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Slevin, F orcid.org/0000-0002-7176-904X, Hanna, CR, Appelt, A orcid.org/0000-0003-2792-9218 et al. (4 more authors) (2022) The Long and the Short of it: the Role of Short-course Radiotherapy in the Neoadjuvant Management of Rectal Cancer. Clinical Oncology, 34 (5). E210-E217. ISSN 0936-6555

https://doi.org/10.1016/j.clon.2021.12.004

Abstract

Total mesorectal excision (TME) is the cornerstone of treatment for rectal cancer. . Multiple randomised trials have demonstrated a reduction in local recurrence rates with the addition of pre-operative radiotherapy, either as a one-week hypofractionated short course (SCRT) or a conventionally fractionated long course (LCRT) schedule with concurrent chemotherapy. There is also increasing interest in the addition of neoadjuvant chemotherapy to radiotherapy with the aim of improving disease-free survival.

The relative use of SCRT and LCRT varies considerably across the world. This is reflected in, and is likely to be driven in part by, disparity between international guideline recommendations. In addition, different approaches to treatment may exist both between and within countries, with variation related to patient, disease and treatment centre and financial factors

In this review, we will specifically focus on the use of SCRT for the treatment of rectal cancer. We will discuss the literature base and current guidelines, highlighting the challenges and controversies in clinical application of this evidence. We will also discuss potential future applications of SCRT, including its role in optimisation and intensification of treatment for rectal cancer.

Keywords (max 6): rectal cancer; pre-operative radiotherapy; short course radiotherapy; hypofractionated radiotherapy

Statement of search strategies used and sources of information

PubMed and Google Scholar were searched without limitations on multiple occasions between 21st April 2021 and 12th August 2021 for terms including, but not limited to, 'rectal cancer', 'short course radiotherapy', 'long course radiotherapy', 'chemoradiotherapy', 'hypofractionated radiotherapy' and 'radiotherapy'. Further references were identified by manually examining the references lists of relevant publications.

Introduction

Approximately 2 million new cases of colorectal cancer are diagnosed each year globally, around a third of which are located in the rectum[1]. Total mesorectal excision (TME) is the cornerstone of treatment for rectal cancer, but multi-modality management with the addition of radiotherapy and/or chemotherapy is now commonly used, especially for locally advanced disease. Randomised trials have demonstrated that pre-operative radiotherapy reduces the risk of locoregional recurrence when delivered either as a one-week hypofractionated short course (SCRT) with immediate surgery, or conventionally fractionated long course

concurrent with fluoropyrimidine chemotherapy (LCRT) with delayed surgery[2-8]. More recently, SCRT with delayed surgery (for example, by 4-8 weeks) has emerged as an additional treatment option[9]. Potential advantages of SCRT compared with LCRT include no requirement for concurrent chemotherapy, better treatment compliance and resource/cost benefits[10-12].

Despite low local recurrence rates now achievable with multi-modality approaches to treatment, important challenges to rectal cancer management remain including high rates of distant relapse (around 30% in high risk patients) and treatment-related morbidity. There is a need to better understand which patients might benefit from treatment de-escalation, for example omission of either neoadjuvant therapies or surgery, and which patients may require systemic treatment approaches to reduce distant metastases.

This review will specifically focus on the use of SCRT for the treatment of rectal cancer. We will discuss the literature base, current guidelines and highlight the challenges and controversies in clinical application of this evidence. We will also discuss potential future applications of SCRT, including its role in optimisation and intensification of treatment for rectal cancer.

The current evidence base supporting use of SCRT in rectal cancer

Figure 1 illustrates key randomised trials of SCRT for rectal cancer.

(i) SCRT for non-margin threatening rectal cancer

Evidence for reduced local recurrence with pre-operative SCRT versus surgery alone in patients with resectable rectal cancers was established in the Swedish (pre-TME era) and Dutch TME trials[5, 8]. Prior to this, the trial by Frykholm et al had also demonstrated reduced local recurrence with pre-operative SCRT versus a longer course of radiotherapy delivered adjuvantly[13]. Later, the UK CR07 trial compared pre-operative SCRT with selective use of post-operative LCRT for circumferential resection margin (CRM) positive tumours and demonstrated superiority of the pre-operative, short-course approach[7]. Three randomised trials have since compared pre-operative SCRT and LCRT[9, 14, 15].

