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Short-Course Radiation Therapy Versus Long-Course Chemoradiation in the Neoadjuvant Treatment of Locally Advanced Rectal Cancer: New Insights from Randomized Trials

Thomas D. Mullen[1] · **Edward Y. Kim**[1] · **Smith Apisarnthanarax**[1]

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Abstract
Purpose of Review Examine prospective evidence supporting preoperative short-course radiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) for locally advanced rectal cancer and discuss recently published data that are helping to clarify the utility of SCRT.
Recent Findings SCRT with early surgery results in lower pCR rates, lower severe acute toxicities, no difference in late toxicities, and no apparent difference in local control, DFS, and OS when compared with LCRT. When surgery is delayed after SCRT, cancer outcomes appear equivalent, including pCR rates. The addition of full-dose systemic therapy with SCRT prior to surgery is attractive to further downstage patients, particularly in patients at high risk of distant relapse.
Summary Increasing randomized evidence is accumulating to support the use of SCRT as an acceptable preoperative treatment approach for locally advanced rectal cancer. Increasing the interval from SCRT to surgery and/or adding systemic doses of chemotherapy may mitigate potential concerns related to SCRT. More mature data and future results of ongoing randomized trials will help clarify the oncologic equivalence and safety of SCRT followed by preoperative chemotherapy.

Keywords Rectal cancer · Radiation therapy · Neoadjuvant · Preoperative · Short-course · Long-course

Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

✉ Smith Apisarnthanarax
apisarn@uw.edu

[1] Department of Radiation Oncology, University of Washington, 1959 NE Pacific Street, Box 356043, Seattle, WA 98195-6043, USA

Abbreviations

APR	Abdominoperineal resection
CAPOX	Capecitabine-oxaliplatin
CRM	Circumferential resection margin
DFS	Disease-free survival
EORTC	European Organization for Research and Treatment of Cancer
FOLFOX	Fluorouracil-leucovorin-oxaliplatin
FU	Fluorouracil
LCRT	Long-course chemoradiotherapy
LR	Local recurrence
MRI	Magnetic resonance imaging
NR	Not reported
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall survival
pCR	Pathologic complete response
SCRT	Short-course radiotherapy
TROG	Trans-Tasman Radiation Oncology Group

Introduction

The treatment of locally advanced rectal cancer is notable in that two valid neoadjuvant approaches have been studied in parallel and found beneficial in improving local control. The two approaches, short-course hypofractionated radiotherapy (SCRT) and long-course chemoradiation (LCRT) have been researched extensively. SCRT typically involves a hypofractionated treatment to 25 Gy in 5 fractions over 1 week. LCRT refers to conventionally fractionated radiation therapy to 45–50 Gy in 1.8–2.0 Gy fractions given 5 days per week given with 5-fluorouracil (5-FU)-based chemotherapy. Each regimen is used in different parts of the globe: for example, SCRT in Sweden and Poland, and LCRT in Germany, the UK, and the USA.

Emerging data regarding SCRT may dramatically change the enthusiasm for this approach, particularly when combined with neoadjuvant systemic therapy. In this review, we will describe the rationale of each approach and further explore the emerging randomized evidence comparing the two approaches.

Randomized Trials of SCRT Versus LCRT

Several trials have investigated the utility and safety of SCRT versus LCRT (Table 1). It is important to note that these trials compared SCRT followed by immediate surgery to LCRT followed by a delayed surgery. The first randomized phase III trial was published by Bujko et al. in 2004 [3]. Three hundred twelve patients with palpable T3 or T4 tumors without sphincter involvement were randomized to 25 Gy in 5 fractions or 50.4 Gy in 28 fractions with concurrent 5-FU and leucovorin from 1999 to 2002. Surgery including TME was performed within 7 days and 4–6 weeks, in the SCRT and LCRT arms, respectively. The pathological complete response (pCR) rate was 0.7% for SCRT and 16% for LCRT. Although rates of positive circumferential radial margins (CRM) were higher in the SCRT compared to the LCRT arm (12.9 vs. 4.4%, $P = 0.017$), no differences in rates of sphincter preservation, local control, or OS were observed [4]. Acute toxicity was reportedly lower in the SCRT (grades 3–4 3.2 versus 18.2%), and late toxicity was not significantly different when looking at all toxicities. However, small/large bowel late complications were seen in 5.1 and 1.4% of patients receiving SCRT and LCRT, respectively. This trial is notable for including low rectal tumors and having equivalent oncologic outcomes in each arm—despite a difference in pCR and a higher rate of positive CRM with SCRT.

