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Locally recurrent rectal cancer: improving radiation treatment

Piqeur, F.

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LOCALLY RECURRENT RECTAL CANCER

Improving *radiation* treatment

Floor Piqeur

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Locally recurrent rectal cancer

Improving *radiation* treatment

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Promotor

Prof. Dr. C.A.M. Marijnen

Copromotores

Dr. J.W.A. Burger	Catharina Ziekenhuis, Eindhoven
Dr. H.M.U. Peulen	Catharina Ziekenhuis, Eindhoven

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Chapter 1

Introduction and thesis outline

Rectal cancer affects up to 3000 patients each year in the Netherlands.[1] Following the introduction of total mesorectal excision (TME) and the use of (chemo)radiotherapy in advanced rectal cancer, local control for patients with primary rectal cancer has improved significantly. In both intermediate and advanced disease, neoadjuvant treatment is used to increase the chances of a radical surgical resection (R0) and decrease the chance of local recurrences.[2] For patients with intermediate disease, short-course radiotherapy, consisting of 5 fractions of 5Gy (5x5Gy), can be considered. In case of advanced disease, neoadjuvant treatment is recommended, consisting of either 5x5Gy followed by consolidation chemotherapy, or full course chemoradiotherapy (CRT) (25x2Gy or 28x1.8Gy), combined with twice daily capecitabine. In the past decades, the use of radiotherapy in the primary setting has expanded with the introduction of organ-preservation strategies.[3]

The incidence of locally recurrent rectal cancer (LRRC), defined as recurrent disease within the small pelvis after partial or total mesorectal excision, has decreased following improvements in primary cancer treatment, but 6-12% of patients will still develop LRRC.[4–6] At LRRC diagnosis, 40-60% of patients will present with distant metastases.[7–9] The diagnosis and management of LRRC patients is highly complex and usually requires a multimodal approach by an experienced multidisciplinary team. LRRC management is complicated due to heterogeneity of patient presentation and previous treatment. Due to the loss of anatomical boundaries, LRRC can present in numerous different locations, such as the pelvic side wall, the anastomosis, or in the presacral area. Previous TME surgery also means that in LRRC, structures beyond the mesorectum are involved by definition.

The variation in primary rectal cancer treatment means some patients presenting with LRRC will previously have undergone extensive neoadjuvant treatment followed by surgery, whereas others will develop recurrent disease after surgery alone.
These variables greatly complicate standardization of recommendations. Not all modalities can be used in all patients, and it is questionable whether tumour biology after such varying primary treatment pathways is comparable between patients.

After LRRC diagnosis, the first obstacle often faced in LRRC management is staging. Due to the distortion or loss of normal anatomical plans and boundaries (i.e., the mesorectal fascia) after primary surgery, local recurrences can present anywhere within the small pelvis.[10,11] Although the CT-thorax abdomen is effective for the diagnosis of distant metastases

and may help identify progression of tumour in the small pelvis, its soft-tissue discrimination is insufficient for LRRC staging. The gold standard modality for LRRC staging is therefore the T2-weighted MRI, with additional diffusion-weighted imaging (DWI).[10–15] The MRI has proven pivotal in adequate staging, as it is highly sensitive, specific and accurate in regard to LRRC.[16–19] An FDG-18 PET-CT is not formally recommended in each (suspected) LRRC, but is often used as a trouble-shooter in cases of clinical doubt, for example in patients in which a LRRC is suspected, but no suspicious lesion can be seen on CT.[12,14,19–21] However, there are still concerns regarding the risk of false positives due to infectious or inflammatory causes, as well as false negatives, mainly in low cell-density mucinous tumours.
Even with the modalities mentioned at hand, staging can remain challenging. Differentiation between postoperative (inflammatory) changes, fibrosis and tumour requires extensive radiological expertise. These uncertainties not only influence adequate staging at baseline but can also cause challenges in several different aspects of LRRC treatment, such as surgery and radiotherapy planning.

A second obstacle lies in establishing the intent of treatment. In the Netherlands, there is general consensus that patients with non-metastatic, (borderline) resectable LRRC are deemed eligible for curatively intended treatment.[22] For patients with evident irresectable disease or extensive metastatic disease, there is a general consensus that palliative or best-supportive care is the most appropriate treatment. However, many patients will fall in a grey area between these two clear clinical scenarios, due to patient or disease characteristics. For example, to date, there is no consensus on how to define oligometastatic disease in LRRC, and general definitions of oligometastatic disease can also vary significantly.[23] Therefore, it is difficult to determine up-front which patients with low-burden metastatic disease will or will not benefit from curatively intended treatment, further complicating recommendations.

For now, treatment with curative intent for LRRC in the Netherlands generally consists of neoadjuvant CRT followed by surgery.[22] This involves either full-course CRT (25x2Gy or 28x1.8Gy) in patients who are radiotherapy naive, or chemo reirradiation (15x2Gy) in patients who have previously received (chemo)radiotherapy for their primary tumour. In both cases, radiotherapy is combined with twice-daily concomitant capecitabine. The ratio of RT-naive versus reirradiation patients with a local recurrence is approximately 30:70.[24]

Although there has been relative consensus regarding the indication of CRT for LRRC, there has been a lack of awareness regarding radiotherapy delivery, exampled by the absence of LRRC delineation guidelines. In primary rectal cancer, national and international guidelines have been formulated specifying treatment details, such as areas to be incorporated in target volumes and margins to be used.[25] No such guidelines exist for LRRC, introducing even more heterogeneity in LRRC management. For surgery, similar issues are present. Although there is consensus that surgery should be performed for patients with resectable disease in a curative setting, there are no guidelines on how extensive the performed surgery should be, other than that a radical surgical resection (R0-resection) should be aimed for.[13] Additionally, there is no clear consensus on when or how to perform additional intra-operative radiotherapy (IORT), meaning its use is often dependent on availability.[12,13,26–28]

In recent years, the use of induction chemotherapy for LRRC has increased. A handful of retrospective cohorts have suggested that the use of induction chemotherapy can influence tumour response rate.[29–32] More pathological complete responses were seen in patients receiving induction chemotherapy followed by CRT, compared to patients only receiving CRT. However, so far, this has not translated into an overall survival benefit, and toxicity has not yet properly been investigated, meaning its place in LRRC treatment is still unknown.[24]

A last obstacle is that robust data to base treatment decisions on are lacking for LRRC. Only a handful of (non-randomized) prospective trials are available for this population of patients. The data that are available often stem from retrospective cohorts and consensus statements, that are subject to biases. Therefore, there is an evident need for robust, high-level, prospective data to steer clinical decision making in this complex patient population.

Due to all the aforementioned factors, LRRC management has proven to be a clear clinical challenge. Fortunately, two prospective phase-3 randomized controlled trials for LRRC patients have been initiated in recent years, namely the PelvEx II and the GRECCAR-15 trial.[33,34] Both trials include patients with (borderline) resectabel LRRC, without distant metastases. The biggest difference in trial population is that the GRECCAR-15 trial only included patients that have previously undergone radiotherapy for primary rectal cancer. The GRECCAR-15 trial was investigating the benefit of reirradiation after induction

chemotherapy but before surgery, whereas the PelvEx II trial is investigating the benefit of induction chemotherapy prior to CRT or chemo reirradiation and surgery. Unfortunately, the GRECCAR-15 trial has recently been closed due to slow accrual.

Ultimately, prospective randomized controlled trials as well as two prospective single arm reirradiation trials, will increase the availability of high-level evidence in the coming years.[35,36] Additionally, the PelvEx II trial has made it a clear goal to establish strong research networks, to facilitate multidisciplinary collaboration and accelerate related research. Within the PelvEx II trial, several initiatives have been taken to ensure uniformity in radiological reporting, radiotherapy treatment delivery and surgical resections, some of which are highlighted within this thesis.

An important step towards improving treatment for LRRC in general, is to reach a clear consensus on how to approach these patients. The aim of this thesis was therefore to achieve standardization of LRRC care and to further improve quality of care, with a specific focus on radiotherapy. The first part of this thesis addresses efforts to standardize LRRC care. The second part of this thesis focusses on improving quality of radiotherapy for LRRC patients. The last part of this thesis describes oncological outcomes for LRRC.

Chapter 2 describes the development of a radiotherapy manual for LRRC. Several meetings were held with an expert radiologist, expert radiation oncologists and expert colorectal surgeons to discuss and standardize radiotherapy treatment for LRRC, based on consensus.
Chapter 3 details the national guideline for LRRC treatment that was developed based on an extensive narrative literature review, to further standardize LRRC care. This guideline incorporates recommendations for LRRC diagnosis, patient selection, and treatment and advocates for centralization of expertise in dedicated referral centres.
To investigate where delineation variations for radiotherapy may occur, a multidisciplinary delineation study was performed (**Chapter 4**). This delineation study provides insight into when delineation variations occur and can aid in tailoring radiotherapy treatment recommendations to specific recurrence types. Moreover, it investigates the clinical benefit of a multidisciplinary approach to radiotherapy delineation, incorporating a radiologist to the clinical workflow.
As substantiating data for the delineation guideline are lacking, a retrospective analysis of local re-recurrences was performed in **Chapter 5**. This in-depth analysis of individual cases provide insights into where local treatment for LRRC may have failed, and forms

hypotheses on how to further improve treatment, hopefully eventually improving local control.

Within the PelvEx II trial, prospective peer-review of all CRT delineations for trial patients is performed. In **Chapter 6**, preliminary results and "lessons learnt" from this quality assurance programme are described. By doing so, the initially instated radiotherapy guideline can be continuously improved.

As described, radiotherapy is also used intraoperatively for LRRC treatment. In **Chapter 7**, a retrospective analysis is performed, to compare postoperative complications before and after IORT dose escalation. This was implemented to improve local control by escalating the dose of IORT on potentially involved resection margins. However, it is important to ensure that further dose escalation can be performed safely.

In **Chapter 8**, oncological outcome of patients with a pathological complete response following neoadjuvant radiotherapy is described and compared to LRRC patients without a complete response. This retrospective analysis has established a pathological complete response as an additional prognostic factor for oncological outcome.

Lastly, in **Chapter 9**, oncological outcomes of patients with re-recurrent rectal cancer are evaluated, highlighting the importance of careful patient selection.

