

Guidelines

ESTRO recommendations for the use, planning and delivery of reirradiation in locally recurrent rectal cancer – Endorsed by ASTRO

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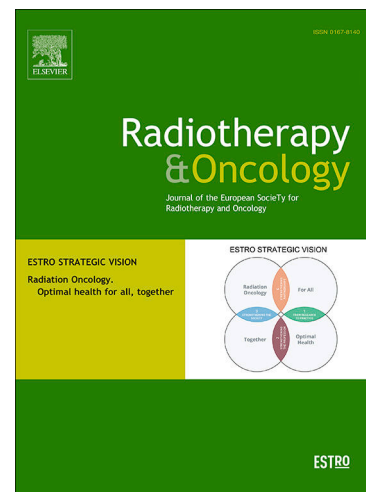
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Title page

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Abstract

Background and purpose

Reirradiation for locally recurrent rectal cancer (LRRC) has historically been restricted by concerns regarding significant adverse effects, particularly with reirradiation doses (in EQD2Gy) ≥ 30 Gy. Advances in radiation technology now enable safer delivery, renewing interest in (chemo)reirradiation as part of multimodal management. Given the scarcity of prospective data and the considerable variability in radiotherapy approaches, there is a clear need for recommendations to enhance treatment homogeneity and quality.

Methods

A writing committee was established by the Lower Gastrointestinal Cancer Sub-Committee of the European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee. We performed a systematic literature review following PRISMA guidelines; aiming to answer 14 key questions regarding the indications, planning and delivery of reirradiation in LRRC. Recommendations were based on available evidence or expert consensus and graded using the American Society for Radiation Oncology (ASTRO) grading system.

Results

Careful patient selection, consideration of treatment intent, treatment planning taking into account prior rectal cancer treatment, organ dose guidance and patient goals are essential to optimize outcomes and minimize adverse effects. The key questions guided a summary of appropriate literature and a series of recommendations to support the implementation of reirradiation in LRRC into routine clinical care. Almost all levels of evidence were low with recommendations mostly based on low quality of evidence or expert opinion, underscoring the urgent need for prospective studies and registry data.

Conclusions

(Chemo)reirradiation in LRRC can be applied in the context of neoadjuvant treatment, definitive treatment and palliation, to increase radical resection rate, enhance local control and improve symptom control. Optimal patient selection, along with advanced imaging and precision techniques, is essential to maximize the therapeutic benefit while minimizing harm. In the absence of high-level evidence, these recommendations represent expert consensus and provide practical guidance to ensure the safe and consistent delivery of (chemo)reirradiation in routine clinical practice.

Keywords

Reirradiation, locally recurrent rectal cancer, treatment planning, delivery, recommendations.

Introduction

In the setting of locally recurrent rectal cancer (LRRC), radiotherapy has typically been used either in neoadjuvant setting, to facilitate radical (or R0) resection, in the definitive setting for local tumour control and symptom control or for symptom control alone in palliation. Radiotherapy naïve patients generally receive (chemo)radiation (C)RT up to 50 Gy as in primary rectal cancer. However, the majority of patients with LRRC previously have received radiotherapy for their primary rectal cancer and may therefore be offered reirradiation (1, 2). Before the introduction of conformal and image-guided radiotherapy, the management of LRRC with reirradiation was associated with significant adverse effects, raising valid concerns about delivering reirradiation doses (in EQD2Gy) ≥ 30 Gy (3, 4). Significant advances in radiotherapy technology now facilitate the delivery of much more precise and conformal treatments. As a result, there is a renewed international interest and increasing use of reirradiation in this setting (5, 6).

The patient population offered reirradiation for rectal cancer is heterogeneous. The most common indication is after previous preoperative (C)RT and total mesorectal excision (TME). Local recurrence occurs in approximately 5-10% of patients after curative surgery and the optimal oncological treatment is further radical surgery. This is a significant undertaking, often requiring exenteration with removal of adjacent organs. Pelvic exenteration has a 30-40% major complication rate, causes a significant drop in quality of life (QoL) which takes an average of 1 year to recover and achieves a median survival of ~37 months and 5-year survival of ~30% (7). Achieving a radical (R0) resection is the most important prognostic factor (7-9), however due to the technical challenges caused by previous multimodality treatment, R0 rates are relatively low at 55–80% (7-10). Therefore, (chemo)reirradiation is often used to optimise outcomes (11). Neoadjuvant (chemo)reirradiation can improve R0 resection rates or even achieve pathological complete response (pCR) (12-14). Delaying surgery for neoadjuvant treatment also helps identify the ~20% of patients who develop early metastatic disease, thus avoiding futile operations (15). Despite surgery being the optimal oncological treatment, more than half of patients with LRRC will not undergo curative surgery due to unresectable tumour, metastases, comorbidity or patient choice (16). Of those with LRRC in situ, 86% are symptomatic with 3-year survival rates of ~30% (16-18). Symptoms result in very poor QoL and include pain, mucus discharge, rectal bleeding, fistulas, abscesses, ureteric or bowel obstructions, lymphoedema and faecal discharge (19, 20). Reirradiation can be used in unresectable patients as definitive treatment for local control and symptom control or for symptom relief in palliation (17, 21).

Several consensus statements and guidelines address the use of rectal reirradiation. Expert groups have recommended the use of neoadjuvant (chemo)reirradiation for LRRC before radical surgery (22, 23). The 2017 European Society for Medical Oncology (ESMO) guidance noted reirradiation as safe for selected patients, though this was not discussed in the latest version (24, 25). The US National Comprehensive Cancer Network (NCCN) guidance only adds a footnote for cases with prior radiotherapy (10). ESTRO-ACROP and GEC-ESTRO provide recommendations on intraoperative radiotherapy (IORT) and salvage brachytherapy (26, 27). Further radiotherapy guidance and protocols have been provided by ongoing/closed trials and prospective audits (28-32). Importantly, the PelvEx II Phase III trial (NCT04389086)

group published a contouring guideline for rectal cancer reirradiation in 2022 (33). A recent discussion article from US colleagues also highlights the challenges of reirradiation in LRRC (34). However, none of these resources provide sufficient detail to empower a multidisciplinary team (MDT) to safely implement routine reirradiation.

Consequently, the ESTRO Guidelines Committee nominated a writing group to develop practical recommendations for rectal cancer reirradiation, supplementing existing ESTRO guidelines for IORT and brachytherapy in LRRC (26, 27). We aimed to perform a systematic review, summarize the relevant literature and define a hands-on approach detailing the supporting level of evidence and the strength of recommendation. Our goal is to empower an MDT to safely implement and deliver external beam (chemo)reirradiation in LRRC, improve treatment-homogeneity and to facilitate research and development in this complex setting.

Methods

These recommendations, their scope and the composition of the writing panel were approved by the ESTRO Guideline Committee and developed in accordance with the Guidelines Committee Procedures Policy (35). The multidisciplinary writing panel consisted of an international group of 12 experts in LRRC and (re)irradiation: 4 radiation oncologists, 2 clinical oncologists, 1 surgeon, 1 radiologist, 2 medical physicists, 1 radiation therapist (RTT), and an early career researcher undertaking a PhD in LRRC reirradiation. The writing panel was chaired by HP.

The initial meeting identified 14 key questions to be addressed by these recommendations, represented by the subheadings below, with member(s) of the group with relevant expertise identified to lead each subheading. These key questions are detailed in Appendix I.

The systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (36). Relevant studies were identified on MEDLINE and PubMed using a combination of terms related to locally or locoregionally recurrent cancer and rectal cancer, restricted to English language full papers published after 2000 (i.e. after introduction of TME surgery) and ≥ 10 patients (full search string in Appendix II). There was no exclusion based on dose delivered. Further papers were identified through reference lists and writing panel expertise. The PRISMA flow chart is shown in Figure 1. A full list of reports selected for review are detailed in Appendix III. A list of definitions is given in Appendix IV. Reirradiation in LRRC after previous rectal cancer radiotherapy is almost solely Type 1 as defined by Andratschke et al.(37)), given the lack of pelvic organs causing risk of toxicity from cumulative doses without overlap of treated volumes. However, these recommendations do in principle apply to Type 2 reirradiation for LRRC.

Each subheading lead reviewed relevant publications and drafted recommendations. Drafts were then reviewed and edited by the writing panel. The American Society for Radiation Oncology (ASTRO) grading system was used to rate evidence quality and recommendation strength (38). The strength of the recommendations was classified by the group, considering the quality of evidence, the specific wording of the recommendation (e.g. use of the word “consider”), the risk of harm, the feasibility, existing consensus and the alternative treatments in each setting. Therefore, it is

possible to apply a “strong” recommendation despite low levels of evidence. Unanimous agreement was reached following discussion for the grading of all recommendations.

