



Controversy

Should we favour the use of 5 × 5 preoperative radiation in rectal cancer

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ABSTRACT

The management of patients with “locally advanced rectal cancer” (LARC) is evolving from the original aim of reducing local recurrence. Current practice recognises the importance of surgical technique, high-quality pre-operative imaging, and integration of neoadjuvant systemic chemotherapy. Contemporary protocols focus on improving survival and avoiding radical surgery with organ preservation strategies. Both short course pre-operative radiotherapy (SCPRT) with immediate surgery and long-course chemoradiation (LCCRT) are standard neoadjuvant strategies, both demonstrating similar efficacy in preventing local recurrence, distant metastases and improving disease-free survival (DFS). SCPRT is highly cost-effective with high compliance rates, hence is gaining traction in Europe and East Asia, partly because of inherent flexibility in timing and the ability to add neoadjuvant systemic chemotherapy as there is a delay to surgery. SCPRT is currently not being exploited to its full extent – particularly in the USA where uptake is approximately 1% of neoadjuvant treatments for rectal cancer. We analyse the use of induction, concurrent and consolidation chemotherapy with SCPRT in a total neoadjuvant therapy (TNT) approach.

Introduction

On confirmation of a rectal cancer diagnosis, treatment depends on clinical staging using examination, computerised tomography and magnetic resonance imaging. Options include surgical resection, radiation therapy and chemotherapy or a combination with the aim of reducing local recurrence risk and increasing the chance of a clear resection margin. The current standard treatments for locally advanced rectal cancer (LARC) in Europe include long-course chemoradiation (LCCRT) using 45–50.4 Gy in 25–28 fractions with concurrent fluoropyrimidine chemotherapy followed by total mesorectal excision (TME) after 6–10 weeks, or short course preoperative radiotherapy (SCPRT) with 5 × 5 Gy and immediate surgery. These two different schedules have been used in parallel in Northern Europe for over 20 years, based on 3 pivotal trials [1–3]. SCPRT requires a short overall treatment time (OTT) - usually 5 consecutive days with immediate surgery within 2–5 days, and is associated with high compliance and low toxicity [1,2,4]. SCPRT also confers lower cost because of fewer fractions compared to LCCRT.

SCPRT reduced 5-year local recurrence (LR) rate from 27% to 11% in the Swedish [1] from 11% to 5% in the Dutch TME [2,5,6] and from 12% to 5% in the Medical Research Council (MRC) CR07 [4,7] compared with surgery alone or surgery and selective postoperative radiotherapy or chemoradiotherapy.

Data on long-term complications and quality of life (QOL) is sparse [8,9]. Early SCPRT trials using older outdated radiotherapy techniques showed high late complication rates [10]. No differences in late toxicity rates were observed between SCPRT and LCCRT in the randomised trials [11,12]. More recent single-institution reports document 58% long-term adverse effects (10% Grade 3) [13].

In the Dutch TME trial postoperative radiotherapy/chemoradiotherapy treatment was administered to only 56/120 (47%) patients with a positive CRM in the surgery-only group, and 53/77 (69%) in the selective chemoradiation arm of CR07 (19% receiving RT alone and 9% no RT at all). The postoperative RT doses mandated in CR07 were low (45 Gy), compared with the German trial, which mandated 55.8 Gy [3]. Hence, in the vast majority in both trials the true comparison was between 5 × 5 Gy with immediate TME versus TME alone.

Prospective studies comparing SCPRT and LCCRT using similar study protocols in clinically determined T3/T4 or node-positive resectable rectal demonstrated no differences in long-term oncological outcomes [11,12]. A recent Cochrane meta-analysis confirmed better local control after SCPRT versus surgery alone, but no reduction in distant metastases [14]. Another meta-analysis reports LCCRT significantly increased the pCR rate compared with SCPRT [15].

Thus current ESMO and NCCN guidelines accept either schedule to prevent local recurrence [16,17], but large variations in their use are reported across Europe [18,19]. LCCRT is favoured in Southern Europe

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and the United States, where a survey of radiation oncologists reported LCCRT was the preferred option of 96% of responders [20]. Concerns expressed included the omission of concurrent chemotherapy with 5×5 Gy, the reduced chance of significant down-staging with the traditional short interval between RT and surgery – thus precluding sphincter-sparing options, and a perceived heightened risk of late toxicity based on the large individual fractions. Analysis of the National Cancer Database 2004–2014 showed 42,336 patients with rectal cancer of whom 41,867 (98.9%) were treated with LCCRT and only 469 patients (1.1%) with SCPRT [21].

Yet in Europe there is a growing trend to integrate NACT universally with a TNT approach in rectal cancer, which has been exploited with SCPRT in both the Polish 2 trial [22] and RAPIDO trial [23] based on experience of adding chemotherapy to LCCRT [24–26].

We explore the advantages and disadvantages of SCPRT and LCCRT considering short-term endpoints such as pCR, rates of positive CRM (≤ 1 mm) or R0/R1 resection rates. We examine SCPRT and immediate surgery, SCPRT with 4–8 weeks delay and SCPRT with delay filled with consolidation systemic chemotherapy. We investigated longer-term outcomes including local recurrence, rate of distant metastases, sphincter-sparing, colostomy rate, disease free survival (DFS) and overall survival (OS). Our working hypothesis was that LCCRT would offer better clinical and pathological response compared to SCPRT alone, but this pattern might be reversed when chemotherapy is added.

Search strategy

Relevant studies published up to May 2019 were systematically searched within the PubMed, Medline, Cochrane and EMBASE databases with key search words: “rectal cancer” AND “preoperative long course chemoradiotherapy” OR “preoperative short course radiotherapy” OR “ 5×5 Gy”. Relevant articles and reviews were examined to identify further studies of interest, and 493 studies were originally included. For consistency, we specifically excluded studies using schedules with 4×5 Gy or 5×4 Gy. A total of 302 articles remained after eliminating duplicates and irrelevant articles – see consort diagram (Fig. 1). We chose the topics in selected articles for this descriptive review.

