How to Select for Preoperative Short-course Radiotherapy, While Considering Long-course Chemoradiotherapy or Immediate Surgery, and Who Benefits?

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Abstract

The management of patients with locally advanced rectal cancer (LARC) has evolved with the aim of reducing local recurrence and improving survival. Current practice has developed from refinements in surgical technique, the availability of different types of preoperative imaging, the selective or blanket use of neoadjuvant treatment (usually radiation) and sophisticated efforts exploring multimodality treatments to achieve organ preservation. Both short-course preoperative radiotherapy (SCPRT) and long-course chemoradiation (CRT) are considered standard neoadjuvant strategies, which are advocated in different parts of the world. New techniques in the delivery of radiotherapy, such as intensity-modulated radiotherapy (IMRT), may allow more precise dosing to the target volume (tumour and/or locoregional lymph nodes) and limit radiation doses to critical normal structures; however, current schedules of SCPRT and CRT impact on late function, and if they do not improve survival in resectable cancers, can they be omitted in selected cases?

Keywords

Rectal adenocarcinoma, neoadjuvant radiation, chemoradiation, chemotherapy, short-course preoperative radiation, long-course chemoradiation

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In patients with locally advanced rectal cancer (LARC), not involving the mesorectal fascia (MRF), surgery with total mesorectal excision (TME) is the standard of care. Prior to the TME era, high rates of local recurrence (LR) were observed after radical surgery, and 10–40 % of patients required a permanent stoma, even for tumours arising in the mid/upper rectum. In the 1990s, randomised trials[1–3] established short-course preoperative pelvic radiotherapy (SCPRT) using 5 x 5 Gy as a component of the curative treatment of resectable and early rectal cancers. These historical trials reported LR rates of 20–30 % after surgery alone, reflecting the suboptimal surgical practice at the time.

Two subsequent trials examined whether SCPRT simply compensated for poor surgical technique, i.e. whether SCPRT still reduced LR if TME was performed. By then, it was recognised that the risk of LR, after a potentially curative resection, is mainly explained by microscopic tumour cells within 1 mm of the circumferential resection margin (CRM).[4] Hence, in the control group in the event of a histopathological involved CRM, postoperative RT or chemoradiotherapy was intended in the Dutch TME study[5] and CR07 trial,[6] respectively. Both trials confirmed a reduction in LR, but overall survival (OS) was not improved, and the risk of metastases predominated over LR.[5–8]

During the same period, the strategy of postoperative fluorouracil (5FU)-based chemoradiation (CRT) for patients with stage II or III rectal cancer[9] was extrapolated to the preoperative setting. Randomised trials of preoperative 5FU-based CRT demonstrated an improvement in locoregional control,[10–12] but not disease-free survival (DFS) or OS. However, in more advanced unresectable/borderline cases, CRT improved resectability and DFS.[13] The German trial also led to the recognition that preoperative CRT is more effective and less morbid than postoperative CRT.[10] With the benefit of preoperative imaging (computed tomography [CT], transrectal ultrasound and magnetic resonance imaging [MRI]) to stage and define the ease of resectability, neoadjuvant CRT has been widely extended, particularly when the CRM is predicted to be compromised.

Hence, different strategies for treating LARC have developed independently in different countries, shaped by local experts and

Table 1: Randomised Studies of SCPRT

Trial	Number	Stage	Chemotherapy	Adjuvant Chemotherapy	Local Recurrence	RFS/DFS	5-year OS
Polish SCPRT[25]	155	cT3–T4	None	Optional	Crude 9 %	4-year DFS 58 %	4-year OS 67 %
Polish CRT[26]	157	cT3–T4	5FU/FA	Optional	Crude 14 %	4-year DFS 56 %	4-year OS 66 %
TROG SCPRT[27]	163	II–III	None	Mandated FUFA 6/12	3 years 7.5 %	5-year RFS 64 %	5-year 74 %
TROG CRT[27]	163	II–III	PVI 5FU 225 mg/m^2	Mandated FUFA 4/12	3 years 4.4 %	5-year RFS 61 %	5-year 70 %
Latkauskas SCPRT[34]	37	II–III	None	Not stated	Not stated	Not stated	Not stated
Latkauskas CRT[35]	46	II–III	5FU/FA	Not stated	Not stated	Not stated	Not stated
Pach 2012[36] SCPRT immediate 7–10 days	77	I–III	None	Not stated	1.5 %	Not stated	63 %
Pach 2012[36] SCPRT delayed 4–5 weeks	77	I–III	None	Not stated	7 %	Not stated	73 %

