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Tumour Review

Dutch national guidelines for locally recurrent rectal cancer

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ABSTRACT

Due to improvements in treatment for primary rectal cancer, the incidence of LRRC has decreased. However, 6–12% of patients will still develop a local recurrence. Treatment of patients with LRRC can be challenging, because of complex and heterogeneous disease presentation and scarce – often low-grade – data steering clinical decisions. Previous consensus guidelines have provided some direction regarding diagnosis and treatment, but no comprehensive guidelines encompassing all aspects of the clinical management of patients with LRRC are available to date. The treatment of LRRC requires a multidisciplinary approach and overarching expertise in all domains. This broad expertise is often limited to specific expert centres, with dedicated multidisciplinary teams treating LRRC. A comprehensive, narrative literature review was performed and used to develop the Dutch National Guideline for management of LRRC, in an attempt to guide decision making for clinicians, regarding the complete clinical pathway from diagnosis to surgery.

Introduction

After the introduction of total mesorectal excision (TME) and neo-adjuvant treatment, the incidence of locally recurrent rectal cancer (LRRC) has decreased, but 6–12 % of patients will still develop LRRC after primary rectal cancer.[1–5] At diagnosis, 40–60 % of patients present with distant metastases.[6–9] Detection of LRRC can be a challenge in itself, due to distorted anatomical planes and absence of the mesorectal fascia after primary rectal cancer surgery, the extra-luminal location of recurrences, and the presence of fibrosis or chronic inflammatory changes within the pelvis. Heterogeneity of presentation, prior treatment, and tumour biology are further complicating factors in LRRC treatment. Literature regarding LRRC is limited, meaning decisions are often based on low-grade evidence from retrospective cohorts, consensus statements, and a handful of single-arm prospective trials. Fortunately, prospective randomized controlled trials for LRRC patients have been initiated, which will likely increase the level of evidence in the coming years.[10,11].

Due to the aforementioned factors, LRRC management can be challenging. Recommendations have been included in several consensus guidelines, such as the beyond-TME, the PelvEx collaborative and the ESMO guideline.[12–14] However, the scope of these guidelines are more focussed on the management of locally advanced rectal cancer and not specifically on LRRC. Moreover, these guidelines did not represent all disciplines associated with LRRC.

We aim to provide a narrative literature review and guideline for LRRC on behalf of the Dutch Colorectal Cancer Guideline Committee, to guide decision making in the complete clinical pathway. The definition used for LRRC within this guideline is recurrent disease in the lesser pelvis, following partial (PME) or total (TME) mesorectal excision of

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rectal or distal sigmoidal cancer, including local recurrences originating from lymph nodes.[12] Residual or regrowing tumour after local treatment or organ-preservation strategies are not considered a LRRC. This guideline will become a module within the Dutch Colorectal Cancer Guidelines and can be of value for a worldwide multidisciplinary audience in the absence of a comprehensive international LRRC guideline.

Methods

The Dutch Colorectal Cancer guideline committee consists of the following disciplines: Surgery, Internal Medicine, Geriatrics, Gastroenterology, Radiation Oncology, Pathology, Radiology, Nuclear Medicine, and Nursing. All committee members are mandated by their national societies. The guideline consists of 79 modules, including one on LRRC. Modules are developed in a structured way. Clinical questions with corresponding PICOs are formulated. Existing (inter)national guidelines and systematic reviews are retrieved, reviewed for relevant content, and summarized. Individual studies are used to complement the prior two sources whenever applicable. A guideline draft with proposed recommendations is written by primary committee members, sometimes with external experts. This is reviewed by all committee members and discussed during regular meetings. Documents are revised until consensus is reached and all members agree on its final version. The module is then sent to all members of relevant national societies for commentary feedback. After a rebuttal phase, modules are authorized by the national societies and published online at www.richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc.

Relevant literature regarding diagnosis, treatment and prognosis was retrieved from MEDLINE and EMBASE. The search was performed on 21–02-2023 and repeated on 04–08-2023. Articles published in English were included. Articles from before the introduction of TME were excluded, as were articles already described in systematic reviews or *meta*-analyses. The search and number of results can be found in the supplementary material. All recommendations are summarized in Table 1.

Expert centres

Clinical evaluation of patients with (suspected) LRRC should be performed in specialized multidisciplinary teams (MDTs), given the complex, heterogeneous disease (Fig. 1), and the limited data available. Patients should be discussed pre-treatment in a centre with a dedicated MDT, as this is assumed to improve oncological outcome and can aid in management of (life changing) aspects of treatment.[2,12–15] An expert centre should have sufficient LRRC-specific expertise in radiology, surgical oncology, radiation oncology, medical oncology, and pathology. Individual surgeons and surgical teams should be experienced in performing extended multivisceral resections and should have access to appropriate perioperative care facilitating management of complications for patients undergoing advanced surgery.

Diagnosis and (response) evaluation

Obtaining a histological biopsy can be challenging in LRRC. A growing or suspicious lesion in the lesser pelvis, detected on MRI, combined with increasing CEA-levels or suggestive F18 FDG PET/CT imaging should be deemed enough for diagnosis if MDT-consensus is reached. To our best knowledge, no data on false negative biopsies is currently available. In clinical practice the value of biopsies seems limited, as negative biopsies in patients with evident radiological and biochemical signs of recurrence are frequently encountered, and biopsies can be technically challenging, especially in extra-luminal recurrences. An F18-FDG PET/CT can be used as an adjunct imaging technique for diagnosis, as described below. Alternatively, a waiting period of three months with repeated imaging can be considered a valid alternative to detect disease progression and confirm the diagnosis.