The Trans-Tasman Radiation Oncology Group (TROG) 01.04 trial also examined the question of SCRT followed by early surgery versus LCRT with delayed surgery. The primary endpoint—3-year LR rate—was not different at 7.5 and 4.4% ($P = 0.24$), respectively. Five-year DFS and OS were also not different. Pathologic complete response rates were 1 versus 15% for SCRT and LCRT, respectively. Similar to the Polish I trial, lower rates of acute toxicity were seen in the SCRT arm (1.9 versus 27.1% Grade 3+) and late Grade 3+ toxicity was not significantly different [6]. Subgroup analysis of patients with distal tumors (<5 cm from anal verge, $n = 79$) revealed a cumulative incidence of LR of 12.5% for SCRT versus 0% for LCRT ($P = 0.26$). Although not statistically significant, the authors raise the concern of not having sufficient power to detect a true difference in this subgroup.

A smaller study conducted in Egypt (Table 1) similarly showed lower rates of acute toxicity with SCRT but no difference in 2-year oncologic outcomes [9]. The Berlin Cancer Society initiated a study in 2007 randomizing patients to SCRT versus LCRT [10, 11] and has reportedly closed to accrual as of 2009, but no results are yet published [12].

In summary, in comparison to LCRT, SCRT with early surgery results in lower pCR rates, lower severe acute toxicities, no difference in late toxicities at 5 years of follow-up, and no apparent difference in local control, DFS, and OS. Taken together, these data suggest that the major disadvantage of SCRT is lack of down-staging (e.g., pCR or tumor shrinkage sufficient to change rates of sphincter preservation or regression of an anticipated positive circumferential resection margin), whereas a distinct advantage is appreciated in terms of treatment time and acute toxicity. However, whether tumor down-staging is necessary or sufficient to improve oncologic or surgical outcomes is unclear. Nevertheless, increasing the interval time to surgery and/or the inclusion of neoadjuvant systemic therapy may ameliorate the lack of down-staging seen in SCRT and has been the subject of additional study.

Timing of Surgery After SCRT

As stated above, a shortcoming of SCRT followed by early surgery has been a lack of appreciable pathologic down-staging compared to LCRT [13]. Although not explicitly reported in the initial Stockholm trials, the rate of down-staging with SCRT would be expected to be nil given the short interval to surgery. Conversely, rates of pCR in the preoperative LCRT arms of the German, French, and EORTC trials were 8, 11, and 14%, respectively [14–16]. The potential benefits of down-staging include the ability to achieve a higher rate of sphincter preservation [14] and improved local control [17–19]. However, actual clinical benefit of down-staging on these outcomes is controversial.

Down-staging is likely a result of both adequate tumoricidal therapy as well as sufficient time for tumor regression. The Stockholm III trial was initiated to test the latter and compared patients undergoing SCRT followed by early surgery (1–7 days) versus SCRT followed by delayed surgery (28–56 days) [20]. Increased pCR rates (11.8 vs. 1.7%) as well as improved tumor regression grade were seen in the delayed surgery arm [21]. However, rates of positive CRM were no different. Notably, those in the immediate surgery arm who had an unplanned delay in surgery (11–17 days after SCRT) experienced a higher rate of postoperative complications such as wound infection and anastomotic leak [20]. Failure and survival outcomes are not yet available for this cohort. Therefore, based on pathologic response and postoperative surgical complications, the ideal timing of surgery after SCRT may be at least 3–4 weeks after SCRT.