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

Table 2: Potential Difference Between SCPRT and Long-course Preoperative CRT

	Short-course (SCPRT)	Long-course (CRT)
Total radiation dose	25 Gy in 5 fractions	45–50.4 Gy in 25–28 fractions
Fraction size/number	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
Recommended overall time to surgery following treatment	3–7 days	6–12 weeks
Downsizing/downstaging	Not unless surgery delayed 11–12 weeks from start of SCPRT	Yes, approximately 50 %
Concomitant chemotherapy	No	Yes
Acute toxicity	Obscured if immediate surgery	10–24 % G3
Late toxicity	<10 %	<10 %

BED = biologically effective dose; CRT = chemoradiation; SCPRT = short-course preoperative radiotherapy.

regional biases based on the results of individual national trials. Both SCPRT and long-course CRT are considered standard strategies, which are fervently advocated in highly polarised arguments. Sometimes there are perverse incentives in terms of reimbursement that partly drive these selections.

Ideally, we should individualise available treatments, based on clinical, imaging and molecular characteristics. This strategy could select patients more likely to respond to RT/chemotherapy/targeted agents or could spare patients from treatment that may not be needed, or is unlikely to be effective. Imaging can accurately determine the local disease extent and the presence of metastatic disease. The prospective multicentre MERCURY trial established that MRI measured extramural primary tumour extent was equivalent to measurement in the resection specimen.[14] MRI can also identify macroscopic extramural vascular invasion and a CRM at risk (<1 mm).

There has been a long-standing debate on whether to improve surgical quality or utilise RT.[15] The majority of LRs historically reflected inadequate mesorectal resection,[16] which is a common finding on postoperative MRI after partial mesorectal excision.[17] Currently, optimal quality-controlled surgery, in terms of TME in the trial setting, can be associated with LR rates of less than 10 %, whether patients receive RT or not.[7] Factors that compromise the performance of good-quality TME are well recognised and include patient- and disease-related aspects and the surgeon's case volume.[18]

This review attempts to evaluate the individual advantages relating to SCPRT or long-course CRT. The question as to whether there is a group of patients who do not need RT because the benefit is so marginal is also addressed. It represents an individualised approach to the use of radiation therapy, with speculation on future applications and developments.

Rationale for the Different Approaches

Short-course Preoperative Radiotherapy

SCPRT represents a flexible schedule of a short accelerated and hypofractionated intensive RT, administering 25 Gy in five fractions over 5 days. According to the linear quadratic formula, this schedule is equivalent to 21 x 2 Gy fractions in terms of acute and late effects, assuming an α/β of 10 Gy for acute effects and 3 Gy for late effects.

Three trials prior to the introduction of TME[1,3,19] compared SCPRT followed by immediate surgery with surgery alone. The Uppsala trial[20] compared SCPRT and immediate surgery with initial surgery followed by postoperative split-course RT for patients with Dukes B and C histology. All trials showed a significant reduction in LR with SCPRT and contributed to the current acceptance of SCPRT. In the Swedish Rectal Cancer Trial,[3] LR was reduced from 27 % to 11 % ($p<0.001$) and 5-year survival increased from 48 % with surgery alone, to 58 % after SCPRT and surgery, respectively ($p=0.004$).[3] A recent report confirms that the benefits shown are sustained after 13 years of follow up.[21]