In the Polish I trial, no significant difference in local recurrence or survival between the fractionation schedules was observed between SCRT and LCRT for operable (T3/4) tumours, although better downstaging was achieved with LCRT[14]. Similarly, the TROG 01.04 trial found no difference in local recurrence or survival but did report better downstaging and rates of pathological complete response (pCR) with LCRT and a trend to reduced local recurrence for distal tumours treated with LCRT[15]. It should be acknowledged that neither study was powered to directly compare rates of tumour downstaging/pCR between treatment arms. More recently, the Stockholm III trial demonstrated no significant difference in local recurrence rates between SCRT and immediate surgery, SCRT and delayed surgery, or LCRT (without concurrent chemotherapy)[9]. The number of local recurrences was low

across all three arms (2-5.5%, P=0.48), with distant disease the predominant pattern of failure (23-30%, P=0.40).

(ii) SCRT for margin-threatening rectal cancer

LCRT has traditionally been preferred to treat tumours in which the mesorectal fascia is threatened (≤1 mm) or involved[12]. This consensus developed following trials of LCRT which demonstrated evidence of downstaging in locally advanced tumours, including in patients with irresectable tumours, and because of high local recurrence rates in CRM positive patients treated with SCRT in the Dutch TME and CR07 trials[2-4, 6, 7, 9]. More recently, there has been interest in the use of SCRT with delayed surgery in this context, following preliminary evidence that SCRT followed by delayed surgery for patients unsuitable for LCRT could result in tumour downstaging[16-18].

SCRT and delayed surgery also offers an opportunity to deliver systemically active chemotherapy as part of a total neoadjuvant therapy (TNT) approach, although questions remain regarding the duration of chemotherapy, whether chemotherapy should be used prior to or following radiotherapy and the most appropriate duration of delay. In a long-term analysis of the phase III Polish II trial, which evaluated patients with fixed T3 or T4 disease and compared SCRT followed by three cycles of 5-fluorouracil/oxaliplatin (FOLFOX) chemotherapy before TME to LCRT and TME, superiority of the SCRT arm for radical surgery rate, local control or survival outcomes was not demonstrated[19].

In contrast, the recently reported RAPIDO phase III trial evaluated patients with at least one of the following criteria: T4 disease, EMVI, N2 disease, lateral nodal metastases or involved mesorectal fascia. The trial compared SCRT followed by six cycles of capecitabine/oxaliplatin (CAPOX)/nine cycles of FOLFOX chemotherapy and delayed TME to LCRT/TME/adjuvant chemotherapy[20]. RAPIDO reported significantly reduced disease-related treatment failure in the SCRT arm (24% versus 30%, P=0.019), with improved pCR rates (28% versus 14%, p<0.0001) and a reduction in distant relapse in the SCRT arm (20% versus 27%, P=0.0048). The results of another similar trial to RAPIDO, STELLAR, were recently presented, pending its formal publication[21]. No significant difference in disease-free survival at 3 years between SCRT followed by chemotherapy versus LCRT was observed (64.5% versus 62.3%), although the combined rates of pCR and complete clinical response (cCR) appeared higher for the SCRT followed by chemotherapy arm (22.5% versus 12.6%, P=0.001).

Additional questions remain regarding TNT, including whether LCRT or SCRT-based TNT is superior and which patients might benefit most from each approach. Approximately 60% of patients in RAPIDO had threatened/involved mesorectal fascia at diagnosis, but whether these patients accounted for the majority of local failures remains uncertain[20]. In addition, although there are evaluations of LCRT and neoadjuvant chemotherapy (for example, the PRODIGE-23 and OPRA trials (NCT02008656)), a direct comparison between SCRT and LCRT TNT is yet to be

reported[22]. Such an approach is currently being tested in the ACO/ARO/AIO-18.1 clinical trial (NCT04246684). A recently published systematic review and meta-analysis of TNT versus LCRT pre TME, which included the RAPIDO, PRODIGE-23 and POLISH II trials, suggested improvements in outcomes such as pCR in favour of the TNT approach[23].

Toxicity considerations related to SCRT

After publication of the Stockholm I and II trials, concern was raised regarding increased acute and late radiotherapy toxicity with hypofractionated schedules. Large, two-field techniques were used in these historical trials, which could account for the extent of toxicity that was observed[10, 24, 25]. The Dutch TME trial demonstrated that short-term side effects compared to no radiotherapy included a slight increase in surgical complications, but otherwise SCRT with immediate surgery was well tolerated[26]. The timing of surgical intervention to remove the rectum shortly after radiation, and the absence of chemotherapy, may both reduce acute toxicity that might otherwise occur[10].