A Lithuanian trial was conducted between 2007 and 2013 to compare SCRT with delayed surgery versus LCRT with the same delay (6 weeks) with primary endpoints of down-staging and pCR response rates. Preliminary data were published in

Table 1 Published randomized trials of SCRT with immediate surgery versus LCRT

Trial	MRC C07 [1, 2]	Polish trial I [3–5]	TROG 01.04 [6, 7••, 8]	Egyptian trial [9]
Years	1998–2005	1999–2002	2001–2006	2007–2009
N	1350	312	326	32
Inclusion	Operable rectal	T3-T4 N0-2 M0 without sphincter involvement	T3 N0-2 M0	T2-4 N0-2 M0
Neoadjuvant therapy arms	1. 5 Gy × 5 2. Selective post-op 1.8 Gy × 25 with 5-FU	1. 5 Gy × 5 2. 1.8 Gy × 28 with 5-FU	1. 5 Gy × 5 2. 1.8 Gy × 28 with 5-FU	1. 5 Gy × 5 2. 1.8 Gy × 25
Interval RT to surgery	Median 27 days RT to surgery	1. Within 1 week of RT 2. 4–6 weeks from RT per protocol	1. 3–7 days from RT 2. 4–6 weeks from RT	1. Within 1 week 2. 4–6 weeks
pCR	NR	0.7 vs. 16.1%	1 vs. 15%	0 vs. 13.4% ($P = 0.15$)
Acute complications	More pts in preoperative arm who got APR had perineal wound healing problems than APR pts in post-op	Gr3-4: 3.2 vs. 18.2%	Gr3-4: 1.9 vs. 27.1%	Any toxicity: 0 vs. 37.9% ($P = 0.002$)
Median follow-up	4 years	4 years	5.9 years	18 months
Failure outcome	3-year LR: 4.4 vs. 10.6% ($P < 0.01$)	4-year LR: 10.6 vs. 15.6% ($P = 0.21$)	3-year LR: 7.5 vs. 4.4% ($P = 0.24$) 5-year LR: 7.5 vs. 5.7% ($P = 0.51$)	Cumulative LR: 14.2 vs. 6.7%
Survival outcome	3-year DFS: 77.5 vs. 71.5% ($P = 0.01$) 3-year OS: 80.3 vs. 78.6% ($P = 0.40$)	4-year DFS: 58.4 vs. 55.6% ($P = 0.82$) 4-year OS: 67.2 vs. 66.2% ($P = 0.96$)	5-year DFS: NR, but not different by log-rank ($P = 0.47$) 5-year OS: 74 vs. 70% ($P = 0.62$)	2-year DFS: 61 vs. 83% ($P = 0.83$) 2-year OS: 64 vs. 66% ($P = 0.39$)
Late Gr3+ toxicity	NR	10.1 vs. 7.1% ($P = 0.36$)	5.8 vs. 8.2% ($P = 0.53$)	Any late toxicity: 3.4 vs. 3.4%
Patient-reported QOL	Increased fecal incontinence in pre-op arm	No difference in anorectal or sexual function	No difference between arms	NR

APR Abdominoperineal resection, *DFS* disease-free survival, *FU* fluorouracil, *LR* local recurrence, *NR* not reported, *OS* overall survival, *QOL* quality of life, *RT* radiotherapy

2012 on pCR rates showing improved down-staging with LCRT [10]. A recent update, however, showed this difference to be non-significant (4.4% SCRT versus 11.1% LCRT, $P = 0.11$) [22]. At a median follow-up of 3.3 years, neither LR nor OS was different. When compared to Stockholm III, the pCR rate of the Lithuanian trial with SCRT is disappointing, but it adds support to the concept of adding therapy between the completion of radiation therapy and surgery to improve tumor response.

Neoadjuvant SCRT Plus Sequential Chemotherapy

Adjuvant chemotherapy is a key component of therapy for locally advanced rectal cancer. Phase III data support the use of 5-fluorouracil and platinum-based chemotherapy in the adjuvant setting [23]. Several studies have begun to examine the utility of providing the same chemotherapy in the preoperative setting for high-risk rectal cancer in the hopes of increasing chemotherapy compliance, providing early treatment of occult micrometastases, and perhaps further down-staging of tumors [24]. This strategy has already been examined in the setting of neoadjuvant LCRT and provided favorable preliminary results in terms of down-staging and chemotherapy compliance [24, 25]. Given that delayed surgery improves pCR and down-staging, several researchers have examined the utility of shifting the indicated adjuvant chemotherapy to the neoadjuvant setting, thereby providing full-dose systemic therapy while also allowing sufficient time for tumor response to SCRT (Table 2).