Subsequent trials were designed to test whether SCPRT still reduced LR if TME was performed. The Dutch trial[6] and the Medical Research Council CR07 trial[5] compared routine SCPRT and immediate surgery against initial surgery with a policy of selective postoperative treatment restricted to patients with involvement of the CRM (the Dutch trial used RT alone and CR07 concurrent 5FU-based CRT). Both trials showed a sustained reduction in LR (10–11 % to 4–5 %) in the SCPRT group. However, the number of patients who were intended to, and actually received postoperative RT in the Dutch trial, is not known[6] whereas in the CR07 trial there were no details on compliance in the 53/77 patients who received selective postoperative CRT. Hence, it is not clear (as it is in the German study) whether the majority of recurrences occurred in the treated or non-treated patients. Adjuvant chemotherapy was not

Table 3 : 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 CRT 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 CRT 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 predictive of response to CRT?	
Response may define good/bad prognostic groups	May overtreat some good prognosis patients
Improves overall survival?	No evidence that NACT offers better DFS over post-op adjuvant

CRT = chemoradiation; DFS = disease-free survival; NACT = neoadjuvant chemotherapy; SCPRT = short-course preoperative radiotherapy.

used in the Dutch trial, whereas the majority of patients with stage III disease (84 % versus 87 % for SCPRT and selective CRT arms, respectively) received 5FU chemotherapy in the CR07 trial.[5] In the CR07, doses of RT mandated were low (45 Gy) compared with standard postoperative CRT trials, e.g. the German trial mandated 55.8 Gy postoperatively.[10] Of the 53/77 patients with a positive CRM in the selective arm who received chemoradiotherapy, 19 % received RT alone and 9 % no RT.

SCPRT is now favoured in Scandinavia, the Netherlands and the UK for resectable cancers where staging MRI suggests a conventional TME should enable a curative resection without margin involvement, i.e. tumour shrinkage is not required.

Advantages of Short-course Preoperative Radiotherapy

Compliance is high because toxicity (nausea, diarrhoea, proctitis, tenesmus, urinary frequency, dysuria, erythema/desquamation of the perineum in low rectal cancers) is usually only experienced after treatment is completed. The short overall treatment time (OTT), with immediate surgery (ideally within 7 days), leaves an insufficient interval to express the pelvic normal tissue reactions from radiation and avoids the accelerated repopulation that may occur in the latter part of CRT. Other advantages include consequent high compliance and low cost.

Decisions on the requirement for postoperative adjuvant chemotherapy can be made without modification of the pathological stage or effacement of the nodes. In contrast to fluoropyrimidine-based CRT, adjuvant chemotherapy with systemically active regimens, such as FOLFOX, can be started with minimal delay, if deemed necessary, within a few weeks of diagnosis.

Disadvantages of Short-course Preoperative Radiotherapy

SCPRT is criticised because this schedule does not allow concurrent integration of preoperative chemotherapy, although it could be argued that standard CRT does not utilise fully systemic doses of chemotherapy. The SCPRT schedule does allows some integration of induction,[22] concurrent[23] and consolidation chemotherapy[24,25] prior to, during and following SCPRT, respectively. SCPRT also only partly compensates for a positive CRM.[23,24]

Is Short-course Preoperative Radiotherapy Currently Employed in an Optimal Way?

The Polish trial and the TROG-0104 trial demonstrate that the interval to pathological assessment influences the rate of response.[27–29] Although size may diminish,[30] no reduction in tumour or nodal classification is expected if the interval is less than 10 days.[31] Yet, some downstaging is observed if surgery is delayed for more than 10 days.[31,32] Surprisingly, T-stage downstaging was observed in the CR07 trial (or perhaps the arms were imbalanced at randomisation),[5] but overall, the Dutch TME trial found no significant difference in tumour node metastasis (TNM) classification between SCPRT and surgery alone groups[6,30] and so the aim of SCPRT is simply to reduce the risk of pelvic recurrence. Further extension of the interval following SCPRT to surgery of at least 6 weeks does demonstrate significant histopathological response and downstaging.[33–35]

A small randomised controlled trial in patients with resectable stage II and III rectal adenocarcinoma[36] compared the downstaging achieved after long-course CRT or SCPRT, followed by delayed surgery (see *Table 1*). Surgery was performed 6 weeks after in both groups. Fewer patients achieved early pTstage (pathological complete response [pCR] or pT1) in the SCPRT group (3 % versus 22 %; p=0.03), which suggests the interval to maximal response after SCPRT may need to be longer, i.e. 12 weeks after the start of treatment.[36,37]