Practical considerations of (chemo)reirradiation in LRRC

The benefit-risk ratio of reirradiation will depend on the specific patient scenario. In a 50-year-old patient with a LRRC near structures where radical surgery may be difficult, 4 years after (C)RT and TME, reirradiation has a much higher benefit-risk ratio than in an elderly asymptomatic patient with LRRC, which is stable and detected incidentally while monitoring established metastatic disease. In scenario 1, reirradiation should be delivered with neoadjuvant intent to facilitate a radical operation ; in scenario 2, the morbidity of reirradiation may outweigh any benefits and could be held in reserve for when symptoms develop and the benefit-risk ratio will be higher.

Multiple factors affect the benefit-risk ratio and the radiotherapy planning and delivery. Dose previously delivered to organs of interest (OOI) drive the feasibility of safe delivery of further radiotherapy. Importantly, this will depend on not just the previous prescription dose or maximum dose delivered to any given OOI; but also on the location of previous dose relative to the new treatment target and the volume of OOI previously irradiated. Time interval between previous irradiation and reirradiation is known to impact tissue and functional recovery for some pelvic organs. Preclinical evidence suggests that some organs, for example the spinal cord, recover in time and dose dependent manner; however in others, such as in the bladder, there is no long-term recovery (39, 40). Similar to head and neck carcinoma (H&N) recurrences, LRRC and adjacent OOI are often less mobile and fixed, as well as the anatomy of OOI being very altered compared to at the time of primary (C)RT, due to interim surgery. These challenges result in increased fibrosis and poorer tolerance of reirradiation relative to de novo irradiation in H&N cancer; they are likely to impact LRRC in a similar way (41). In this setting previous systemic therapy can also have a negative impact on the tolerance of reirradiation (42, 43). Care must be taken to identify whether previously irradiated OOI, or parts of OOI, remain in situ or have been removed. For example, if all large bowel in a previously irradiated volume has been resected, any large bowel in the vicinity of reirradiation volumes can be regarded as radiotherapy-naïve.

Planned treatments for LRRC, such as surgery, are also relevant for normal tissue as target coverage considerations. For patients set to undergo pelvic exenteration, potential adverse events related to normal tissues scheduled for removal may be less critical - although it must be acknowledged that not all patients who start neoadjuvant (chemo)reirradiation will ultimately proceed to surgery (15, 44). Additionally, identification of sites at high risk of a margin positive (R1/2) resection during multidisciplinary discussions can guide contouring and dose planning. Given the complexity of clinical decision making, reirradiation should always be discussed within a site-specific multidisciplinary team (MDT) involving radiation and medical oncologists, surgeons, radiologists, and - if available - palliative care physicians.

Central to this decision-making process are the patients. As most patients with LRRC ultimately die of the disease, treatment discussions should include the full range of options—from neoadjuvant or definitive treatment to palliation and best supportive care—highlighting goals, expected outcomes, risks, and potential impact on QoL. Planning and delivery of reirradiation should involve a multi-professional radiotherapy team (MPT) of radiation oncologists, physicists, RTTs, and expertise in reirradiation radiobiology (understanding and application of biological principles, e.g. tissue repair, residual injury, time interval and changed tolerance).

General recommendations

General Recommendations	Strength of recommendation	Quality of Evidence
All patients should be discussed in a specialist MDT with experience in rectal reirradiation, preferably including both radiation and medical oncologists, surgeons, radiologists, and – if available – palliative care physicians	Strong	Expert Opinion [§]
The benefits, risks and uncertainties of reirradiation should be discussed with patients, including the aims of different treatments and their impact on QoL	Strong	Expert Opinion [‡]
Planning and delivery of reirradiation should involve an MPT of radiation oncologists, physicists, RTTs and expertise in reirradiation radiobiology	Strong	Expert Opinion [§]
Consider dose, time interval and adverse effects from previous irradiation, previous surgery and previous systemic therapy	Strong	Expert Opinion [*]

*Where expert opinion is noted, the following rationale has been applied * indicates safety, † indicates feasibility, § indicates consensus and ‡ indicates patient values.*

Dose and fractionation

Table 1 and 2 details all identified retrospective series and two prospective trials delivering (chemo)reirradiation using linac based photons in LRRC (2-4, 12-14, 45-61). The extended version of both tables is provided in Appendix V. While there are ongoing concerns about the safety of reirradiation after a full course of (chemo)radiation, these publications, many of which use historic radiotherapy techniques, generally show feasibility and acceptable rates of adverse events (62). Most papers simultaneously report outcomes of neoadjuvant, definitive and palliative treatment intent. Although the boundaries between these groups are not always well-defined nor consistent in the literature reports, we nonetheless used this categorization for the purpose of structuring the summary below. Here, neoadjuvant (chemo)reirradiation refers to (chemo)reirradiation with the intent of proceeding to radical surgery; definitive (chemo)reirradiation refers to (chemo)reirradiation aiming to achieve cCR or prolonged local control (LC) and symptom control; and palliative reirradiation is reserved for symptom relief in patients with a limited life expectancy. A graphical summary of treatment options is provided in Figure 2. Guidance for treatment planning and delivery for standard external beam radiotherapy are described in subsequent sections.

Neoadjuvant (chemo)reirradiation

Valentini et al. reported a phase II trial of 59 patients with resectable LRRC where patients received 40.8 Gy in 1.2 Gy/fraction twice daily (BID) with concurrent 5-fluorouracil (14). At 4-6 weeks after (chemo)reirradiation 66% underwent surgery. R0 and R1 resection was achieved in 21/30 patients and 3/30 respectively. pCR was seen in five patients (13%). Seven patients showed late adverse events including skin fibrosis, impotence, urinary complications requiring nephrostomy and a small bowel fistula requiring surgical diversion. Five-year overall survival (OS) was 66.8% in R0 resected patients. In a systematic review of reirradiation in LRRC with and without surgery involving 744 patients pooled grade ≥ 3 acute and late complication rates of 11.7% and 25.5% were reported (17). LC was higher with surgery, but differences were modest. One, two and three-year LC rates in those that underwent surgery versus those with (chemo)reirradiation alone were 84% versus 72%, 64% versus 55% and 47% versus 45% respectively, with a 3-year OS rate of 51.7% in the operated group. Tao et al. reported a retrospective series of (chemo)reirradiation (48), an update on a previous series by Das et al. (56), using a total dose of 30-45 Gy (88% received 39 Gy) in 1.5 Gy/fraction BID with 91% receiving concurrent chemotherapy. Total dose delivered was based on retreatment interval, with 30 Gy if <1 year versus 39 Gy if >1 year. In total 66% (43/65) of patients underwent surgery, and about 50% of them received IORT. An R0 resection was achieved in 67%. Three-year OS was 63% for those that underwent surgery, 3-year rate of grade 3-4 toxicity was 54% and included wound complications, pelvic abscess, small bowel or urinary obstructions, anastomotic strictures, proctitis or cystitis.

The pCR rate reported following EQD2Gy $_{\alpha/\beta=10\text{Gy}}$ doses of approximately 30-40 Gy are 8-17% (14, 48, 63). Although mostly retrospective data, lack of pathological confirmation in some patients, and a total neoadjuvant treatment (TNT) strategy in the Voogt et al. cohort, these data suggest that doses up to 30-40 Gy may achieve

complete response with favorable long-term outcome in a small proportion of patients. However, as we cannot reliably identify complete responders after neoadjuvant treatment, surgery remains standard in these patients.

Based on the literature, and in keeping with PelvEx, Beyond TME and ESMO guidance; the routinely used doses for neoadjuvant (chemo)reirradiation in LRRc should be 30 Gy in 1.8-2 Gy fractions with an optional IORT boost if clinically and logistically appropriate (22-24), a hyperfractionated regimen of 40.8 Gy in 1.2 Gy BID fractions as per Valentini et al., or 30-39 Gy in 1.5 Gy BID fractions as per Tao and Das et al. (14, 48, 56).