Several notable phase II trials have also been published in the Netherlands, Korea, and the USA examining SCRT plus preoperative chemotherapy and show promising results (Table 2) [27•, 28, 29]. A major commonality of these trials is the inclusion of stage IV patients who may benefit from abbreviating radiotherapy and early initiation of full-dose systemic therapy. Impressive rates of pCR ranging from 11 to 26% were seen, and acute toxicity was commensurate with what is typically seen with full-dose systemic therapy (e.g., mainly hematologic). Together, these data supported further development of randomized trials to compare SCRT plus chemotherapy to LCRT.

The most notable randomized results come from the Polish Colorectal Study Group [26••]. From 2008 to 2014, 541 patients with T3N+, T4, or clinically fixed rectal cancer without distant metastases were randomized to receive either SCRT followed by FOLFOX4 × 3 cycles then surgery or LCRT with concurrent FOLFOX chemotherapy followed by surgery. The median time between initiation of radiotherapy and surgery was 12.4 weeks in both arms. For those undergoing surgery, pCR rates were 16 versus 12% for SCRT plus chemotherapy and LCRT, respectively ($P = 0.17$). Rates of grades 3–4 toxicity were not different between arms (23 versus 21%). At a median follow-up of 2.9 years, cumulative LR rates for those who received an R0-R1 resection were 7 and 5%, respectively. Distant metastasis free survival, DFS, and late toxicity were similar at 3 years. However, there was a statistically significant difference in 3-year OS favoring SCRT (73 versus 65%, $P = 0.046$). It is unclear what accounts for the lack of correlation between DFS and OS, but the authors suggest that patients who failed in the LCRT arm had a higher risk of death compared to those who failed in the SCRT arm. Several potential explanations for this phenomenon were provided by the authors, namely immunologic effects and worse adherence to therapy in the LCRT arm. It will be important to see if the difference is maintained at long-term follow-up.

The STELLAR trial is currently being conducted at multiple institutions in China. This trial randomizes patients with non-metastatic clinical T3-4 or N+ rectal cancer to receive SCRT followed by capecitabine and oxaliplatin for 4 cycles versus LCRT; surgery is planned at 4 weeks versus 6–8 weeks following completion of neoadjuvant therapy. The study is designed for a non-inferiority comparison with 3-year DFS as the primary endpoint. Although not yet published, preliminary data presented at the 2016 American Society of Clinical Oncology Annual Meeting indicate pCR rates of 25.7 and 7.9%, respectively [30]. Grades 3–4 acute toxicity during the entire neoadjuvant period occurred in 28.4% (primarily driven by toxicities during the period between SCRT and CAPOX) versus 5.2% of patients, respectively. In summary, it appears that adding systemic doses of chemotherapy in the neoadjuvant setting along with preoperative SCRT substantially adds to the down-staging of tumors at the expensive of increased toxicity in the preoperative setting. However, more mature data with longer follow-up are needed.

Patient Selection

Tumor Stage

Many of the trials discussed above have used different inclusion criteria, but the most common factor for inclusion is a clinical T3 or T4 rectal tumor. Based on these criteria, SCRT and LCRT appear to be equivalent in terms of local control and DFS [4, 7••]. However, in the Polish I trial, patients were classified as T3/T4 based on physical exam findings (circumferential or tethered on digital rectal exam) without endoscopic ultrasound or MRI [4]. The TROG 01.04 trial enrolled clinical T3 patients (staged by MRI or ultrasound) and excluded T4 lesions [7••]. Whether SCRT is appropriate for T1-2 node-positive tumors remains undetermined: the Berlin Cancer Society Trial and the STELLAR Trial are currently accruing such patients. No results have been published for the former, and the latter has only presented preliminary results.

