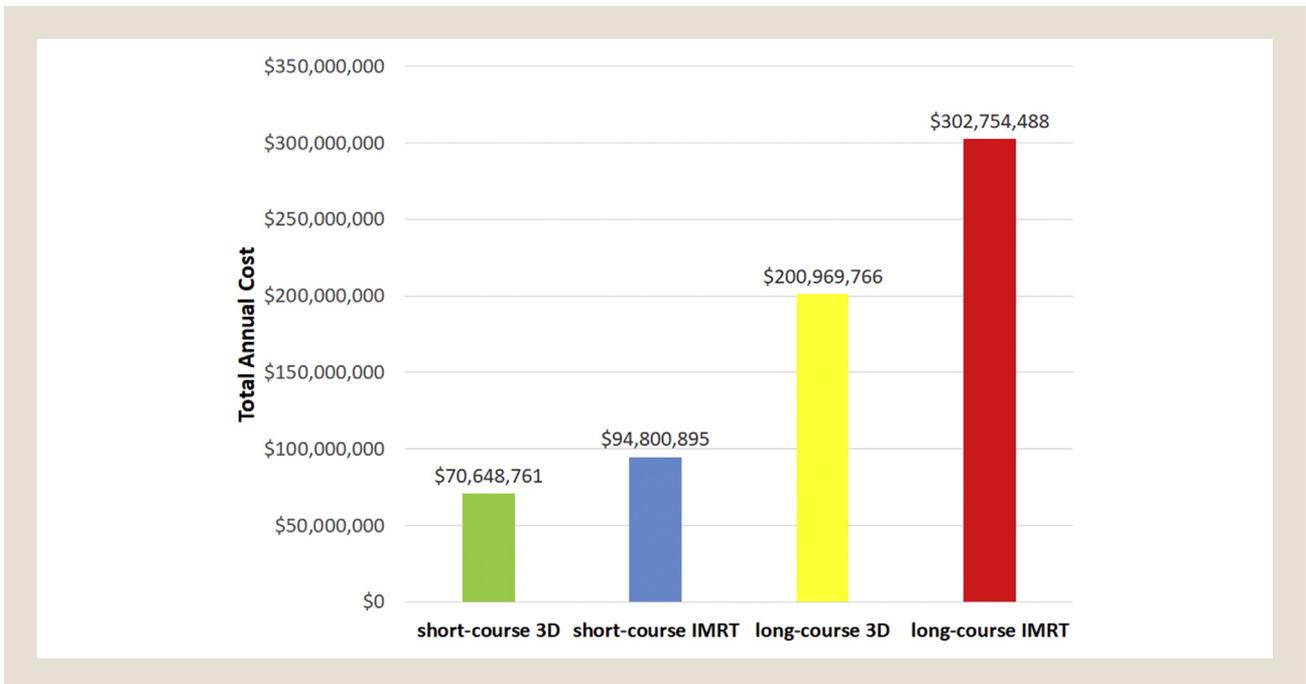
Abbreviations: CPT = Current Procedural Terminology; IMRT = intensity-modulated radiotherapy.  
<sup>a</sup>The total cost per code includes the professional component and technical charge when applicable.

**Figure 1** Target Population Estimation by the Surveillance, Epidemiology, and End Results Database



Abbreviations: EBRT = external beam radiotherapy; RT = radiotherapy.