Results

We found 13 relevant studies directly comparing SCPRT and LCCRT; 7 randomised prospectively [11–13,21,22,27–35] (one only published in abstract with no oncological outcomes) [34] and 6 retrospective analyses [36–40] and a prospective phase II [41]. One randomised study compared long and short intervals after SCPRT to surgery and long course radiotherapy alone [42–45] pivotal trials comparing SCPRT and LCCRT are compared in Tables 1 and 2.

SCPRT vs LCCRT

The 2 different approaches (SCPRT and LCCRT), when randomly compared in patients with resectable cancers, have similar perioperative complications, late effects, local recurrence rates, DFS and OS [11,12,27]. Early *meta*-analyses showed no difference in local recurrence, DFS or OS, but LCCRT resulted in significantly higher pCR, down-staging and higher acute toxicity [46,47]. Another *meta*-analysis suggests SCPRT with delayed surgery is as effective as LCCRT in terms of sphincter preservation, local recurrence, and is associated with similar grade 3/4 acute toxicity, R0 resection rate and down-staging [14]. More recent *meta*-analyses confirm that SCPRT reduces local recurrence compared to surgery alone and suggest that SCPRT may also reduce overall mortality, but not necessarily after TME [14,48] with no differences apart from pCR rates [49]. Some therefore recommend SCPRT with delayed surgery (after an interval of more than 4 weeks) [50] rather than immediate surgery, because of the higher pCR and fewer postoperative complications.

SCPRT and immediate surgery

Both the Polish and TROG-0104 trials showed the interval to surgery or definitive pathological assessment influences both the rate of pCR and CRM positivity [11,12,27]. Although tumours may shrink within days [51], no reduction in tumour or nodal classification occurs unless the interval is more than 10 days [52,53]. A small Egyptian randomised study showed no significant differences in local control, distant metastases, sphincter-sparing, local recurrence, DFS or OS,

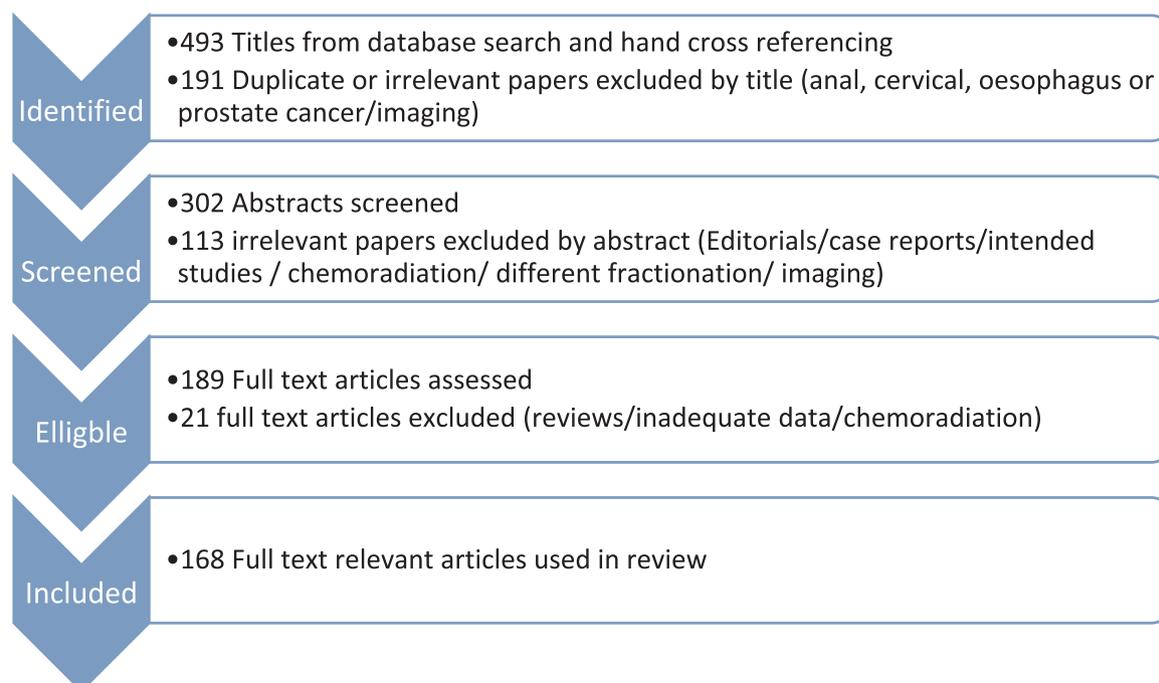


Fig. 1. Flow chart of selection process of articles included in the review.

Table 1
Direct randomised trials comparing SCPRT and LCCRT in resectable rectal cancer.

	Polish Colorectal Cancer Group (Bujko 2004 [27], Bujko 2006) [11]		Trans-Tasman Radiation Oncology Group (TROG-01) (Ngan 2012) [12]	
	5 × 5 Gy SCPRT + TME	50.4 Gy with 5FU bolus + TME	5 × 5 Gy SCPRT + TME 6 cycles adj CT	50.4 Gy with 5FU ci + TME 4 cycles adj CT
No. of patients	155	157	163	163
Loco-regional failure rate	9%	14.2%	7.5%	4.4%
5 year DFS	58%	55%	73%	70%
Overall 5 year survival	67%	62%	74%	70%
Grade 3–4 late toxicity	10.1%	7.1%	5.8%	8.2%

Table 2
Randomised studies of SCPRT versus LCCRT.