Table 2 Selected trials of SCRT plus neoadjuvant chemotherapy versus LCRT

Trial	Polish trial II [26••]	Washington University phase II [27•]	Korean phase II [28]	Dutch stage IV trial [29]	STELLAR trial [30]	RAPIDO trial [31]
Years	2008–2014	2009–2012	2011–2014	2006–2010	2015–present	2011–present
N	541	80	32	50	93	NR
Inclusion	T4 or fixed cT3 N0-2 M0	T3-4 N0-2 M0-1	T3 (84%) T4 (16%)	T3N1-2 (64%) T4N1-2 (14%) 84% metastatic to liver only	T3-4 or N+, M0	T4 or N2[a]
Neoadjuvant therapy arm(s)	1.5 Gy × 5 → FOLFOX4 × 3 cycles 2. 1.8 Gy × 28 with concurrent FOLFOX	5 Gy × 5 → FOLFOX × 4 cycles	mFOLFOX6 × 4 → 5 Gy × 5 → mFOLFOX6 × 4	5 Gy × 5 → CAPOX-bevacizumab × 6	1. 5 Gy × 5 → CAPOX × 4 2. 2 Gy × 50 Gy with concurrent capecitabine	1 (Arm B). 5 Gy × 5 → CAPOX × 6 2 (Arm A). 1.8 Gy × 30 with concurrent capecitabine
Interval RT to surgery	Median 12.4 weeks from start of RT in both arms	Mean 17.3 weeks from start of RT	Median 14 weeks	24–28 weeks per protocol	1. ~17 weeks 2. 6–8 weeks	1. ~22–24 weeks 2. 6–8 weeks
pCR	16 vs. 12% ($P = 0.17$)	25%	11%	26%	25.7 vs. 7.9%	NR
Acute complications	Gr3-4: 23 vs. 21%	Gr3-4 non-hematologic: 20% Gr3-4 hematologic: 27%	Gr3+: Neutropenia 28% Nausea 3% Diarrhea 6%	No Gr3+ events during or after RT Gr3-4 events: 39%	Gr3-4: 26.6 vs. 5.9%	NR
Median follow-up	2.9 years	26 months (mean)	30 months	32 months	NR	NR
Failure outcome	Cumulative local failure: 22 vs. 21% ($P = 0.82$) Distant metastasis: 30 vs. 27% ($P = 0.25$	Cumulative LR: 5%	Cumulative LR 3%	2-year LR for R0: 6%	NR	NR
Survival outcome	3-year DFS: 53 vs. 52% $P = 0.85$) 3-year OS: 73 vs. 65% ($P = 0.046$)	Cumulative DFS: 87% Cumulative OS: NR	2-year PFS: 17% 2-year OS: 65%	2-year OS: 80%	NR	NR
Late Gr3+ toxicity	8 vs. 6%	26%	12.5% anastomotic leak	NR	NR	NR
Patient-reported QOL	NR	NR	NR	NR	NR	NR

[a] Additional inclusion criteria apply—see reference 27

DFS disease-free survival, *FU* fluorouracil, *LR* local recurrence, *NR* not reported, *OS* overall survival, *QOL* quality of life, *RT* radiotherapy

Nodal Stage

There is currently no evidence that nodal stage is relevant for the use of SCRT versus LCRT apart from its general prognostic aspect. Nodal stage has not been a primary inclusion or exclusion criterion for many of the aforementioned trials besides the ongoing STELLAR [30] and RAPIDO [31] trials, and none of the published trials have shown nodal stage to be a predictive factor for any recurrence or survival outcomes. There is limited data regarding pathologic lymph node response, but in the Polish II trial of SCRT plus sequential chemotherapy versus LCRT, no difference in ypN stage was seen between arms [26••]. In total, there is insufficient data to acknowledge any difference in lymph node clearance between SCRT and LCRT or the use of node positivity as a criterion for one approach over the other.

Location Within Rectum

Distal tumors are at a higher risk of LR than proximal tumors [32]. The reason for this appears to be multifactorial, as the distance from the anal verge, the type of resection, and the presence of a positive CRM are all independent predictors of recurrence [33]. Only the latter two are potentially modifiable by preoperative treatment. LCRT was shown to increase the rate of sphincter preservation in one trial—although rates of APR versus anterior resection were not different between arms [14]. Other studies have not shown significant differences in sphincter preserving surgeries between patients treated with SCRT versus LCRT [3, 7••].

Rates of positive CRM could be decreased by preoperative treatment through tumor regression. Although SCRT with immediate surgery results in little or no down-staging, LCRT or SCRT with delayed surgery increases down-staging and rates of pCR compared to SCRT or surgery alone [7••, 20]. Furthermore, the Polish I trial showed decreased positive margins with LCRT compared to SCRT [4]. Conversely, neither preoperative SCRT nor post-operative LCRT can compensate for a positive CRM [1, 34].