Table 1
Summary of Dutch National Guideline recommendations for LRRC.

	Summary of recommendations
Expert teams	
1	Discuss all patients with a possible local recurrence in an expert MDT prior to starting neoadjuvant treatment, to determine intent of treatment and treatment strategy.
2	Expert centres should be defined as centres with a specialized LRRC expert MDT, consisting of specialized radiologists, surgeons, radiation oncologists, medical oncologists and pathologists.
3	Surgical teams should be experienced in performing extensive multivisceral resections when treating LRRC.
Treatment intent	
4	Patients with resectable local recurrences or recurrences that potentially will become resectable after neoadjuvant treatment are eligible for treatment with curative intent.
5	Patients with distant metastases are not eligible for treatment with curative intent. However, patients with low-burden, oligometastatic disease with prolonged and sustained response may be considered for treatment with curative intent.
Staging and restaging	
6	The diagnosis LRRC should be made clinically based on a suspicious or growing lesion on MRI, combined with a suggestive F18-FDG PET/CT or rising CEA and MDT-consensus. Pathological verification can be used in addition, but should not overrule MDT-consensus.
7	Locoregional (re)staging should be done by T2-weighted MRI with DWI (highest b-value $\geq$ b800). Be aware that the field of view may need to be adjusted to ensure the whole recurrence is visualized.
8	Perform a CT-thorax-abdomen to assess the presence of distant metastases in case of a LRRC.
9	An F18-FDG PET/CT can be used as a problem solver to establish the diagnosis. Alternatively, a waiting period of 3 months with repeated imaging can be used to confirm the diagnosis.
10	Perform restaging (distant and locoregional) after neoadjuvant treatment with MRI and CT-thorax-abdomen.
11	Use standardized radiological reporting for locoregional staging at all timepoints and report at least tumour location, size and type, in addition to all structures (possibly) involved by either tumour or (residual) fibrosis.
12	An assessment of (possible) resectability should be performed at all timepoints given the consequences for treatment intent.
Neoadjuvant treatment	
13	Full-course neoadjuvant chemoradiotherapy (25x2Gy or 28x1.8 Gy with concomitant capecitabine (825 mg/m^2 bid)) is recommended for radiotherapy naïve patients in a curative setting.
14	Chemo reirradiation (15x2Gy with concomitant capecitabine (825 mg/m^2 bid)) is recommended for patients previously irradiated in the lesser pelvis in a curative setting.
15	Delineate target volumes using the consensus-based delineation guideline agreed upon by expert centres, to make sure that all surgical resection margins are incorporated within the target volumes.
16	There is no indication for neoadjuvant systemic treatment outside of clinical trials.
Surgical treatment	
17	All patients with a LRRC undergoing surgery should be operated on in expert centres.
18	Only patients in whom an R0-resection is considered feasible should undergo surgery.
19	There is no indication for surgical resection in patients with (new) irresectable locoregional disease or new metastases after neoadjuvant treatment.
20	There is no indication for debulking surgery in patients in whom an R2-resection is expected.
21	Consider the use of IORT in all patients with (potentially) involved or narrow resection margins.
22	Only consider curatively intended surgery in oligometastatic patients after a prolonged interval of good response to systemic therapy.
23	There is no indication for adjuvant treatment.
Non-operative management	
24	Consider chemoradiotherapy (full-course or reirradiation) for patients with irresectable local recurrences, with the goal of achieving local control and reducing symptom burden.

For locoregional evaluation, MRI is the gold-standard.[12–14,16–18] The T2-weighted MRI has a high sensitivity (80–91 %), specificity (86–100 %), and accuracy (95 %) in LRRC.[19,20] Evaluation can be challenging due to extensive prior treatment in the pelvis, consisting of surgery +/- radiotherapy and/or chemotherapy. The MRI