Late toxicity from SCRT compared to surgery alone is well recognised, and includes increased rates of faecal incontinence, bowel dysfunction, urinary incontinence, infertility and sexual dysfunction[10]. Based on more recent trials, late toxicity appears to be broadly comparable between LCRT and SCRT[12]. For example, in the Polish I trial, severe late toxicity was 10% versus 7% (P=0.36) for LCRT and SCRT respectively[14]. In TROG 01.04, severe late toxicity was 8% versus 6% (P=0.53) for LCRT and SCRT respectively[15]. In Stockholm III, SCRT with delayed surgery was associated with significantly fewer post-operative complications than SCRT with immediate surgery (OR 0.61, 95% CI 0.45-0.83, P=0.001)[9]. Conversely, severe radiation acute toxicity was significantly worse in the SCRT and delayed surgery arm in the pooled comparison of the two SCRT arms, with admission rates of 7% versus <1% for SCRT and delayed surgery versus SCRT and immediate surgery respectively (OR 24.67, 95% CI 3.31-183.72, P<0.0001). This perhaps explains why SCRT and delayed surgery has not been universally adopted. No difference was observed between the three arms in Stockholm III for late toxicity.

The treatment technique used in Stockholm III was 3 or 4 field 3-dimensional conformal radiotherapy and the superior border was higher than in other clinical trials (mid L5 or 1-1.5 cm superior to the sacral promontory)[27]. Increasingly, rectal cancer radiotherapy is being delivered using highly conformal intensity-modulated radiotherapy (IMRT). This has the potential to reduce acute and late toxicities, although at present limited published data exist concerning OAR constraints for SCRT delivered using IMRT and how these are associated with development of clinically-significant toxicities[28]. Given the potential for intensification of treatment using SCRT (see **Future directions**), determining the most appropriate OAR constraints should be a priority for further research.

Reasons for variation in practice

Currently, there is recognised hetereogeneity in practice both within and across geographical locations regarding if and how radiotherapy and chemotherapy are used in the neoadjuvant setting to treat rectal cancer, and this variation is likely driven by a number of factors[29, 30].

Differences exist between guidelines regarding definitions of high-risk disease, which influences the recommendations made regarding particular interventions. For example, UK guidelines focus more on threat to mesorectal fascia whereas a number of factors are included in European/US guidelines[31-34]. A summary of national/international guideline recommendations stratified by tumour stage and other risk factors is shown in **Table 1**.

This variation also extends to the eligibility criteria for randomised trials, which presents a challenge to clinical decision-making when attempting to apply published evidence outside of the trial setting. There are also gaps in the evidence base, with an absence of direct comparisons between particular treatments, for example TNT using SCRT or LCRT. This means that in some circumstances, clinical decision-making depends on extrapolation from what evidence is available. Organ preservation is emerging as a therapeutic approach in rectal cancer (see **Organ preservation** section), although the avoidance of radical surgery remains under investigation in clinical trials and adoption of these approaches will likely vary between centres[35].

There is potential variation in experience and expertise between multidisciplinary and surgical teams, which could influence decision-making regarding use of pre-operative treatments. A culture of favouring certain treatments may also exist in some institutions. This could itself be related to a number of factors, including the perceived ability for certain patient populations to tolerate/comply with particular treatments and geographical factors including distance from treatment centres and associated travel times. Participation by centres in particular clinical trials and whether the infrastructure is in place to deliver certain treatments, such as immediate surgery could also influence familiarity with and choices of treatment. Decision-making could also be influenced by differences in re-imbursement and cost/resource utilisation factors within healthcare systems. Previous analyses in USA have demonstrated the potential for considerable economic savings with SCRT compared with LCRT[10, 30, 36].

It may be understandable that heterogeneity in practice exists. An example concerns the use of SCRT in non-margin threatening node positive disease. In the Netherlands and Sweden, SCRT is selectively used for these tumours following multidisciplinary team discussion, based on the historical randomised trials of SCRT performed in these countries which demonstrated a relative risk reduction in local recurrence to all rectal cancers (see **Figure 1**). In contrast, increased use of magnetic resonance imaging (MRI) in contemporary trials means that there is now greater clarity regarding clinical disease stage. This information can help determine which patients are most likely to benefit from pre-operative radiotherapy and theoretically reduces morbidity through decreased use of multi-modality treatment. For example, the MERCURY group advocates for the selective use of LCRT, rather than SCRT, by

using the diagnostic MRI to identify prognostic factors such as threat to mesorectal fascia and location of the primary tumour[37, 38]. In a recent observational study using the MERCURY recommendations, the majority of 149 patients with low or intermediate risk disease (as stratified by UK guidelines) received TME alone, with local recurrence observed in only 2% of patients[33, 39].

