Locally recurrent rectal cancer: improving radiation treatment

Piqeur, F.

Chapter 5

Analysis of re-recurrent rectal cancer after curative treatment of locally recurrent rectal cancer

Piqeur F, Coolen L, Nordkamp S, Creemers DMJ, Tijssen RHN, Neggers-Habraken AGJ, Rutten HJT, Nederend J, Marijnen CAM, Burger JWA, Peulen HMU.

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ABSTRACT

Background and purpose: Substantiating data guiding clinical decision making in locally recurrent rectal cancer (LRRC) is lacking, specifically in target volume (TV) definition for chemoradiotherapy (CRT). A case-by-case review of local re-recurrences (re-LRRC) after multimodal treatment for LRRC was performed, to determine location of re-LRRC and assess whether treatment could have been improved.

Materials and methods: All patients treated with curative intent for LRRC at the Catharina Hospital Eindhoven from October 2016 onwards, in whom complete imaging of (re-)LRRC and radiotherapy was available, were retrieved. Patients were discussed in plenary meetings with expert colorectal surgeons, radiation oncologists and radiologists. Each case was classified based on re-LRRC location, whether it was in accordance with the (current) radiotherapy protocol, and whether multimodal management would have been different in retrospect.

Results: Thirty-three cases were discussed. LRRC treatment was deemed suboptimal in 17/33 patients, due to different target volumes (13/17) and/or different surgery (9/17). 15/33 (46%) of re-LRRC developed in-field of the prior radiotherapy TV, possibly showing RT-resistant disease. Other re-LRRCs developed out-field (n=5, 15%), marginally (n=6, 18%), or in a combined fashion (n=7, 21%). In retrospect, 48% of cases were irradiated in line with current TV recommendations. TVs of 13/33 cases would have been altered if irradiated today.

Conclusion: This study highlights room for improvement within current standard-of-care treatment for LRRC. Different surgical management or TVs may have improved outcome in up to half of discussed cases. Further delineation guideline development, incorporating the results from this study, may improve oncological outcome, specifically local control, for LRRC patients.

INTRODUCTION

Locally recurrent rectal cancer (LRRC) is a highly complex disease requiring multidisciplinary management. Outcomes for patients with LRRC who are treated with a curative intent remain poor, with a five year overall survival rate of 30%.[1–3] Moreover, three year local control rates vary from 19%-64%, despite maximal local treatment.[1,2,4–6] Several factors are known to influence oncological outcome, such as type of neoadjuvant treatment, achieving a pathological complete response and whether or not a radical surgical resection (R0) is achieved.[1,7] The treatment for LRRC consists of neoadjuvant chemoradiotherapy (nCRT) followed by surgery.[8–10] The randomized controlled trial PelvEx II is currently investigating the potential benefit of induction chemotherapy in addition to nCRT, hypothesizing that more R0 resections can be achieved.[11]

Up to 70% of patients presenting with LRRC have previously undergone radiotherapy for primary rectal cancer, meaning nCRT is usually limited to a dose of 15x2Gy, combined with 5FU-based chemotherapy.[6,12,13] In the 30% RT naive patients, full course chemoradiotherapy is advised.[8–10,14] Target volume delineation of LRRC can be challenging, due to factors such as difficult interpretation of radiology, extensive postoperative changes within the small pelvis and heterogeneity of disease. Moreover, for individual clinicians, target volume delineation can be hampered by a low exposure to LRRC, given only 4-11% of patients will develop LRRC after primary rectal cancer.[3] As no delineation guideline existed to guide clinicians in LRRC delineation, a consensus-based delineation guideline was developed.[11,15]

To optimize the currently instated guideline, robust prospective data regarding target volumes is essential. In the meantime, a better understanding of locoregional treatment failure after (re)irradiation may aid in improving LRRC treatment, by improving local control rates or reducing toxicity. Thorough analyses of local recurrences have contributed to changes in delineation guidelines for primary rectal cancer, by determining at-risk areas for recurrences, allowing for a reduction of target volumes, therefore potentially reducing toxicity.[16] It is therefore plausible that a thorough review of local re-recurrences (re-LRRC) after LRRC treatment on a patient per patient basis may enhance our understanding of locoregional treatment failure in LRRC.

The purpose of this hypothesis-generating study is to evaluate the location of re-LRRC in comparison to previous LRRC target volumes. By doing so, we may increase our

understanding of locoregional re-recurrences, which may be caused by suboptimal treatment, or rather poor tumour biology.