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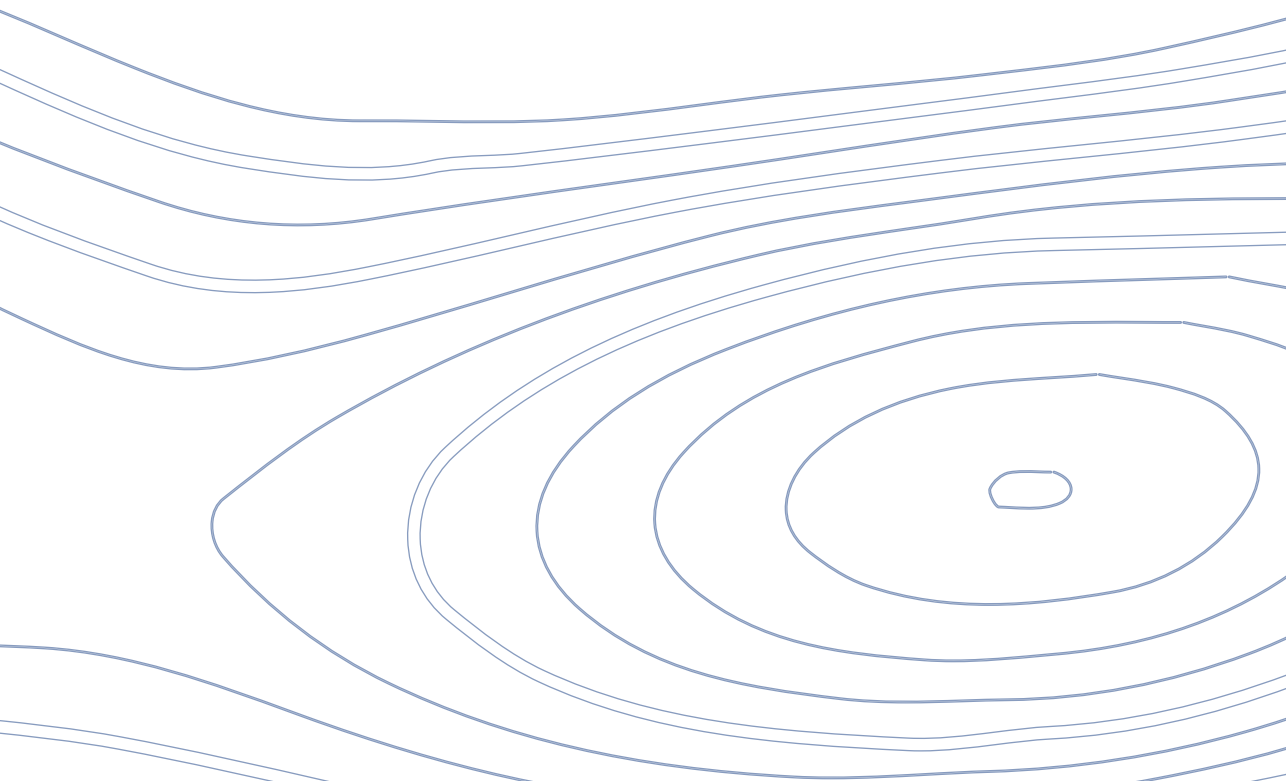
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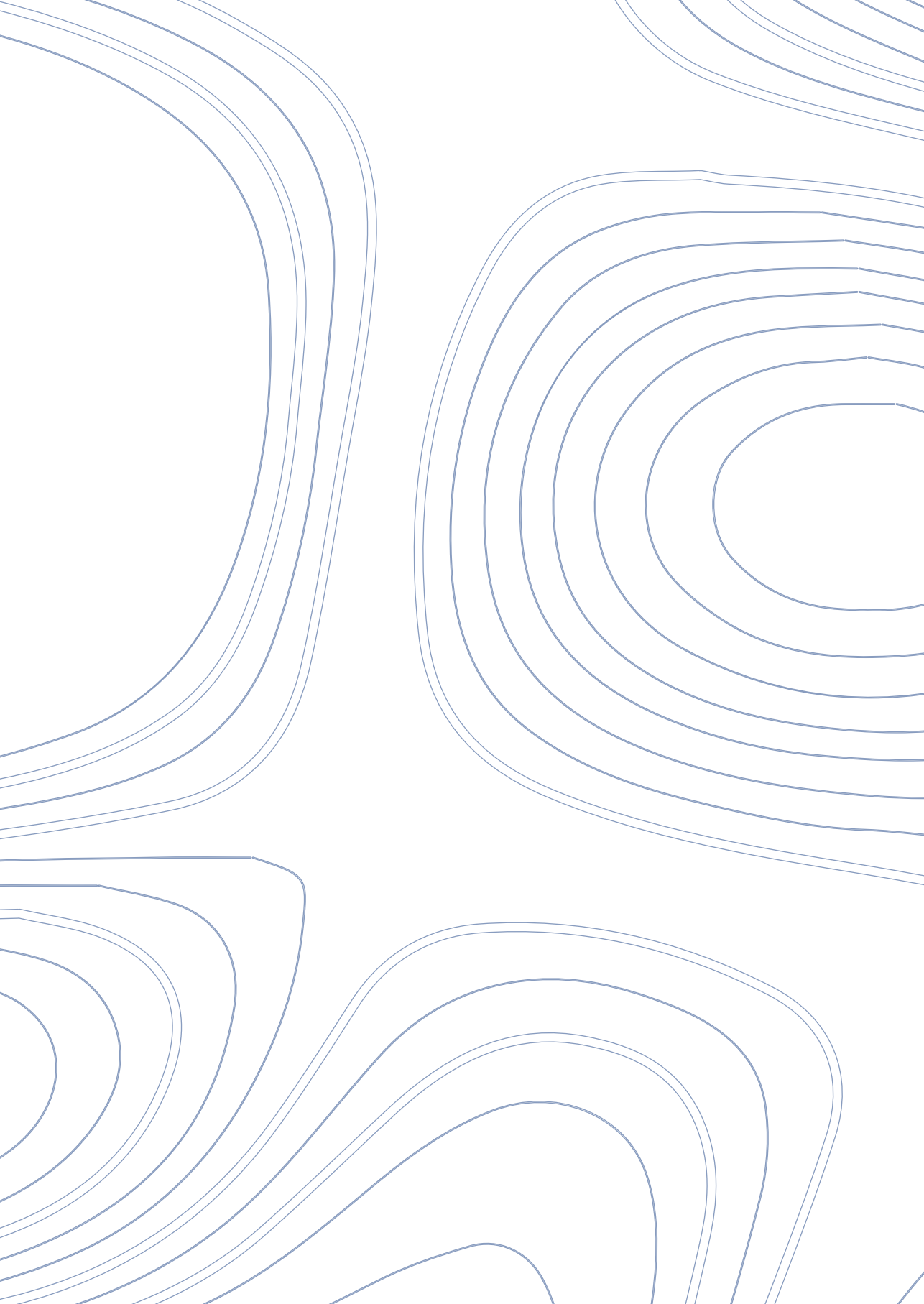
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Part I

Standardizing locally recurrent rectal cancer care





Chapter 2

Development of a consensus-based delineation guideline for locally recurrent rectal cancer

Piqeur F*, Hupkens, BJP*, Nordkamp S, Witte MG, Meijnen P, Ceha HM, Berbee M, Dieters M, Heyman S, Valdman A, Nilsson MP, Nederend J, Rutten, HJT, Burger JWA, Marijnen CAM, Peulen HMU.

**Both authors contributed equally.*

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ABSTRACT

Background and purpose: Neoadjuvant chemoradiotherapy (nCRT) is used in locally recurrent rectal cancer (LRRC) to increase chances of a radical surgical resection. Delineation in LRRC is hampered by complex disease presentation and limited clinical exposure. Within the PelvEx II trial, evaluating the benefit of chemotherapy preceding nCRT for LRRC, a delineation guideline was developed by an expert LRRC team.

Materials and methods: Eight radiation oncologists, from Dutch and Swedish expert centres, participated in two meetings, delineating GTV and CTV in six cases. Regions at-risk for re-recurrence or irradical resection were identified by eleven expert surgeons and one expert radiologist. Target volumes were evaluated multidisciplinary. Inter-observer variation was analysed.

Results: Inter-observer variation in delineation of LRRC appeared large. Multidisciplinary evaluation per case is beneficial in determining target volumes. The following consensus regarding target volumes was reached.
GTV should encompass all tumour, including extension into organs at risk if applicable. If the tumour is in fibrosis, GTV should encompass the entire fibrotic area. Only if tumour can clearly be distinguished from fibrosis, GTV may be reduced, as long as the entire fibrotic area is covered by the CTV.
CTV is GTV with a 1 cm margin and should encompass all at-risk regions for irradical resection or re-recurrence. CTV should not be adjusted towards other organs. Multifocal recurrences should be encompassed in one CTV. Elective nodal delineation is only advised in radiotherapy naive patients.

Conclusion: This study provides a first consensus-based delineation guideline for LRRC. Analyses of re-recurrences is needed to understand disease behaviour and to optimize delineation guidelines accordingly.

BACKGROUND AND PURPOSE

In the past decades, treatment outcome of locally recurrent rectal cancer (LRRC) has improved significantly.[1–5] Intensification of neoadjuvant treatment for LRRC is used to improve oncologic outcome.[1,2,6,7] Currently, neoadjuvant chemoradiotherapy (nCRT) is an integral part of LRRC treatment.[2,8–16] In radiotherapy naive patients, nCRT is advised to downstage tumour volume and increase the likelihood of a radical resection (R0), which is the most important prognostic factor for survival.[1,4] Reirradiation in the setting of LRRC is feasible and safe, confirmed by low toxicity rates seen in the first prospective reirradiation feasibility trial for LRRC performed by Valentini et al.[17] Although reirradiation does show encouraging results, the clinical benefit of reirradiation is yet to be proven, as it has not yet shown an effect on overall survival.[2,8,10–14,18] Two ongoing randomized controlled trials (RCT) are investigating the role of neoadjuvant treatment for LRRC. The PelvEx II trial is investigating the benefit of chemotherapy preceding nCRT, hypothesising that additional preoperative chemotherapy will lead to more R0 resections.[19,20] The GRECCAR 15 trial is investigating the benefit of reirradiation after induction chemotherapy and will also assess percentage of R0 resections as primary endpoint.[20]

Although the use of full course nCRT is promising and the role of reirradiation for LRRC is being studied, there is no consensus on target volume definition for LRRC. Delineation is hampered as diagnostic imaging is more difficult to interpret due to altered anatomy after primary surgery, multifocality of disease, invasion of surrounding structures, and the presence of fibrosis. Supporting evidence is also lacking. Additionally, clinicians often have limited exposure to LRRC due to the low incidence of disease, as only 6-10% of patients with rectal cancer develop a local recurrence.[1,2,21] These factors could contribute to inadequate target volume delineation with possible geographical miss. Furthermore, a large interobserver variability in target volume delineation can be expected.