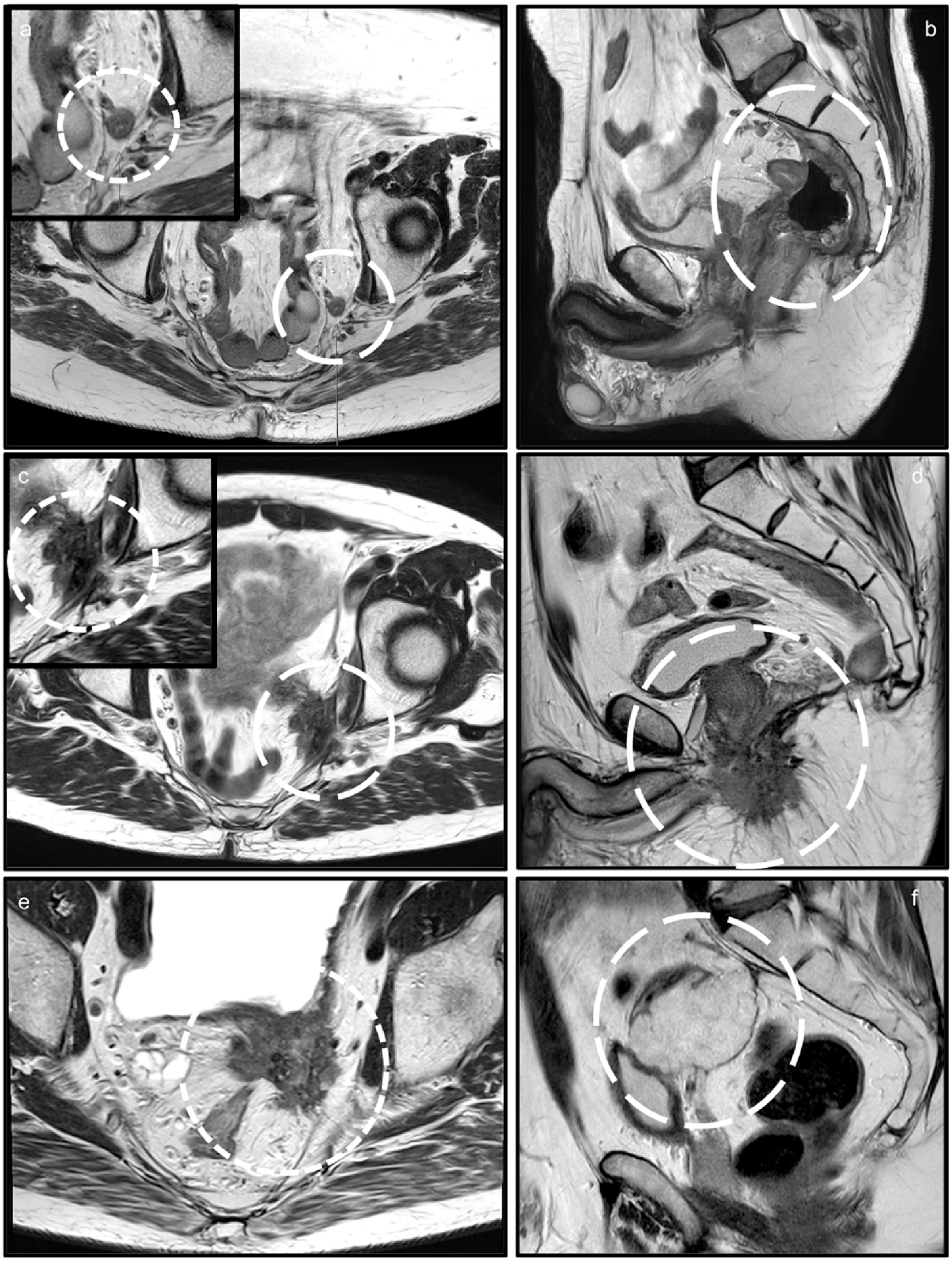

Fig. 1. Heterogeneity in local recurrences as seen in 6 individual patients with LRRC, with (a) a lateral nodal recurrence in the obturator space (b) a presacral recurrence concurring in a pre-existent abscess after anastomotic leakage, (c) a lateral recurrence involving the pelvic side wall and sciatic nerve, (d) a perineal recurrence also involving the prostate, (e) an anastomotic recurrence also involving the bladder, ureter and internal iliac vasculature, (f) a mucinous recurrence with involvement of the bladder, sigmoid and presacral fascia.

has a high negative predictive value for tumour invasion into surrounding structures, but the positive predictive value (PPV) varies, as a result of difficult differentiation between postoperative changes, fibrosis, and tumour.[16,21] Diffusion weighted imaging (DWI) can improve accuracy compared to T2-weighted images alone, as it aids in discerning tumour from fibrosis.[17,22–25] Assessment of mucinous tumours can also be challenging, as the high signal intensity on T2-weighted images and limited or absent diffusion restriction can impair recognition or differentiation from postoperative changes.[17,26] It is important to pay attention to the recurrence location during MRI-acquisition, as the standard field of view often needs to be adjusted to ensure depiction of the whole recurrence. Given the variation in recurrence locations and the necessary repeated imaging, it is advised not to angulate the MRI, to maximize comparability.

An F18-FDG PET-/CT can be helpful in case of diagnostic uncertainty.[27,28] A pooled analysis by Yu et al. of 26 studies investigating a F18-FDG PET/CT compared to a CT-thorax-abdomen, showed a high sensitivity (94 %) and specificity (94 %) for LRRC detection (AUC 0.98).[29] Systematic reviews by Maas et al. and Lu et al. also showed improved sensitivity and specificity of F18-FDG PET and F18-FDG PET/CT in identifying a LRRC.[27,30] Accordingly, an F18-FDG PET/CT is recommended in cases with clinical doubt, for example in patients with a rising CEA, but without a suspicious lesion on CT.[12,14] The limitations of F18-FDG PET/CT lie in identifying small lesions and in false positives due to infectious or inflammatory causes.[20] There is also a risk of false negatives, especially in mucinous tumours due to lower cell density and mucin production.[19] F18-FDG PET/MRI has been introduced, yielding promising results in LRRC detection: high sensitivity (94 %), specificity (94 %) and accuracy (94 %). It also provides a high sensitivity for detection of distant metastases (96 %).[31] However, hybrid PET-MRI is currently scarcely used due to its low availability, lack of evidence and concerns about the quality of MRI in such hybrid systems.