Another small randomised study[38] also investigated the impact of the interval between SCPRT and surgery on OS, and recurrence rate (see *Table 1*). Counterintuitively, a lower rate of systemic recurrence was observed in patients operated on with the longer interval of 4 to 5 weeks after SCPRT (2.8 % versus 12.3 %) than in patients with the shorter interval of 7 to 10 days (p=0.035). No differences in LR rates were observed (p=0.119).

Developments in Short-course Preoperative Radiotherapy

Integration of Chemotherapy

In contrast to long-course RT, synchronous 5FU-based chemotherapy is less easily combined with SCPRT. To our knowledge, only one study has been reported attempting to integrate chemotherapy into SCPRT (5 x 5 Gy).[23] Hence, some investigators have modified SCPRT (5 x 5 Gy) to a hyperfractionated RT regimen with a view to reducing late effects,[39–41] and potentially integrating chemotherapy. A further study also modified SCPRT in rectal cancer to deliver twice-daily

Table 4: Advantages and Disadvantages of SCPRT and CRT

Advantages of Chemoradiation	Disadvantages
Early partial treatment (5FU) of micrometastases	Delivery of less than full systemic doses
May prevent repopulation during radiotherapy	Delays full systemic adjuvant chemotherapy 18–26 weeks
Tumour will have intact blood supply	Worse compliance to chemotherapy treatment
Potential for organ sparing if downstaged	Expensive
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	
Advantages of SCPRT	**Disadvantages**
Excellent compliance (>90 %)	No downstaging if immediate surgery
Cheap	No potential for organ sparing if downstaged
Tumour will have intact blood supply	Does not increase chance of curative resection
Allows chemotherapy within 10 days prior to surgery (RAPIDO)	Only partially compensates for a positive CRM
Trials show improved local control	

5FU = fluorouracil; CRM = circumferential resection margin; CRT = chemoradiation; SCPRT = short-course preoperative radiotherapy.

fractions of 2.9 Gy to a total dose of 29 Gy in 1 week immediately prior to surgery.[42]

Extending the Interval to Surgery

SCPRT followed by local excision of small, radioresponsive tumours in elderly patients achieves an acceptable LR rate.[43] A complete, or near complete, pathological response in the primary may predict complete response in the pelvic/perirectal lymph nodes. A good response was observed in 67.2 % of patients treated in the short-course group, and LR at 2 years (median follow-up) was 11.8 %, although SCPRT may compromise functional outcomes.[44] This SCPRT strategy is tested in the current UK-TREC trial (transanal endoscopic microsurgery [TEM] and Radiotherapy in Early Rectal Cancer), where patients with early rectal cancer (T1–2N0) are randomised between radical TME surgery and SCPRT with delayed local excision at 8 to 10 weeks. Caution is needed for very low tumours where local excision/TEM surgery results in exposure of the external sphincter or levator, thus potentially compromising any subsequent surgery.

Two small retrospective studies in locally advanced tumours[33,34] (with 46 and 41 patients, respectively) and a prospective phase III trial[35] show that short-course RT with delayed surgery for several weeks can result in substantial downstaging and achieve an R0 resection for most patients. Hence, several alternative sequencing approaches have been examined.

There have been reports of neoadjuvant chemotherapy administered for four cycles, followed by preoperative SCPRT 1 week after chemotherapy completion, delivering a lower dose of 20 Gy in five fractions over 1 week. Surgery was performed the following week.[45] Late toxicity of grade 3 and above was observed in 9 % of patients.