METHODS AND MATERIALS

All patients treated for LRRC with curative intent from October 2016 until March 2022 at the Catharina Hospital Eindhoven (CHE) were screened from an existing retrospective database. Patients with re-LRRC were included if complete imaging of (re)-LRRC and LRRC radiotherapy data were available in a DICOM format. Re-LRRC is defined as a second recurrence within the small pelvis after surgical resection of LRRC. Patients with distant metastases at any stage were not excluded as long as LRRC was treated with (intended) radical surgery. All available data and imaging were anonymized. The study was approved by the Catharina Hospital Eindhoven (nWMO-2021.099).

Induction chemotherapy for LRRC was standard in the CHE until November 2020. Therefore, most patients received 3-4 cycles of CAPOX (capecitabine and oxaliplatin), or 4-6 cycles of FOLFOX (5-FU, leucovorin, oxaliplatin) or FOLFIRI (5-FU, folinic acid, irinotecan), followed by nCRT. This consisted of either full-course CRT (25x2Gy) for RT naive patients or chemo reirradiation (15x2Gy) for patients previously irradiated for primary rectal cancer, both with concomitant capecitabine. At the time of treatment, radiotherapy target volumes were not standardized. In general, target volumes for RT naive patients often mirrored those of LARC.[17] Target volumes for reirradiation patients often consisted of gross tumour volume (GTV), with a 1cm margin to the clinical target volume (CTV) and an additional 1 cm margin to the planning target volume (PTV).[18–21] Surgery was planned within 10-14 weeks after CRT, generally combined with intraoperative radiotherapy, as described in previous publications.[22,23]

Data regarding patient, tumour and treatment characteristics of primary, recurrent, and re-recurrent rectal cancer were collected from patient records. Recurrence locations were classified as primarily central, anterior, posterior, or lateral, based on the radiological checklist used in the PelvEx II trial, as shown in the supplementary material (S1). A rigid bone match was performed of the LRRC planning CT, containing original target volumes, to all other available imaging of the local recurrence and re-recurrence (MRI and/or F18-FDG-PET/CT). An abdominal radiologist delineated the re-recurrences on available imaging. Matching and delineation was performed using RayStation ® (Version 12A-SP1-R, RaySearch Laboratories AB, Sweden, Released 2022).

Plenary meetings were held with two colorectal surgeons (PB, HR), a radiation oncologist (HP), and two colorectal radiologists (JN, LC), all with extensive expertise in LRRC. A second round was held with the prior and an additional radiation oncologist (CM), blinded for previous conclusions. In both rounds, patient information and matched imaging were presented to initiate discussion.

The location of each re-recurrence was compared to prior radiotherapy treatment volumes. Re-LRRC was deemed; (a) in-field if it was (mostly) covered by previous target volumes and it was agreed that the origin of the re-LRRC was most likely within the CTV of previous radiotherapy; (b) marginal if the re-LRRC was (mostly) within the 50% isodose line, but the origin of the re-LRRC was most likely outside of the CTV; (c) out-field if it was largely or not at all covered by previous radiotherapy. If individual lesions of a multifocal re-recurrence could be classified into two or more categories, this was classified as a combined re-recurrence (for example in case of a combination of one out-field lesion, one marginal lesion).

Each re-recurrence was additionally scored on the following items: (1) Management was suboptimal in retrospect (yes/no); (2) Radiotherapy target volumes should have been different in retrospect (yes/no); (3) Surgical management should have been different in retrospect (yes/no); (4) Administered radiotherapy was in line with the current PelvEx-II guideline (yes/no)[15]; Discussion was held until consensus was reached in all domains.

Categorical data were presented as absolute numbers with percentages. Continuous data are reported as medians with an interquartile range (IQR). No statistical comparisons were performed given the small sample size.

Table 1. Baseline characteristics of the first local recurrence (LRRC) and local re-recurrence (re-LRRC).