In primary rectal cancer, a delineation guideline of Valentini et al. has been widely adopted and has proven to reduce interobserver variability.[22,23] However, to our knowledge, no delineation guidelines have been drawn up for LRRC.

The aim of this study is to develop a consensus-based delineation guideline for LRRC by multidisciplinary delineation workshops in order to decrease delineation variability, to optimize radiotherapy treatment consistency within the PelvEx II trial and to provide radiation oncologists with a guideline for clinical practice.[24]

MATERIALS AND METHODS

Dutch expert LRRC treatment centres were invited to participate in this study. Expert centres were defined as centres with a dedicated LRRC multidisciplinary tumour board, treating at least 10 patients per year. One radiation oncologist of every Dutch expert centre was asked to delineate three cases of LRRC (cases 1.1-1.3). Dutch participants were instructed to delineate gross tumour volume (GTV), and clinical tumour volume (CTV) according to their own discretion or local guidelines. No margins were specified. Participants received information on patient history, prior treatment, tumour characteristics and imaging for each case. Cases were selected to represent diverse disease presentations, but all cases met PelvEx II inclusion criteria, meaning all patients had confirmed LRRC after mesorectal resection, deemed resectable by the treating surgeon. Tumours invading in the neuroforamina or in the cortex of S2 and upwards and tumours encasing the sciatic nerve are considered irresectable.[25] Table 1 shows a summary of case characteristics. Case information is presented in the supplementary material (S1).

All delineations were reviewed and discussed multidisciplinary, with radiation oncologists, surgeons and a radiologist. The participating radiologist and surgeons were asked to identify tumour and regions at risk for re-recurrence or involved resection margins. Following the first meeting, the delineation guideline was drafted. All Dutch radiation oncologists received the concept guideline to review before the second meeting. They were asked to delineate three more cases (cases 2.1-2.3), including one repeat (case 2.1 was a repeat of case 1.2) to test guideline adherence. During the second meeting, the guideline was adjusted based on the discussion. Following the second meeting, the guideline was approved by all participants.

The delineation study was repeated in Sweden. Radiation oncologists from 3 expert sites were invited to participate and were instructed to delineate according to local practice. No other instructions were provided, however, participants received the Dutch guideline prior to delineation, introducing potential bias. After two meetings with Swedish participants, the final version of the guideline was drafted.

Table 1. Summary of case characteristics, representing diverse disease presentation in LRRC

	Meeting	Prior radiotherapy	Radiotherapy naive	Location **	Unifocal	Multifocal
Case 1.1	1	X		Lateral, near the pelvic wall	X	
Case 1.2*	1	X		Posterior	X	
Case 1.3	1	X		Axial/central		X
Case 2.1*	2	X		Posterior	X	
Case 2.2*	2		X	Posterior	X	
Case 2.3	2	X		Lateral, obturator loge	X	

* Case 1.2 is repeated as case 2.1 to test guideline adherence. Case 2.2 is derived from the same patient as case 1.2 and 2.1, but case information was altered to represent a radiotherapy naive patient.
** Location[25]: Lateral: involving the bony pelvic sidewall or sidewall structures including the iliac vessels, pelvic ureters, lateral lymph nodes, pelvic autonomic nerve, and sidewall musculature; posterior: involving the sacrum and coccyx; axial/central: not involving anterior, posterior, or lateral pelvic sidewalls.

After guideline completion, delineation variation was calculated. The following analyses had no impact on the development of the guideline but were used to demonstrate delineation variation. Analyses were performed on Dutch and Swedish data separately, to account for potential bias. Delineations were triangulated into a 3D mesh structure, by use of in-house software (Match42). Median surfaces of contours were constructed to encompass each point defined as target volume by at least 50% of radiation oncologists. Subsequently, analyses were performed in reference to the computed median delineations. Interobserver agreement was evaluated using the Dice similarity coefficient (DSC), which is a measure for overlap, for each GTV and CTV in reference to the computed median.[26] A DSC of 1.0 signifies a perfect overlap between two delineations, whereas a DSC of 0.0 signifies no overlap.[26]

The distance between the median delineation and radiation oncologist's delineation was evaluated using Hausdorff distances (HD).[26] The HD is defined as the maximum of all smallest distances from each point on one delineation to the other. A smaller value of HD corresponds to less variation. The maximum distance, i.e., the HD100%, is sensitive to outliers. Therefore, the HD98% (98th percentile) was used in analysis, to reduce the effect of single outliers.

Comparisons of median DSC and HD98% were performed by Wilcoxon sign rank test and Mann-Whitney U test. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0, IBM Corp. Released 2017. Armonk, NY: IBM Corp.

RESULTS

Six Dutch expert centres (Catharina Hospital Eindhoven, The Netherlands Cancer Institute, Amsterdam University Medical Centre, Maastro, Haaglanden Medical Centre and University Medical Centre Groningen) participated in the Dutch meetings. Delineations were performed by five Dutch radiation oncologists (HP, PM, HC, MB, MD). Four colorectal surgeons (JB, KH, JM, AA) and one radiologist (JN) specialized in colorectal imaging were present.
Three Swedish expert centres (Karolinska Institute, Sahlgrenska University Hospital and Skåne University Hospital) and the Dutch PelvEx II Quality Assurance (QA) team (HP, PB, CM, HR, JN, BH, FP) participated in the Swedish meetings. Other Dutch participants did not attend Swedish meetings. Delineations were performed by three radiation oncologists (SH, AV, MN). Five Swedish colorectal surgeons were present (EA, ML, PN, PB, HI).
Median and range of DSC and HD98% of Dutch and Swedish delineations can be found in table 2 and 3 respectively. Median DSC of GTV for Dutch and Swedish participants ranged from 0.57-0.76 and 0.64-0.87 respectively, suggesting a large variation in GTV contours. The smallest DSC in Dutch contours, i.e., the largest variation, was seen in the multifocal recurrence (case 1.3) (0.57 (0.36-0.67)), and in the recurrence located in fibrosis (case 1.2) (0.59 (0.41-0.81)). Less variation was seen in Swedish contours.
Median DSC of CTV in Dutch and Swedish participants ranged from 0.75-0.87 and 0.85-0.90 respectively. HD98% shows large outliers in Dutch contours, with median HD98% up to 2.05cm (0.98cm-2.96cm) and 2.87cm (0.78cm-3.54cm) in cases 1.2 and 2.2 respectively. Less outliers were seen in Swedish contours (median HD98% 0.57cm-1.68cm).
When comparing CTV of case 1.2 and 2.1 for Dutch delineations i.e., before and after a guideline, median DSC is equal (0.82 and 0.81 respectively (p=0.345)), but the range suggests a decreasing trend (0.27-0.84 to 0.73-0.87 respectively). The same pattern is seen in median HD98%, with a median HD98% of 2.05cm (0.98-2.96cm) in case 1.2 and 1.34cm (1.1-1.85cm) in case 2.1 (p=0.225).

Based on defined at-risk regions and consensus delineations, the following guideline was drawn-up. A step-by-step consensus delineation with MRI and FDG-PET is shown in figure 1. All consensus delineations are shown in figure 2. Performed delineations per case are described in the supplementary material. Table 4 provides a summary of recommendations.

Table 2. Median, minimum and maximum DSC and HD98% of radiation oncologist's GTV and CTV in reference to calculated median GTV and CTV for Dutch participants.

	Case description		N	DSC			HD 98% (cm)		
				Median	Min	Max	Median	Min	Max
1.1	Recurrence near the pelvic wall	GTV	5	0.76	0.58	0.92	0.84	0.32	1.12
		CTV	5	0.75	0.28	0.86	1.54	0.86	2.87
1.2	Presacral recurrence	GTV	5	0.59	0.41	0.81	1.27	0.64	2.26
		CTV	5	0.82	0.27	0.84	2.05	0.98	2.96
1.3	Multifocal recurrence	GTV	4	0.57	0.36	0.67	0.75	0.64	1.10
		CTV	4	0.84	0.64	0.94	1.14	0.77	3.20
2.1	Presacral recurrence, repeat	GTV	5	0.66	0.49	0.83	1.22	0.63	1.57
		CTV	5	0.81	0.73	0.87	1.34	1.17	1.85
2.2	Presacral recurrence, RT naive	GTV	4	0.66	0.40	0.84	1.20	0.97	1.87
		CTV	4	0.68	0.74	0.90	2.87	0.78	3.54
2.3	Lateral recurrence	GTV	4	0.76	0.33	0.83	0.56	0.43	1.21
		CTV	4	0.87	0.35	0.89	0.64	0.55	3.38

Table 3. Median, minimum and maximum DSC and HD98% of radiation oncologist's GTV and CTV in reference to calculated median GTV and CTV for Swedish participants.

	Case description		N	DSC			HD 98% (cm)		
				Median	Min	Max	Median	Min	Max
1.1	Recurrence near the pelvic wall	GTV	3	0.87	0.63	0.95	0.37	0.15	1.57
		CTV	3	0.89	0.80	0.96	0.63	0.19	1.40
1.2	Presacral recurrence	GTV	3	0.80	0.58	0.89	0.83	0.76	2.13
		CTV	3	0.85	0.82	0.94	0.76	0.48	2.03
1.3	Multifocal recurrence	GTV	3	0.72	0.11	0.77	0.31	0.13	2.14
		CTV	3	0.90	0.77	0.91	1.68	0.76	2.34
2.1	Presacral recurrence, Repeat	GTV	3	0.73	0.72	0.88	0.99	0.71	1.41
		CTV	3	0.87	0.80	0.93	0.85	0.78	1.80
2.2	Presacral recurrence, RT naive	GTV	3	0.86	0.70	0.91	0.78	0.43	1.26
		CTV	3	0.87	0.79	0.90	1.58	1.50	4.28
2.3	Lateral recurrence	GTV	3	0.64	0.52	0.86	0.57	0.33	0.71
		CTV	3	0.88	0.71	0.91	0.57	0.51	0.98