For assessment of distant metastases, the standard modality is still a contrast CT. Although the incidence of distant metastases is higher in patients with LRRC than in primary rectal cancer, there is no clear evidence supporting the need for routine F18-FDG PET/CT over CT in LRRC for detection of distant metastases. This is probably because bone metastases are relatively rare in colorectal cancer, for which the F18-FDG PET/CT has a higher accuracy than CT alone.[32,33].

Classification of LRRC is not yet standardized. Many classifications have been described in the literature but not one has been sufficiently validated for clinical use.[19] A degree of standardisation may however improve treatment quality for patients with LRRC.[12–14,16,19] A comprehensive description of all involved pelvic structures is of the utmost importance for assessing resectability, surgical planning and radiotherapy delineation.[13] It is therefore advised to adhere to some form of standardized reporting, describing at least the location, size and type of tumour, as well as providing information on all (possibly) involved surrounding structures. A suggested radiological checklist can be found in the supplementary material.[10].

Evaluation after neoadjuvant treatment is advised, because of the prognostic value and the implications for surgery and for patient selection, i.e., in whom no further surgical benefit is expected. This is the case in patients with an expected irradical resection and/or with new distant metastases. A cohort by Hagemans et al. describes 447 LRRC patients, 244 of whom started treatment with curative intent.[28] Fifty-one patients dropped out after neoadjuvant therapy (21 %), mainly due to new distant metastases (63 %), but also due to irresectable disease, and clinical deterioration. Refraining from surgery in these patients is the most important reason to perform re-evaluation.

Response assessment may also provide prognostic information, as a higher response to neoadjuvant treatment correlates to the chance of achieving an R0-resection and to better oncological outcomes.[34] There is no optimal method for response evaluation and reports are highly variable between readers. Only 1 cohort study to date investigates the use of MRI tumour regression grade (mrTRG) in LRRC, compared to pathological tumour regression grade (pTRG).[35] A high PPV of 95 % was seen for a good response (pTRG 1–2), provided evaluation was done by an expert radiologist. Underestimation of response was low, but overestimation was observed in 17 % when using the mrTRG versus the pTRG. Moderate variation was noted between radiologists, highlighting the need for expertise. The use of a PET/CT for response evaluation is described in one cohort, reporting a PPV of 63 % for a major response (pTRG 1–2), 43 % for a partial response (pTRG 3) and 36 % for a poor response (pTRG 4–5).[36] In 45 % of patients, PET/CT correctly assessed response, but underestimation was seen in 32 % and overestimation in 23 %. Data reporting the PPV for pCR assessment are lacking, while this might have therapeutic implications.

At present, neither the mrTRG or response evaluation using PET/CT can be formally recommended, nor are data available regarding the value of PET/CT in addition to MRI. It is however recommended to provide a response estimate based on T2-weighted MRI and DWI. It is also advised to describe the extent of residual tumour and fibrosis, as it cannot be guaranteed that there are no remaining areas of residual tumour within fibrosis. The extent of residual fibrosis is therefore essential for proper surgical planning. Given the lack of prospective data determining the ideal interval for response assessment, it is recommended to follow the same timing of evaluation as for primary rectal cancer (6–8 weeks after finishing chemoradiotherapy).[37].

Systemic therapy

There is no prospective data on the value of induction or consolidation chemotherapy in LRRC. Three retrospective cohorts describe the use of induction chemotherapy (ICT) in LRRC, showing that ICT may increase the likelihood of an R0 resection and pCR, which are both prognostic factors.[34,38,39] The most recent study shows favourable results in 345 operated patients.[40] A pCR rate of 30 % was reported after ICT and full-course chemoradiotherapy (CRT), 17 % after ICT and reirradiation, 17 % after full-course CRT alone and 9 % after reirradiation alone. An improved OS (HR 0.41, $p < 0.001$), DFS (3-year 56 % vs 26 % ($p < 0.001$) and LRFS (3-year 82 % vs 44 %, $p < 0.001$) was seen in patients with a pCR compared to patients without a pCR.

In turn, a comparative study between two expert centres with differing treatment strategies showed no difference in oncological outcomes.[41] Of the 184 patients, 84 were treated with ICT. All but two patients (1 %) received neoadjuvant chemoradiotherapy (nCRT), but reirradiation was more prevalent in patients receiving ICT (75 % ICT+, 45 % ICT-, $p < 0.001$), and resections were less extensive (24 % pelvic exenterations ICT- vs 18 % ICT+, $p = 0.007$). The proportion of R0 resections was similar (ICT + 71 %, ICT- 79 %, $p = 0.302$), as was pCR rate (16 % ICT + vs 11 % ICT-, $p = 0.388$). No difference was seen in OS, LRFS or MFS.

Based on the current data, it cannot be determined whether the improved outcomes are due to ICT, or due to the selection of patients with a favourable tumour biology. Also, the adverse effects of ICT, such as toxicity, delay of CRT and surgery, and possible progression under chemotherapy are underreported. Prospective data are needed to answer questions regarding the indication, timing, and optimal type of chemotherapy, and possible (additional) use of targeted therapy. For now, there is no formal indication for neoadjuvant systemic treatment. Results from the PelvEx II trial are awaited.[10].