Proceeding to systemic 'consolidation' chemotherapy following SCPRT is a rational approach which fits with De Ruysscher's Principle of SER (the interval between the start of treatment and the end of RT) which ideally should be as short as possible.[46] Preliminary results of SCPRT followed by four courses of systemic chemotherapy (FOLFOX) in 44 evaluable patients (4 cT4 and 40 cT3) have been reported showing histopathological downstaging to ypT0-2 in 75 % of patients, and 30 % to ypT0.[24]

An interim analysis can be made of a Polish trial in which patients with unresectable fixed cT3, cT4 or locally recurrent rectal cancer without distant metastases were randomised to either 5 x 5 Gy, followed by three courses of FOLFOX4, or 50.4 Gy delivered in 28 fractions concurrently with 5-FU, leucovorin and oxaliplatin. Surgery in both groups was performed 12 weeks after the beginning of radiation and 6 weeks after neoadjuvant treatment. pCR was observed in 21 % of the patients in group one and in 9 % in group two, but acute toxicity was similar.[4,7] The overall resection rate and microscopically radical resection rate were 77 % and 73 % in the experimental group versus 83 % and 71 % in the control group. Postoperative complications were similar (27 % in the experimental group and 16 % in the control group).

The Dutch Colorectal Group treated patients presenting with rectal cancer and synchronous resectable metastases with SCPRT, followed by six cycles of capecitabine and oxaliplatin, plus bevacizumab in the M1 phase II trial.[48] They reported high response rates and radical (R0) resection was achieved in 80 % of the patients. Hence, the Polish trial[47] and the M1 trial[48] both support the hypothesis that systemic chemotherapy has activity on the primary tumour and may contribute to locoregional response compared with short-course alone with a planned 'waiting period' without chemotherapy.

Based on these promising results, the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial is currently recruiting.[25] The trial randomly assigns patients with LARC to SCPRT, followed by six cycles of capecitabine, plus oxaliplatin and then TME, compared with fluoropyrimidine-based preoperative long-course chemoradiotherapy and TME.

Long-course Preoperative Chemoradiotherapy

Long-course preoperative CRT is preferred in the US and southern Europe as the standard of care for patients with clinical stage II and III rectal cancer.[49] CRT is advocated because it achieves sphincter-sparing procedures and integrates systemic chemotherapy at an early timepoint.[49] However, this notion is somewhat counterintuitive from a functional point of view as addition of CRT to a low anastomosis has additive deleterious effects on neo-rectal and anal canal function. Also, subsystemic doses of chemotherapy are usually required in CRT. The

rationale for long-course CRT is to achieve additive local and systemic effects using a concurrent fluoropyrimidine, thereby inducing downstaging/downsizing and, sometimes, tumour sterilisation. The optimal interval to surgery after CRT, if downstaging is required, remains unproven.[50]

Published randomised trials have shown a significant impact of preoperative versus postoperative CRT on local control, but no effect on OS. CRT is more appropriate and can also facilitate a curative resection for cases where the surgeon considers the tumour unresectable and/or the CRM/MRF is breached or threatened on MRI imaging. In these circumstances, even technically optimal surgery is unlikely to achieve a curative resection. Preoperative 5FU-based CRT has shown favourable effects on recurrence-free survival (RFS), and cancer-specific survival with a trend to improved OS.[13] CRT can also achieve eradication of tumour (i.e. pCR) in 8–40 % of patients, depending on cT and cN stage initially treated. Also, there is increasing enthusiasm for a non-operative approach in the event of a complete clinical response.[51]

It remains unclear why increasing response is useful to a patient unless the tumour is initially borderline resectable or unresectable, i.e. the CRM is threatened or there is disease outside the MRF. Alternative indications include the rectal cancer proving likely on histology to be radioresistant (signet ring), the aim being to perform a lesser operation, i.e. sphincter sparing or local excision, or, finally, in terms of organ-sparing, i.e. to avoid surgery completely. Hence, outside of the above indications, dose escalating the radiation with a simultaneous integrated boost, brachytherapy or contact therapy is unlikely to achieve anything additional other than downstaging.[52]

Similarly, attempting to enhance the chemo-radiosensitivity with additional cytotoxic chemotherapy, such as oxaliplatin[53–57] or irinotecan, is also unlikely to prove of benefit. Therefore, patients need to be selected for CRT, which simultaneously combines early cytotoxic chemotherapy treatment with a locoregional treatment. The advantages of CRT in the preoperative setting include the potential to increase the likelihood of a R0 resection, less acute toxicity and enhanced radio-sensitivity due to better oxygenated cells, as opposed to hypoxic cells in scar tissue in the postoperative setting. In addition, although unvalidated, the preoperative approach may define good and bad prognostic groups.[58–61]