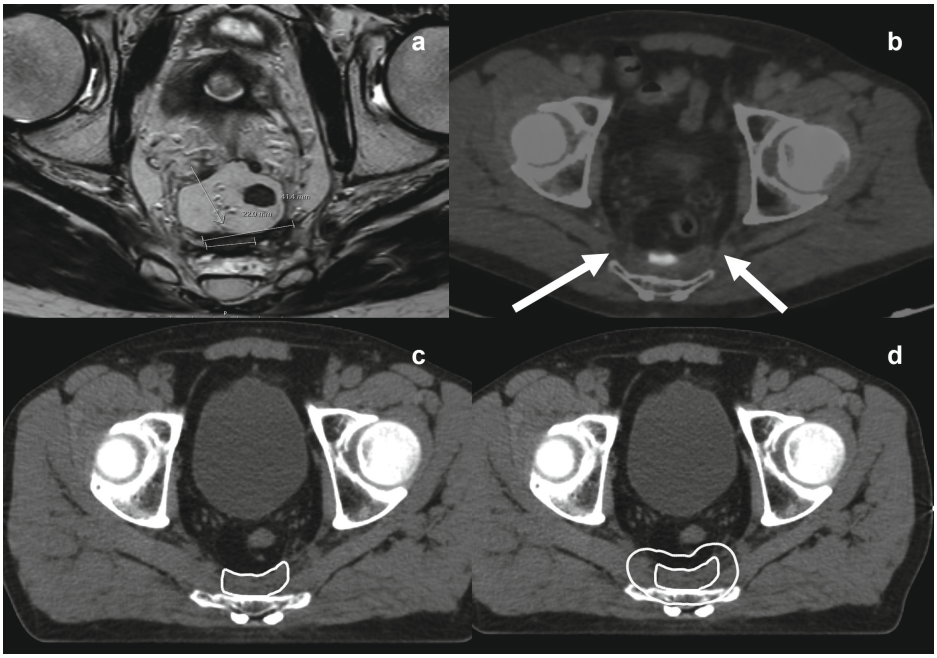


Figure 1. Consensus delineation for case 1.2 (and 2.1)

A: MRI imaging of local recurrence.
B: PET imaging of local recurrence, surgical at-risk regions (i.e., sacrospinous ligament) highlighted by white arrows
C: GTV delineation (complete fibrosis)
D: CTV delineation (GTV + 1cm, expanded to encompass at-risk surgical region)

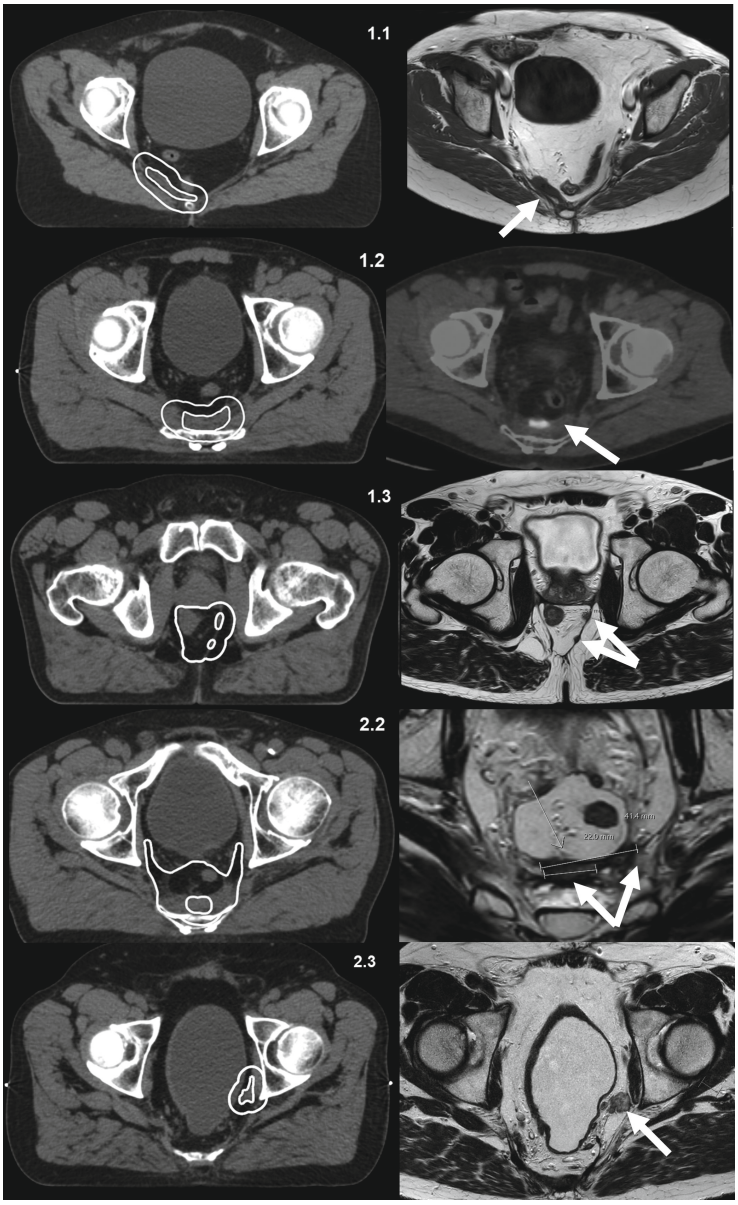


Figure 2. Consensus-based GTV and CTV for cases 1.1-2.3 (on the left), with diagnostic MRI (case 1.1, 1.3-2.3) or PET (case 1.2) imaging on the right.

1.1: Recurrence near the pelvic wall

1.2 (repeated as 2.1): Recurrence located in fibrosis (with black-and-white PET)

1.3: Multifocal recurrence

2.2: RT naive patient with elective CTV delineation as in locally advanced rectal cancer

2.3: Lateral recurrence

GTV should be determined based on a multidisciplinary consensus with expert radiologists and surgeons. We advise a pelvic MRI, preferably in combination with FDG-PET or CT. All tumour that can be seen at baseline staging must be delineated. This information should be derived from at least diagnostic imaging, supplemented by clinical examination or endoscopic findings. Only involved areas of surrounding organs should be included in the GTV. For example, it is not necessary to encompass the entire bladder at involved levels. In patients receiving induction chemotherapy prior to nCRT, there may be tumour regression. In case of major regression, adjustment towards other structures is allowed. In case of a complete response, there will still be a GTV, i.e., the tumour bed or fibrosis after induction chemotherapy.

If the tumour is located in fibrosis (case 1.2 and 2.1), the entire fibrotic area should be covered by the GTV. Only if distinguishing tumour from fibrosis seems straightforward and highly accurate, GTV may be reduced to encompass only distinguished tumour, as long as the complete fibrotic area is covered by the CTV.

CTV includes GTV with a margin of 1 cm. In case of chemotherapy preceding nCRT, all pre chemotherapy GTV must be included in the CTV. Given the recurrent nature of the tumour and the loss of anatomical boundaries due to previous surgery, no adjustment of the CTV towards organs at risk (OAR) is allowed. The only exception is the pelvic bones, where adjustment of the CTV is allowed if bony invasion is clearly not present, i.e., adjustment of the CTV towards the acetabulum in case of a presacral recurrence. Consequentially, the CTV may extend into the pelvic bones. In case of a multifocal recurrence (case 1.3), all locations should be combined in one CTV, with logical anatomic boundaries. Small separate islands should be avoided. The upper and lower limit are one centimetre beyond the most cranial and caudal GTV.
It is strongly advised to consult with the surgeon to determine at-risk resection margins and surgery type when delineating CTV. Extension of the CTV to encompass all resection margins is strongly advised. Specific attention is needed for adequate coverage of at-risk tissue that will not be surgically removed. If the tumour is located in fibrosis, sufficient inclusion of the dorsolateral area should be regarded. No elective nodal delineation is recommended in patients undergoing reirradiation.

In radiotherapy naive patients, in contrast to patients undergoing reirradiation, elective nodal irradiation is advised, mirroring recommendations for primary rectal cancer by

Valentini et al,[27] with allowance for national adjustments (case 2.2). Anatomical changes due to previous treatment should be considered.

PTV volume ensures coverage of the CTV considering the systematic and random set-up errors, changes over time in the patient geometry and movement of internal organs that may occur. Since the required margin is dependent on local image guidance protocols, the extent of this margin should be determined according to local policy (between 5mm and 10mm is recommended).

It is strongly recommended to delineate all OARs, as in primary rectal cancer, i.e., the femoral heads, the bladder, the small bowel, and the anus. Currently, reliable data on OAR constraints are lacking and are highly dependent on the volume and location of the recurrence, thus no optimization objectives can be given yet. The priority should be target volume coverage. Priority of optimisation should be as followed: CTV > PTV > Bowel Bag > Bladder > Other OAR.

Table 4. Recommendations for GTV, CTV and PTV delineation in LRRC.

GTV	General recommendations	• Delineate all macroscopically visible tumour in primary staging • Delineate only visibly involved areas of surrounding organs • If tumour is located in fibrosis, encompass complete fibrotic area • Consult with a dedicated radiologist to determine the extent of the GTV
	Additional recommendations	*In case of induction chemotherapy* • In case of major regression, adjustment towards other non-involved structures is allowed • In case of a complete response, GTV should still be defined (i.e., remaining tumour bed or fibrosis) *In case of tumour located in fibrosis* • Only if tumour and fibrosis can clearly be distinguished, it is optional to reduce the GTV to visible tumour, as long as the fibrosis is completely covered by the CTV

CTV	General recommendations	• Consult with the treating surgeon to determine surgical resection margins at risk for irradical resection and discuss planned type of surgery
		• CTV = GTV + 1cm margin
		• An additional margin of 0.5cm in dorsolateral region is recommended
		• Combine multifocal recurrences into one CTV
		  • Use logical anatomical boundaries
		  • Stay 1 cm beyond the most cranial and caudal GTV
		• Do not adjust CTV towards other organs

	Additional recommendations	*In case of induction chemotherapy* • All pre chemotherapy GTV must be included in the CTV *In radiotherapy naive patients* • Additional elective nodal delineation is advised: adhere to national guidelines for locally advanced rectal cancer • Consider anatomical changes due to prior surgery *In patients undergoing reirradiation* • No additional elective nodal delineation is advised
PTV	General recommendations	• Apply the PTV margin according to local protocol • Recommended margin between 5mm and 10mm

DISCUSSION

In this study we developed a delineation guideline for LRRC based on six cases, delineated by eight radiation oncologists during four multidisciplinary meetings. It was endorsed by a multidisciplinary team of rectal cancer experts responsible for conducting the international multicentre RCT PelvEx II.[28] The most important conclusion is that multidisciplinary evaluation of individual cases is necessary to define target volumes. The current guideline provides a first step towards an evidence-based guideline, setting a common and

reproducible standard for delineation in all PelvEx II centres. The guideline will be improved based on the ongoing QA programme, multidisciplinary discussions within the PelvEx II trial and follow-up information on developed re-recurrences. Reproducibility and applicability will be investigated within the trial, anticipating a larger case mix.