Trial	No	Stage	Chemo	Adjuvant chemotherapy	Local recurrence	5 year RFS/DFS	5 year OS
Polish SCPRT [11,27]	155	cT3-T4	None	Optional	Crude 9%	DFS 58%(4 year)	67%(4 year)
Polish CRT [11,27]	157	cT3-T4	5FU/FA	Optional	Crude 14%	DFS 56%(4 year)	66%(4 year)
TROG SCPRT [12]	163	II-III	None	Mandated FUFA 6/12	3 years 7.5%	RFS 64%	74%
TROG [12] CRT	163	II-III	PVI 5FU 225 mg/m ²	Mandated FUFA 4/12	3 years 4.4%	RFS 61%	70%
Latkauskas/Karevice [31,33] 2017 SCPRT	75	II-III	None	No adjuvant	4/68 (6%)	DFS 45%	62%
Latkauskas/kairevice [31,33] 2017 CRT	75	II-III	5FU/FA	4 cycles FUA post-op	5/72 (7%)	DFS 67%	79%
Pach 2012 [30] SCPRT immediate 7–10 days	77	I-III	None	Not stated	1.5%	Not stated	63%
Pach 2012 SCPRT[30] delayed 4–5 weeks	77	I-III	None	Not stated	7%	Not stated	73%

SCPRT = short course preoperative radiotherapy; LCCRT = long course chemoradiation; RFS/DFS relapse free survival/disease free survival; OS = overall survival; FUFA = 5FU and folinic acid.

although LCCRT achieved significantly better down-staging [29].

Another randomised study assigned 150 patients with stage II–III resectable disease to SCPRT with delayed TME at 6–8 weeks versus conventional LCCRT (50 Gy/25 fractions and TME after 6–8 weeks) followed by 4 cycles of postoperative adjuvant chemotherapy [31,33]. The DFS curves separate at about 18 months, showing a statistically significant difference between LCCRT and SCPRT ($P = 0.013$) with 5-year DFS 67% and 45% respectively. Curves for OS separate earlier at 12 months and 5-year OS was 79% in LCCRT ($n = 72$) and 62% in the SCPRT ($n = 68$) groups respectively ($P = 0.015$). These survival curves are inverted (DFS differences appear after OS differences) and not compatible with standard classical curves from landmark studies showing a benefit of adjuvant chemotherapy in colon cancer [54,55], suggesting poor stratification between the 2 groups despite randomisation.

Local recurrence

In the Swedish Rectal cancer trial, the benefit in OS persisted after 13 years – with a rate of 38% in the irradiated group versus 30% after surgery alone ($P = 0.008$). The cancer-specific survival rate was 72% v 62% ($P = 0.03$), and local recurrence rate 9% v 26% ($P < 0.001$) respectively [56].

The Dutch TME trial reported the LR rates at 5 years were 5.6% after SCPRT and TME and 10.9% after TME alone ($P < 0.001$) [5]. Subgroup analyses showed SCPRT significantly reduced LR among patients with involved nodes, low cancers 5–10 cm from the anal verge, and uninvolved CRMs. At 12 years' follow-up, [6] 10-year LR rates of 5% for SCPRT + TME versus 11% for TME alone were reported. Distant failure rates (25% vs 28%) and OS rates (56% vs 57%) were similar (see Table 3).

Early response endpoints

There are no standard internationally accepted intervals between SCPRT and immediate or delayed surgery. The Dutch TME [2] and Polish [27] trials had median OTT from start of SCPRT to surgery of

only 8 days, and CR07 a median of 9 days [4]. TROG 0104 does not state the OTT, but the protocol mandated the interval from the first day of radiotherapy to surgery not to exceed 11 days, recommending radiotherapy be given in 5 consecutive days starting on a Monday or Tuesday [12].

Pathological complete response (pCR)

Studies where surgery takes place within a week of completion of SCPRT are associated with few cases of pCR (Table 1). If surgery is performed slightly later (at a median of 13 days) pCR rises to 5% [57]. With longer intervals of 4–8 weeks pCR rises to 10%. The rate of tumour regression grade (TRG) 1–2 increases if the interval is prolonged further from 16.7%, if < 6 weeks to 54.3%, when > 8 weeks [58]. PCR rates are even higher- in the range of 16–28% if consolidation chemotherapy is also integrated prior to surgery [22,40].

Circumferential resection margin

A meta-analysis with over 17,500 patients showed a CRM of ≤ 1 mm in rectal cancer to be a strong predictor of local recurrence (HR 2.7 [95% CI 1.72 to 4.35]), distant recurrence (HR 2.78 [95% CI 1.85 to 4.35]), and OS (HR 1.72 [95% CI 1.27 to 2.27]) [59].

In the Dutch TME trial CRM + rates (≤ 1 mm) were 16% and 18% in the SCPRT and immediate surgery and surgery alone arms respectively. SCPRT did not significantly reduce local recurrence in patients with a positive CRM (9.3% vs. 16.4%, $p = 0.08$), with local recurrence rate of 17% and 30% after low anterior resection or abdominoperineal resection, respectively [60].

In CR07 an involved CRM was reported in 128 (11%) patients – 10% after SCPRT and 12% with selective postoperative LCCRT, but CRM margin positivity rate fell during the trial as surgical quality improved [8]. For patients with an involved CRM, 3-year local recurrence was 13.8% after SCPRT and 20.7% after selective postoperative LCCRT (NS). If data from both Dutch and CR07 trials were combined, the effect of SCPRT on local recurrence would probably have been significant in patients with an involved CRM. Subsequent reports from CR07 with

Table 3
Potential differences between SCPRT and long-course preoperative LCCRT.

	Short-course (SCPRT)	Long-course (LCCRT)
Total radiation dose	25 Gy in 5 fractions	45–50.4 Gy in 25–28 fractions
Fraction size/number of fractions	5 Gy in 5 fractions	1.8–2 Gy in 23–28 fractions
Radiation duration	1 week	5–5.5 weeks
BED, late effects	66.7 Gy	72–84 Gy
Overall treatment time till surgery	3–7 days	10–14 weeks
Down-sizing/down-staging	Not unless surgery delayed 11–12 weeks from start of SCPRT	Yes - approx 50%
Concomitant chemotherapy	No	Yes
Acute toxicity	Obscured if immediate surgery	10–24% G3
Late toxicity	< 10%	< 10%

Table 4
Advantages and disadvantages of Neoadjuvant Chemotherapy prior to SCPRT or chemoradiation.