Definitive (chemo)reirradiation

The non-operated cohort in the study by Valentini et al. reported a response rate (CR + partial response (PR)) of 44.1% with a symptomatic response rate of 83.3% (14). Five-year OS was 22.3% in patients without surgery, or with surgery and an R1/2 resection. Cai et al. also published a prospective trial where 22 patients were treated with intensity modulated radiotherapy (IMRT) up to 39 Gy in 1.3 Gy/fraction twice daily. They reported a response rate of 40.9%, and a symptom relief response of 86.4%, with grade 3 acute and late adverse events of 16.6% and 22.7% respectively. The Lee et al. systematic review reported a pooled symptomatic relief response of 75.2% in 413 patients, without differentiation between operative and non-operative cases. In the non-operative group (n=283) 1-, 2-, and 3-year OS rates of 63.5%, 34.2%, and 23.8% were reported (17). As detailed above, LC rates were only marginally lower than those achieved with radical surgery. Another systematic review (including seven studies) noted that >80% of patients reported symptomatic relief of pain, bleeding and gastrointestinal symptoms (62). The non-operated group in Tao et al. reported a 3-year freedom from local progression rate and OS of 30% and 20% respectively (48). Late toxicity grade 3-4 toxicity occurred in 16%. Of patients with symptoms, 70% (21/30) experienced improvement of symptoms with a median duration of symptom control of 10 months (range, 1–24). Only two studies escalated dose >50 Gy with improved LC at the cost of increased severe late adverse events (3, 4).

The studies listed in Table 1 and 2 reporting on definitive (chemo)reirradiation suggest that factors associated with increased LC include small tumour or GTV, good performance status, and doses >50 Gy EQD2Gy _{$\alpha/\beta=10$ Gy}. The duration of symptom control in these series ranged from 6 to 12 months, with most reporting responses lasting 10 months.

Altogether, the data suggests that definitive reirradiation has clinical benefit with acceptable adverse effects with doses from 30-40 Gy either with BID or standard fractionation.

Palliative reirradiation

Palliative reirradiation is commonly described in clinical series, where it is used to achieve local control and has been associated with meaningful symptom control lasting

several months (46, 47, 49). If this involves patients experiencing symptoms, with a short life expectancy of <6 months and/or a poor performance status WHO ≥ 2 , once-daily treatment schedules without concurrent chemotherapy are more patient friendly. In the absence of data supporting a specific regimen, 1×8 Gy or 5×4 Gy appear to be reasonable options consistent with other palliative indications, while maintaining the cumulative EQD2Gy $_{\alpha/\beta=3\text{Gy}}$ well below 90 Gy, thereby ensuring good tolerability.

Dose and fractionation recommendations

Recommendations	Strength of recommendation	Quality of Evidence
Consider neoadjuvant (chemo)reirradiation to improve R0 resection rates	Strong	Expert Opinion [§]
Neoadjuvant (chemo)reirradiation dose		
• 40.8 Gy in 1.2 Gy/fraction twice daily	Strong	Low
• 30-39 Gy in 1.5 Gy/fraction twice daily +/- IORT	Strong	Low
• 30 Gy in 1.8-2 Gy/fraction daily +/- IORT	Strong	Low
Non-resectable/operable: consider definitive (chemo) reirradiation for prolonged local control	Strong	Expert Opinion [§]
Definitive (chemo)reirradiation dose with schedules as used in neoadjuvant setting	Strong	Low
Standard palliative regimens in patients with symptoms, poor performance (WHO ≥ 2) and prognosis (<6 months) e.g. 1x8 Gy and 5x4 Gy	Strong	Low

*Where expert opinion is noted, the following rationale has been applied * indicates safety, † indicates feasibility, § indicates consensus and ‡ indicates patient values.*

Advanced radiotherapy techniques or modalities

In addition to standard conformal techniques, other external beam techniques or modalities are routinely applied in the reirradiation setting of LRRC, and these are summarized below. Use of these is heavily dependent on expertise, availability, appropriate quality assurance, reimbursement of costs, travel distance, and expected benefit, in addition to appropriate patient selection as suggested below. There are few data to guide selection of these techniques.

IORT and endorectal brachytherapy are not covered in these recommendations, as they are fully described in the ESTRO/ACROP and GEC-ESTRO guidelines, respectively (26, 27). In summary, IORT delivers a single fraction electron or brachy boost of 10-15 Gy, generally combined with previous neoadjuvant external beam (chemo)reirradiation. According to the ESTRO guidelines for IORT in LRRC, an IORT boost is considered for LRRC with persisting tumour adherence after neoadjuvant chemoradiotherapy, inadequate radial margins (close <1 mm), and a high risk of relapse. Endorectal brachytherapy can be used for patients not covered by these recommendations, as salvage treatment for a small local intraluminal regrowth following definitive (C)RT, in patients who are inoperable or chose to avoid surgery.

Stereotactic reirradiation

Stereotactic Body Radiotherapy (SBRT) delivers potentially ablative doses and may provide an alternative to surgery for patients unfit or unwilling to have surgery or for carefully selected patients by the MPT with LRRC. In rectal reirradiation it is most often used for 1-3 discrete lesions <5 cm. It can be delivered when the lesions of LRRC are adjacent to OOI such as bowel or bladder, provided there is no direct invasion based on imaging and/or endoscopy. The most common site for SBRT is a lateral sidewall recurrence, but it can be used in any compartmental recurrence for example central presacral recurrences, anterior prostate recurrences or posterior sacral recurrences. Given the high fraction dose and generally small PTV margins, daily online image guidance is essential to ensure proper target coverage. Moreover, there should be careful discussion within the MPT regarding prioritisation, which in SBRT most often concerns prioritisation of the OOI. In case of close proximity to mobile OOI, such as bowel, online adaptive strategies are preferable.

Johnson et al. published a LRRC retrospective multicentre cohort of 68 patients and 81 lesions, with a median GTV volume of 13.4 cm³ (range 0.6–121.7cm³), treated with

a conservative dose of 30 Gy in 5 fractions for isolated recurrence (21, 64). With a median follow-up (FU) of 28 months, the 2-year OS was 77% with a median OS of 38.7 months. Defoe et al. reported a single centre retrospective series of 14 patients with presacral recurrence treated with 36 Gy in 3 fractions or 12-18 Gy in 1 fraction with Cyberknife (65). The median GTV volume was 52.5 cm³ (range 19 – 110 cm³). With a median FU of 16.5 months, outcomes were similar, with 2-year OS and LC rates of 78.8% and 68.2% respectively. There were no reported G3-5 toxicities.

The safety of SBRT in the previously irradiated pelvis was addressed in two publications (not limited to LRRC). The 2021 Delphi consensus regarding pelvic SBRT reirradiation supported its use after multidisciplinary review (66). In addition, the DESTROY-1 trial recently published the outcomes from the SBRT reirradiation arm (67). This phase I trial delivered SBRT reirradiation to 49 lesions in the pelvis in 5 fractions, up to a maximum of 45 Gy in patients who previously received >60 Gy or in locations with previous small intestinal irradiation, or 50 Gy in patients after <60 Gy. Two patients experienced grade 4 adverse effects, namely a soft tissue abscess in the acute setting which was treated surgically, and late skin ulceration after cumulative EQD2Gy _{$\alpha/\beta=3\text{Gy}$} = 170 Gy. No Grade 3 or 5 toxicity was reported.

Proton therapy

The potential to decrease integral radiation dose is important for reirradiation. Consequently, charged particle therapy, with less entrance dose and rapid dose fall-off, is of obvious interest to potentially decrease the risk of adverse effects and/or to allow for dose escalation. However, clinical studies have yet to show the actual value of proton or other charged particle therapy in comparison to standard photon reirradiation.

Appendix VI summarises the literature on proton therapy for LRRC (68-73). Based on these studies, a 2024 review and consensus statement from the Particle Therapy Co-Operative Group (PTCOG) gastrointestinal subcommittee on lower GI tract malignancies discusses clinical situations in which PBT should be considered. They achieved consensus on recommending proton therapy for “patients requiring reirradiation for local-regional recurrence”. Strength of consensus recommendation: strong, Overall quality of evidence grade: moderate, Oxford level of evidence: 3).

One trial reported favourable early adverse effects using proton therapy for reirradiation in LRRC with preserved QoL (74). At least three further prospective non-randomized trials are ongoing, exploring radiation doses from 70.4 Gy in 16 fractions, 65 Gy in 52 fractions or maximum tolerance dose (NCT03098108, NCT04827732, NCT04695782).

Carbon ion therapy

Carbon ion therapy (CIRT) provide physical properties similar to protons but may be especially relevant for addressing the radioresistance of LRRC, as its higher linear

energy transfer (LET) leads to increased relative biological effectiveness (RBE) and enhanced cell death.

Several phase I and phase II studies have investigated the use of CIRT in the treatment of LRRC (Appendix VII) (75-86). A systematic review from 2020 concluded that CIRT is promising in improving outcomes in LRRC, but there is a need for multi-institutional prospective clinical trials (87). One single arm Phase II trial is ongoing, delivering 74 Gy in 20 fractions of CIRT for LRRC in China (NCT05807984).