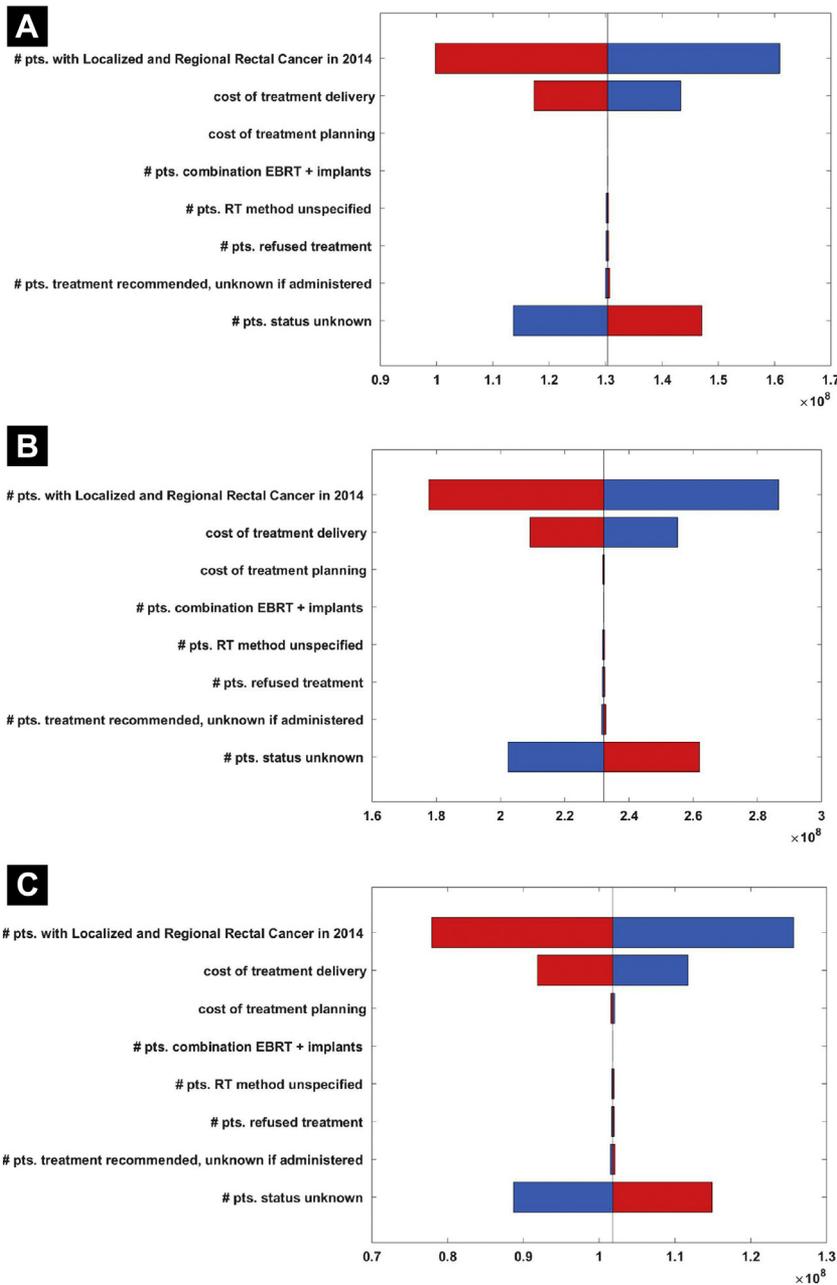
**Figure 2** Total Annual Cost to United States Healthcare Payers by Fractionation Scheme and Planning Method



Abbreviation: IMRT = intensity-modulated radiotherapy.

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**Figure 3** Univariate Sensitivity Analysis for Various Parameters' Impact on Total Cost of Treatment by Fractionation Scheme and Planning Method. A, CRT-3D Versus SCR-3D; B, CRT-IMRT Versus SCR-3D; C, CRT-3D Versus CRT-IMRT; D, SCR-3D Versus SCR-IMRT; E, CRT-3D Versus SCR-IMRT; F, CRT-IMRT Versus SCR-IMRT



Abbreviations: CRT = long-course chemoradiotherapy; 3D = 3-dimensional; EBRT = external beam radiotherapy; IMRT = intensity-modulated radiotherapy; RT = radiotherapy; SCR = short-course radiotherapy.

capecitabine and continuous infusion fluorouracil, respectively). With SCR, the annual US cost to healthcare payers is approximately \$70,648,761 and \$94,800,895 for SCR-3D and SCR-IMRT, respectively (Figure 2). Adopting SCR as the standard of care could lead to an annual savings of \$106,168,871 to \$232,105,727.