Advantages of Neoadjuvant Chemotherapy	Disadvantages
Early treatment of micro-metastases with chemotherapy	May delay definitive SCPRT or LCCRT treatment
Allows delivery of chemotherapy at full systemic doses	May reduce compliance to chemoradiation component
Easier to assess clinical response to chemotherapy agents	
Response may be even higher in primary tumours than that reported for metastatic disease	
Better compliance to chemotherapy than postoperative adjuvant chemotherapy	May cause more surgical morbidity
May enhance oxygenation/radio-response	May select radio-resistant clones
May facilitate radical LCCRT if shrinks	May allow distant/sanctuary site seeding
Potential for organ sparing if downstaged	
Potential for curative resection if downstaged	Uncertain effect on local control
Response to chemo may predict response to LCCRT	
Response may define good/bad prognostic groups	May over-treat some good prognosis patients
May Improve overall survival	No evidence that NACT offers better DFS over postop adjuvant chemotherapy

8 years follow-up showed no statistical difference in DFS or OS [61].

In the Polish trial, involved CRM rates of 12.9% and 4.4% were reported for SCPRT and LCCRT respectively, ($P = 0.017$) [27], but this difference did not impact on local recurrence or distant metastases in the different arms. Hence, a positive CRM after SCPRT and immediate surgery has only weak prognostic relevance, but with longer intervals to surgery, CRM involvement becomes a stronger predictive factor for loco-regional recurrence, over six times higher than tumour-free margins (HR 6.45; CI 2.37–17.6], $p = 0.0003$) [57].

Morbidity and mortality after SCPRT and immediate surgery

In the Dutch TME trial [2] surgical mortality rates were higher after RT + TME compared with TME alone (3.5% vs 2.6%) and postoperative complications were also higher (48% versus 41%). Anastomotic leakage rates were similar (13% and 12%). In the Polish trial [27] 2/138 (1.5%) died during or after LCCRT prior to surgery, but none during or after 5 x5 Gy. In the TROG 0104 trial there was no 30-day operative mortality [12]. Hence, many use the 5 x 5 Gy schedule for radiotherapy treatment of the elderly.

SCPRT and a delay until surgery

Most of the randomised trials show an OTT to surgery of 8–12 days [1,2,4,62,63]. As explained above, this schedule does not lead to down-staging, but retrospective evidence suggested that SCPRT and delayed surgery could achieve down-staging in less fit patients [64,65].

In a study from Uppsala University, 37/46 patients (80%) with non-resectable/T4 disease +/- metastases underwent SCPRT with delayed surgery [65]. R0 resection was achieved in 32/37 (86%) of those resected and a pCR rate of 4/37 (10.8%). In a similar UK study, where 22/41 (51%) of patients had tumour < 2 mm from the mesorectal fascia (MRF) and 20/37 (47%) had MRF involvement on MRI [66], resection was achieved in 26/37 (63%), and 22/26 (85%) had R0 resections with a 2/26 (7.8%) PCR rate. Hence some authors have proposed routinely extending the interval between radiotherapy and surgery to increase the rate of pCR and CCR [67].

The Stockholm III randomised phase III trial prospectively compared SCPRT with standard 1-week delay to surgery, SCPRT with a 4–8 week delay, and long-course radiotherapy alone with a 4–6 week delay in resectable cancers. The design was amended to allow randomization of patients to the SCPRT comparison only. Despite the increase down-staging and pCR rates from delaying surgery, no differences in the rate of metastases was reported for the arms operated immediately within 7 days of SCPRT or 4–8 weeks later [42].

A population based study from the nationwide Netherlands Cancer registry reported on rectal cancer patients diagnosed 2005–2014, and receiving radiation therapy (RT, 5 x 5 Gy; N = 764) or chemoradiation therapy (LCCRT; n = 5070) followed by total mesorectal excision after an interval of 5–15 weeks. A good response (ypT0-1 N0) was reported in 17.5% of patients treated with RT and in 22.6% of patients treated with LCCRT (OR 0.70, 95% CI 0.51–0.95). However, pCR was achieved significantly less commonly after SCPRT (9.3%) than LCCRT (17.5%) [68]. In multivariable analysis, histological subtype, clinical stage and distance to anus were identified as independent predictors for tumour response (see Table 4).

Population data mirror these findings when outcomes from each approach in Norway and Sweden were contrasted [19].

A smaller phase III trial with a similar design randomized 154 patients to SCPRT with surgery 7–10 days after the last fraction or to SCPRT with surgery 4–5 weeks later [30]. Counterintuitively, a lower rate of systemic recurrence was observed in patients operated after a longer interval of 4–5 weeks (2.8% vs 12.3%) than in patients with the shorter interval of 7–10 days, ($P = 0.035$). A population based analysis gave support to this, showing a non-significant improvement in OS for a longer interval after SCPRT [69].

A further randomized controlled trial [31] compared patients with rectal cancer treated with SCPRT and LCCRT, both with delayed surgery. No differences in perioperative outcomes, such as R0 resection rate or sphincter-preserving surgery and long-term outcomes were seen except for an improvement in DFS, down-staging at surgery (12.6 vs 39.1%) and pCR (2.7% vs 13.1%) in patients who received LCCRT (see Table 5).

If SCPRT is used simply to prevent local recurrence, randomised and

Table 5
Advantages and disadvantages of SCPRT and LCCRT.

Advantages of Chemoradiation	Disadvantages
Early partial treatment (5FU) of micrometastases May prevent repopulation during radiotherapy Tumour will have intact blood supply Potential for organ sparing if downstaged Potential for curative resection if downstaged Potential for brachytherapy boost Potential for avoiding radical surgery (Habr-Gama) Avoids surgery for resistant/progressive tumours Response may define good/bad prognostic groups Trials show improved local control Trials with oxaliplatin show reduced rates of metastatic disease at surgery	Delivery of less than full systemic doses Delays full systemic adjuvant chemo 18–26 weeks Worse compliance to chemotherapy treatment Expensive
Advantages of Short course preoperative RT Excellent compliance (> 90%) Cheap Tumour will have intact blood supply Allows chemo within 10 days prior to surgery (RAPIDO) Trials show improved local control	Disadvantages No downstaging if immediate surgery No potential for organ sparing if downstaged Does not increase chance of curative resection Only partially compensates for a positive CRM

single arm phase II studies confirm it is safe in oncological terms to delay surgery for 4–8 weeks rather than immediate surgery [41,42,44] because similar rates of local recurrence, distant metastases, RFS and OS are reported. However, a delay seems to be associated with less surgical morbidity and greater down-staging than when SCPRT is followed by immediate surgery [43].