Advanced radiotherapy techniques or modalities recommendations

Recommendations	Strength of recommendation	Quality of Evidence
SBRT can be considered for 1-3, small, discrete lesions of LRRC , without invasion of GI tract or bladder; as an alternative to surgery in centres with experience	Conditional	Low
Consider protons for neoadjuvant or definitive (chemo)reirradiation in centres with experience and availability	Conditional	Low
Consider carbon ions for neoadjuvant or definitive (chemo)reirradiation in centres with experience and availability	Conditional	Low

Radiotherapy planning

Imaging for treatment planning

An essential part of the pre-treatment workup includes sourcing/requesting previous treatment details, including as complete radiotherapy data as available (37). Data should preferably include full 3D imaging, structures, and dose distributions. If full 3D data is not available, then as much information as possible should be sourced to recreate previous dose distributions. The expected planning and delivery technique

should be considered, for example SBRT or hyperfractionated treatment; to facilitate the optimal planning process.

Supine positioning is superior in maintaining stability for pelvic IMRT and proton/particle treatment (88-90). In rectal cancer patients, where anatomical changes between primary (C)RT and (chemo)reirradiation are likely significant, patient comfort and day-to-day reproducibility should be prioritised. Any attempts to reproduce a prone treatment position from previous RT may compromise the safe and accurate delivery of complex reirradiation plans. Individual bladder and bowel protocols will be required depending on the site of the recurrence, plan for surgery, and adjacent OOI, and should be discussed and agreed with the MPT (91).

Where available, multi-modality planning scans, e.g. MRI/PET, should be acquired in the treatment position, on a flat couch and registered with the RT planning CT scan (92). Intravenous contrast should be used where clinically appropriate, to aid delineation, ensuring scanning levels provide coverage of relevant OOI. All relevant diagnostic imaging should be available and can be used as a visual aid, but The Institute of Physics and Engineering in Medicine (IPEM) recommend they should not be registered to planning imaging if not conducted in the treatment position, due to potential errors in registration (92). Further guidance on MRI and PET imaging is available in Appendix VIII.

Target Volumes

The only published delineation guideline for LRRC was developed for the PelvEx II trial where reirradiation is delivered in the neoadjuvant setting (33, 93). The guideline was written with multidisciplinary input from a radiologist, radiation oncologists and surgeons with expertise in LRRC. As no other delineation guidelines exist, and it has been developed by a large MDT with expertise in neoadjuvant (chemo)reirradiation, it is strongly recommended to follow these guidelines when performing target volume delineation for LRRC, especially in the neoadjuvant setting. Deviations from the guideline may be warranted if there is a different treatment goal. Interrogation of relapse rates, particularly sites of relapse on completion of the trial, will inform practice in due course, however the trial guideline remains a common reference point.

The gross tumour volume (GTV) includes all visible tumour and surrounding fibrosis, as well as the entire abscess in case of tumour location within an abscess. For intraluminal recurrence, the full circumference is included. In the neoadjuvant setting, a 1 cm GTV to clinical tumour volume (CTV) margin is used, with an additional 0.5 cm in certain directions based on surgical input. PTV margins typically range from 5-10 mm, depending on imaging and setup protocols. See Appendix VIII for further information on imaging of LRRC.

In a retrospective study of 33 patients with re-recurrence who had previously undergone reirradiation without contouring guidance, 17/33 (52%) were not delineated in accordance to the current guideline. In 10 of these 17 cases, a multidisciplinary team deemed that, in retrospect, delineations would have been altered to be in accordance with the PelvEx guidelines, generally resulting in larger target volumes (94). This is in line with preliminary PelvEx II data, reporting that up to 50% of the GTV and/or CTV

required expert revision (93), resulting in a refinement of the contouring guidance and reinforcing the need for review by specialist radiation oncologists.

Dose planning, prioritization and cumulative dose evaluation

Evaluation of previous and cumulative dose

All previous dose distributions should be rescaled to equieffective dose (typically equieffective dose $\text{EQD2Gy}_{\alpha/\beta=3\text{Gy}}$) for normal tissue cumulative dose evaluation (95), see ESTRO Reirradiation Physics Working Group for detailed, site-agnostic recommendations for cumulative dose evaluation for reirradiation (96) and the ReCOG consensus statement for dose reporting guidance (97). If full 3D data are not available, then as much information as possible should be sourced to map previous field borders and irradiated volumes onto current imaging; and, if a suitable beam model is available, to recreate previous dose distributions for 3D dose evaluation.

Most methods for cumulative dose evaluation depend on registration of previous treatment imaging to current images (96). This is particularly challenging in the pelvis due to previous surgery, general changes in internal organ position (e.g. for bowel) and filling (e.g. for bladder), and changes in treatment position (typically from prone to supine). Rigid image registration is useful when evaluating dose distributions in limited areas (typically high dose areas near the retreatment target volume), provided that this is the focal area for the registration, but is unlikely to be valid for larger pelvic volumes. Deformable image registration (DIR) has shown promise for the evaluation of cumulative pelvic dose distributions (98, 99), but will often fail for very mobile and deformable organs (such as bowel) or in cases of substantial tissue loss (e.g. after surgery). In this case, point dose evaluation, based on maximum previous dose to sub-volumes of the OOI in vicinity of the new target is usually most helpful; see (96). A visual inspection of image registrations and mapped dose distributions are essential to ensure plausibility before attempting to evaluate cumulative dose, especially in the setting of major anatomical changes e.g. due to surgery.

Note that where the whole or substantial parts of pelvis have previously received a homogeneous dose (e.g. for 3- or 4-field box techniques), and the new target is fully contained within this previously irradiated volume, simple evaluations based on prescription doses may be useful to guide clinical decision making (100). This may, e.g., be relevant for reirradiation targets planned for 30 Gy in 1.8-2 Gy fractions, following previous 3D conformal radiotherapy to 45-50 Gy (i.e. where the cumulative $\text{EQD2Gy}_{\alpha/\beta=3\text{Gy}}$ is <90 Gy).

Dose planning

Dose planning for reirradiation of LRRC is inherently challenging and difficult to standardise. Non-standard pelvic anatomy due to surgical intervention(s), recurrence location in organs without clear boundaries, significant variation in target position and shape, and the need to account for and evaluate previous radiation dose in treatment planning, all add to the complexity. IMRT allows selection of gantry angles to utilise sharp beam penumbras, whereas VMAT is optimally delivered using half or quarter arcs to avoid unnecessary dose to previously irradiated tissues. All reirradiation with

neoadjuvant, definitive intent should be delivered using IMRT/VMAT or similar inverse planned technique.

Treatment planning will depend on the exact position of the new target relative to the original target and high dose volumes to OOI. When the volume is completely within the previous treatment volume (e.g. local recurrence in anastomosis), optimisation should proceed as for 'de novo' treatments with subsequent evaluation of cumulative equieffective dose to OOI. If no high dose overlap in critical OOI exists (e.g. inguinal node recurrence in exit dose of previous pelvic beams), careful field/arc arrangements are required to avoid entry/exit dose through previously irradiated volumes. A partial overlap with previous targets or high dose volumes (e.g. recurrence in external iliac node on edge of previous PTV) may make it challenging to achieve full target coverage while keeping OOI doses within tolerance, particularly if cumulative doses of $\text{EQD2Gy}_{\alpha/\beta=3\text{Gy}} > 90 \text{ Gy}$ are planned. In this case, joint planner–physician decision-making is necessary to weigh tumour control against risk of normal tissue adverse effects, keeping patient preferences and therapeutic aims in mind. A number of different strategies can routinely be employed to take into account the total dose received in previous treatment courses (background or bias dose) during the optimisation process, as summarised in Table 3 (29, 31, 101-106). Where image registration is considered (locally) reliable, possibly the most useful approach involves up-front generation of isodose structures from previous dose distribution, representing relevant dose levels (e.g. 100%, 85%, 70% of previous prescription dose, or clinically relevant normal tissue dose levels in equieffective dose); mapped to the current imaging and included as avoidance or optimisation volumes in plan optimisation (Table 3, option 1). Where image registration is not reliable (or available), the preferred alternative approach is to optimise using the previous maximum point dose to OOI (or sub-volume of OOI in vicinity of new target) to establish 'remaining' dose available for plan optimisation objectives (Table 3, option 2).

Prioritisation

The physician should specify patient-specific OOI dose guidance and indicate whether PTV coverage may be compromised to respect them. For neoadjuvant treatment, areas at risk of positive resection margins (R1/2) should be prioritised for target coverage in treatment planning, whereas OOI planned for surgical removal may be deprioritised.

Normal tissue dose guidance

The clinical publications that offer suggestions of dose guidance are detailed in Table 4.