Interobserver variation in GTV delineations was large, suggesting that interpretation of diagnostic imaging is challenging in LRRC, especially in tumours located in fibrosis (case 1.2), and multifocal recurrences (case 1.3). Though current literature suggests high sensitivity and specificity for LRRC detection by FDG-PET and MRI (sensitivity 94-98% and 80-91%, specificity 96-98% and 86-100% respectively),[29] less evidence is available on determining the extent of pelvic disease and on accuracy of delineations. Previous studies show that understaging of disease by radiologists is common, particularly in tumours located in fibrosis or invading in surrounding structures.[30–32] This poses the question how accurate GTV delineation in LRRC currently is. A learning curve in assessment of recurrences is reported in radiologists, in whom exposure to LRRC may be higher compared to radiation oncologists, especially when referred to non-expert radiation oncology clinics for nCRT.[31,33] Therefore, possible future strategies could be demarcation of GTV by expert radiologists, to improve GTV delineations, or delineation of CTV based on known surgical at-risk regions, to ensure adequate CTV coverage, regardless of GTV.

Complete coverage of fibrosis by the GTV is advised, as the risk of irradical resection in fibrotic tissue was deemed high by participating surgeons. This is in line with research performed in primary rectal cancer by Tanaka et al., that concluded that there is a high rate of remaining cancer cells within fibrosis.[34] It is likely that this is similar in LRRC. Moreover, the accuracy of MRI and PET as diagnostic imaging within fibrosis is currently unknown. Therefore, a contouring approach with a reduction of GTV to encompass only PET-positive tumour within fibrosis, whilst covering the remaining fibrosis within the CTV, should remain the exception rather than the rule.

In case 1.3, a multifocal recurrence, not all foci were delineated as GTV by all participants, suggesting that possible tumour miss may occur clinically. Reassuringly, less variation was seen in CTV, as all foci were delineated within one CTV. The rationale behind this is that visible foci of multifocal recurrences may only be the tip of the iceberg and may be of a different aetiology than, for example, a lymph node recurrence. Multifocality may be a first manifestation of peritoneal metastatic disease in the pelvis or may be due to tumour

seeding or tumour spill. There may also be additional foci present, although not yet visible, which led to the recommendation of combining all foci into one CTV, demarcated by logical anatomical boundaries.

Elective nodal delineation was discussed. For patients undergoing reirradiation, CTV is based on GTV with an adequate margin to achieve maximal local control. Elective nodal delineation may be beneficial in counteracting microscopic nodal metastases, but as there is no evidence of benefit yet, this is not advised. In addition, at-risk regions for micro metastases or lymph node recurrences cannot be defined yet, as drainage of the pelvis may be substantially altered. Lastly, extensive additional reirradiation may cause high doses on OARs, increasing toxicity risk.

On the contrary, elective nodal delineation is advised in radiotherapy naive patients, where the benefit of elective irradiation does seem to outweigh the possible risk of toxicity or exceeding critical OAR doses. An analysis of re-recurrence patterns may provide information needed to define elective target volumes.

No recommendations for OAR constraints were given, as robust data for OAR constraints in reirradiation are lacking. Additionally, OAR are often resected during surgery, especially when the OAR are adjacent to at-risk margins and thus in close proximity to the irradiated target volume. This was recently confirmed by Nordkamp et al., comparing surgical strategies in two tertiary referral centres for LRRC. Merely 23% of all LRRC patients underwent TME surgery without additional resections and in patients undergoing reirradiation, that percentage is even lower (18%).[35] Therefore, priority should be placed on adequate target coverage rather than on sparing OAR.

A future priority in treatment planning may be bone marrow sparing, as data in primary rectal cancer, show that CRT can cause haematological toxicity, leading to dose reductions or treatment interruptions that are associated with worse oncological outcomes.[36,37] However, these findings have not yet translated to clinical practice in the form of constraints.

This study is hampered by several limitations. First of all, LRRC is a heterogeneous disease, with varying presentations. Therefore, it is challenging to develop a guideline with wide applicability. Consequently, all delineations of patients treated in the PelvEx II study are prospectively evaluated within a QA programme, in which delineations are reviewed prior

to nCRT. Observations made within the PelvEx II trial will be used to improve the guideline where necessary. Second, conclusions are limited due to the small number of cases and observers, especially regarding variation. Interobserver variation and the potential benefit of a guideline should be studied in larger case series with multiple observers before conclusions can be drawn. Third, there is scarce literature discussing target volume definition in LRRC and the location of re-recurrences. Although this emphasizes the importance of this study, there are no prospective data to support the current recommendations. Lastly, the cases presented in this study were selected to represent diverse disease presentation but had to adhere to PelvEx II inclusion criteria. Therefore, it may not be applicable to irresectable tumours treated with palliative intent.

As described earlier, the most important conclusion is that multidisciplinary evaluation of individual cases was deemed essential. The presence of an expert radiologist proved indispensable to optimize identification of the recurrence. Surgical oncologists were needed to identify areas at particular risk for positive resection margins. In general, it is advised to incorporate surgical at-risk areas into the CTV, to maximize volume reduction and improve chances of achieving a R0 resection, specifically in dorsolateral direction in presacral or lateral pelvic recurrences.

CONCLUSION

This study provides a first multidisciplinary, consensus-based delineation guideline for LRRC Analyses of re-recurrences are needed to further understand disease behaviour and recurrence patterns and to optimize delineation guidelines accordingly.

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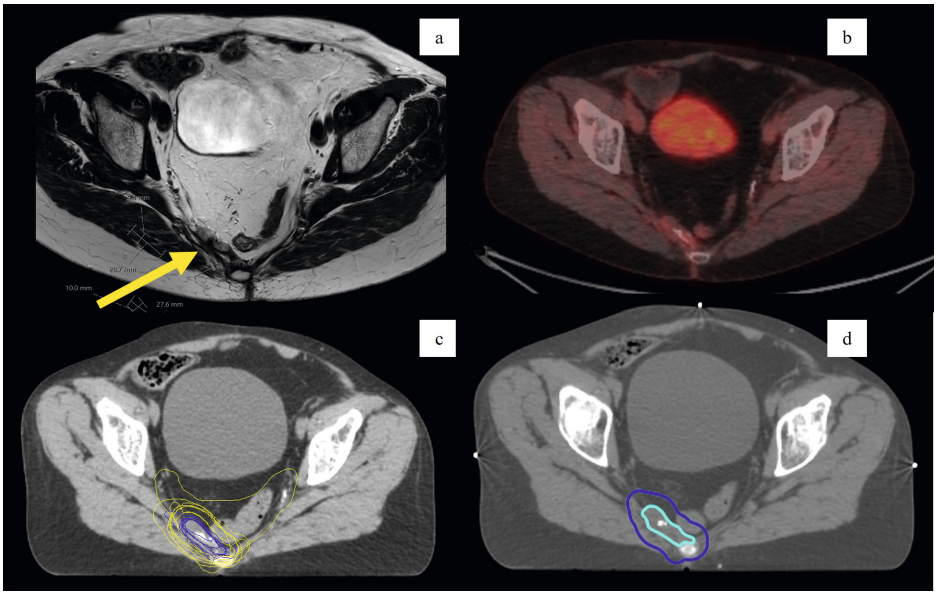
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SUPPLEMENTARY DATA OF CHAPTER 2

Case 1.1: Unifocal* local *recurrence near the pelvic wall

60-year-old woman with a history of a T3N2 rectal cancer, for which she was treated with neoadjuvant chemoradiotherapy and a low anterior resection. Patient presented with a unifocal local recurrence located on the right pelvic wall. Patient received induction chemotherapy, consisting of 4 courses FOLFOX, but showed no response. Patient was referred for preoperative chemo reirradiation followed by resection.



Supplementary figure 1. Local recurrence near the pelvic wall (case 1.1)

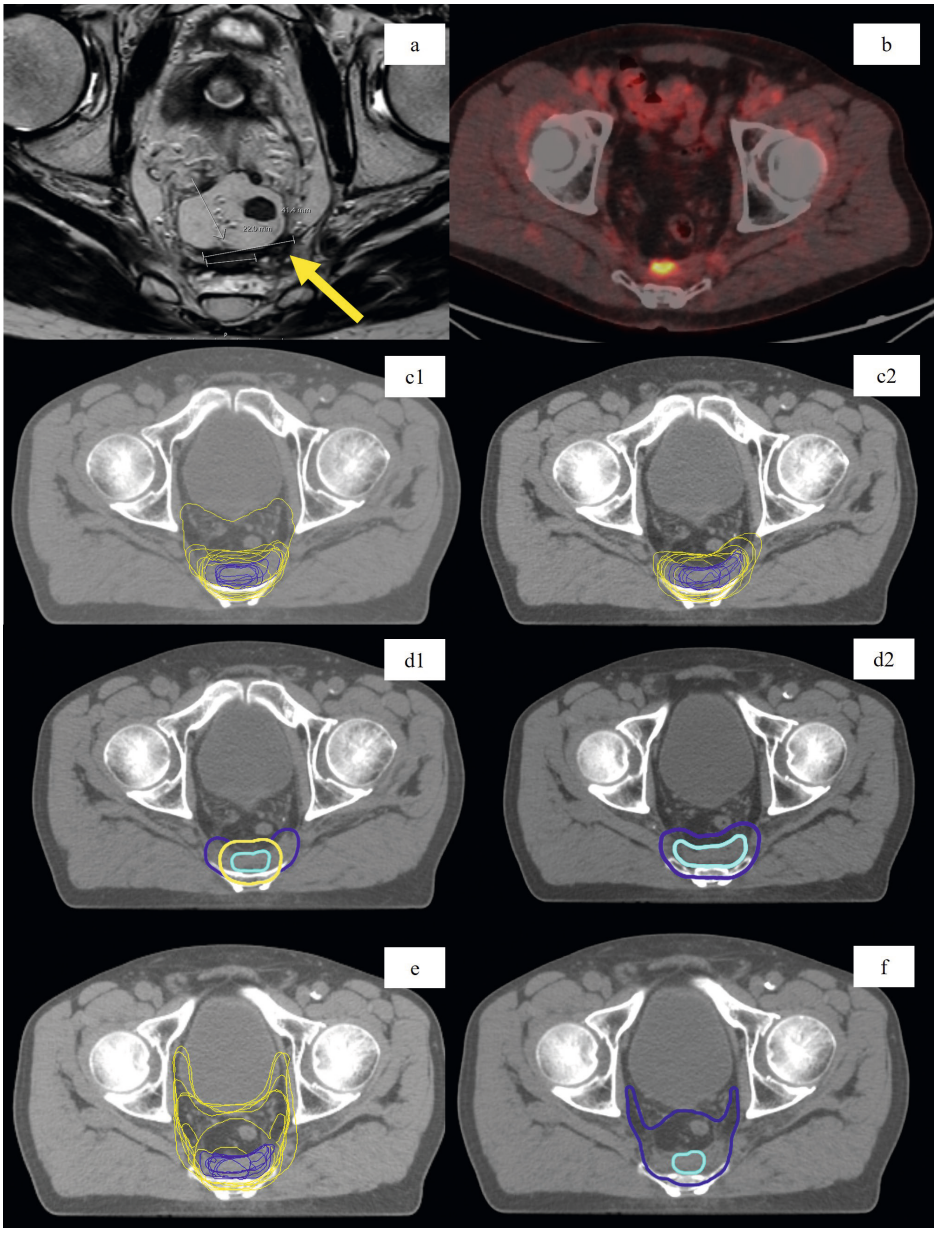
a + b. MRI + PET imaging of local recurrence

c. Dutch and Swedish GTV (blue) and CTV (yellow) delineations

d. Example of consensus delineation of GTV (light blue) and CTV (dark blue)