In 2131 patients eligible for analysis from the Dutch ColoRectal Audit (DCRA), the incidence of anastomotic leakage was significantly higher in patients who received SCPRT and underwent surgery within < 4 days (10.1% vs 7.2% $p = 0.018$) [70]. A meta-analysis specifically examining the interval to surgery and surgical morbidity after SCPRT considered immediate surgery (< 4 weeks) vs delayed surgery (> 4 weeks) [71]. The study found neither LCCRT nor SCPRT increased the incidence of anastomotic leakage (AL) after anterior resection of mid and low rectal cancer. Nor did the interval to influence the risk of AL (see Table 6).

SCPRT in the context of metastatic disease/SCPRT as palliation

Liver metastases from rectal cancer can present either synchronously, or metachronously. Only approximately 20% of these will be suitable for surgical resection. Hence, neoadjuvant chemotherapy is usually required, but controversy remains regarding the role of pelvic radiotherapy. Individual trials show metastatic disease in LARC confers an increased risk of local recurrence [2]. Indeed, a meta-analysis used multivariate analysis to show a hazard ratio of 16.2 (95% CI, 5.4–48.6, $P < 0.001$) and 20.26 (95% CI, 7.43–55.28, $P < 0.001$) at 2- and 5-

year follow-up, respectively [72]. An individual patient-data meta-analysis showed an improved survival if the primary were resected [73]. SCPRT is effective in controlling primary-related symptoms, avoiding a colostomy in a substantial proportion of patients particularly if followed by systemic chemotherapy [74]. Early reports from a Dutch group demonstrated that SCPRT, with consolidation chemotherapy followed by surgery, was an effective alternative to traditional LCCRT - thereby addressing the primary tumor early with no undue delay in the initiation of systemic therapy. The primary endpoint of R0 resection was achieved in 66%, and 26% overall achieved a pCR [75]. An update at years 8.1 years showed 16/50 patients (32%) were still alive and 14/50 (28%) were disease-free. Of 36 patients who received radical treatment, only 2/36 (5.6%) suffered local recurrence [76].

Retrospective studies of patients treated with upfront chemotherapy then SCPRT, demonstrated that, amongst patients who underwent surgery, there was a pCR rate of 13.6% and a down-staging rate of 45.5% [77].

Retrospective evidence suggests better outcomes with SCPRT and consolidation chemotherapy than LCCRT in terms of OS in patients with metastatic rectal cancer (34.8 vs. 20.2 months, $P = 0.010$) despite similar rates of down-staging [78]. The authors recommend planned SCPRT should be the preferred radiation approach for managing metastatic rectal cancer (see Table 7).

Hence, SCPRT followed by consolidation chemotherapy is most frequently used, although upfront chemotherapy followed by SCPRT has been trialled in a small US study [79], and a Korean study used four cycles of mFOLFOX6 induction and consolidation before and after

Table 6
Trials studying short course radiation in localized rectal cancer.

Study	Regimen	No. of Patients
Stockholm 1	Arm 1: 5 × 5 Gy with immediate surgery	424
	Arm 2: surgery alone	425
Stockholm 2	Arm 1: 5 × 5 Gy with immediate surgery	272
	Arm 2: surgery alone	285
Swedish trial	Arm 1: 5 × 5 Gy with immediate surgery	585
	Arm 2: surgery alone	583
Uppsala	Arm 1: 5 × 5.1 Gy with immediate surgery	235
	Arm 2: selective postoperative radiotherapy for patients with stage B/C, 60 Gy in 30 fr	236
Dutch TME trial	Arm 1: 5 × 5 Gy with immediate surgery	924
	Arm 2: selective postoperative radiotherapy for patients with positive margins (11%), 50.4 Gy in 28 fr	937
MRC CR07	Arm 1: 5 × 5 Gy with immediate surgery	674
	Arm 2: selective postoperative LCCRT for patients with positive circumferential margin (9%), 45 Gy in 25 fr +5-FU	676
Polish trial	Arm 1: 5 × 5 Gy with immediate surgery	155
	Arm 2: 50.4 Gy in 28 fr with concomitant CT weeks 1 & 5	157
TROG 01.04	Arm 1: 5 × 5 Gy with immediate surgery	163
	Arm 2: 50.4 Gy and 5-FU 225 mg/m ² /day followed by surgery at 4–6 weeks	163

Table 7
Short Course Preoperative Radiotherapy (5 × 5 Gy) and immediate surgery.

Trial	Number in trial	No of patients in SCPRT group	Patients characteristics/stage	Interval from start of SCPRT to surgery (days)	+ CRM rate	pCR rate %
Prospective Randomised phase III						
Polish Trial (Bujko 2004 [27], Bujko 2006) [11]	312		T3-T4 N0-2 M0 without sphincter involvement		13%	0.7%
CR07 (Sebag-montefiore 2009) [4]	1350		Operable rectal cancer	9		Not reported
Egyptian trial (Eitta 2010) [29]	32		T2-4 N0-2 M0			0%
TROG 01.04 (Ngan 2012) [12]	326		Resectable T3 N0-2 M0			1%
Retrospective studies						
Vironen 2005 [39]		42	Resectable stage II/III	Within 7 days	Not stated	0%
Krajcovicova 2012 [37]	N/A	96	Resectable stage II/III	3–5 days	Not stated	0%
Skora 2018 [57]	N/A	210	Resectable stage II/III	Median 13 days	Not stated	10/210 4.8%

radiotherapy in a sandwich approach, which reported local tumour down-staging in 54% [80].