Baseline characteristics (n=33)		**LRRC**	**%**	**Re-LRRC**	%
Gender	Male	23	70	23	70
	Female	10	30	10	30
Age at diagnosis	Mean (SD)	65 (8)	-	67 (9)	-
Interval*	Median (IQR)	26 (14-40)	-	9 (6-14)	-
Multifocal	Yes	9	27	19	58
	2 lesions	*7*	*78*	*10*	*53*
	>2 lesions	*2*	*22*	*9*	*47*
Size of the tumour	Median (IQR) (mm)	28 (22-35)	-	35 (25-68)	-
Primary involved compartment	Central	12	36	4	12
	Anterior	1	3	2	6
	Posterior	9	27	14	42
	Lateral	10	30	7	21
	*Multicompartmental***	1	3	6	18
Metastases at diagnosis	Yes	7	21	22	67
Treatment intent of LRRC	Curative	33	100	3	9
	Palliative	-	-	30	91

**Interval from surgery for LRRC to (re-)recurrence in months*

***A multicompartmental classification is only given if the recurrence is too diffuse to define one primary compartment. Where possible, multifocal recurrences were also classified to a primary compartment.*

RESULTS

A total of 33 patients with re-LRRC were discussed during four plenary sessions and two second readings. Twenty-four patients presented with a unifocal local recurrence (73%). Twenty-six patients did not have metastases at diagnosis (79%). Twenty-four patients (73%) received induction chemotherapy. Neoadjuvant chemoradiotherapy consisted of chemo reirradiation in 23 patients (70%) and full course chemoradiotherapy in ten patients (30%). In 25 patients, either a pathologic complete response (pCR) or an R0-resection was achieved (76%). Patient and treatment characteristics are summarized in Tables 1 and 2, respectively.

Table 2. Treatment characteristics of LRRC

Treatment characteristics LRRC (n=33)		n=	%
Induction chemotherapy	Yes	24	73
Neoadjuvant chemoradiotherapy	15x2	23	70
	25x2	10	30
Consolidation chemotherapy	Yes	4	12
Type of surgical resection*	Resection n.o.s.	10	30
	APR	14	42
	LAR	2	6
	Total exenteration	7	21
Additional intraoperative treatment	HIPEC	1	3
	IOERT	30	91
Post-operative complications	No	10	30
	Clavien-Dindo I-IIIa	17	52
	Clavien-Dindo IIIb-V	7	21
Pathology	pCR	4	12
	R0, but not pCR	21	64
	R1	8	24

**APR: an abdominoperineal resection; LAR: low anterior resection; TE: total exenteration (TE), defined as a rectal resection with additional resection of the bladder and either prostate and vesicles or ovaries, vagina and uterus; Resection n.o.s.: a resection not otherwise specified, without formal bowel resection.*

The majority of re-LRRC cases presented in-field of the LRRC target volumes (n=15, 46%). Five (15%) re-LRRCs were deemed out-field, and six marginal (18%) in relation to the LRRC target volumes. In the remaining seven cases (21%), the multifocal nature of the re-recurrence resulted in a combination of classifications. In two cases, there were in- and out-field lesions; three cases had marginal and out-field lesions; one case had in-field and marginal lesions; and one case of re-LRRC presented so diffusely within the small pelvis that several lesions were in-field, marginal, and out-field. Examples of in-field, marginal, out-field and combined re-recurrences can be found in figure 1.

Table 3. Outcome of multidisciplinary discussions, presented separately for in-field and not in-field re-recurrences (i.e., marginal, out-field, or combined). *Different management can mean either different radiotherapy and/or different surgery.

		In-field (n=15)		Not in-field (n=18)		Overall (n=33)	
Radiotherapy LRRC	15x2	10	67%	13	72%	23	70%
	25x2	5	33%	5	28%	10	30%
In-line PelvEx	Yes	10	67%	6	33%	16	48%
Different management*	Yes	6	40%	11	61%	17	52%
Different RT	Yes	4	27%	9	50%	13	39%
Different surgery	Yes	3	20%	6	33%	9	27%

In patients who underwent reirradiation for LRRC, 44% presented with an in-field re-LRRC (n=10). In patients who received full course CRT, the percentage of in-field re-LRRCs was similar at 50% (n=5). The distribution of out-field, marginal and combined re-LRRCs was also similar amongst reirradiation (respectively n=3 (13%), n=5 (22%), n=5 (22%)) and full course CRT patients (respectively n=2 (20%), n=1 (10%), n=2 (20%)).