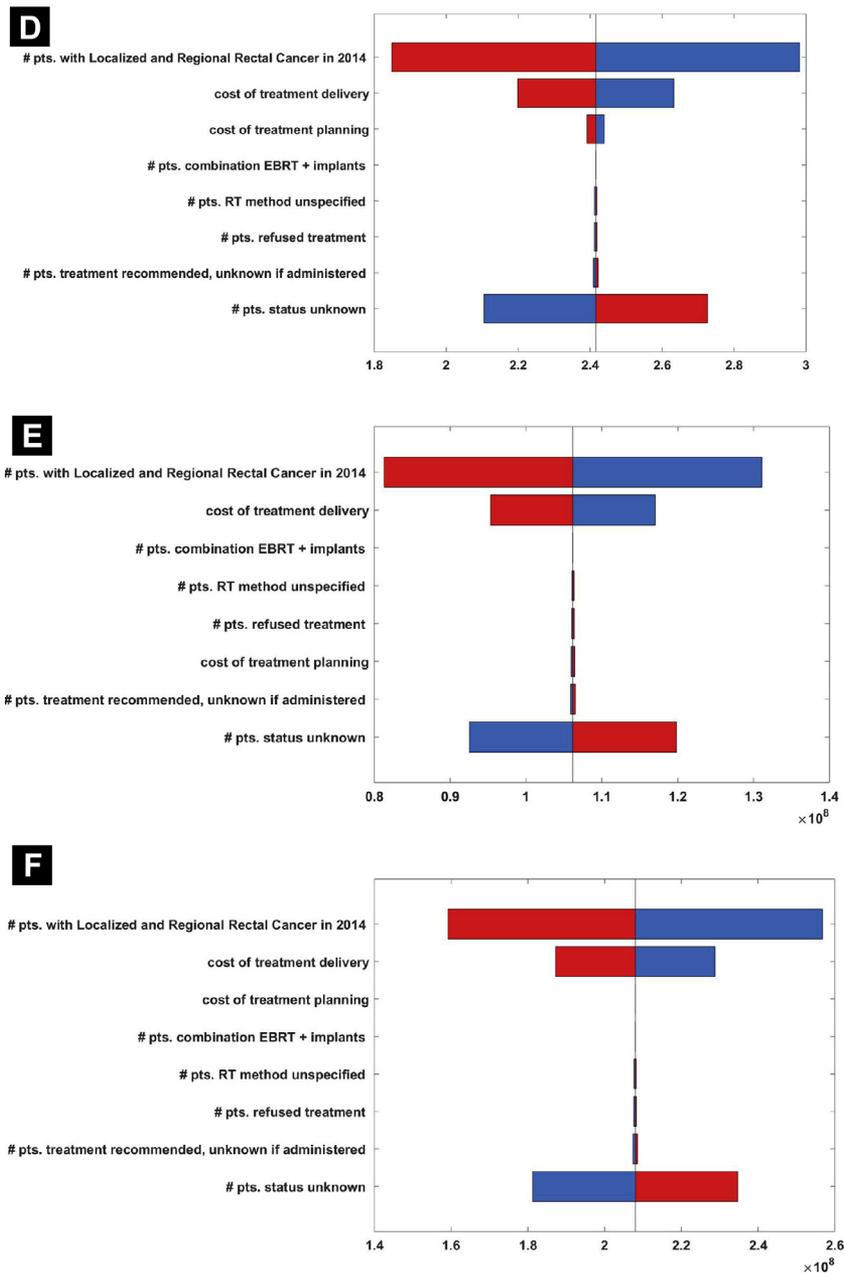
The univariate sensitivity analysis (Figure 3) demonstrates that the model variables with the greatest potential impact on the

differences in annual cost of each fractionation scheme are the target population size, IMRT treatment delivery, and number of fractions.

## Discussion

We performed an estimation of the impact of fractionation and treatment planning method on the annual cost of radiation therapy

Figure 3 continued



for localized and regional rectal cancer in the US. We have shown that the annual cost could be decreased between 53% and 77% with SCR and that IMRT increases the cost of CRT by approximately 34% to 50%. These differences are mostly attributed to the total number of fractions per treatment course and the higher cost of IMRT. The relevance of this analysis is dependent on the clinical equivalency between standard CRT and SCR, which has been proven in several randomized trials<sup>7,8,13</sup> as well as on the lack of proven benefit with IMRT.<sup>10</sup> Also, from the patient's perspective, a shorter treatment course would be more convenient with lower travel expenses and a shorter absence from work.

Although there may be more acute toxicity with CRT,<sup>7</sup> there is no difference in late toxicities.<sup>7,8</sup> It seems then that toxicity may have an indirect minor effect on the difference in cost.

A very relevant question with locally advanced disease is whether SCR can effectively downstage tumors. In a study evaluating SCR with delayed surgery, tumor regression was visible on magnetic resonance imaging in 74% of patients and the pathologic T and N stages were significantly lower than clinically assessed at presentation.<sup>21</sup> The Stockholm III trial compared early versus delayed surgery after SCR, and found that downstaging was significantly more common with delayed surgery.<sup>22</sup> It appears that SCR can also

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achieve tumor shrinkage. Although it is known that tumor regression is prognostic with CRT,<sup>22</sup> it seems that higher rates of pathologic complete response or downstaging with CRT do not lead to superior outcomes compared with SCR.<sup>8</sup>