Advantages of Chemoradiation

Preoperative CRT can downstage fixed/unresectable tumours and result in higher curative resection rates being achieved, thereby reducing the risk of LR.[12,13] Using MRI criteria, it is possible to predict where there is a high risk that the surgeon will not able to perform an R0 resection and will leave gross macroscopic or undetected microscopic tumour in the pelvis.

Two European trials (EORTC 22921 and FFCD 9203) demonstrated that the addition of concurrent 5FU/LV to long-course radiation was associated with an acceptable increase in acute toxicity and resulted in pathological downstaging. Both trials reported similar findings, with a significant reduction in the rate of LR from 15 % to 8–10 %, but with no difference in DFS or OS.[11,12] The German rectal cancer trial (AIO) compared preoperative versus postoperative 5FU CRT.[10] The rate of LR was 12 % with postoperative CRT compared with 6 % in the preoperative CRT arm. Acute and late toxicity was also significantly less with the preoperative approach, although the dose of RT was higher (55.8 Gy) in the postoperative arm.

These three trials[10–12] shifted the approach in Europe and much of the US from selective postoperative CRT based on histopathology to a more blanket, but imaging-based, selection of patients for preoperative CRT. The relevance of this strategy has been further strengthened by the results of the NSABP-R03 trial,[62] which also randomised preoperative versus postoperative CRT, but only recruited 267 of its planned patient target number (n=900). Five-year locoregional recurrence was 10.7 % in each treatment arm (p=0.693). A significant improvement of 5-year DFS (65 % versus 53 %; p=0.011), and a non-significant improvement in 5-year OS (75 % versus 66 %; p=0.065) were also observed for the preoperative arm.

By contrast, in more advanced unresectable/borderline cases, CRT improved resectability and DFS.[13] Distant metastases still occurs in at least 30 % of cases.[11,12,59] Nevertheless, due to the improved pCR and locoregional control, 5FU-based preoperative CRT, followed by TME, has become the standard of care in patients with LARC. A Scandinavian trial of 207 patients with nonresectable or locally recurrent rectal cancer[13] randomised patients to receive CRT with 50 Gy plus 5FU/LV versus long-course RT alone (50 Gy). In this more advanced, high-risk group, a statistically significant reduction in local failure, time-to-treatment failure and cancer-specific survival was observed in patients who received preoperative CRT.

Disadvantages of Chemoradiation

Current fluoropyrimidine-based CRT is relatively expensive due to the large number of treatments (25–28 daily fractions) compared with SCPRT (5 x 5 Gy). CRT delivers less than full systemic doses and has no impact on DFS or OS. Finally, CRT delays full systemic adjuvant chemotherapy for 18–26 weeks from the diagnosis of an advanced cancer until the postoperative adjuvant setting where oxaliplatin (FOLFOX or XELOX) can be delivered at systemic doses (see *Table 4)*.

Concurrent chemotherapy usually consists of 5FU, either as a continuous infusion in combination with leucovorin, or using an oral fluoropyrimidine, such as capecitabine or UFT-oral. Initial enthusiasm was stimulated by phase I/II trials and the efficacy of oxaliplatin in dealing with distant micro-metastases in the adjuvant setting in colon cancer.[63,64] However, these combinations have yet to show a benefit in terms of improving outcome in resectable rectal cancer.[53–55,58,57]

Direct Comparison of the Two Approaches (Short-course Preoperative Radiotherapy and Chemoradiation)

Phase III trials have reported a direct comparison between SCPRT and immediate surgery, and preoperative CRT and surgery after an interval.[27,29] The Polish trial randomised 312 patients with resectable rectal cancer between 1999 and 2002. The trial aimed to evaluate the hypothesis that the downstaging effects of preoperative CRT with a 4 to 6-week delay to surgery would increase the rate of sphincter-preserving resection compared with SCPRT and immediate surgery. However, no difference was observed for the primary end point of sphincter-sparing. The 5-year rate of LR was 9 % and 14 % (p=0.17) for SCPRT and CRT, respectively, with no significant difference in DFS or OS.