In 4 out of 7 patients with a combined re-recurrence, that is presenting with a multifocal re-recurrence that could not be classified into an in-field, out-field or marginal category, there was a history of an R1 resection of the initial recurrence (Table S2). R1 resections preceded two (13%), zero (0%), and two (33%) in-field, out-field, and marginal re-recurrences, respectively. Metastases at re-LRRC diagnosis were mainly seen in patients presenting with either in-field or combined re-LRRC (n=12 (80%) and n=6 (86%), respectively), but were less frequent in out-field or marginal re-LRRC (n=2 (40%) and n=2 (33%), respectively).

Overall, 17/33 patients would have been managed differently in retrospect (52%) (table 3), similarly distributed across all re-LRRC locations. In the majority, different target volumes would have been advised (n=13), as described below. A wider resection (i.e., a total pelvic exenteration) would have been advised in 9 cases in which surgery was deemed inadequate.

Sixteen cases (48%) were delineated in accordance with the currently instated delineation guideline, whereas 17 were not. In 10/17 cases, delineations would be altered to be in accordance with the current guideline. In the remaining 7/17 cases, non-accordance could be explained by patient-specific factors, and therefore would not have been altered in retrospect. Reasons include but are not exclusively; extensive small bowel within the

small pelvis limiting elective target volume area; recurrences above S1/S2 in which elective rectal irradiation was omitted; or cases in which editing towards OAR would have been accepted.

In an additional 3 cases, target volume alterations were suggested even though delineation was performed in accordance with the currently instated delineation guideline, totalling 13 cases in which alterations were suggested. In one case, it was agreed that elective delineation of all obturator nodes could have been performed in a patient undergoing reirradiation for a lateral nodal recurrence, even though currently no elective target volumes are advised in reirradiation. This was discussed given that the tumour re-recurred within the lateral compartment, at the margins of previous target volumes. In two cases, the guideline was deemed not extensive enough in retrospect, as fibrosis was not covered by the GTV but only just by the CTV (figure 2), and a pre-existing abscess was not completely delineated as GTV. In both cases, the GTV would have been expanded in retrospect, even though the current guideline would not have recommended it.