Multiple studies show that distal tumors are at still at a higher risk of recurrence even when treated with SCRT or LCRT [7••, 35, 36]. However, whether SCRT is equivalent or inferior to LCRT for these tumors is controversial. The Polish I trial notably included only palpable rectal tumors which undoubtedly accounts in some part for the higher rates of recurrence in this study [4] (4-year LR 10.6% SCRT versus 15.6% LCRT, $P = 0.21$). This is compared to others reporting rates <10% [1, 7••, 26••]. Despite the inclusion of these distal tumors, the Polish I trial showed no statistically significant difference in LR between SCRT and LCRT, although this was not the primary endpoint of the trial. This is in contrast to the TROG 01.04 data, where the authors suggest that there is either no difference or a clinically important difference favoring LCRT based on the wide confidence intervals reported—with a 12.5% cumulative LR with SCRT versus 0% LR with LCRT among 79 patients with distal tumors [7••, 37]. The SCRT arm of the TROG study had a higher proportion of distal tumors on pretreatment exam (30 versus 19%, $P = 0.025$ by chi-square analysis of the published data). The pathologic specimens also demonstrated a similar difference. However, the rates of positive margins or type of surgery were not different between arms, suggesting this imbalance may have had little impact on outcomes [7••].

Advances in the use of MRI for staging have led to improved preoperative assessment of CRM involvement and, through better patient selection, improved rates of positive pathologic CRM [38]. A notable feature of the most recently initiated SCRT versus LCRT trials is a requirement of MRI for clinical staging, whereas this has not be extensively utilized in past trials [30, 31].

Late Toxicity and Quality of Life

An in-depth discussion of the myriad late effects of radiation therapy for rectal cancer is beyond the scope of this article. The reader is referred to an excellent systematic review on the subject was published by Birgisson in 2007 [39]. Late toxicities seen in patients treated with radiation therapy include gastrointestinal (Gl), neurologic, rectal, anal, urinary, and sexual dysfunction. Patients are also susceptible to bone fractures, thromboembolism, and secondary malignancy. Assessment of late toxicity due to pelvic radiation therapy is confounded by the impact of surgery and less so by chemotherapy. Most studies use the Radiation Therapy Oncology Group/EORTC and LENT-SOMA scales to rate and record toxicity [40, 41]. Data from recent studies including chemotherapy after SCRT are lacking (e.g., the Polish II trial)—mostly due to their immaturity. Late toxicity, particularly GI, is relevant in the SCRT versus LCRT discussion since LCRT advocates have voiced concern for potential increase in late toxicities with SCRT due to a higher dose per fraction.

Gastrointestinal Toxicity

Late changes in bowel function after radiotherapy can include frequent bowel movements, incontinence, ileus, obstruction, and fistula. In the Polish I trial, late toxicity of any grade occurred in 28.3% of SCRT and 27.0% of LCRT patients ($P = 0.81$); severe late toxicity occurred in 10.1 and 7.1% of patients respectively ($P = 0.36$). Grade 3+ GI toxicity occurred in 5.1 versus 1.4% of patients, most of which was ileus or fistula. Health-related quality of life (HR-QOL) data were later published with a median time since surgery of 12 months [5]. Approximately two thirds of patients reported anorectal dysfunction such as frequent bowel movements and mild

incontinence, but no significant differences were noted between treatment arms. A majority of patients (~60%) rated their quality of life related to anorectal function as "Bad but acceptable."

In the TROG study, late grade 3+ GI toxicity occurred in 3.2 and 5.1% of patients treated with SCRT and LCRT, respectively ($P = 0.53$) [7••]. Patient-reported HR-QOL data are not yet available for this cohort but are expected. In total, there is no conclusive evidence that rates of severe GI toxicity are significantly higher with SCRT.