The Trans-Tasman Radiation Oncology Group (TROG 01.04) trial randomised 326 patients between SCPRT (5 x 5 Gy) and immediate

surgery, and preoperative CRT and interval to surgery to compare the rate of LR. Adjuvant chemotherapy with 5FU and folinic acid for 6-monthly cycles was planned to start 4 to 6 weeks postoperatively in both arms. The mature trial results confirm similar outcomes for SCPRT and LCRT for distant recurrence, OS and late effects.[29] Cumulative incidences of LR at 5 years were 7.5 % for SCPRT and 5.7 % for long-course CRT respectively (p=0.51). However, for distal tumours, 6/48 SCPRT patients and 1/31 CRT patients had a LR, respectively (p=0.21).[29]

The major conclusion from analysis of the two trials discussed above is that they were underpowered, either individually or in combination, to detect a clinically relevant, but small, difference in LR, i.e. 5 %. This would have need approximately 1,800 patients in total. Neither trial, therefore, provides sufficient evidence to definitively compare efficacy between SCPRT and CRT. The Polish trial reported no significant difference for severe late toxicity with rates of 10 % and 7 % for SCPRT and CRT, respectively (p=0.17). In the TROG 01.04 trial, crude late G3-4 toxicity rates are similar, i.e. 5.8 % for SCPRT and 8.2 % for CRT, respectively (p=0.53).[29] In the Polish trial, quality of life (QoL), anorectal and sexual functioning did not differ in patients receiving short-course RT compared with those receiving CRT,[65] although the details and documentation are poor.

Toxicity and Quality of Life of Short-course Preoperative Radiotherapy and Chemoradiation

Much of the concern for many clinicians, particularly those in the US, is the potential risk of enhanced acute and late toxicity from the large individual 5 Gy fractions within the SCPRT regimen.[49,66,67] This view was originally raised by the reports from the Stockholm I and II trials that showed a significant increase in postoperative mortality and venous thromboembolism, pelvic and femoral neck fractures, small bowel obstruction and postoperative fistulae. Possibly the two-field large treatment volumes were responsible.

SCPRT and CRT appear broadly comparable in terms of reported acute toxicity,[68] with the exception of acute neurogenic pain, which is observed in <1–2 % of patients receiving SCPRT and is usually reversible.[69,70] In the Swedish rectal cancer trial, 14/897 patients discontinued SCPRT due to neurotoxicity.[3] With a more limited field size, these side effects were not observed in the CR07 trial,[5] and have not been reported after CRT.

Data from the Polish trial demonstrated 18 % acute toxicity with CRT, compared with 3 % with SCPRT respectively (p=0.001).[27] The provisional reports from the TROG trial demonstrated a similar pattern,[71] although much of the acute toxicity is obscured by the timing of surgery.

The Dutch TME study demonstrated more perineal complications following SCPRT and APER (18 % versus 29 %; p=0.008). In the postoperative period, many patients who had SCPRT become leucopenic, which may increase the risk of postoperative complications and death.[72] Elderly patients aged over 75 years who were operated on 4 to 7 days after RT had a higher chance of dying due to non-cancer-related causes during the TME-trial compared with an interval of up to 3 days.[73]

Toxicity after SCPRT has been well-documented.[74] Effects on sexual function,[75] urinary incontinence,[76] bowel function[77] and faecal incontinence[78,79] have been reported. SCPRT impacts on continence-related QoL compared with patients treated with surgery alone.[80] These complications may depend on the size of the radiation field, shielding, the OTT, the fraction size and the total dose.

The Dutch study after 11 years follow-up reported a higher risk of second malignancy from SCPRT. Few publications have reported late complications after preoperative CRT. After a median of 4.6 years follow up,[81] the EORTC 22921 trial reported low QoL scores for sexual functioning, which were more severe in males than females.