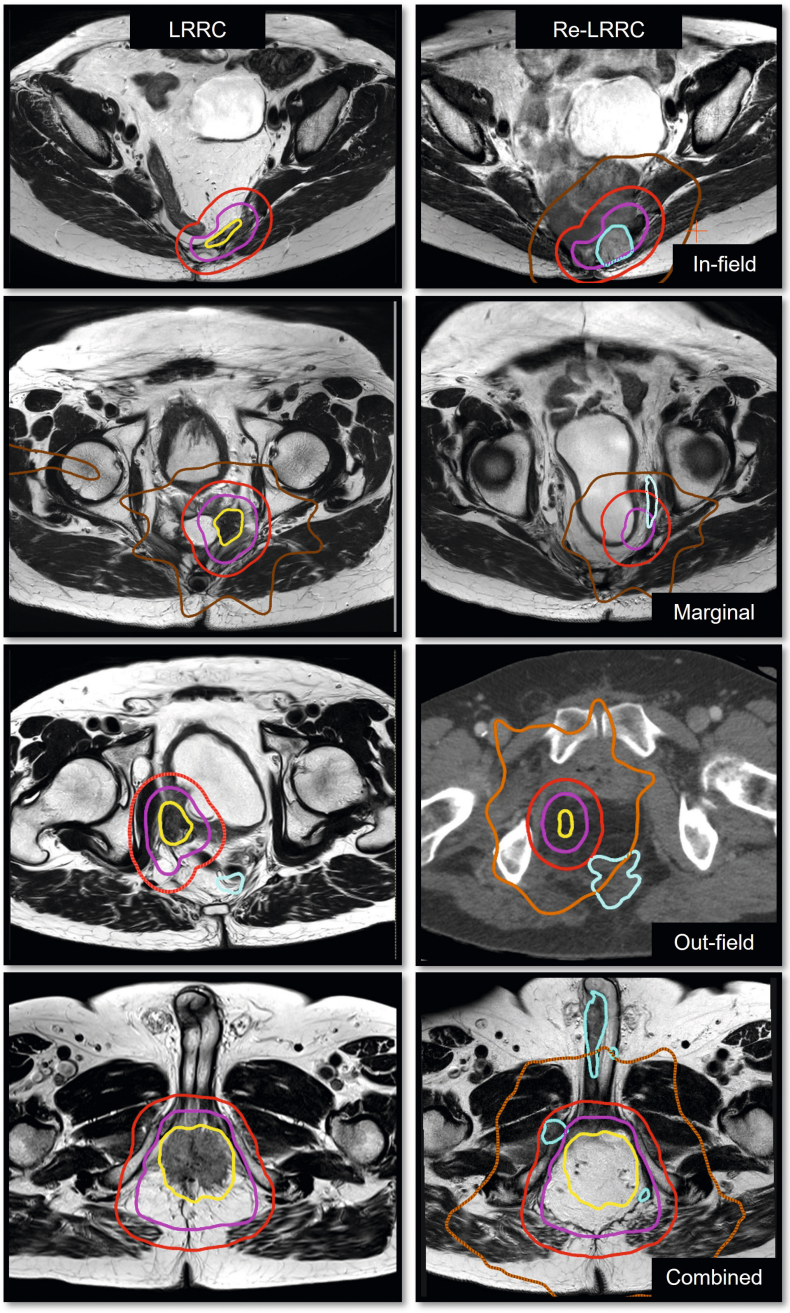

Figure 1. Examples of re-recurrences deemed in-field, marginal, out-field or combined compared to LRRC target volume. MRI or CT of the LRRC is shown on the left, and the re-LRRC on the right. GTV (yellow), CTV (pink), and PTV (red), as well as the 50% isodose line (brown) is shown for the recurrence. The re-LRRC is shown in blue. Target volumes may seem different from left to right as different slices were chosen for better visualisation.

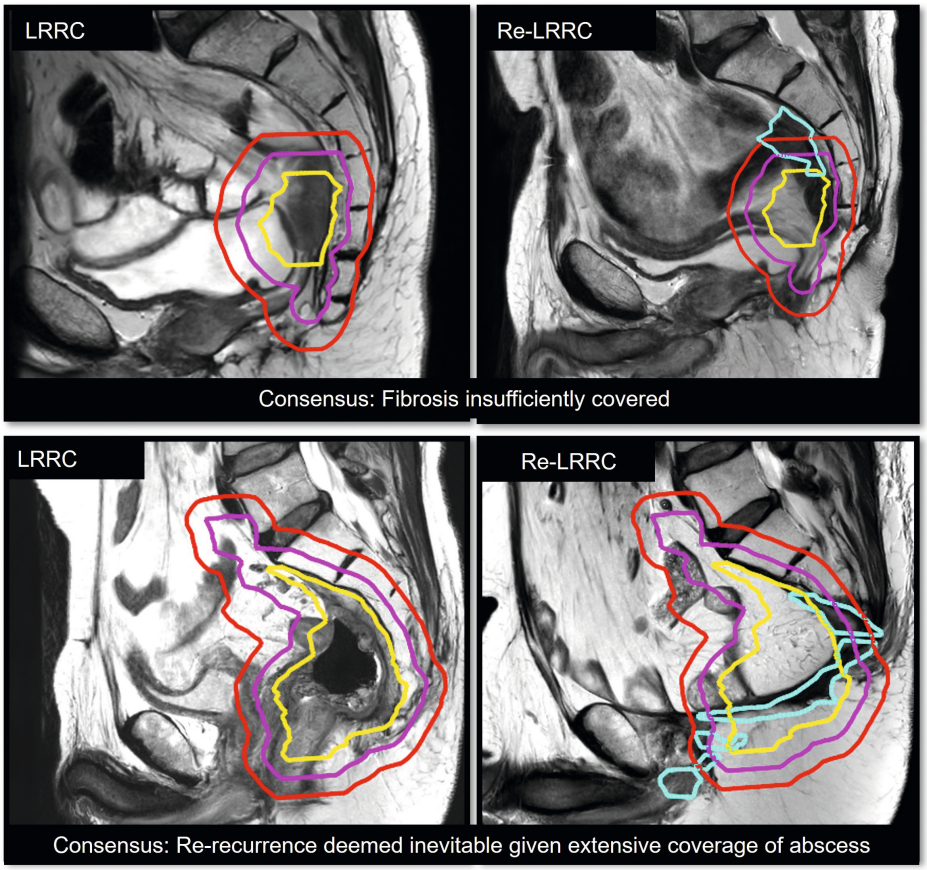

Figure 2. Two examples of discussed cases with different conclusions. For both cases, LRRC imaging is shown on the left, re-LRRC imaging on the right. LRRC target volumes are shown in yellow (GTV), pink (CTV) and red (PTV). The local re-recurrence is delineated in blue. In the top case, the re-recurrence was considered marginal and therefore treatment was deemed suboptimal, as target volumes would have been delineated different in retrospect, even though they were in line with current PelvEx II delineation guidelines. In the lower case, the developed re-recurrence was completely in-field and as such deemed inevitable.