Immunotherapy

There are rapid developments in the field of immunotherapy in colorectal cancer, especially in patients with mismatch repair deficient (dMMR) tumours. A prospective phase-2 study of 16 patients (12 in follow-up) with stage 2–3, dMMR primary rectal cancer showed a clinical complete response rate of 100 % after 9 cycles of dostarlimab (500 mg/3 weeks, intravenously), omitting CRT and TME surgery in all 12

patients. No evidence of disease progression was reported in any patient in follow-up (median 12 months (range 6–25)).[42] It is likely that immunotherapy could be beneficial for (especially) dMMR LRRC patients. No formal recommendations can be made yet, as direct evidence for LRRC is lacking.

Adjuvant chemotherapy

Adjuvant chemotherapy does not seem to improve oncological outcomes after intentional curative resection of LRRC, despite the high risk of distant metastases.[2,43] Therefore, there is no indication for adjuvant chemotherapy.

Chemoradiotherapy

Two groups of patients are distinguished in regards to CRT for LRRC, namely RT-naïve patients and patients undergoing reirradiation, differing in treatment options and prognosis. The ratio of RT-naïve patients versus reirradiation patients in recent cohorts is about 30:70.[44] Neoadjuvant chemoradiotherapy (nCRT) is used in LRRC to induce preoperative downstaging and increase the likelihood of an R0 resection.[1–4,28,45] The chance of achieving a pCR should be an additional argument for the use of nCRT (9 % pCR after chemo re-irradiation, 17 % pCR after full-course CRT).[40] In both full-course CRT and reirradiation, radiotherapy is combined with concomitant capecitabine (825 mg/m^2, bidaily), in the Netherlands. In case of toxicity concerns, Teysuno (25 mg/m^2 bidaily) is recommended. Radiotherapy without a radiotherapy sensitizer can be used in case of remaining toxicity concerns in regard to concomitant chemotherapy. Fluorouracil-based chemotherapy can also be considered as an alternative to capecitabine.

In RT-naïve patients, several retrospective cohorts have shown a beneficial effect of full-course nCRT on the number of R0 resections and oncological outcomes. In a study by Bosman et al., 63 % R0 resections was achieved after full-course CRT. An improved LRFS was seen compared to up-front surgery (3-years 70 % vs 35 % $p = 0.003$), with a trend towards improved OS (3-years 50 % vs 32 % $p = 0.062$).[46] Dijkstra et al. showed similar outcomes, with 68 % R0 resections after full-course CRT, 5-year OS of 32 % and a 5-year DFS of 26 %.[47] In line with international guidelines, full-course nCRT is recommended in patients with LRRC, both in patients with resectabel disease and in patients requiring preoperative downstaging.[12,14] For RT-naïve patients, the same dose is used as for primary advanced rectal cancer, namely 25x2Gy or 28x1.8 Gy.[12–14,48].

In patients who previously received pelvic radiotherapy, the use of chemo-reirradiation is advised.

Two studies showed an increased R0 resection rate after chemo-reirradiation compared to up-front surgery (56 % vs 42 % ($p < 0.001$) and 43 % vs 26 % ($p = 0.001$) respectively), without a difference in oncological outcomes.[43,46,49] Sun et al. further showed that in patients with an irresectable LRRC, reirradiation (30–36 Gy) can lead to enough downstaging to make patients eligible for surgery (25 %). In sixteen of the eighteen patients who underwent surgery following reirradiation, an R0 resection was achieved.[50] Although an association between chemo-reirradiation and improved oncological outcomes cannot be demonstrated yet, there is evidence for an increased likelihood of an R0 resection.

Internationally, the use of chemo-reirradiation remains controversial due to toxicity concerns. Its use is considered in the ESMO and Beyond-TME guidelines.[12,14] The most recent data suggest that reirradiation is safe. Toxicity varies between cohorts, but acute toxicity (≥Gr3) in up to 31 % of patients has been reported.[1,4,49,51] This is seen particularly in older cohorts or in patients with irresectable tumours irradiated with higher doses (40 Gy) than usual in the Netherlands.[52,53] The same is seen with regard to late toxicity, with reported ≥ Gr3 toxicity of 0–48 %.[54–56] A large retrospective cohort study (n = 377) reported no difference in postoperative complications between patients predominantly treated with total neoadjuvant therapy versus up-front surgery (32 % versus 30 %, $p = 0.742$).[44].

Chemo-reirradiation toxicity is also decreasing over time, due to improved techniques and smaller margins, as mentioned below, allowing for better sparing of the organs at risk (OAR). [1] This is described in a review by Guren et al, in which treatment interruptions or stops decrease from > 30 % in the first (chemo)-reirradiation studies, to 4 % in the most recent studies. In the recent cohort of Dijkstra et al, no grade 4–5 toxicity after chemo reirradiation is seen, and grade 3 toxicity is reported in only 6 %.[47] Chemo-reirradiation was completed by 97 %.

In reirradiation, there is variation in dose due to concerns about the cumulative dose and OAR. Some studies use hyperfractionation (1.2–1.5 Gy, 2x/d) to facilitate an increased tumour dose without increasing late toxicity, as in the benchmark trial by Valentini et al, prescribing reirradiation up to 40.8 Gy (+/- resection).[57] Currently, there is no clear evidence of an efficacy or toxicity difference between hyperfractionation and conventional fractionation up to 30 Gy for LRRC.[51] As there is extensive Dutch experience with 30 Gy chemo-reirradiation (+/- intraoperative radiotherapy), the use of conventional fractionation up to 30 Gy is recommended (15x2Gy), in line with the ESTRO-ACROP recommendations.[48].