Adding chemotherapy to SCPRT in LARC

SCPRT has been criticised because the schedule is unlikely to allow concurrent integration of preoperative chemotherapy without excess toxicity. Because more down-staging was observed if surgery was delayed after SCPRT [44,65] some have advocated delaying surgery even further to 12 weeks from the start of SCPRT and filling this interval with chemotherapy using FOLFOX. The sequence of SCPRT or LCCRT followed by systemic chemotherapy is attractive because this achieves high compliance with the radiation component. Prolonging the interval between LCCRT or SCPRT and TME has been shown to increase pCR rates, but the interval has varied from 6 to 20 weeks with longer durations if consolidation chemotherapy was also administered (see Table 8).

Postoperative adjuvant chemotherapy in rectal cancer following LCCRT or SCPRT is acknowledged to be administered inconsistently between individuals and centres, and is often tolerated poorly. Hence, SCPRT with delay of 4–12 weeks provides an interval to surgery, which accommodates the systemic therapy that has been traditionally administered post-operatively.

Induction chemotherapy prior to 5 × 5 Gy in LARC alone

Up-front NACT is an attractive concept because it allows delivery of chemotherapy agents, when the primary tumour is treatment-naïve with an intact vasculature, undisturbed by radiation or surgery and has not yet upregulated resistance mechanisms.

Few trials have investigated induction chemotherapy followed by SCPRT. An observational study examined NACT followed by SCPRT (using only 5 × 4 Gy) then immediate surgery, recruiting 67 patients

with cT3-4 tumours [81]. Patients received eight weeks of NACT (initially 5-FU-based for 28 patients then oxaliplatin-5FU for 39). Histopathological down-staging compared to clinical staging was reported in 51% of patients, but no patient achieved pCR.

In the COPERNICUS trial, patients with resectable cancers (mrT2/T3a/T3b) where the mesorectal fascia (MRF) was not threatened, and/or extramural vascular invasion (EMVI) was present, were treated with four cycles of FOLFOX prior to SCPRT and immediate surgery. Sixteen weeks of post-operative adjuvant chemotherapy (AC) were also intended. 60 patients were recruited and 57 patients completed protocol treatment. Compliance with NACT was excellent, with a median dose intensity for both fluoropyrimidines and oxaliplatin of 100% compared with postoperative adjuvant at 63% and 45% respectively. pCR was reported in 7/57 tumours (12%) [82].

Concurrent chemotherapy with SCPRT

Concerns for excess acute toxicity have generally deterred investigators from adding concurrent chemotherapy to SCPRT, but a small study gave concomitant chemotherapy using a 5-FU infusion extended over 96 h, with SCPRT using intensity modulated radiation therapy (IMRT). Following completion, 4 cycles FOLFOX6 were administered. Of the patients who proceeded to TME, 9/10 (90%) achieved an R0 resection, but none achieved pCR [83].

The Korean Radiotherapy Oncology Group (KROG) 10–01 Phase II trial evaluated SCPRT with concurrent chemotherapy administered over 5 days using bolus 5-fluorouracil (400 mg/m²/day) and leucovorin followed by surgery after 4–8 weeks [84]. YpCR was observed in only 1/71 (1.4%) of patients. Down-staging occurred in 20 (28.2%) patients, but severe (grade ≥ 3) acute toxicity was reported in 27/71 (38%) patients.

Another small study combined IMRT with concurrent and consolidation 5FU chemotherapy, with bolus 5-FU day 1 and 5 and a

Table 8
Short Course Preoperative Radiotherapy (5 × 5 Gy) and delayed surgery: Randomised phase III trials.

Trial	Nature of study	No of patients in SCPRT group	Patients characteristics/stage	Interval from start of SCPRT to surgery (weeks)	pCR rate %
Veenhof 2007 [69]	Population	108	Resectable stage II/III	7	12
Radu 2008 [65]	Retrospective	24	Unresectable/T4 or unfit	7.7	10
Hatfield 2009 [66]	Retrospective	43	Unfit for 5FU	9	8
Erlandsson 2019 [45]	phase III	335	Easily Resectable stage II/III	4–8 Median 6.4	10.9
Pach 2012 [30]	phase III	154	Resectable stage I-III	4–5	10
Pettersson 2012 [42]	Retrospective	112	Unresectable/T4 or unfit	8	8
Latkauskas 2012 [31]	phase III	83	Resectable stage II/III	7.1	3
Krajcovicova 2012 [37]	Retrospective	96	Resectable stage II/III	3–5 days	0
Bujko 2013 [111]	Prospective phase II	64	Small ≤ 3 cm stage I/II	8	36% (23/64)
Yeo 2013 [84]	Prospective phase II	71	Resectable stage II/III	8	1
Faria 2014 [100]	Prospective phase II	52	Resectable stage II/III	8.4	10

continuous infusion on days 1 and 2. Surgery was performed 8 weeks after completion [38]. A down-staging rate of 47.4% and a pCR rate of 21.1% were reported [38] with acceptable acute toxicity – perhaps reflecting the use of infusional rather than bolus 5FU.

Two phase-1 studies examined SCPRT with concurrent capecitabine alone or capecitabine and sodium valproate on days 14–21 followed by surgery 8 weeks later [85]. A pCR was achieved in 6/28 (21%) patients. The schedule was considered feasible and capecitabine 825 mg/m²/bd, is being used in an ongoing phase-2 trial.

A Russian study used SCPRT with concurrent capecitabine, local hyperthermia and rectal metronidazole [86]. Sixteen of 80 patients (20%) patients had pCR. A further phase 2 single-arm prospective trial used SCPRT with concurrent and consolidation chemotherapies including capecitabine and oxaliplatin [87] with TME at least 8 weeks after radiotherapy. Concurrent oxaliplatin 85 mg/m² and oral capecitabine 825 mg/m² BD were given during SCPRT with one cycle of XELOX consolidation chemotherapy 3–4 weeks after completion. A pCR was achieved in 8/26 (30.8%) patients who underwent surgery or 8/33 (24%) overall. However, 7/33 (21.2%) patients experienced G3 proctitis. These results confirm that concurrent chemotherapy and SCPRT is associated with substantial toxicity.