IMRT has proven to be cost-effective in the treatment of several clinical scenarios<sup>23-26</sup>; however, its role in rectal cancer has not yet been well-defined. IMRT generally allows a more conformal dose delivery. However, costs are significantly higher than 3D, and robust efficacy data are lacking. In a retrospective report comparing IMRT with 3D planning, IMRT was associated with significantly less toxicities, hospitalizations, emergency department visits, and treatment breaks with no negative impact on outcomes.<sup>22</sup> In another retrospective report, patients treated with IMRT had significantly less gastrointestinal toxicity without negatively impacting outcomes.<sup>27</sup> Radiation Therapy Oncology Group (RTOG) 0822 was a phase II trial for CRT-IMRT with concurrent capecitabine and oxaliplatin. This study was compared with the RTOG 0247 trial, which used the same chemotherapy regimen with non-IMRT pelvic radiotherapy with no significant toxicity benefit to IMRT.<sup>10</sup> However, the addition of oxaliplatin is known to increase gastrointestinal toxicity,<sup>28</sup> and thus, these results are difficult to interpret. An ASTRO panel rated IMRT as “may be appropriate” for advantages such as reduced toxicity and disadvantages such as the higher financial costs.<sup>29</sup> In a study of treatment patterns based on the prospective NCCN Colorectal Cancer Database between 2005 and 2011, 80% of patients were treated with CRT-3D and 17% with CRT-IMRT. Although IMRT use increased from under 13% before 2009 to over 30% in 2010, there was significant variability in its use among institutions.<sup>30</sup> IMRT may be attractive when higher doses per fractions are used, such as short-course RT and in specific clinical scenarios such as re-irradiation, patients with medical comorbidities such as inflammatory bowel disease, or a pelvic kidney, which may be associated with higher toxicity from pelvic radiotherapy.

There are multiple limitations of our study. First, estimating the target population of patients receiving radiation is extremely difficult. We used data from 2014, but multiple trends may cause this estimation to be inaccurate. We did not account for indirect personal costs such as transportation-related expenses and loss of work. Ongoing trials could change the treatment paradigm in the future. For example, the Preoperative Radiation Or Selective Preoperative Radiation and Evaluation before Chemotherapy and Total Mesorectal Excision (PROSPECT) trial is randomizing patient to standard CRT versus perioperative FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) with CRT reserved to poor responders to chemotherapy or poor surgical outcomes.<sup>31</sup> This trial could establish perioperative FOLFOX as an alternative to RT and reduce the number of patients treated. Moreover, SCR is not a part of this trial. On the other hand, the Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial randomized patients between CRT followed by surgery and optional adjuvant CAPOX (capecitabine and oxaliplatin) and SCR followed by neoadjuvant CAPOX and then surgery.<sup>32</sup> In our analysis, we did not account for costs of neoadjuvant or adjuvant chemotherapy, but rather only standard-of-care concurrent chemotherapy. To perform comparisons, we regarded all

patients treated with RT in 2014 as if they were treated with the same fractionation, chemotherapy, and planning method, whereas in reality, there may have been significant heterogeneity. When calculating costs, we referred to the OPPS; however, this represents only one aspect of the US health care system and may under- or overestimate costs. Although data shows that SCR could decrease costs, it is still not considered first-line treatment by most cancer centers in the US.

## Conclusion

SCR may have the potential to save in the region of US \$106 to 232 million annually in the US, likely without impacting outcomes. Although its equivalence with CRT has been shown in several trials, it seems clinicians have largely been reluctant to adopt SCR. Ongoing trials may provide more convincing data and lead to a more widespread use. Lack of evidence showing benefit with costly IMRT should prevent it from being the current standard-of-care. SCR may also lead to lower personal financial toxicity. It would be reasonable for public and private payers to consider which type of radiation is most suited to reimbursement.

## Clinical Practice Points

- The benefit of combined modality treatment for rectal cancer was demonstrated in multiple trials. Preoperative CRT and SCR were found to have equivalent outcomes in 3 randomized trials. IMRT-based CRT has not shown benefit.
- In this study, we assessed the difference in cost between traditional 3D-based CRT, IMRT-based CRT, and 3D-based SCR from the payers' perspective of the US. We have shown that the annual cost could be decreased by 64% to 77% with SCR and that IMRT increases the cost of CRT by 50%. These differences are mostly attributed to the total number of fractions per treatment course and the higher cost of IMRT.
- In recent years, there has been an increasing focus placed on understanding the cost and value of cancer care. As outcomes are similar, there is no difference in late toxicities, and from the patient's perspective, a shorter treatment course would be more convenient, with lower travel expenses and a shorter absence from work. It would be reasonable for public and private payers to consider which type of radiation is most suited to reimbursement.

## Disclosure

The authors have stated that they have no conflicts of interest.

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