Regardless of pre-existing variation in practice, the Covid-19 pandemic has increased the use of SCRT because of the need to minimise hospital visits during the first wave and concerns around reduced surgical capacity, chemotherapy toxicity, and compromise to LCRT with treatment gaps[40, 41]. Despite the obvious challenges presented, the pandemic provides an opportunity to reflect on how the existing evidence can inform clinical practice going forward. A number of initiatives are underway to evaluate the impact of Covid-19 on radiotherapy delivering and patient outcomes, including the CTRad Covid-19 radiotherapy initiative and UK coronavirus cancer monitoring project[40-42].

Organ preservation

There is increasing potential for organ preservation in patients who achieve a cCR following SCRT or LCRT, with or without neoadjuvant chemotherapy, or local excision. These patients might be able to avoid the morbidity, permanent colostomy and impact on quality of life associated with radical surgery[35]. Organ preservation is discussed as a potential treatment approach in European/US guidelines[31, 32, 34]. A recent international Delphi study established consensus recommendations regarding investigation and reporting of organ preservation within clinical trials and routine practice[35]. In this section, we will discuss the evidence for SCRT-based organ preservation.

Concerning early tumours treated with an intentional organ preservation strategy, the TREC feasibility trial randomised patients with T1-2 N0 rectal adenocarcinoma to receive SCRT and delayed transanal endoscopic microsurgery (TEM) versus TME alone[43]. Seventy per cent of patients in the SCRT/TEM arm achieved organ preservation, with 30% obtaining a pCR. Severe toxicities were also significantly reduced compared to TME alone (15% versus 39%, P=0.04) and SCRT/TEM was associated with improved bowel toxicity/function and quality of life. The phase II/III STAR-TREC trial is currently recruiting for patients with T1-3b N0 rectal cancers and will compared standard TME to organ preservation approaches (SCRT or LCRT followed by TEM or watch and wait depending on clinical response, with TME if poor response at first clinical evaluation post-radiotherapy)[44]. Regarding opportunistic organ preservation for patients with a cCR after SCRT, a protocol amendment to the Stockholm III trial introduced tumour regression as a secondary endpoint. This analysis reported promising pCR data with SCRT and delay, although the trial was not adequately powered to directly compare its three arms for this endpoint[16]. Many of the clinical trials which have included organ preservation have focused on LCRT and earlier stage rectal cancers[35]. However, the promising pCR data reported in the RAPIDO trial suggests that there could be a role for increasing the delay to surgery after SCRT, and using chemotherapy in this gap as part of an organ

preservation for locally advanced tumours[20]. The multicentre phase III ACO/ARO/AIO-18.1 trial (NCT04246684) is currently recruiting, and will compare SCRT with LCRT-based TNT with selective organ preservation for patients with a cCR.

There remain a number of unresolved questions regarding radiotherapy for organ preservation, including the impact of site and stage of the tumour, whether SCRT, LCRT or local radiotherapy (contact or brachytherapy) should be used, if chemotherapy should be added and whether this should precede or follow LCRT, how to optimise radiotherapy and, for local excision, the type of minimally invasive surgery that should be performed[35, 43, 44]. In addition, the optimum methods for assessment of clinical response, the impact of a cCR or pCR on survival outcomes and the most appropriate time-period for response assessment remain to be determined.

Future directions

1. Dose escalation

There is the potential to optimise the delivery of SCRT and to expand its application in the management of rectal cancer. For example, the use of IMRT could reduce toxicity and daily online image guidance for motion management can permit a reduction of elective volume planning target volume (PTV) margins and improve accuracy of treatment delivery[28]. There appears to be a dose-response relationship in rectal cancer, meaning that for selected patients, for example where the aim is organ preservation or where there are involved lymph nodes outside of the TME volume, there could be a value in boosting the primary tumour and/or nodal disease beyond 25 Gy[29, 45]. Such an approach was used in a small number of patients in a phase II trial of SCRT and delayed surgery, where a boost to provide a total dose of 30 Gy was delivered[46], but larger trials are awaited. This approach to dose escalation could be of theoretical benefit to those patients who have little or no clinical response to pre-operative therapy, even to TNT. For example, in RAPIDO, approximately 10% of patients in both arms had an R1/2 resection, with minimal downstaging achieved[20]. The increasing use of IMRT and online image guidance could facilitate the safe and effective delivery of dose escalation strategies[28].