Chemoradiation/Short-course Preoperative Radiotherapy in the Context of Metastatic Disease

In a further study of patients with stage IV rectal cancer and low volume systemic metastases, 115 patients were examined, 65 (56 %) of whom received preoperative CRT and 50 (44 %) of whom did not. There were no significant baseline differences between the two groups and no significant difference in the rates of locoregional recurrence (12.3 % versus 12 %), with median survival of 27 versus 34 months for patients treated with RT or those not treated.[82] The initial palliative effect of SCPRT in stage IV rectal cancers, followed by systemic chemotherapy, appears sufficiently effective to avoid surgery, even if the tumour is close to obstructing.[83] This strategy allows earlier administration of full systemic chemotherapy, compared to CRT.

Advanced rectal cancers (primary, recurrent or metastatic) are often associated with neuropathic pain, bleeding, a mucinous discharge, frequency of defecation, tenesmus and obstruction. SCPRT can alleviate symptoms, restore function, and improve QoL. SCPRT is quick to administer and acceptable to even those patients with poor performance status, limited mobility or who are elderly.

Data on Omission of Radiation Therapy in Rectal Cancer

Improvements in the surgical technique have resulted in a reduction in the LR rate from 30 % in the 1980s to between 5 %–10 % currently. Even lower rates are currently achieved in both stage II and III in some specialist centres,[84–87] particularly if the quality of surgery is optimised. New emerging data[88] shows that it is possible to substitute RT with chemotherapy in selected cases, with low risk features on initial staging.

Selection of Patients Most Likely to Benefit from Preoperative Radiotherapy (Short-course Preoperative Radiotherapy or Chemoradiation)

The National Institute of Health and Clinical Excellence colorectal guidelines (http://guidance.nice.org.uk/CG/Wave16/2) identifies three levels of risk for LR. If the pelvic MRI demonstrates cT1, T2 or T3a disease without adverse features, such patients can omit RT, provided staging and surgery are optimised. Many consider this approach controversial.

If the primary tumour is staged radiologically as T4b (involvement of another organ) or is predicted to breach or threaten (<1 mm) the margins in terms of the MRF, levator or external sphincter complex, CRT is the treatment of choice. However, in older or frail patients, treatment using 5 x 5 Gy with a long delay of 6–12 weeks is an alternative option. Since inadvertent perforations and positive CRMs are observed more commonly in low rectal cancers, CRT is often advocated for low tumours. Upper rectal cancers rarely require RT[6,89] and the greatest benefit of SCPRT seems to be in patients with mid-rectal tumours.[8]

In practice, the majority have resectable T3 disease with no predicted threat to the CRM. Here the balance between risk and benefit must be carefully considered. The routine blanket use of either SCPRT or CRT, as recommended on publication of the CR07 trial, represents substantial

overtreatment. In this setting, current evidence from trials that compared SCPRT and preoperative CRT suggests that the two approaches are broadly similar in their ability to lower the risk of LR,[28,29] so both are acceptable options. Both approximately halve the rate of LR but do not impact on DFS or OS. This finding probably reflects the observation that the majority of patients within these trials were node negative, i.e. low risk.

Hence, this patient group can be considered for, but may not need, either SCPRT or CRT if the MDT recognises that optimised surgery is being performed by the surgeon (units where surgeons are performing good-quality TME in at least 70 % of cases), and the predicted margins are >2 mm. By contrast, although SCPRT/CRT does compensate for suboptimal surgery, it does not compensate entirely.

In contrast to CRT with a long interval to allow downsizing, SCPRT allows definitive surgery to take place within days and allows the rapid use of systemically active chemotherapy (FOLFOX). Recent trials of SCPRT have included patients with cT3 and/or N+ disease who also underwent sequential or postoperative chemotherapy, allowing a more relevant comparison with CRT and blurring some of the advantages of CRT. Many surgical units are now only employing SCPRT or CRT in 15–20 % of cases.

Conclusion

Further research is needed to identify patients either at excess risk of radiation-related toxicity or whose cancers are more or less likely to benefit from preoperative radiation and/or fluoropyrimidine chemotherapy. ■

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