The most common deviations from the current delineation guideline were (multiple deviations per case possible); (a) not encompassing all GTV's in one CTV (n=5) in multifocal recurrences; not keeping at least a one-centimetre margin from GTV to CTV (n=4); not encompassing all fibrosis (n=3); and editing the CTV towards organs at risk (OAR) (n=4).

Patients who were treated in line with the current guideline were most often patients undergoing reirradiation (n=13/16, 81%). The majority of these re-LRRCs reoccurred in-field

(n=10/16, 63%). Patients not treated in line with the current guideline more frequently underwent full course chemoradiotherapy (7/17, 41%).

DISCUSSION

To the best of our knowledge, the current manuscript is the first to perform an in-depth review of re-recurrences after curatively intended treatment for LRRC on a patient-per-patient basis. Importantly, in half of discussed patients (17/33), at least one point of possible treatment improvement was noted. Extensive deliberation among a multidisciplinary expert team showed how improvements in our current standard of care could be achieved.

Interestingly, 15/33 (46%) of the discussed re-LRRCs occurred in-field, with no difference in patients undergoing reirradiation or full course CRT (respectively 10/23 (44%) and 5/10 (50%)). This may imply a therapy-resistant aetiology of disease, in which radiotherapy could never prevent a re-recurrence. This idea may be strengthened by the fact that patients with in-field re-LRRCs more often presented with synchronous distant metastases (12/15 (80%)), contrary to patients presenting with marginal or out-field re-recurrences (2/6 (33%) and 2/5 (40%)). In the majority of these cases, locoregional failure may be considered a result of unfavourable tumour biology rather than treatment failure.

Another striking observation based on re-LRRC location is the overrepresentation of previous R1-resections (4/7) in patients later presenting with combined location re-recurrences. This group of patients also presented more often with synchronous distant metastases (6/7 (86%)) at re-LRRC diagnosis. One hypothesis as to why this may be is that previous surgery was not extensive enough, causing an R1-resection and subsequent local and distant recurrence. However, a recent study by Nordkamp implies that although extending surgery may lead to an increased R0 resection rate, it does not improve metastasis free or overall survival.[6] Therefore, it may also be that the initial R1-resection is merely a symptom of poor tumour biology rather than treatment failure, leading to a locoregional recurrence and distant recurrences, whatever neoadjuvant or surgical treatment is applied.

LRRC target volumes would have been delineated differently in retrospect in a majority of cases. Importantly, most suggested alterations have already become standard practice in PelvEx II study centres, such as encompassing complete fibrosis into the GTV and refraining from editing towards organs at risk, to account for the invasive nature of LRRC.[15]

However, based on the case discussions, some additional radiotherapy target volume suggestions could be made. For example, 2 cases of LRRC in abscesses were not completely irradiated at the time of the LRRC. From an etiological point of view, it makes sense to consider the entire abscess cavity as tumorous, as cells can easily spread in the circulating fluid. The cellular microenvironment of an abscess may also be conducive to tumoral growth due to the upregulation of growth factors.[24,25] In both cases, we observed that the re-LRRC recurred within or along the borders of the prior abscesses. Therefore, there was consensus that abscesses containing tumour should ideally be deemed GTV.

Another suggestion was discussed in case of lateral recurrences. Three very similar lateral nodal recurrences were observed in this study in patients undergoing reirradiation, who did not receive reirradiation on additional elective target volumes. Two of the three lateral recurrences re-recurred marginally within the lateral compartment. In both cases, it was hypothesized that the nodal recurrence may have developed due to lymphogenic spread of the primary tumour and therefore, elective delineation of the lateral compartment was discussed for patients with (nodal) lateral recurrences undergoing reirradiation. When raising concerns regarding the potential additional toxicity, it was agreed that surgical resection of the lateral compartment may potentially have a higher chance of complications than more extensive reirradiation.[26] Consensus was reached that in (primarily) lateral recurrences, elective delineation of the complete lateral compartment (i.e., obturator nodes) can be defended in patients undergoing reirradiation. For RT naive patients, elective delineation of the lateral compartment is already advised.
Both these suggestions could be considered when further developing the currently instated delineation guideline. However, these suggestions should also be re-evaluated in larger, ideally prospective datasets of re-recurrences following curative treatment for LRRC.