Genitourinary Toxicity

Serious late urinary toxicity is rare after radiotherapy for rectal cancer. Most commonly reported symptoms include increased frequency and incontinence [39]. In the Polish I trial, grade 3+ bladder toxicity occurred in 1.4 vs. 0.7% of patients in the SCRT and LCRT arms, respectively. HR-QOL analysis did not specifically address urinary symptoms accept for "emptying difficulties" of which there was a high percentage (83 versus 88%), though no significant difference between arms. Late GU toxicity was not described in the TROG study [7••].

Decline in sexual function was also addressed in the Polish I study where 24 versus 22% of men had "a lot" of sexual decline after SCRT and LCRT, respectively. For women, rates were 15 and 38% ($P = 0.10$) [4]. Based on these data, no difference in late sexual function between SCRT and LCRT is apparent, though more research is necessary.

Technical Aspects of SCRT and LCRT

Radiotherapy techniques for SCRT have been relatively uniform across published studies. The initial trials of preoperative SCRT versus surgery alone used 2D techniques and more extensive fields than modern series. For example, the Swedish Rectal Study treated para-aortic nodes up to L2 [42]. On the other hand, the Dutch TME study covered up to the sacral promontory, similar to most modern fields and guidelines [43]. All the comparative trials for SCRT versus LCRT have used 2D or 3D conformal techniques with conventional field borders and lymph node coverage, similar to the Dutch TME study. Both TROG and the Polish Colorectal Study Group used 25 Gy in 5 fractions to the entire clinical target volume without a cone-down. Other strategies have been used including a dose-painting "nested" technique employed by the Washington University group [27•].

Biological effective dose (BED) is also important in comparing SCRT to LCRT. The BED for acute responding tissues ($\alpha/\beta = 10$, BED_{10}) of >30 Gy predicts LR [44]. It is notable that 25 Gy in 5 fractions is neither isoeffective to 50 Gy in 25 fractions in terms of acute responding tissues nor late responding tissues ($\alpha/\beta = 3$). Using the linear-quadratic formula [45], 25 Gy in 5 fractions represents a BED_{10} of 37.5 Gy and for late responding tissues ($\alpha/\beta = 3$) a BED_3 of 66.7 Gy. The comparable BED_{10} and BED_3 for 50 Gy in 25 fractions is 60 and 83.3 Gy, respectively. When daily repair and total treatment time (e.g., average LCRT treatment time of 33 days including weekends) are taken into account, the BED_{10} of LCRT is lower at 44.4 Gy. The inclusion of concurrent chemotherapy is expected to increase the BED_{10}, but radiobiologic modeling of this effect in rectal cancer is limited if not nonexistent. Nevertheless, randomized data clearly support the inclusion of concurrent chemotherapy with LCRT for the endpoint of LR [15, 46]. Given the lower BED_{10} with SCRT and the lack of concurrent chemotherapy, it is still somewhat surprising that the trials to date show no difference in oncologic outcomes between SCRT and LCRT. A potential role for immunomodulation in both SCRT and LCRT is interesting, but any advantage of one over the other in this regard is purely speculative at this time [47, 48]. Whether the addition of concurrent chemotherapy to SCRT would add additional benefit is uncertain, and the ability to easily interdigitate full-dose systemic therapy between SCRT and surgery make the latter strategy the most reasonable at this time—and is the subject of ongoing trials.

Practice Patterns

Despite data demonstrating oncologic equivalence and reduced acute toxicity with SCRT compared with LCRT, SCRT is rarely practiced in the USA. In a National Cancer Database Study, only 0.7% of locally advanced rectal cancer patients underwent SCRT [49]. A survey of US radiation oncologists revealed a strong bias towards LCRT, with respondents citing concerns about the lack of tumor down-staging with SCRT and the "need for longer clinical trial follow-up." [50•] However, a majority of respondents also said that they would offer SCRT if patients declined or had a contraindication to chemotherapy, or if there were a significant geographic barrier to receiving LCRT.

The preference for LCRT is not limited to the USA. Elliot et al. examined practice patterns in the Stockholm-Gotland area treated from 2007 to 2010 and found that LCRT was provided for 61% of patients whereas 31% of patients received SCRT [51]. However, patients with early or intermediate rectal cancer were more likely to receive SCRT or no radiotherapy. Another analysis was published concurrently examined patterns in the Netherlands, Sweden, Denmark, Norway,

and Belgium in 2008–2009 [52]. In the Netherlands and Sweden, SCRT was favored for early stage rectal cancers whereas LCRT was favored for T4 or node-positive tumors. Conversely, little radiotherapy was used for stage I tumors in Norway and Belgium, and for more advanced tumors LCRT was the preferred modality.