Consolidation chemotherapy after SCPRT

The rationale of systemic chemotherapy after SCPRT is to enhance response, reduce tumour volume and achieve greater downstaging than with LCCRT alone, with the hope of increasing RO or curative resections and reducing the need for performing multi-visceral resection, which may impact favourably on the rate and severity of Clavien-Dindo surgical morbidity. Previous European studies reported substantial down-staging with high rates of pCR in patients with LARC treated with SCPRT followed by systemic chemotherapy [88], even in the presence of metastatic disease [75]. These findings provided the rationale for the Polish 2 study [22] and the RAPIDO trial [2]. In the USA, a prospective phase II study from Washington University enrolled 76 patients with cT3-4 rectal cancer to receive SCPRT followed by four cycles of mFOLFOX6 sequential chemotherapy prior to surgery (Olsen 2013) [41]. This group treated an elective nodal target volume to 20 Gy, with an integrated boost to 25 Gy to primary tumour and associated mesorectum, followed by 4 cycles of FOLFOX. The original trial reported that at surgery 21/76 (28%) achieved ypT0, and among low risk, PROSPECT eligible patients this rate was 16/38 (42%) [41]. In a subsequent location and TNM stage-matched cohort comparison with patients treated with LCCRT (Markovina 2017) [89]. Patients treated with SCPRT and chemotherapy had greater T-downstaging and superior distant metastasis-free survival and DFS. Delayed surgery did not increase complications from radiation fibrosis.

A retrospective review from Johns Hopkins Hospital (2017–2019) reported on 26 patients treated with SCPRT and mFOLFOX6 starting 2 weeks following completion of the radiation (Jia 2019) [90]. Initial staging showed cT2(5), cT3(16), and cT4(5) with 88% cN+. After treatment, 20 patients were resected with a pCR rate of 7/20 (35%), and 6/9 patients who achieved CCR opted for watch-and-wait.

The Polish 2 trial investigated local down-staging and R0 resection was the primary endpoint [22]. Initial results showed that SCPRT followed by 3 cycles of FOLFOX prior to surgery numerically (but not significantly) improved early surgical outcomes such as R0 resection (the primary endpoint), compared to LCCRT alone. The novel arm did show lower acute toxicity and did not worsen postoperative surgical morbidity and mortality. Somewhat counterintuitively, the DFS rates were almost identical at 53% versus 52% (HR = 0.96, 95% CI 0.75–1.24, P = 0.85) and the cumulative incidence of distant metastases similar (30% versus 27%, P = 0.26), yet an improved OS was reported favouring the novel arm.

The concept of neoadjuvant chemotherapy as consolidation after chemoradiotherapy [24,91,92] or SCPRT [22,23,93] is oncologically

attractive. Yet, early-stage patients (I and II) are unlikely to benefit from chemotherapy (based on adjuvant studies in colon cancer), hence NACT risks a small but unnecessary treatment-related mortality (0.5%) of FOLFOX/XELOX (MOSAIC and SCOT trials) as well as potential long-term toxicity effects from oxaliplatin. In contrast, more down-staging as a result of NACT may increase the chance of organ-sparing in a ‘watch-and-wait’ programme [94].

Further information on the utility of combination SCPRT and consolidation NACT will be available from the similarly designed phase III RAPIDO (NCT01558921) [22] and STELLAR trials (NCT02533271) [93], which will also hopefully inform on the optimal duration of NACT following SCPRT; 3 cycles of FOLFOX (6 weeks) as evaluated in the Polish 2 trial [35], 4 cycles of CAPOX (12 weeks) in the STELLAR trial or 6 cycles of CAPOX (18 weeks) in the RAPIDO trial.

The STELLAR phase III trial randomised patients with LARC between SCPRT and 4 courses of CAPOX (Experimental group) and a standard but curiously permissive LCCRT dose of 45–50 Gy in 25 fractions, concurrent with capecitabine (Control group). The initial analysis cited a pCR rate of 46.7% (7/15) [95]. A subsequent planned interim analysis showed a lower pCR rate of 19% vs 5% in the short-course/CCT group vs the chemoradiation group, respectively, P = 0.029. However, in the short-course/CCT group, overall complete response rate was 30% when patients with CCR who did not proceed to surgery were included with patients with pCR [91]. In contrast to the Polish 2 trial, these latter trials added chemotherapy to impact on systemic disease, and their primary endpoint is 3-year DFS.

The Korean trial ESCORT (NCT03676517) is also currently recruiting, using SCPRT and 2 cycles of XELOX (6 weeks) with pCR as the primary endpoint.

Potential immune effects from SCPRT

Cancers promote an immune microenvironment, which suppresses adaptive host defences by releasing TGF- β in response to irradiation. TGF- β restricts the activity of CTLs and natural killer (NK) cells and recruits immunosuppressive myeloid-derived suppressor cells (MDSCs) and Tregs, which impair activation of CD4+ and CD8+ T cells. By killing cells, radiotherapy produces tumour antigens, oxygen radicals and non-specific immune alarm signals. Such changes depend on total radiation dose, individual fraction size, interval between fractions, total number of fractions and the OTT. Previous studies showed infiltrating CD45-positive cells increase significantly in tumour within a week of SCPRT [96].

Current research focusses on combining immune-modulating therapies (such as checkpoint inhibitors) and defining the optimal RT fraction size and schedule to fit. Larger fractions may exert stronger immune responses than standard 1.8–2 Gy daily fractions. In experimental models doses of 9–10 Gy appear to inflict more damage causing cell kill by indirect/immune effects. SCPRT may therefore be more efficient than LCCRT in triggering both innate and adaptive anti-tumour immunity [97]. This latter study suggested a transient reduction (over weeks) in MDSCs and Tregs to a nadir at 5 weeks after of SCPRT. Interestingly poor responders showed a large decrease in MDSCs but an increase of Treg-PD-1 cells.