Target volumes

There is limited evidence regarding target volumes for LRRC. Information on re-recurrence patterns and at-risk areas is lacking, and due to the heterogeneous presentation in altered anatomy, determining target volumes can be challenging.[2] Only ESTRO-ACROP previously recommended target volumes.[48] Delineation of RT-naive patients is often performed in accordance with LARC. In reirradiation, target volumes of GTV + 1–4 cm margin are often used.[49,58–61] In some series, a larger CTV is used in reirradiation, consisting of GTV with margin, the mesorectal space and the presacral and internal iliac nodes.[47] No comparative cohorts are known.

To overcome these variations, a delineation guideline was developed for LRRC, based on multidisciplinary meetings with expert centres involved in the PelvEx II trial.[10,62] Multidisciplinary involvement in target volume definition is strongly recommended, as interpretation of radiology can prove tricky, and it is of the utmost importance that all surgical resection margins are covered by target volumes. Quality assurance within the PelvEx II trial has already shown that target volumes are changed in up to 50 % of patients after peer-review, highlighting the complexity of delineation (Fig. 2).[63] Since this guideline was developed with the cooperation of several expert centres, it is recommended to delineate as described in the publication, with surgical and radiological input.[62].

There are no studies that predefine OAR constraints for (re-)irradiation in LRRC.[58] Given the well-described tolerance to (re-)irradiation, it is recommended to prioritize target volume coverage. The Dutch consensus regarding priority of planning is CTV > PTV > Small intestine > Bladder > Other OAR.[62] Treatment with IMRT or VMAT is standard of care in the Netherlands.

Adjuvant chemoradiotherapy

Only one review by Fadel et al (2022) reports outcomes after adjuvant CRT (45 % R0).[64] Five-year local control was only 13 %, compared to 49.5 % after nCRT and 5-year OS was only 21 % compared to 35 % after nCRT or 30 % after surgery alone. Adjuvant CRT does not seem to compensate for irradical surgery and therefore has no place in LRRC treatment.

Surgery

Surgical resection of LRRC is the cornerstone of curative treatment. Regardless of prior treatment, an R0 resection is the most important

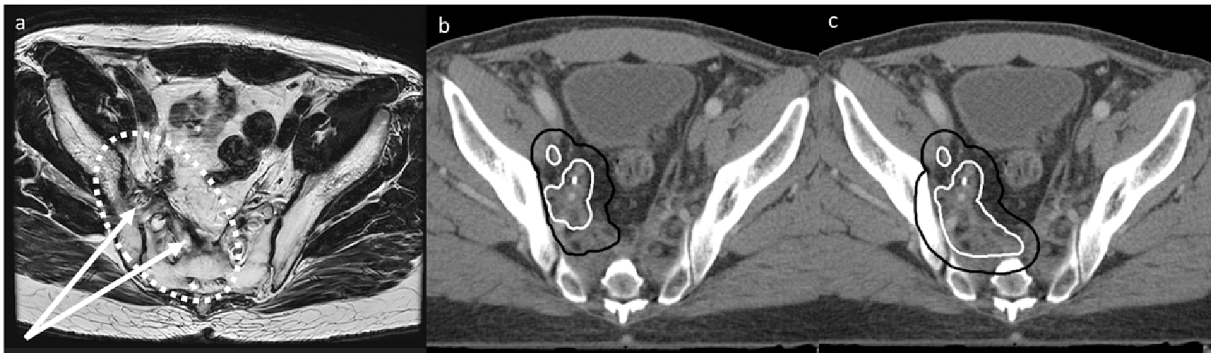

Fig. 2. Example of altered radiotherapy target volumes after peer-review in a multifocal recurrence. It was advised to extend the gross tumour volume (white) from before (b) to after (c) to encompass complete fibrosis as seen on diagnostic MRI (a). Additionally, it was advised not to edit clinical target volume (CTV, black) towards the lateral pelvic side wall, to guarantee that surgical resection margins would be encompassed by the CTV.

prognostic factor in LRRC.[3,4,64–66] An R0 resection is defined as being free from microscopic or macroscopic involvement. An R1 resection is a resection with microscopic positive resection margins, and an R2 resection means that macroscopic tumour has been left behind during surgery.[65] All physically fit patients with a LRRC without distant metastases, in whom an R0 resection is considered feasible, are eligible for curative resection. If an R2 resection is expected, surgery is not recommended as it does not improve oncological outcomes (5-years OS R2 resection 10 % vs non-operative management 4 %, p = 0.282) and appears to deteriorate quality of life (QoL).[28,67].

Surgery often requires extended multicompartmental extra anatomical resections, resulting in a high probability of morbidity and peri- and postoperative complications (37 % ≥grade 3 complications). Reducing the probability of complications can be facilitated by improved techniques, care, and surgical expertise, which is a strong argument for centralization of surgical care.[44,65] The impact of surgery on QoL can be significant and prolonged, often due to pain, gastrointestinal complaints, urinary and sexual dysfunction, and functional complaints of the lower extremities.[67–69] However, omitting surgery can also be accompanied by a reduced QoL, due to pain, fistulation, and tumour mass effect.[68] Preoperative counselling should therefore include QoL aspects. Refraining from extensive surgery in patients with a limited prognosis seems appropriate and should be discussed in a shared decision-making process.