While there is some evidence correlating cumulative dose and associated adverse effects in reirradiation of spinal cord and brain, the majority of evidence for the OOI relevant to our population is based on animal studies, and there is scarcity of data that can be translated to routine clinical work (39). There is no evidence regarding the optimal dose guidance for OOI in rectal (chemo)reirradiation. Based on patient series

reported in the literature, and expert opinion, it is likely that cumulative EQD2Gy _{$\alpha/\beta=3\text{Gy}$} of <90 Gy can be delivered to the planned PTV without any formal OOI constraint calculations with acceptable levels of severe adverse events. However, we acknowledge that this is not a universal safe threshold and should be interpreted in conjunction with organ-specific dose–volume parameters, overlap volume, and clinical intent. Cumulative dose should always be considered in the context of the benefit-risk ratio. For example, in the neoadjuvant setting, where the aim is to improve R0 resection rate and extend life expectancy, dose constraints may be stricter for organs that are not planned for resection, whereas in organs that will be removed during surgery, hotspots in OOI may be deprioritized over target coverage of areas at risk for R1 resections. Conversely, patients receiving repeat reirradiation may accept a higher adverse effects risk when the alternative is poor QoL with uncontrolled pelvic disease. Although there is no optimal dose guidance available, we propose that a reporting set for clinical practice and future publications/registries should be developed, in line with Andratschke et al. and Paradis et al. (37, 97) This should as a minimum include previous dose data availability, cumulative EQD2 method, registration method, time interval, overlap volume, and cumulative D_{max} or equivalent small-volume metrics for bowel, bladder, ureters, cauda/sacral roots where relevant.

Image-guided radiotherapy

Image-guided radiotherapy (IGRT) protocols for LRRC reirradiation have not been primarily investigated in prospective clinical studies and are poorly described throughout retrospective series.

Expert consensus data and results from a pattern of care survey provide some key insights/recommendations for pelvic reirradiation (91, 107, 108). Daily volumetric imaging with cone-beam CT (CBCT) should be acquired and online positional corrections applied. This is most relevant in SBRT but should also be strongly considered in neoadjuvant and definitive (chemo)reirradiation in case of concern regarding specific OOI. Image acquisition settings should be optimised to improve the differentiation between adjacent structures e.g. optimising the kilovoltage (kV) or milliampere-seconds (mAs). MR-guided platforms will enhance target and OOI visualisation in scenarios complicated by fibrosis or anatomical distortion (109). Daily adaptive radiotherapy strategies may enable sparing of mobile bowel adjacent to recurrent disease (109-111). These are especially beneficial in SBRT where an ablative dose is delivered often very close to adjacent OOI and are feasible due to the low number of fractions.

High inter-patient variability requires individualised upfront IGRT protocols in discussion and agreement with the MPT (physician, physicist, and RTT) in accordance with planning prioritisation. The region of interest for image matching should be predefined, including prioritisation of relevant structures. An automatic registration should be performed, followed by soft tissue adjustments based on the agreed protocol. Additionally, isodose lines can be used as a visual guide to high dose regions, although must be used with caution.

Radiotherapy planning and delivery recommendations

Recommendations	Strength of recommendation	Quality of Evidence
Reirradiation treatment planning should account for previous radiotherapy dose, and cumulative equieffective dose to normal tissue should be evaluated	Strong	Moderate
For neoadjuvant (chemo)reirradiation, areas at risk of an R1 resection should be prioritised for PTV coverage, whereas OOI planned for surgical removal may be deprioritised.	Conditional	Expert Opinion [§]
All neoadjuvant or definitive reirradiation should be delivered using IMRT/VMAT or comparative inverse planned technique.	Strong	Expert Opinion [†]
Daily volumetric imaging should be performed daily for SBRT and should be strongly considered for neoadjuvant and definitive (chemo)reirradiation in case of concern regarding specific OOI	Strong	Expert Opinion [*]

Where expert opinion is noted, the following rationale has been applied * indicates safety, † indicates feasibility, § indicates consensus and ‡ indicates patient values.

Concurrent radiosensitizers

Concurrent chemotherapy with capecitabine or 5-fluorouracil has been employed in all published single- and multicentre series of (chemo)reirradiation, where clinically appropriate. Extrapolation from primary rectal cancer trials demonstrating improved response with concurrent oral or intravenous fluoropyrimidines supports its routine use with all hyper- or normofractionated regimens when not contraindicated (e.g. in patients with cardiac or hepatorenal comorbidities). The use of concurrent chemotherapy should not affect the planned dose and fractionation (112, 113). Other concurrent systemic anticancer treatment (SACT) remain experimental, for example a

PD-1 inhibitor in the TORCH-R trial (NCT05628038) (29), or FOLFOX concurrently with (chemo)reirradiation (114).

Multiple single or multicentre series report the use of SACT in addition to (chemo)reirradiation with different aims (63, 114-117). Neoadjuvant therapy has been used as a test of tumour biology, with disease progression identifying patients unsuitable for surgery and redirecting management (117). Voogt et al. used neoadjuvant chemotherapy, as in primary rectal cancer to improve the pCR rate (44). This is being further investigated in PelvEx II, the prospective randomised trial investigating the use of neoadjuvant chemotherapy with the aim of improving R0 resection rate (104). The RETRY trial (NCT05984576) is investigating the use of TNT with adjuvant chemotherapy to improve LC rate (30). The potential impact on progression free survival (PFS) or OS will depend on the regimen used, the line of treatment, previous SACT, molecular markers, mismatch repair status, the disease-free interval, the site, size and number of recurrent deposits. It is beyond the scope of this document to offer any guidance on the use of SACT for LRRC beyond its role as a radiosensitiser.

Regional hyperthermia (RHT) may enhance radiation damage. There is significant in vitro data to support this, and RHT has been delivered in a number of retrospective series published between 1992 and 2003, including both locally advanced rectal cancer (LARC) and LRRC, of which a proportion have had previous radiation (46, 55). These are referenced in Table 1 and 2. Based on the available data, there is no guidance to suggest which patients may benefit. Therefore, we suggest this is considered only in centres with expertise, and ideally within a prospective clinical trial.

Concurrent radiosensitizers recommendations

Recommendations	Strength of recommendation	Quality of Evidence
Concurrent oral or intravenous fluoropyrimidines should be delivered with reirradiation if patient factors allow, in neoadjuvant or definitive reirradiation setting	Strong	Low
Consider regional hyperthermia in combination with reirradiation in centres with experience and availability, ideally within a clinical trial	Conditional	Expert opinion [§]

*Where expert opinion is noted, the following rationale has been applied * indicates safety, † indicates feasibility, § indicates consensus and ‡ indicates patient values.*

Discussion

These recommendations aim to guide clinicians to implement and deliver (chemo)reirradiation in the complex setting of LRRC after previous neoadjuvant (C)RT for rectal cancer. Although there is a lack of high-level evidence, there was very strong agreement among the experts to consider neoadjuvant or definitive (C)RT up to 30-40 Gy, with cumulative EQD2Gy _{$\alpha/\beta=3\text{Gy}$} of 80-90 Gy. This is supported by two prospective phase II trials and two relatively large retrospective studies, although the optimal total dose, fraction size and frequency (once or twice daily) are unknown (14, 47, 48, 56). Given the approach taken in these reports, it may be concluded that there are no strict OOI constraints below the 90 Gy threshold. In practice, the appropriateness of this threshold for a specific patient will be highly dependent on numerous additional factors; such as volume of reirradiation, overlap with and type of OOI, toxicity from prior radiotherapy, and time interval between previous radiotherapy and reirradiation - and whether patients will proceed to surgery, removing most of the reirradiated OOI tissue.

There is no definitive evidence to support one external beam treatment technique or modality over the other, nor the use of daily online volumetric imaging. In the setting of LRRC, day-to-day tumour- and organ motion is very unpredictable, hence our expert view is to strongly recommend the use of daily online imaging. This enables PTV margin reduction and, in combination with treatment planning techniques that result in steep dose fall-off, results in smaller reirradiated volumes and potentially less toxicity.

Hyper- versus standard fractionated regimens have never been compared head-to-head in rectal cancer reirradiation, but evidence from both preclinical and retrospective series suggests that hyperfractionation may result in decreased late adverse effects by repair of sublethal damage between fractions and repopulation from surviving cells (118). In the neoadjuvant setting, there are more long-term survivors, therefore the rationale for twice daily fractionation is most valid, however the theoretical potential benefit in late adverse effects may not outweigh the logistical challenges for both patients and health care providers (40).