Mature results from the Polish 2 trial showing no OS benefit [35] will disappoint many who felt immune mechanisms specific to 5 \times 5 Gy may have explained the previously reported OS benefit.

Dose escalation/altered fractionation of radiotherapy

Investigators have modified SCPRT to a twice-daily hyper-fractionated regimen to reduce late effects [98,99] with the aim of potentially integrating chemotherapy [100]. A further study also modified SCPRT in rectal cancer to deliver twice daily fractions of 2.9 Gy to a total 29 Gy in one week immediately prior to surgery [101]. Dose escalation of SCPRT has been explored using 5 \times 6 Gy [102], which achieved a pCR

rate of 10% with SCPRT alone. Others in a planned phase I trial are extending up to 5×8 Gy followed by 4 cycles of FOLFOX [103].

Discussion

Both SCPRT with immediate surgery and LCCRT followed by TME demonstrate similar efficacy in preventing local recurrence, distant metastases and improving DFS. Extending the interval to surgery after SCPRT is oncologically safe, and is associated with less surgical morbidity. NACT addresses metastatic disease. NACT could also potentially allow less extensive surgery by converting from the necessity for radical surgery (entailing a permanent colostomy) to sphincter-conserving or organ-sparing surgery, or even avoiding surgery altogether. Hence, neoadjuvant chemotherapy followed by SCPRT, and SCPRT followed by chemotherapy are both under investigation. The most promising sequence from the data presented above is SCPRT followed by consolidation chemotherapy. However, further investigations need to determine the optimal interval to start after completion of SCPRT, and the ideal duration/number of chemotherapy cycles prior to surgery.

Clinicians in the USA have expressed concerns about enhanced acute and late toxicity from the large individual 5 Gy fractions [104]. The Stockholm I and II trials used 2-D radiotherapy with large treatment volumes up to the third lumbar vertebra, which are not relevant to modern target delineation. There is no evidence of such toxicity from more modern studies, which is even less likely if IMRT is used.

American studies have attempted to challenge the findings of equivalence between LCCRT and SCPRT trials [11,12] by comparing these schedules in retrospective SEER data and the NCDB [105,106]. Because these databases only capture OS, but not recurrence or cancer-specific survival, these comparisons are liable to the bias inherent in outcome-by-outcome analysis.

SCPRT is cheaper than LCCRT [107]. Cost-effectiveness for SCPRT with immediate surgery and LCCRT and delayed surgery was analysed [108]. Assumed radiation costs were 3 times higher in the base-case analysis, with SCPRT at \$21,669 and LCCRT \$57,933. SCPRT was more cost-effective (incremental cost-effectiveness ratio, \$133 495 per quality-adjusted life-year). However, the focus on sphincter-sparing, which was assumed to be more likely after LCCRT (39%) than SCPRT (19%), partly offsets the above calculations.

In a study [109] examining costs within the Polish 2 trial [22], total direct cost of radiotherapy was calculated by multiplying resource use and unit costs (indirect department costs based on the number of fractions used). They estimated the cost of SCPRT plus chemotherapy much higher than LCCRT (\$78,937 vs. \$38,140). Nevertheless, they concluded that SCPRT plus chemotherapy is still a more cost-effective strategy [109].

A further recent population-based analysis of the total annual cost of radiotherapy for LARC in the USA, calculated LCCRT with 3D or IMRT as \$15,882 and \$23,745 per patient, compared with SCPRT at \$5,458 and \$7,323 per patient, respectively [110]. The authors estimated that adoption of SCPRT had the potential to save between \$106 and \$232 million per annum.

Conclusions

The ability of SCPRT to prevent LR in rectal cancer does not appear substantially different from that of LCCRT. SCPRT is highly cost-effective, and more cost-effective than LCCRT if down-staging is discounted. Stockholm III results suggest that surgery may have less complications with a delay to 4–6 weeks without compromising oncological outcomes, and the delay increases the pCR rates. The regimen is flexible in its positioning and allows integration of NACT, but the optimal sequence and timing of chemotherapy prior to surgery remains unclear. Hence, selecting the ideal interval between SCPRT and surgery should currently take into account many factors including the need for systemically active chemotherapy, the potential for down-sizing/down-staging

whilst limiting its adverse events in terms of acute toxicity and surgical morbidity.

The addition of consolidation chemotherapy with 3 cycles of FOLFOX appears to enhance down-staging and may improve resectability in borderline and unresectable cancers over SCPRT alone, although this strategy has not reduced the risk of distant metastases and does not improve survival. Additional consolidation chemotherapy with more aggressive regimens (FOLFOXIRI or XELOX and bevacizumab) or longer durations have been advocated. However, the long-term oncological benefit of adding chemotherapy to short-course radiotherapy is not currently clear.

Practice points

- When SCPRT and LCCRT are compared clear differences in oncological outcomes (local control, rate of metastases, DFS) or late effects and HrQOL have not been demonstrated.
- LCCRT and delay to surgery achieves more down-staging and a higher rate of pCR than SCPRT alone (5×5 Gy) with delay to surgery, but has not translated into more sphincter preservation.
- The oncological safety of a long interval to surgery after SCPRT compared with surgery within 7 days has been definitively established.
- Modest down-staging is achieved by SCPRT alone if surgery is delayed, which can be enhanced in unresectable cancers by additional systemic doublet (but not single agent) consolidation chemotherapy.
- SCPRT allows the rapid integration of systemic chemotherapy usually starting within 10 days of radiotherapy completion.
- If prevention of local recurrence is the aim of treatment, rather than down-staging, or achieving a complete clinical response (CCR) and avoiding radical surgery, SCPRT is probably the preferred schedule taking into account compliance, patient choice, convenience, acute toxicity, and cost - assuming equivalence of oncological outcomes and late effects.
- In terms of total neoadjuvant therapy, the most promising sequence is SCPRT followed by consolidation chemotherapy
- Further investigations need to determine the optimal interval to start after completion of SCPRT, and the ideal duration/number of chemotherapy cycles prior to surgery.

Declaration of Competing Interest

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