Case 1.2, 2.1 and 2.2: Unifocal* presacral *local recurrence

- Case 1.2: 74-year-old male with a history of a cT3bN0 distal rectal carcinoma, for which he was treated with neoadjuvant chemoradiotherapy and a low anterior resection. Patient was diagnosed with a unifocal presacral local recurrence, for which he received induction chemotherapy consisting of 3 cycles of CAPOX, to which he responded well. Patient was referred for preoperative chemo reirradiation, followed by resection with intraoperative radiotherapy.
- Case 2.1: Repeat of case 1.2, to test guideline adherence
- Case 2.2: Case presented as RT naive patient: 74-year-old male with a history of a cT3bN0 distal rectal carcinoma, for which he was treated with a low anterior resection. Patient was diagnosed with a unifocal presacral local recurrence, for which he received induction chemotherapy consisting of 3 cycles of CAPOX, to which he responded well. Patient received no chemoradiotherapy for primary rectal cancer. Patient was referred for preoperative full course chemoradiotherapy, followed by resection with intraoperative radiotherapy.



Supplementary figure 2. Presacral recurrence (case 1.2 and 2.1 (reirradiation) and 2.2 (RT naive))

a + b. MRI and PET imaging of local recurrence

c. Dutch and Swedish GTV (blue) and CTV (yellow) delineations of case 1.2 (c1) and 2.1 (c2)

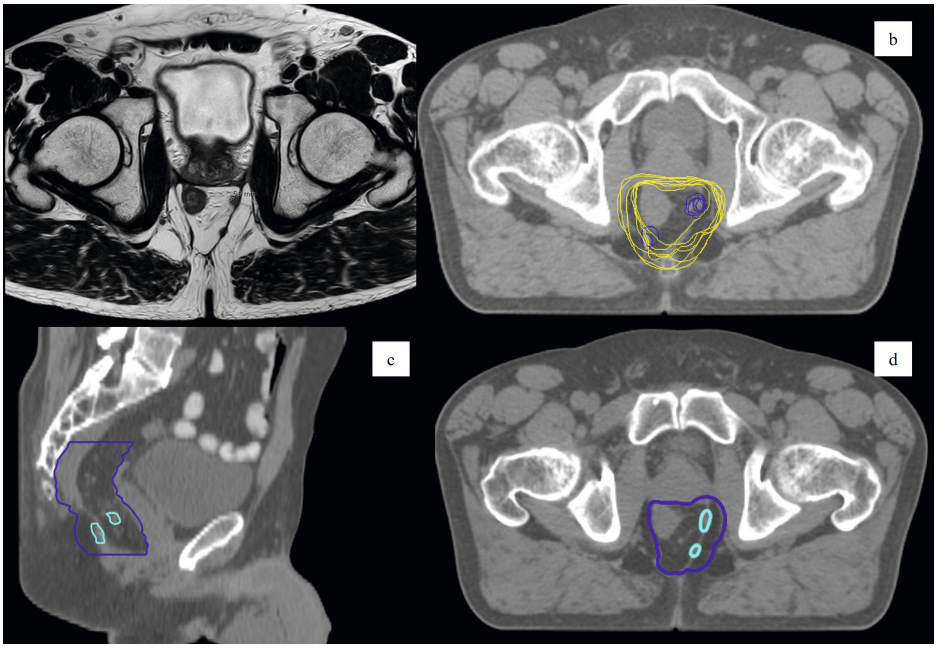
d. Example of a consensus delineation of GTV (light blue) and CTV (dark blue) if tumour can be distinguished from fibrosis (d1) or cannot be distinguished from fibrosis (d2).

e. Dutch and Swedish GTV (blue) and CTV (yellow) delineations in case of a RT naive patient

f. Example of a consensus delineation of GTV (light blue) and CTV (dark blue) of case 2.2 (RT naive)

Case 1.3: Multifocal local recurrence

52-year-old male with a history of a cT3N0 distal rectal carcinoma, for which he was treated with preoperative chemoradiation and a laparoscopic rectal resection. Patient presented with a multifocal local recurrence, consisting of 4 tumour deposits in the mesorectum. Patient received induction chemotherapy, consisting of 3 courses CAPOX to which a metabolic response could be seen. Patient was referred for chemo reirradiation.

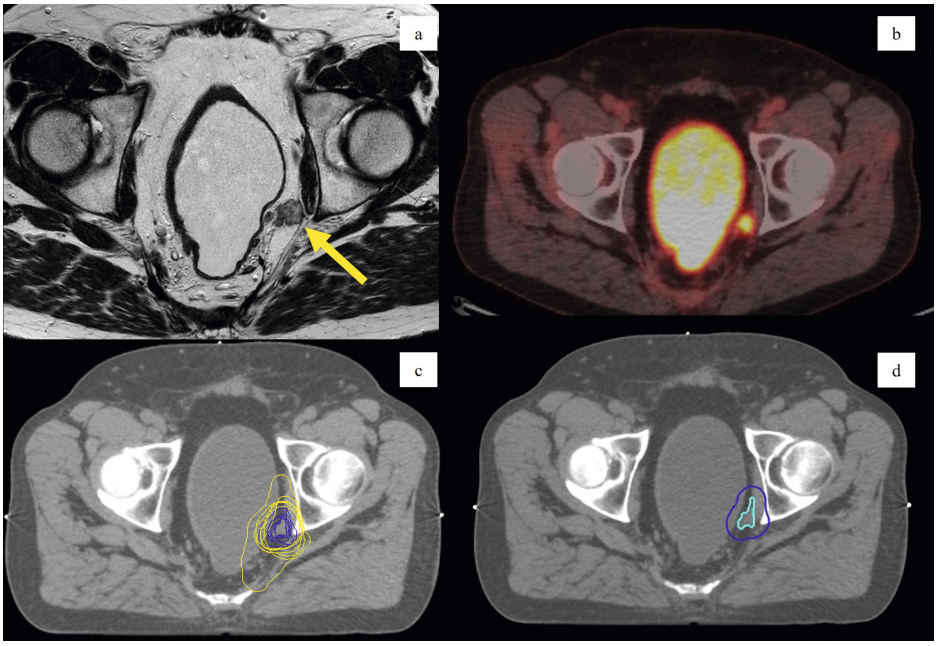


Supplementary figure 3. Multifocal recurrence (case 1.3)

a. MRI imaging of local recurrence
b. Dutch and Swedish GTV (blue) and CTV (yellow) delineations
c. Example of consensus delineation of GTV (light blue) and CTV (dark blue) in sagittal view
d. Example of consensus delineation of GTV (light blue) and CTV (dark blue) in transversal view

***Case 2.3: Unifocal lateral* recurrence**

68-year-old male, with a history of a cT2N0 distal rectal carcinoma, for which he was treated with neoadjuvant chemoradiotherapy and a rectum amputation. Patient was diagnosed with a unifocal lateral local recurrence. Patient was treated with induction chemotherapy, consisting of 4 courses of CAPOX. Patient was referred for chemo reirradiation.



Supplementary figure 4. Lateral recurrence (case 2.3)

a + b. MRI and PET imaging of local recurrence

c. Dutch and Swedish GTV (blue) and CTV (yellow) delineations

d. Example of consensus delineation of GTV (light blue) and CTV (dark blue)

Chapter 3

Dutch National Guidelines for Locally Recurrent Rectal Cancer

Piqeur F, Creemers, DMJ, Banken E, Coolen L, Tanis PJ, Monique M, Roef M, Marijnen CAM, van Hellemond IEG, Nederend J, Rutten HJT, Peulen HMU, Burger JWA

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ABSTRACT

Due to improvements in treatment for primary rectal cancer, the incidence of locally recurrent rectal cancer (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 neoadjuvant 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 extraluminal 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 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, Gastro-enterology, 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.

RESULTS

Expert centres

Clinical evaluation of patients with (suspected) LRRC should be performed in specialized multidisciplinary teams (MDTs), given the complex, heterogeneous disease (figure 1), and the limited data available. Patients should be discussed before 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 extraluminal 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

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 ≥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 28x1.8Gy with concomitant capecitabine (825mg/m^2 bid)) is recommended for radiotherapy naive patients in a curative setting.

14 Chemo reirradiation (15x2Gy with concomitant capecitabine (825mg/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 and 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.