Conclusion

(Chemo)reirradiation can be applied in the context of neoadjuvant treatment, definitive treatment and palliation, to increase radical resection rate, enhance local control and symptom control, and relieve symptoms, respectively. Despite its increasing role (6), reirradiation is still underused due to concerns about adverse effects. Optimal patient selection, along with advanced imaging and precision delivery techniques, is essential to maximize the therapeutic benefit while minimizing harm. Safe delivery requires expertise, or close mentorship from experienced teams, as well as ongoing training, data collection, and audit. Participation in national and international databases and trials (e.g. ReCare, UK SABR audit, PelvEx II, ReRad, RETRY, PRIOR), and collaborations (ReCOG), is strongly encouraged to improve evidence, standardization, and outcomes (5, 6, 31). The choice of modality and technique depends on institutional experience, available equipment, and patient characteristics. In the absence of high-level evidence, these recommendations represent expert consensus and provide practical guidance to ensure the safe and consistent delivery of (chemo)reirradiation in routine clinical practice.

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Figure Headings

Figure 1. PRISMA diagram of publication selection.

Figure 2. Decision Tree.

LRRC - Locally recurrent rectal cancer; XRT - radiotherapy; CRT –

chemoradiotherapy; IORT – intraoperative radiotherapy; SABR – stereotactic ablative
body radiotherapy; BID – twice daily treatment.

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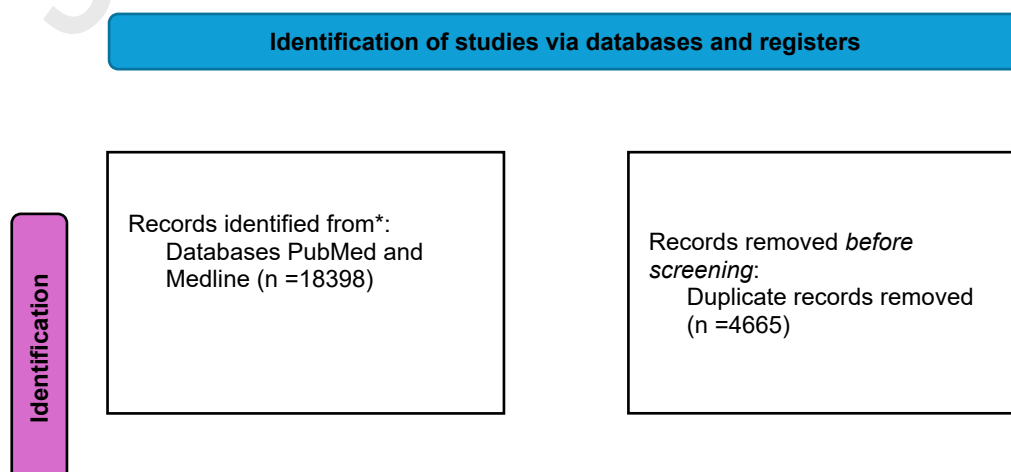
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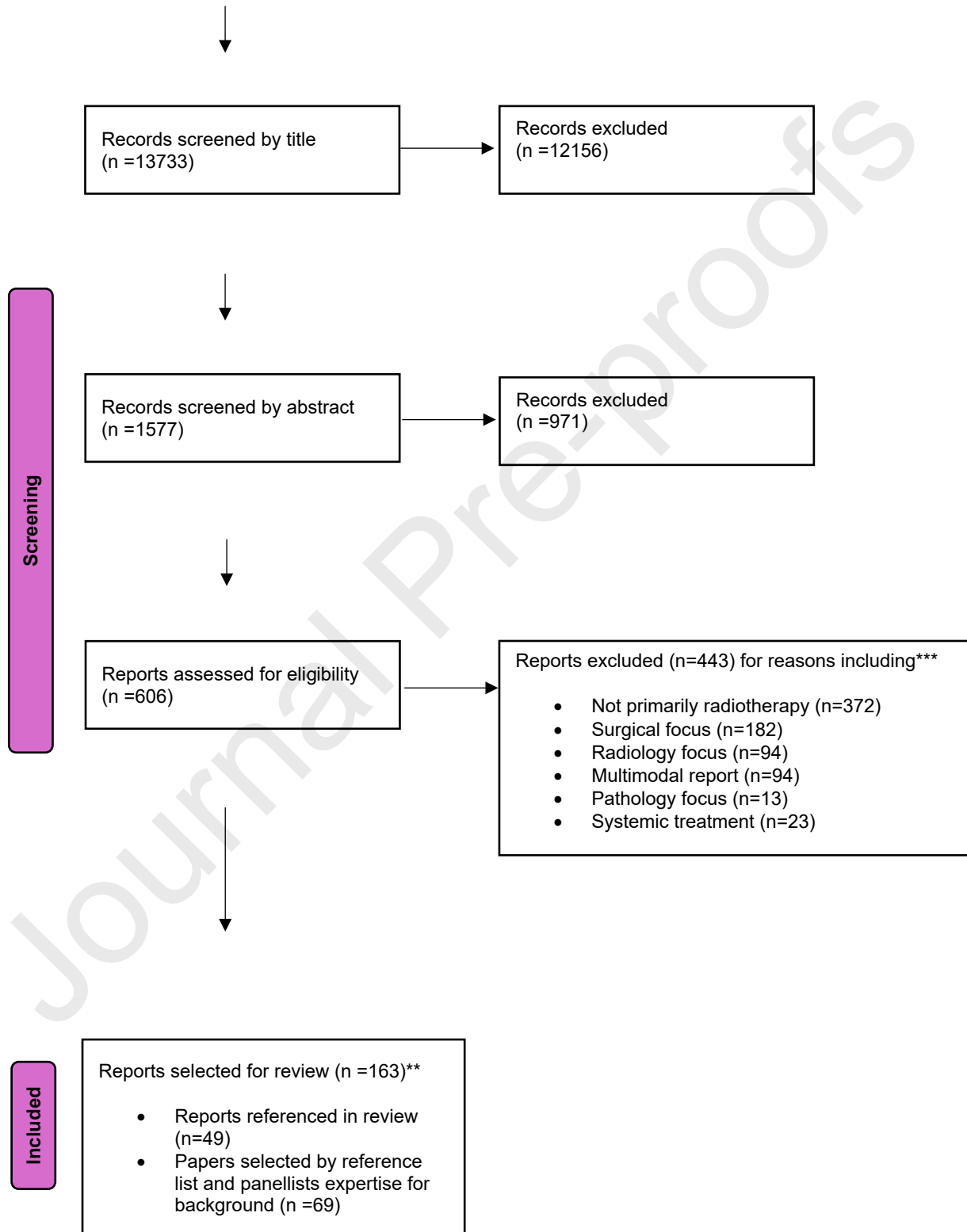
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Figure 1

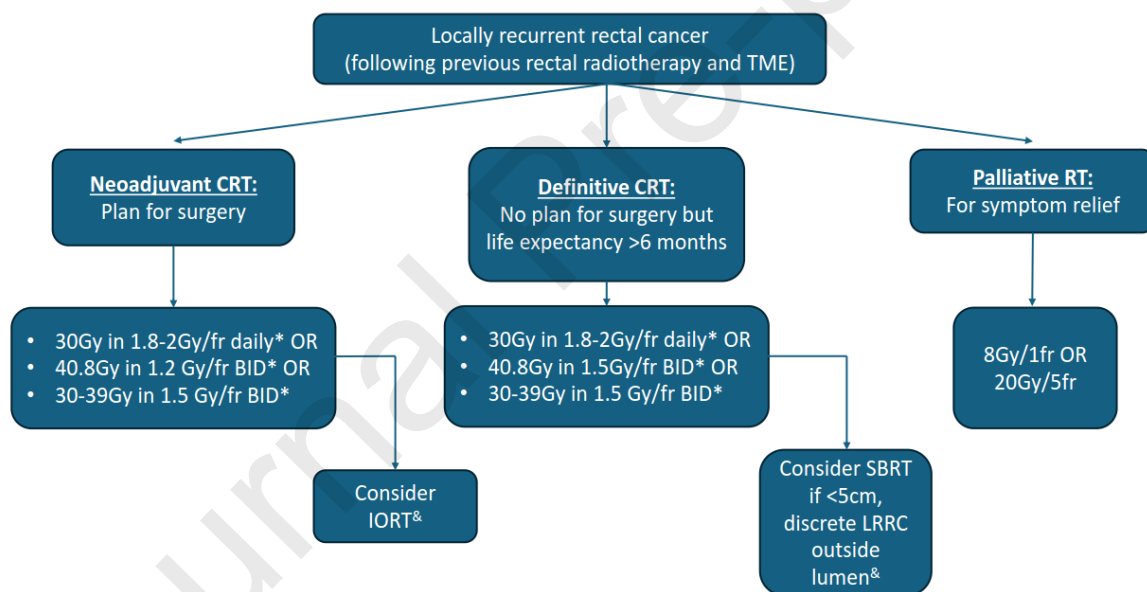




*Initial search was performed as broadly as possible to include all literature on locally recurrent rectal cancer (LRRC). Search was based on full-text information rather than title specific, as information regarding recurrent rectal cancer is often enclosed in articles primarily focussing on primary rectal cancer. Subsequently, the focus was progressively refined to specifically target studies and data pertaining to reirradiation for LRRC as a treatment strategy.