Defining absolute surgical contraindications is delicate based on current literature, given the developments in peri- and postoperative safety, and the heterogeneous presentation. QoL should also be considered when determining the size of surgical resection, even if surgery is technically feasible. Previously mentioned contraindications for curative resection are summarized in Table 2.[10,12,13] Determining resectability requires thorough expertise and should be done in properly equipped expert centres. It is recommended to consider areas of fibrosis adjacent to tumour as potentially malignant and therefore include these in the surgical plan.[13].

Table 2
Summary of contra-indications for curative resection of LRRC, as mentioned in the Beyond-TME and PelvEx collaborative guidelines.

Surgical contra-indication	
Bilateral sciatic nerve involvement	Absolute
Circumferential bone involvement (i.e. involvement of bony structures in all directions)	Absolute
Extension of tumour through the sciatic notch	Relative
Encasement of external iliac vessels	Relative
High sacral involvement	Relative
Irresectabel distant metastases	Relative
Predicted R2 resection	Relative

Watch-and-wait

Although a watch-and-wait strategy has been adopted into (inter) national guidelines on primary rectal cancer, no cohorts have been published describing this in LRRC. Also, diagnosis of a complete response after neoadjuvant treatment of LRRC is challenging. Therefore, no recommendations can currently be made on the safety of a watch-and-wait approach in LRRC.

Intra-operative radiotherapy

Evidence for the use of IORT in LRRC is limited and often stems from cohorts of locally advanced and recurrent rectal cancer patients (LARRC). The goal of IORT is to improve local control by boosting the total radiotherapy dose locally, specifically at the area at-risk of tumour residue. A *meta*-analysis from 2021 shows that there may be a reduced locoregional recurrence rate after additional IORT in LARRC (21 % IORT- versus 15 % IORT+, OR 0.55, p = 0.11).[70] Other improved oncological outcomes were not reported. Only one study in this *meta*-analysis also included LRRC patients (n = 104/168), reporting a similar number of recurrences (49 % IORT + vs 44 % IORT-) and a similar OS (both 35 %), despite a lower R0 rate (32 % IORT + vs 48 % IORT-).[71] In a larger but older *meta*-analysis in LARRC, a significant effect of IORT was seen on 5-year local control, DFS and OS (OR 0.22, HR 0.51, HR 0.33, respectively), however the use of nCRT varied widely and should be taken into account when interpreting these results.[72] Both *meta*-analyses report the safety of IORT, observing no difference in neuropathy, urethral stenosis, presacral abscesses, anastomotic leaks, or surgical re-interventions (36 % IORT +, 29 % IORT-).[70,72] An increase in wound complications was reported in Mirnezami et al. (OR 1.86, p = 0.049).

The optimal type of IORT is not known. One direct comparison between two IORT modalities (intraoperative electron radiotherapy (IOERT) and high-dose-rate brachytherapy (HDR-IORT)) has been performed, demonstrating a similar OS (p = 0.747), but an improved LRFS after HDR-IORT (HR 0.6, p = 0.021), potentially due to a higher surface dose of HDR-IORT.[73] More major complications were however reported after HDR-IORT (46 % versus 26 %, p = 0.017). These data do suggest an effect and a dose–response relationship of IORT in general.

The use of IORT is often considered in LRRC, especially in patients at-risk for an R1 resection, despite the fact that there is no clear OS benefit, because of the high morbidity that can arise from locoregional failure. Formal indications for IORT stated by ESTRO-ACROP are (a) (possibly) involved resection margins, aiming to avoid re-recurrences, (2) proximity of the tumour to surrounding organs or (3) (expected) narrow resection margins (<1mm). It is therefore advised to consult a centre with IORT facilities prior to surgery.[12,13,48].

No comparative studies are available to determine an optimal

interval between nCRT and IORT for LRRC. A cohort from Holman et al. showed that the probability of an R0 resection correlated with the interval between nCRT and surgery.[43] The likelihood of an R0 resection increased up to 12 weeks after nCRT, probably due to tumour regression. However, the risk of a local re-recurrence (especially in R1 patients) seemed to increase beyond 7 weeks, implying that a longer interval may be unfavourable. Biologically this makes sense, as IORT should be used as an additional boost and not as a stand-alone therapy. It is recommended to follow the same timeframe to surgery as in primary rectal cancer (6–12 weeks after nCRT), to allow for sufficient tumour regression, whilst also maintaining IORT efficacy.[43,48].

Palliative strategies

CRT can be considered in the palliative setting, in order to achieve local control and to reduce symptom burden.[12,14] Although several palliative studies are outdated and radiotherapy techniques have since improved, an overall palliative effect between 57–100 % is described, with a median duration of palliation of approximately 9 months. An efficacy of (chemo)-reirradiation of 83–94 % is described for symptom relief in LRRC, at median doses of > 30 Gy. [1,51,54] Reirradiation is particularly effective for haemostasis, with a reported success rate of up to 100 %. Local control rates after (chemo) reirradiation vary widely (25–70 %), due to heterogeneity of patients, treatment, and reported outcomes, although a *meta*-analysis by Lee et al. reports three-year local control rates of 45 %.[51].