Nonoperative 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 with or without prior radiotherapy and/or chemotherapy. The MRI 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]

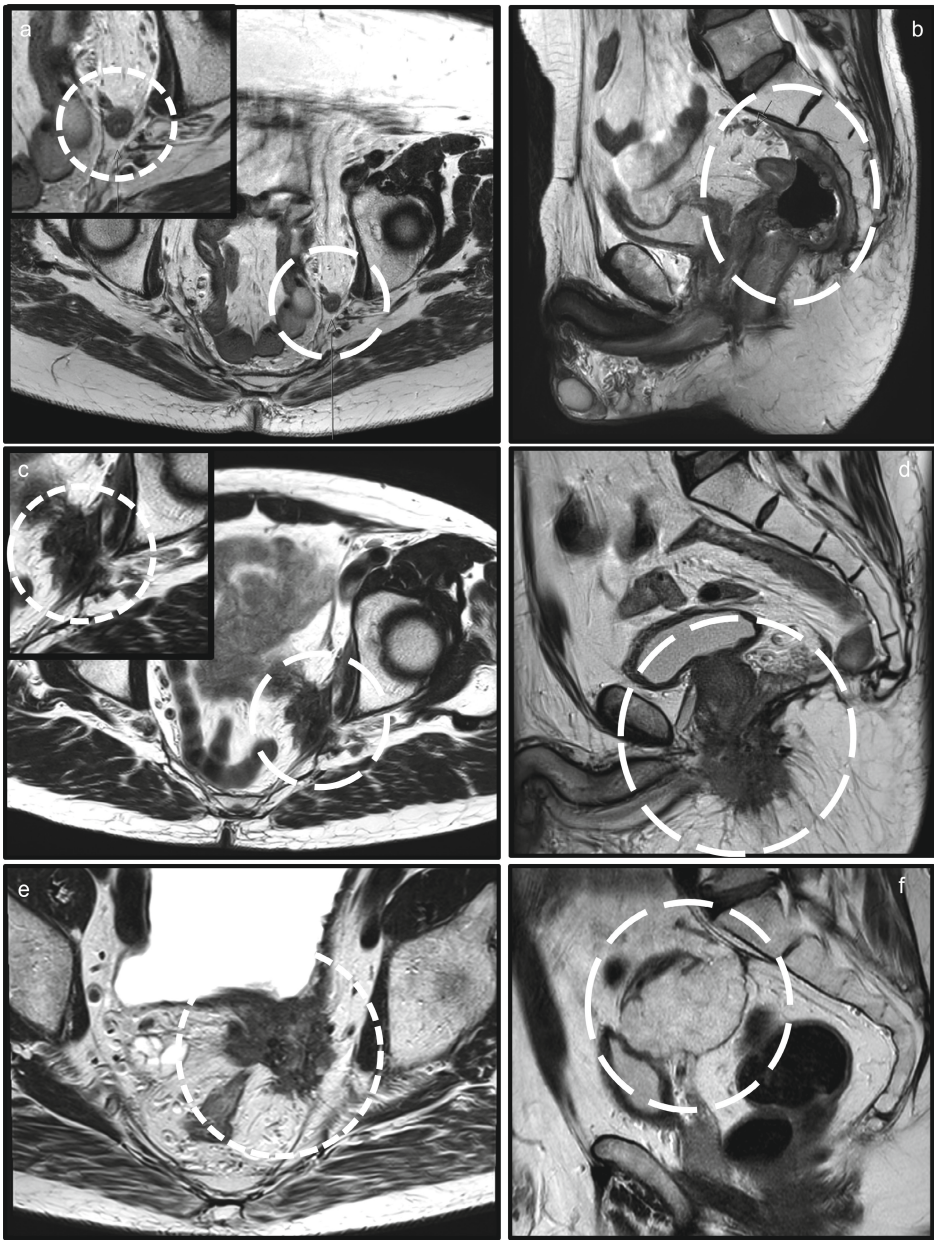


Figure 1. Heterogeneity in local recurrences as seen in 6 individual patients with LRRC, with (a) a lateral nodal recurrence in the obturator space (b) a presacral recurrence concurring in a pre-existent abscess after anastomotic leakage, (c) a lateral recurrence involving the pelvic side wall and sciatic 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.

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 F18-FDG 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, F18-FDG 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 F18-FDG PET/CT can be formally recommended, nor are data available regarding the value of F18-FDG 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 overall survival (OS) (HR 0.41, p<0.001), disease-free survival (DFS) (3-year 56% vs 26% (p<0.001) and local re-recurrence-free survival (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 metastasis-free survival (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 (500mg/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 regard to CRT for LRRC, namely radiotherapy (RT) naive patients and patients undergoing reirradiation, differing in treatment options and prognosis. The ratio of RT naive 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.[2–4,28,45,46] The chance of achieving a pCR should be an additional argument for the use of nCRT (9% pCR after chemo reirradiation, 17% pCR after full course CRT).[40] In both full course CRT and reirradiation, radiotherapy is combined with concomitant capecitabine (825mg/m^2, bidaily). In case of toxicity concerns, Teysuno (25mg/m^2 bidaily) is recommended. Radiotherapy without a radiotherapy sensitizer can be used in case of remaining toxicity concerns in regard to concomitant chemotherapy.

In RT naive 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).[47] 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%.[48] In line with international guidelines, full course nCRT is recommended in patients with LRRC, both in patients with resectable disease and in patients requiring preoperative downstaging.[12,14] For RT naive patients, the same dose is used as for primary advanced rectal cancer, namely 25x2Gy or 28x1.8Gy.[12–14,49]
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.[43,47,50] Sun et al. further showed that in patients with an irresectable LRRC, reirradiation (30-36Gy) 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.[51] 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.[1,4,52,53] This is seen particularly in older cohorts or in patients with irresectable tumours irradiated with higher doses (40Gy) than usual in the Netherlands.[54,55] The same is seen with regard to late toxicity, with reported ≥Gr3 toxicity of 0-48%.[56–58] 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).[45] 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%.[48] 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 (1.2-1.5Gy bid) to facilitate an increased tumour dose without increasing late toxicity, as in the benchmark trial by Valentini et al, prescribing reirradiation up to 40.8Gy (+/- resection).[59] Currently, there is no clear evidence of an efficacy or toxicity difference between hyperfractionation and conventional fractionation up to 30Gy for LRRC.[53] As there is extensive Dutch experience with 30Gy chemo reirradiation (+/- intraoperative radiotherapy), the use of conventional fractionation up to 30Gy is recommended (15x2Gy), in line with the ESTRO-ACROP recommendations.[49]

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.[49] 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.[50,60–63] 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.[48] 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.[10,64] Multidisciplinary involvement in target volume definition is strongly recommended, as interpretation of radiology can prove difficult, 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 (figure 2).[65] 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.[64]
There are no studies that predefine OAR constraints for (re)irradiation in LRRC.[60] 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.[64]

Adjuvant chemoradiotherapy

Only one review by Fadel et al (2022) reports outcomes after adjuvant CRT (45% R0).[66] Five-year local control was only 13%, compared to 49.5% after nCRT and five-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.

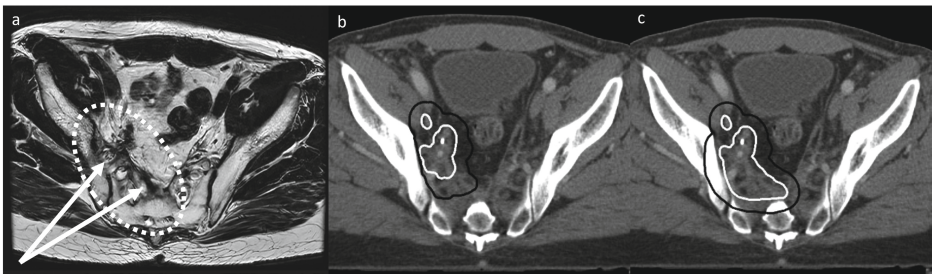


Figure 2. Example of altered radiotherapy target volumes after peer review in a multifocal recurrence. It was advised to extend the gross tumour volume (white) from before (b) to after (c) to encompass complete fibrosis as seen on diagnostic MRI (a). Additionally, it was advised not to edit clinical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

Surgery

Surgical resection of LRRC is the cornerstone of curative treatment. Regardless of prior treatment, an R0 resection is the most important prognostic factor in LRRC.[3,4,66–68] 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.[67] 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).[28,69]

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.[44,67] 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.[69–71] However, omitting surgery can also be accompanied by a reduced QoL, due to pain, fistulation, and tumour mass effect.[70] 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]

Watch-and-wait

Although a watch-and-wait strategy has been adopted into (inter)national guidelines for primary rectal cancer, no cohorts have been published describing this approach 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.

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

Surgical contra-indication	
Poor performance status/medically unfit patients	Absolute
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
Irresectable distant metastases	Relative
Predicted R2 resection	Relative

Intraoperative 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).[72] 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-).[73] In a larger but older meta-analysis in LARRC, a significant effect of IORT was seen on five-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.[74] 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-).[72,74] 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.[75] 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 (1) (possibly) involved resection margins, aiming to avoid re-recurrences, (2) proximity of the tumour to surrounding organs or (3) (expected) narrow resection margins (<1mm). All LRRC patients are at high risk of an R1 resection. It is therefore advised to consult a centre with IORT facilities prior to surgery.[12,13,49]

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 was correlated to 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.[43,49]

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 >30Gy.[53,56,76] 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%.[53]

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 (50-60Gy) for RT naive LRRC, with a 5-year progression-free survival of 35% and a 5-year OS of 54% (without surgery).[77] 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) 48-95Gy, converted EQD2 (α/β=10 Gy) 40-79Gy) in RT naive 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).[78] 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 30Gy reirradiation (5x6Gy) in small recurrences, but toxicity data are lacking.[79] Chung et al. describes outcomes for reirradiation up to a median dose of 50Gy (30-60Gy).[62] 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

(<3.3cm) treated with high dose reirradiation (>50Gy), 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).[80] 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.[81] 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 three-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 three-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.[82] 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.

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SUPPLEMENTARY DATA OF CHAPTER 3

Search Strategy

('locally recurrent rectal cancer'/exp OR ((((local* OR locoregional*) NEAR/2 (recurrence OR recurrent OR recurr*)) OR 'locoregional recurrence'/de) AND ((rect* NEAR/2 (cancer OR tumour* OR tumor* OR maligna* OR carcinoma)) OR 'rectum cancer'/exp))) AND [humans]/lim AND ([embase]/lim OR [medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)

- Search 21-02-2023: 8366 results, of which 221 deemed relevant.
  - 7406 Excluded based on title
  - 538 Excluded based on abstract
  - 201 Excluded based on complete article (21 due to pre-TME data, 8 duplicates, 163 wrong study outcome or population, 9 small cohorts (<10))
- Search 04-08-2023 (from 01-01-2023 onwards): 260 results of which 12 deemed relevant.
  - 243 Excluded based on title
  - 5 Already retrieved from previous search.

Primary research question:

What diagnostic tools are indicated to diagnose locoregional recurrent rectal cancer (LRRC), what determines treatment choice and which multimodal treatment with a curative intent leads to the best outcome?

Defined sub-questions:

1. Is histological or cytological confirmation needed to diagnose LRRC?
2. How should staging and restaging be performed and what elements should be reported in radiological reports?
3. Is there an indication for neoadjuvant systemic treatment for (potentially) resectabel LRRC and what should the neoadjuvant systemic treatment entail?
4. Is there an indication for neoadjuvant chemo (re-)irradiation for (potentially) resectabel LRRC and how should target volumes be defined?
5. How and when should a surgical resection be performed for LRRC?
6. What is the indication for intra-operative radiotherapy for LRRC and what is the optimal interval between neoadjuvant chemo (re-)irradiation and intra-operative radiotherapy?
7. Is there an indication for adjuvant therapy?