Additional Controversies

A major argument for SCRT is the reduction in overall treatment time. Figure 1 illustrates the comparative length of various published neoadjuvant regimens showing overall reduced treatment time with SCRT even with the inclusion of systemic chemotherapy in the neoadjuvant and/or adjuvant setting. By shortening radiotherapy, patients should experience less inconvenience as well incur less overall cost. However, no published data substantiating a cost difference are currently available. Nevertheless, in the absence of excess toxicity or other trade-offs for SCRT, SCRT with delayed surgery should be considered a cost-effective alternative to LCRT. Furthermore, in order consolidate and shorten the overall treatment time of patients receiving SCRT, it is reasonable to provide systemic chemotherapy in the neoadjuvant setting per the Polish II or Washington University Phase II. However, more data is likely needed to change the practice of those habituated to providing LCRT.

As discussed above, some have cautioned about the higher risk of local failure with distal tumors and used this as a basis to recommend against SCRT for these cases [37]. While LCRT is superior to SCRT with immediate surgery in terms of down-staging, SCRT appears to be equivalent to LCRT in terms of LR [3, 4, 7••]. It is still unclear whether tumor down-staging alone is sufficient to improve surgical outcomes and LR. However, this may be moot in an era where SCRT with immediate surgery is being supplanted by SCRT with delayed surgery and possibly intervening preoperative systemic therapy. LCRT appears to be equivalent to SCRT with delayed surgery in this regard [26••]. The ongoing STELLAR and RAPIDO trials (discussed below) will help further clarify this. Therefore, it is difficult to make strong conclusions in either direction regarding the safety of SCRT versus LCRT for distal tumors.

Ongoing Studies

Additional studies are ongoing and will help clarify the role of SCRT in the treatment of locally advanced rectal cancer (Table 2). Only limited preliminary data from the STELLAR trial have been presented so far but are encouraging [30]. The RAPIDO trial has also been initiated in Sweden and the Netherlands to compare LCRT followed by surgery and adjuvant chemotherapy with SCRT followed by chemotherapy and then surgery [31]. The study will be powered at 90% to detect a 10% improvement in 3-year DFS with SCRT compared to LCRT. Other important endpoints will be pCR, LR, acute and late toxicity, and HR-QOL. The trial is currently accruing with no results published or presented as of the writing of this paper.

Conclusions

LCRT has been a well-accepted standard for preoperative treatment in locally advanced rectal cancer for over a decade. The use of SCRT predates LCRT, but the latter has become more widespread mainly due to the increased down-staging and the promise of improved surgical outcomes (i.e., fewer positive margins and increases sphincter preservation). However, when surgery is delayed after SCRT, cancer outcomes appear equivalent, and the additional ability to include full-dose systemic therapy prior to surgery is attractive to further downstage patients, particularly in patients at high risk of distant relapse. While some may see these data as sufficient to change practice in favor of SCRT, others will be hesitant in the absence of additional randomized studies and more mature data. In addition to the already published Polish II trial, the ongoing STELLAR and RAPIDO trials will certainly help clarify the oncologic equivalence and safety of SCRT followed by preoperative chemotherapy.

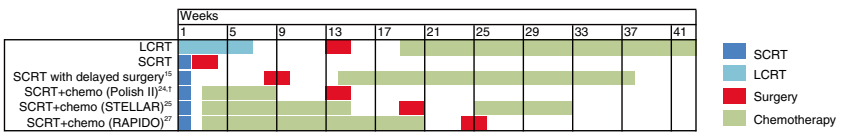

Fig. 1 SCRT and LCRT regimens for locally advanced rectal cancer. Various regimens of SCRT versus LCRT are illustrated. Timing of surgery and chemotherapy is depicted as a range approximating what is acceptable in the referenced protocols. The duration of adjuvant chemotherapy in LCRT and SCRT with delayed surgery regimens is depicted as 6 months. †Adjuvant chemotherapy was not described in the Polish II trial

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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