Definitive RT for LRRC may become an alternative for patients that are ineligible for surgery due to frailty or preference, although there is no Dutch experience with this indication. Watanabe et al. achieved a clinical complete response rate of 17 % after CRT (50–60 Gy) for RT-naïve LRRC, with a 5-year progression-free survival of 35 % and a 5-year OS of 54 % (without surgery).[74] Tanaka et al. describes a 1-year local control rate of 52 %, and 3-year local control rate of 20 % after Intensity Modulated Radiotherapy (biologically effective dose (BED) 48–95 Gy, converted EQD2 ($\alpha/\beta = 10$ Gy) 40–79 Gy) in RT-naïve patients. Tanaka also reports higher local control in patients treated with a higher BED than a lower BED, with an almost significantly different OS ($p = 0.07$). [75] A handful of cohorts also describe definitive reirradiation. Johnstone et al. reported a median PFS of 12 months and a median OS of 39 months after 30 Gy reirradiation (5x6Gy) in small recurrences, but toxicity data are lacking.[76] Chung et al. describes outcomes for reirradiation up to a median dose of 50 Gy (30–60 Gy).[60] 2-year in-field PFS was 49 % and 2-year OS 55 % without surgery, but with a relatively high late toxicity of 42 %. In a sub-selection of patients with small tumours (<3.3 cm) treated with high dose reirradiation (>50 Gy), good tolerance and efficacy was reported.

No data are currently available on achieving long-term local control with chemotherapy in the palliative setting. A retrospective cohort study showed that the locoregional response rate to chemotherapy after reirradiation was significantly less than the response rate of distant metastases not in the irradiated area (10 % versus 41 %, respectively, $p = 0.034$).[77] This suggests a decreased efficacy of chemotherapy after extensive radiotherapy in the pelvis, possibly due to different vascularisation or rigid fibrosis. The use of chemotherapy for locoregional control may not be beneficial after prior radiotherapy.

Distant metastases

When distant metastases are present at diagnosis of LRRC, curative treatment can be initiated only in highly selected cases, as synchronous metastases are associated with a poor prognosis. There is no definition of number or location of metastases eligible for curative treatment, implying that MDT assessment is crucial for patient selection.[28] Van Rees et al. included 535 patients curatively treated for LRRC in two tertiary referral centres.[78] 74 % (n = 398) presented without (a history of) metastases. Synchronous metastases were present at diagnosis of the primary tumour in 4 %, 8 % had a history of metachronous metastases and 13 % presented with synchronous metastases at LRRC diagnosis. A significant difference was seen in 3-year OS; 57 % in patients without (a history of) metastases, 55 % in patients with primary synchronous metastases, 61 % in patients with metachronous metastases and 34 % in patients with synchronous metastases at recurrence diagnosis ($p = 0.021$). The worst outcomes of patients with metastases were observed in patients with synchronous metastases at recurrence, whereas the best outcomes were seen in patients with synchronous metastases at primary diagnosis. In a small subgroup, it was seen that patients with metachronous metastases presenting relatively early after diagnosis of the primary tumour (<1 year) had a better 3-year DFS than patients who had metachronous metastases within a year prior to recurrence diagnosis (48 % versus 22 %, $p = 0.039$).

Indeterminate lung nodules (ILN) do not appear to be of important prognostic value, based on a cohort of 243 LRRC patients, of which 28 % had ILN.[79] The percentage of patients completing curative treatment was comparable amongst patients with and without ILN (ILN + 59 % vs ILN- 65 %, $p = 0.36$), as was OS and PFS. The cumulative incidence of lung metastases was equal (ILN + 31 % vs ILN- 28 % ($p = 0.19$)).

In summary, retrospective cohorts have shown an association between synchronous metastases and a deteriorated OS and oncological outcomes, in already stringently selected patient group. In the described cohort by Van Rees, only 13 % of patients presented with synchronous metastases at diagnosis, whilst population studies have shown that 45 % of LRRC patients have distant metastases at diagnosis.[9] In (highly selected) patients with synchronous metastases where curative treatment is considered, such as low-burden oligometastatic disease, it is recommended to start systemic therapy, to observe tumour biology and to be able to refrain from surgery in patients with progressive disease.

Conclusion

In this article, we describe the Dutch national guideline for LRRC treatment, from diagnosis to multidisciplinary treatment. This guideline highlights the complex nature of the disease and decision making for clinicians treating LRRC.

Declaration of interest

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CRediT authorship contribution statement

Floor Piqeur: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Davy M.J. Creemers:** Writing – review & editing. **Evi Banken:** Writing – review & editing. **Liën Coolen:** Visualization, Writing – review & editing. **Pieter J. Tanis:** Writing – review & editing, Supervision. **Monique Maas:** Writing – review & editing. **Mark Roef:** Writing – review & editing. **Corrie A.M. Marijnen:** Conceptualization, Writing – review & editing, Supervision. **Irene E.G. van Hellemond:** Writing – review & editing. **Joost Nederend:** Writing – review & editing, Visualization. **Harm J.T. Rutten:** Conceptualization, Writing – review & editing, Supervision. **Heike M.U. Peulen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration. **Jacobus W.A. Burger:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2024.102736.

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