** Appendix VI shows all papers deemed relevant regarding reirradiation specifically. Of the 163 studies that were deemed relevant to reirradiation specifically, 49 were referenced in the final paper.

*** Each report may have multiple exclusion reasons.



*consider treatment delivery using protons / carbon ions / hyperthermia in centres with experience, ideally in clinical trials.

& should be performed in centres with expertise, ideally in clinical trials.

Table 1 Details of local control and overall survival within identified photon studies

Journal Pre-proofs								
Author	Year	Study Design	No. of patients	ReRT (%)	Interval between courses (months)	Median dose (Gy per fractionation)	No. of patients undergoing radical surgery (%)	Control (LC) Survival (OS)
Dijkstra et al. [2]	2021	Retrospective	35	100%	65 (53-72)	30.0-30.6Gy/1.8-2.0	35/35 (100%)	3-year and 5-year LRFS: 50.7% and 50.7% 3-year, 5-year OS: 65% and 21%
Koom et al. [3]	2012	Retrospective	22	100%	26 (5-72)	50.2Gy (30-66Gy)/1.8-3	5/22 (23%)	Median LPFS 16 months. 2-year LPFS: 32% Median OS: 21 months. 2-year OS: 50%
Chung et al [4]	2019	Retrospective	41	100%	NR	50Gy (30-60)/2 (1.2-6)	9/41 (22%)	Median IPFR 23.3 months. 2-year IPFR: 49.4% Median OS: 33.8 months. 2-year OS: 55.3%
Bosman et al. [12]	2014	Retrospective	135	100%	34 (7-198)	30.0-30.6Gy/1.8-2	135/135 (100%)	1-year, 2-year and 3-year LC: 100%, 93.7% and 85.9% Median OS: 26 months. Median OS in non-surgical patients and surgical patients: 16 and 60 months respectively
Holman et al. [13]	2016	Retrospective	565	46%	38 (3-235)	30Gy (5-39.6Gy)/2	256/256 (100%)	3-year, 5-year local re-recurrence 3-year, 5-year OS: 54% and 31%

									ce: 46% and 52%
Valentin i et al. [14]	2006	Prospective	59	100%	27 (9-106)	40.8Gy/1.2 twice daily	39/59 (66%)	1-year, 3-year, 5-year LC: 76.3%, 46.6% and 38.8%	Median OS:42 months. 5 years OS:39.3% 5-year survival of non-surgical or R2 resection and surgical patients with R0/R1 resections: 22.3% and 65 % respectively
Susko et al. [45]	2016	Retrospective	33	100%	39 (25-50)	30Gy/1.8-2	14/33 (42 %)	2-year LPFS:15.7%	Median OS: 23 months. 2-year OS: 48% Median OS of non-surgical and surgical patients: 13 and 32 months respectively
Juffermans et al. [46]	2003	Retrospective	54	100%	22 (4-97)	30Gy/4	0/54 (0%)	NR	Median OS:10 months. 1-year, 2-year OS:43% and 6%
Cai et al. [47]	2014	Prospective	22	100%	48.6 (36-62)	39Gy/1.3	0/22 (0%)	1-year, 2-year LPFS:	Median OS:19 months. 1-year, 2-

								67% and 10.7%	year OS:86% and 27 %
Tao et al. [48]	2017	Retrospective	102	100%	30 (5-789)	39Gy (30-45Gy)/1.5	46/102 (45%)	2-year, 3-year LC: 51% and 40%. LC in non-surgical group and surgical group at 1-year: 62.5% and 86.8%; 2-year: 35.7% and 69%; 3-year 30.4% and 47.8% respectively	Median OS:30 months. 2-year, 3-year OS:61% and 39%. Median OS for non-surgical and surgical patients: 17 and 47 months respectively. OS at 3-year for non-surgical and surgical: 63% and 20% respectively
Lingarddy et al. [49]	1997	Retrospective	52	100%	24 (3-86)	30.6Gy (19.8-40.8Gy)/1.8 or 1.2	0/52 (0%)	NR	Median OS:12 months. 2-year, 3-year OS:25% and 14 %
Ng et al. [50]	2013	Retrospective	56	100%	30 (8-176)	39.6Gy (20-39.6Gy)/1.8	12/56 (21%),	NR	Median OS:19 months. Median OS for non-surgical and surgical patients:15 and 30 months respectively.

Haddock et al. [51]	2001	Retrospective	51	100%	22 (9-51)	25.2Gy (5.01-50.4Gy)/NR	51/51 (100%)	2-year, 3-year LC: 61% and 45%	Median OS:23 months. 1-year, 2-year, 3-year OS:74.9%, 48% and 28%
Kim et al. [52]	2010	Retrospective	12	100%	NR	45Gy/1.8	12/12 (100%)	NR	3-year OS in surgical patients:50.9%
Sun et al. [53]	2012	Retrospective	72	100%	25 (13-77)	36-56.4/1.2	18/72 (25%)	NR	Median OS:32 months. 3-year OS:45.1%
Mohiuddin et al. [54]	2002	Retrospective	103	100%	19 (2-86)	34.8 (15-49.2)/NR	34/103 (33%)	LC at end of FU for surgical patients: 15/34 (44.1%)	Median OS:26 months. 5-year OS:19%. Median OS in non-surgical patients and surgical patients: 14 and 44 months respectively. 5-year OS in non-surgical patients and surgical patients: 15% and 22% respectively
Milani et al. [55]	2008	Retrospective	24	100%	34 (11.3-112.4)	39.6Gy (30-45Gy)/1.8	0/24 (0%)	1-year, 2-year, 3-year LPFS: 61%,	Median OS:27 months. 1-year, 2-year, 3-

								30% and 15%	year OS:87%, 60% and 30%
Das et al. [56]	2010	Retrospective	50	100%	28 (5-354)	30-39Gy/1.5 twice daily	18/50 (36%)	3-year FFLP in non-surgical and surgical patients: 21% and 47% respectively	Median OS:26 months. 2-year, 3-year, 5-year OS: 56%, 39% and 25%. Median OS in non-surgical patients and surgical patients: 16 and 60 months respectively. 3-year OS in non-surgical patients and surgical patients: 27% and 66% respectively
Youssef et al. [57]	2016	Retrospective	31	100%	40 (10-308)	39Gy (n=15) twice daily. 30.4Gy (27-40Gy) (n=16) once daily.	9/31 (29%)	1-year, 2-year LC: 61.3% and 47.3%	Median OS:22 months. 1-year OS in non-surgical patients and surgical patients: 59% and 67% respectively

Table 2.
Details of
acute
and late
toxicity
within
identified
photon
studies

Al-Haidari et al. [58]	2020	Retrospective	67	100%	64 (31-80)	30-45Gy/1.2-1.5 twice daily.	20/67 (29.9%)	NR	Median OS:16 months. 3-year OS: 32%. Median OS in non-surgical patients and surgical patients: 9 and 39 months respectively. 3-year OS in non-surgical patients and surgical patients: 16% and 62% respectively
Dresen et al [59]	2008	Retrospective	147	38.8%	28 (3-207)	30.6Gy / 1.8	147/147 (100%)	5-year LC:49.5%	Median OS: 28 months. 5-year OS: 31.5%
Vermaas et al. [60]	2008	Retrospective	11	100%	22 (9-117)	27-40 Gy/1.8-2 Gy	11/11 (100%)	1-year, 3-year LC: 66% and 27%	1-year, 3-year OS:77% and 51%.
Park [61]	2019	Retrospective	24 (+1 anus)	100%	43 (12-2149)	45Gy (36-60 Gy)/NR	11/25 (44%)	NR	2-year, 3-year OS: 55% and 50%

Reference	Year	Acute toxicity	Late toxicity
Dijkstra et al. [2]	2021	G3 5.7%. Obstruction: 1/35 Diarrhoea: 1/35	G3 26 %. Infection: 2/35 (6 %) Insufficiency fracture 1/35 (3 %) Neurological toxicity 6/35 (17 %) Renal toxicity 1/35 (3 %)