2. Optimising combinations of pre-operative radiotherapy and systemic therapy

Despite improvements in local control achieved with pre-operative therapies, survival after rectal cancer remains largely dependent on distant disease relapse. Therefore, there is the potential to better optimise delivery of systemic therapies. This could include a combination of chemotherapy and novel systemic therapies such as immune checkpoint inhibitors alongside pre-operative radiotherapy, an approach which is currently being investigated in several early phase trials[47]. The randomised phase II PRIME-RT trial (NCT04621370) is currently evaluating the addition of durvalumab to FOLFOX chemotherapy after either SCRT or LCRT for patients with locally advanced rectal cancer. The single arm phase II TARZAN trial

(NCT04017455) is evaluating a combination of immune checkpoint and tumour vasculature inhibition through the addition of atezolizumab and bevacizumab to pre-operative RT.

3. Use of MRI-guided radiotherapy

MRI-guided radiotherapy for SCRT has been shown to be feasible and could provide several opportunities including superior soft tissue contrast for target volume delineation, online image guidance to account for internal motion and to permit PTV margin reduction, functional imaging to guide dose escalation and imaging biomarkers of treatment response[48, 49]. MRI could help predict which patients are more or less likely to respond to RT, which could aid decision-making regarding intentional organ preservation strategies and where de-escalation/intensification of treatment should be considered[50].

4. SCRT in the management of metastatic disease

There is increasing interest in SCRT in the definitive management of patients with metastatic rectal cancer. Where synchronous liver and/or lung metastases are seen, the primary tumour is often also locally advanced[51]. LCRT to the primary tumour risks progression of distant metastases, and therefore SCRT plus neoadjuvant chemotherapy provides the benefit of potentially downstaging both primary and metastatic sites simultaneously, which may facilitate radical surgery to all sites of disease. This approach was evaluated in the Dutch M1 phase II trial, which treated patients with SCRT and six cycles of CAPOX/bevacizumab[52]. Seventy-two per cent of patients proceeded to radical surgery, with median overall survival in this group of 4.4 years after a median follow up time of 8.1 years. A question remains regarding the sequencing of chemotherapy in relation to radiotherapy for patients with symptomatic metastatic disease. While the delay to commencing chemotherapy after SCRT may be relatively short (~4 weeks), delivery of chemotherapy before radiotherapy has the potential to achieve more rapid symptomatic improvement, in addition to obtaining control of systemic disease. In a previous phase II study of patients with locally advanced disease investigating TNT, the majority of patients experienced a radiological response after completion of chemotherapy but also a symptomatic response after only a single cycle (median time to complete resolution of symptoms was 32 days)[53].

A concern regarding patients with metastatic disease, in whom surgery will not be performed, is achieving sufficiently prolonged local control of the primary disease if SCRT is used. This is especially relevant for patients with low volume or oligometastatic disease, with a 5-year survival of approximately 40%[54]. For this group of patients, some clinicians may favour LCRT. For patients with a larger burden of metastatic disease, a number of phase II trials of SCRT followed by palliative chemotherapy suggest that the SCRT approach may still provide effective and durable palliation, including in patients with estimated rates of overall survival of 40% at 3 years[55, 56].

Conclusion

As the management of rectal cancer increases in complexity, it is important to consider the value of therapeutic interventions, including SCRT. When initially introduced, SCRT was generally combined with immediate surgery but in recent practice SCRT and delayed surgery has been preferred. Increasingly, SCRT is combined with neoadjuvant chemotherapy as part of TNT and impressive outcomes have been reported, including a reduction in distant metastatic disease. Questions remain regarding the optimum combination and sequence of treatments, whether SCRT or LCRT-based approaches should be preferred, and which patients are most likely to benefit. Looking to the future, SCRT has the potential to further optimise the management of rectal cancer, including as part of intentional and opportunistic organ preservation strategies and approaches to intensification of treatment.

Figure 1 caption

A flow chart summarising randomised trials which have evaluated SCRT in the management of rectal cancer

CSS, cancer-specific survival; DFS, disease-free survival; LC, local control; LCRT, long course radiotherapy; MRF, mesorectal fascia; MRI, magnetic resonance imaging; OS, overall survival; pCR, pathological complete response; R0, microscopically clear resection margin; SCRT, short course radiotherapy; TME, total mesorectal excision

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