Overall, target volumes were often deemed too conservative in retrospect, in part due to toxicity concerns, mainly in patients undergoing reirradiation. Fortunately, there is growing evidence that reirradiation is very well tolerated, with the most recent cohorts showing Grade 3 or higher acute toxicity of maximally 6% after 15x2Gy.[2,18,27–29] Considering the aggressive nature of disease and the fact that up to 50% of patients develop a local re-recurrence in follow-up, we would advise not letting toxicity concerns outweigh target volume coverage.[1,6,7,30]

Several locoregional re-recurrences were deemed inevitable. For some patients, optimal target volumes and surgery seem to have been insufficient to prevent disease relapse. Unfortunately, up to two-thirds of patients with LRRC will eventually develop distant metastases despite advancing treatment options, highlighting unfavourable biology.[4,6,13,30,31] Neoadjuvant radiotherapy should however not be withheld, as it can give physicians a window of time to observe the biological nature of the disease. Thus, physicians may be able to select patients more effectively for curative surgery.

A limitation of the current study is the small sample size. Only a small sub selection of our re-LRRC patients could be included, namely patients for whom all imaging, RT-planning information, and surgical information was available locally. As the goal of the study was merely to generate hypotheses, the small sample size was less of an issue. Furthermore, as mentioned, only patients in whom it was known that a re-LRRC had developed were selected. We do not report the number of patients who were treated similarly but did not develop re-LRRC. Moreover, there is no way of knowing whether the selected individuals would have had a different outcome if they had been treated as discussed. Therefore, all noted observations should only be interpreted as hypothesis generating. No conclusions should be drawn without confirmative studies with larger sample sizes, including patients with and without re-LRRC.

CONCLUSION

This critical review of re-LRRC after treatment with curative intent for LRRC highlights room for improvement within the scope of the current standard-of-care treatment for LRRC. Suboptimal treatment may have played a role in over half of discussed cases, of which the majority was due to different target volumes. Further delineation guideline development, incorporating the results from this study, may improve clinical outcomes, specifically local control for LRRC.

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SUPPLEMENTARY DATA OF CHAPTER 5

Table S1. Radiological checklist for LRRC, redacted from the PelvEx II trial.

Compartment	Structures/organs
Primary compartment involved	Central/Anterior/Posterior/Lateral/**Multicompartmental
Central involvement (yes/no)	Anastomosis (if applicable)
	Levator ani muscle
	Puborectalis muscle (left/right/both)
	Sphincter complex
	Gluteal muscle (left/right/both)
	Perineum
Anterior involvement (yes/no)	Vagina (anterior/posterior wall; introitus; portio; not applicable)
	Cervix (if applicable)
	Uterus (if applicable)
	Ovaries (if applicable)
	Prostate (if applicable)
	Seminal vesicles (if applicable) (left/right)
	Urinary bladder (dome; trigonum; not applicable)
	Peritoneum
	Small bowel
	Colon
	Omentoplasty
Posterior	Presacral fascia
	Periosteum/cortex
	Marrow
	Neuroforamen S1-S2
	Neuroforamen S3-S5
Lateral	Ureter (left/right)
	Sciatic nerve
	Lumbosacral plexus
	S1-S2 nerve roots
	S3-S5 nerve roots
	Sacrospinous ligament (left/right/both)
	Piriformis muscle (left/right/both)
	Obturator compartment (left/right/both)

Table S2. Notable differences in clinical characteristics between patients presenting with in-field, out-field, marginal and combined re-recurrences.

		In-out-marginal							
		In-field		Out-field		Marginal		Combined	
		n=15	%	n=5	%	n=6	%	n=7	%
Complication >=Gr3	Yes	9	60%	1	20%	1	17%	1	14%
	No	6	40%	4	80%	5	83%	6	86%
Abscess in follow-up for LRRC?	Yes	5	33%	0	0%	0	0%	1	14%
	No	10	67%	5	100%	5	83%	6	86%
Radicality of resection	R0	12	80%	5	100%	4	67%	3	43%
	R1	2	13%	0	0%	2	33%	4	57%
	Unknown	1	7%	0	0%	0	0%	0	0%
Metastases at re-LRRC diagnosis?	Yes	12	80%	2	40%	2	33%	6	86%
	No	3	20%	3	60%	4	67%	1	14%