Koom et al. [3]	2012	G3 Diarrhoea 9%	Grade 3–4 toxicity 8/22 (36%)– Small bowel obstruction 4/22 (18%), Fistula 1/22 (5%), Urinary stricture 6/22 (27%), Haematologic 3/22 (14%)
Chung et al [4]	2019	G3 Diarrhoea 7%. No G4.	42% G3 or higher. G3 Fistula 17%, G3 Bowel obstruction 17%, GU tox 10%, G4 Fistula 2%, G4 Bowel obstruction 5%.
Bosman et al. [12]	2014	Diarrhoea (95% grade 1-2, 5% grade 3-4), Neutropenic sepsis (1%, grade 3-4) G3-4 Gastrointestinal toxicity 3%	G3-4 Clavien Dindo 30d complications 5.3% in reirradiated group
Holman et al. [13]	2016	Grade 3 toxicity of 5.1%	NR
Valentini et al. [14]	2006	G3 5.1%, no G4.	Skin fibrosis 2/59 Impotence 2/59 Urinary incontinence/dysuria 2/59 Small bowel obstruction 1/59. In total 7/59=12%, no grading reported.
Susko et al. [45]	2016	G3-4 2/33 (6%). Fistula 1/33 (3%) Ureteral obstruction 1/33 (3%)	7/33 (21 %) incl. Ureteral obstruction, Small bowel obstruction, and Enterocutaneous fistula formation
Juffermans et al. [46]	2003	Diarrhoea (n=1), limited epidermolysis (n=4), Toxicity skin (n=3, grade I), Toxicity bladder (n=7, grade I), Toxicity bowel (n=6, grade I)	
Cai et al. [47]	2014	Acute and late G3 5/22=23%. Diarrhoea 2/22 (9%) Cystitis 1/22 (5%) Radiation dermatitis 1/22 (5%) Intestinal obstruction 1/22 (5%)	Acute and late G3 5/22=23%. Chronic severe diarrhoea 2/22 Small bowel obstruction 1/22 Dysuria with nephrostomy 2/22
Tao et al. [48]	2017	Only surgical toxicity reported.	G3-4 late tox=34%. The non-surgery group included Small bowel obstruction (n = 3), Urinary obstruction/hydronephrosis (n = 2), Pain (n = 1), Diarrhoea and Dehydration (n = 1), and Fistula formation (n = 1).

Lingareddy et al. [49]	1997	G3: Severe diarrhoea 10/ 52 (19%) Moist desquamation 4/52 (8%) Mucositis 2/52 (4%). No RTOG G4.	G3: Small bowel obstruction 9/52 (17%) Cystitis 3/52 (6%). RTOG G4: Fistula (recurrence) 4/52 (8%) and Skin ulceration 1/52 (2 %)
Ng et al. [50]	2013	G3 7/56 (13%). Skin 3/56 (5%) Gastrointestinal 5/56 (9%) Mucositis 1/56 (2%)	Infection/abscess/drainage/discharge 4/12, Fistula 1/12, Urinary infection/retention 2/12, Small bowel obstruction 1/12, Delayed wound healing 1/12, Skin ulceration 1/43
Haddock et al. [51]	2001	Peripheral neuropathy 32% (16/52); 7 mild, 5 moderate, 4 severe. Ureteral narrowing/obstruction 7/51.	
Kim et al. [52]	2010	No G3 or higher radiation-induced Urinary toxicities, Neuropathy or Osteonecrosis with G3 or higher.	
Sun et al. [53]	2012	G3-4 Diarrhoea 10% and Granulocytopenia 8%	Mild Skin fibrosis 4/72 (5.6 %) Mild urinary incontinence/dysuria 4/72 (5.6 %) G3 or severe: Small bowel obstruction 1/72 (1.4 %)
Mohiuddin et al. [54]	2002	G3: Diarrhoea 15% Moist desquamation 8% Mucositis 4%. G4 6% (not specified)	Chronic severe diarrhoea (G3) 18/103 (17%) (10 patients required parental nutrition) Small bowel obstruction 15/103 (15%) Fistula (recurrence) 4/103 (4%) Skin-ulceration 2/103 (2%)
Milani et al. [55]	2008	Skin: G1 (20.8%), G2 (12.5%). Gastrointestinal: G1 (4.2%), G2 (37.5%), G3 (12.5%). Urological G1 (4.2%), G2 (16.7%).	Late: Persistent diarrhoea (4.2%)
Das et al. [56]	2010	G3 Nausea/vomiting: 4%. No G4	Grade 3 toxicity 12/50=24% – Small bowel obstruction, Wound complication, Abscess, Fistula, Ureteral stricture/leakage, haemorrhage, joint disease, nausea Grade 4 toxicity 1/50 (2%) – cystitis.
Youssef et al. [57]	2016	Diarrhoea: G3 (1/31, 3.2%). Total G2 32%; Nausea/Vomiting (n=4), Skin toxicity (n=4), Diarrhoea (n=2)	G3 Sacral insufficiency fracture: 1/31 (3.2 %)

Al-Haidari et al. [58]	2020	G3-4: Skin 4 (6 %) Gastrointestinal 19 (28 %) Genitourinary 12 (18 %) Pain 10 (15 %) Malaise 22 (33 %)	G3-4: Total 25/37=68% Skin 1 (1 %) Gastrointestinal 5 (7 %) Genitourinary 9 (14 %) Pain 5 (7 %) Malaise 15 (22 %)
Dresen et al [59]	2008	Only surgical toxicity reported.	Lower extremity neuropathy 21/57; Ureter stenosis 4/57.
Vermaas et al. [60]	2008	NR	NR
Park [61]	2019	None	G3 12/25 (52%) Small bowel obstruction 4%, Bowel perforation 8%, Fistula 25%.

Table 3: Treatment plan optimisation strategies actively taking previous dose into account as part of the treatment planning process

1) Optimisation structures from previous isodose levels	Up-front generation of isodose structures from previous dose distribution, representing relevant dose levels (e.g. 100%, 85%, 70% of previous prescription dose, or clinically relevant normal tissue dose levels in equieffective dose); mapped to the current imaging and included as avoidance or optimisation volumes in plan optimisation.
2) Optimisation constraints based on previous max OOI doses	Previous maximum point dose to OOI (or sub-volume of OOI in vicinity of new target) subtracted from OOI cumulative maximum dose constraint to establish 'remaining' safe dose (in EQD2Gy). This is subsequently rescaled into current fractionation regime to establish max dose constraint for current plan optimisation.
3) High dose overlap volumes	Initial standard plan optimisation; followed by cumulative equieffective dose evaluation and identification of high dose overlap areas, for which

	new optimisation structures are generated to aid further optimisation.
4) Background / bias dose for plan optimisation	Use of the full previous dose distributions as a 'background' or 'bias' dose directly in plan optimisation. This is not straightforward, as it requires iterative evaluation of cumulative equieffective dose, and although reported in the literature, this approach is not commonly available [101,106].

Table 4. Details of reirradiation publications suggesting constraints

Reference	Published constraints
Cai et al [47]	OOI constraints with no reference to cumulative doses therefore not relevant.
GRECCAR 15 [28]	Trial protocol: • Cumulative bladder dose (α/β not specified) $D_{\max} < 80$ Gy • Cumulative rectal dose (α/β not specified) $D_{\max} < 76$ Gy • Cumulative $V_{40\text{Gy}}$ to small bowel < 200 cc, α/β not specified (optimal constraint)
PelvEx II [104]	Trial protocol: • Optimise dose to PTV with no compromise for OOI (cumulative tumour dose 50 Gy + 30 Gy reirradiation in 2 Gy fractions)

Abusaris et al [105]	Retrospective SBRT cohort delivered as per below with no grade 3-5 toxicity: • Median cumulative rectal $D_{\max}$ EQD2Gy$_{\alpha/\beta=3\text{Gy}}$ <104Gy (65-129Gy) • Median cumulative bowel $D_{\max}$ EQD2Gy$_{\alpha/\beta=3\text{Gy}}$ <98Gy (range 56-144Gy) • Median cumulative bladder $D_{\max}$ EQD2Gy$_{\alpha/\beta=3\text{Gy}}$ <113Gy (range 79-235Gy)
TORCH-R [29]	SBRT Trial protocol: • Cumulative constraints each organ from standard UK SABR consortium guidance [31] plus 15% recovery per year from primary irradiation
UK SABR Consortium Guidance [31]	Guidance document: • Cumulative constraints for each organ using standard UK SABR consortium guidance [96] plus 30% recovery if primary irradiation 6-18 months ago, 50% if >18 months.

Highlights:

- These recommendations guide reirradiation in recurrent rectal cancer
- (Chemo)reirradiation dose: 30-40 Gy in 2 Gy fractions or 1.2-1.5 Gy twice daily
- Consider SBRT for small recurrences and particle therapy at experienced centres
- Cumulative equieffective dose to normal tissue should be evaluated
- IMRT or VMAT and daily volumetric imaging are recommended

Conflict of Interest Declarations

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