8. What local treatment options are there for LRRC patients in the palliative setting?

Outcome measures:

1. Response (on MRI, histological regression, pCR, cCR)
2. Percentage of intended curative treatment
3. Percentage of radical resections
4. Perioperative and postoperative complications
5. Toxicity
6. Overall survival (OS), local recurrence free survival (LRFS), disease free survival (DFS), metastasis free survival (MFS)
7. Functional outcome and QoL
8. Costs

Proposed checklist for radiological reporting (redacted from the PelvEx II trial)

1. Previous surgery: LAR; APR; Other, namely....
2. Focality (number of lesions)
3. Size (if multifocal up to 3 target lesions, greatest size in mm, measured in any plane)
4. Tumour type: solid; mucinous; fibrotic; other (specify)
5. Border: well-defined; lobular/spiculated; irregular
6. Venous invasion (mrEMVI): yes; no; if yes: length in mm
7. Pathological lymph nodes: yes; no
    a. If yes: central; lateral; inguinal; para-aortic; left/right; longest short-axis diameter
8. Primary compartment involved: central; anterior; posterior; lateral
9. Compartments
    a. Centrally involved organs/structures
        i. Anastomosis: yes; no; not applicable
        ii. Levator ani: left; right; both; no; not applicable
        iii. Puborectalis muscle: left; right; both; no; not applicable
        iv. Sphincter complex: yes; no; not applicable
        v. Gluteal muscle: left; right; both; no
        vi. Perineum: yes; no
    b. Anterior involved organs/structures
        i. Vagina; anterior wall; posterior wall; left; right; introitus; no; not applicable
            1) If applicable; invasion of fornix anterior; fornix posterior; fornix lateralis (left/right)

ii. Cervix: yes; no; not applicable
iii. Uterus: yes; no; not applicable
iv. Ovaries: left; right; both; no; not applicable
    1) If yes; is the ovary locally involved or is at a peritoneal metastasis?
v. Prostate: yes; no; not applicable
vi. Seminal vesicles; left; right; both; no; not applicable
vii. Bladder: dome; trigonum; no; not applicable
viii. Peritoneum: yes; no
ix. Small bowel: yes; no
x. Colon: yes; no
xi. Omentoplasty: yes; no; not applicable
xii. Other (e.g. VRAM): yes; no; not applicable

c. Posterior
    i. Most cranial extension: L5; S1; S2; S3; S4; S5; Coccyx
    ii. Involved organs/structures
        1) Presacral fascia: yes; no
        2) Periosteum/cortex: yes; no
        3) Marrow: yes; no
        4) Neuroforamen S1-S2: yes; no
        5) Neuroforamen S3-S5: yes; no

d. Lateral
    i. Height: above piriform muscle; at level of piriform muscle, below piriform muscle
    ii. Location: (mainly) within lateral pelvic fascia; at level of lateral pelvic fascia; (mainly) outside lateral pelvic fascia
    iii. Involved organs/structures
        1) Ureter: left; right; both; no
        2) Sciatic nerve: yes; no
        3) Lumbosacral plexus: yes; no
        4) Nerve roots S1-S2: yes; no
        5) Nerve roots S3-S5: yes; no
        6) Sacrospinous ligament: left; right; both; no
        7) Piriformis muscle: left; right; both; no
        8) Obturator compartment: left; right; both; no
        10. Vessels

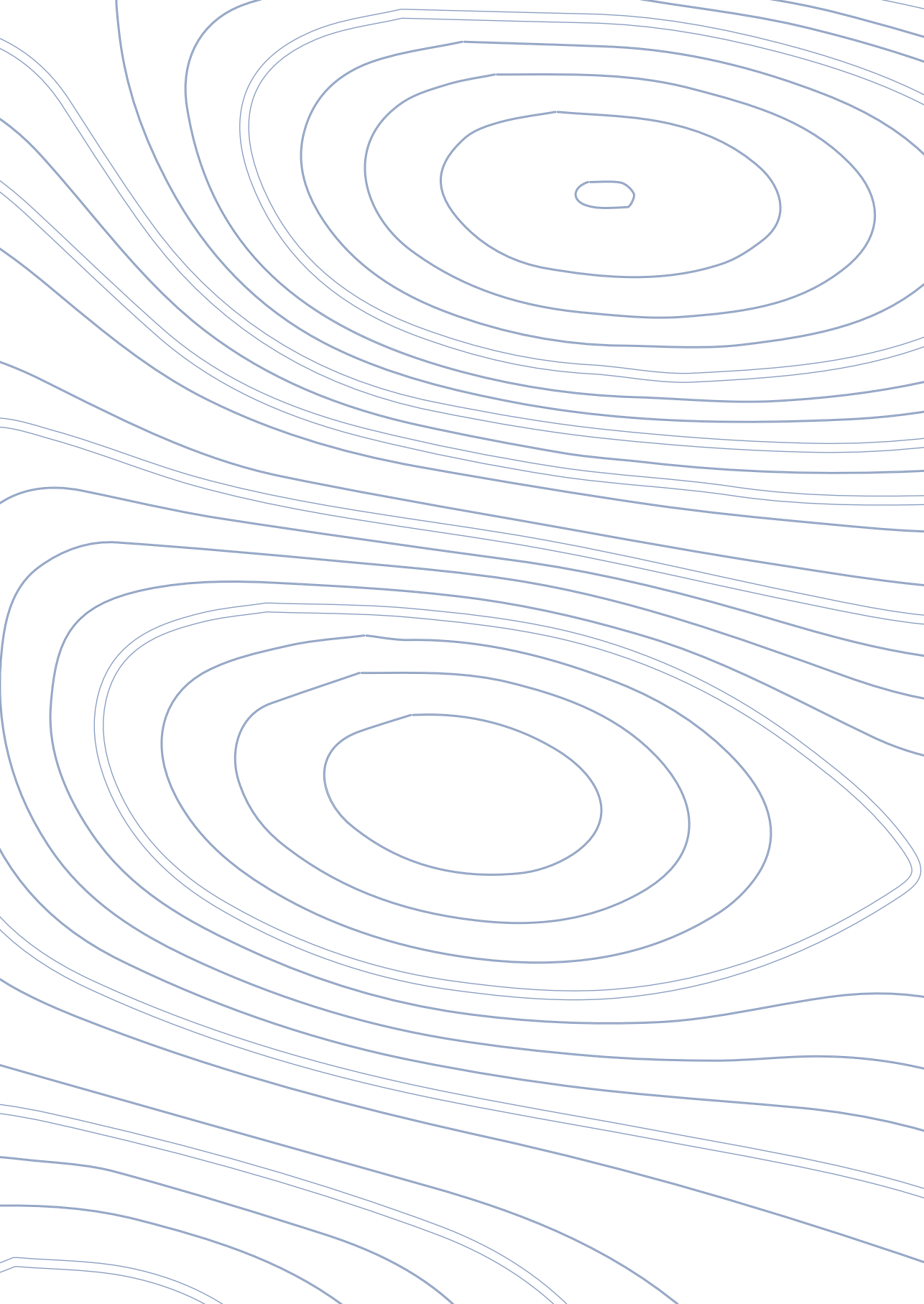
a. Common iliac vein: left; right; both; no

b. Common iliac artery: left; right; both; no
c. Internal iliac vein: left; right; both; no
d. Internal iliac artery: left; right; both; no
e. External iliac vein: left; right; both; no
f. External iliac artery: left; right; both; no

11. Abscess present: yes; no
12. Other complications: yes; no
    a. If yes; please specify
13. (If applicable) Evaluation after chemotherapy/chemoradiotherapy
    a. Overall estimated response
        i. Poor response: limited volume reduction, obvious residual solid mass on T2W and/or persistent mass like diffusion restriction on DWI
        ii. Good response: obvious volume reduction, predominantly fibrosis with only minor residual tumour tissue on T2W and/or small foci of DWI signal
        iii. Complete or near complete response: obvious volume reduction, homogeneous fibrosis without iso-intense nodule or mass and absence of diffusion restriction
        iv. Progression
    b. Extent of residual fibrosis and involvement of surrounding structures (based on previously mentioned checklist)
    c. (Residual) suspect lymph nodes: yes; no
        i. If yes; how many suspect lymph nodes visible and at what location?

Part II

Improving radiotherapy for locally recurrent rectal cancer



Chapter 4

Multidisciplinary approach to target volume delineation in locally recurrent rectal cancer: an explorative study

Piqeur F, van Gruijthuijsen DSC, Nederend J, Ceha H, Stam T, Dieters M, Meijnen P, Bakker-van der Jagt M, Intven M, Verrijssen AE, Cnossen JS, Berbee M, den Hartogh M, Bantema-Joppe EJ, De Kroon M, Paardekooper G, Gielens M, Daniels-Gooszen AW, Lahaye MJ, Lambregts DMJ, Oei SA, Houwers JB, Horsthuis K, Hurkmans C, Rutten HJT, Burger JWA, Marijnen CAM, Peulen HMU.

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ABSTRACT

Background and purpose: Interobserver variation (IOV) in locally recurrent rectal cancer (LRRC) delineation is large, possibly due to different interpretations of imaging. An explorative study was performed to investigate the benefit of additional delineations by expert radiologists.

Materials and methods: 14 cases of LRRC were delineated on planning CT by 8 radiologists (RADs) to construct a median and total radiology contour, followed by 12 radiation oncologists (ROs), without (GTV-) or with (GTV+) the additional contours. IOV was calculated separately for RADs, GTV- and GTV+. The following metrics were used: the Surface Dice Similarity Coefficient (SDSC), Dice similarity coefficient (DSC), and Hausdorff Distance at the 98th percentile (HD98%). The median SDSC, DSC, and HD98% of GTV- and GTV+ were compared. Analyses of IOV in different recurrence types were performed.

Results: Median SDSC, DSC and HD98% significantly improved from GTV- to GTV+ overall, but a significant benefit could not be proven in individual cases. Additional radiological input consistently improved all parameters in 4/14 cases (29%). Subgroup analyses show large IOV in mainly fibrotic and intraluminal recurrences. Little IOV is seen in solitary nodal recurrences.

Conclusion: This study highlights target volume delineation challenges in LRRC. Overall, radiological input reduced IOV amongst ROs in target volume delineation for LRRC. Large differences do however exist amongst recurrence types. A standard terminology for LRRC and close collaboration between radiologists and radiation oncologists seems necessary to reduce IOV and improve quality of care.

INTRODUCTION

Neoadjuvant chemoradiotherapy (nCRT) in locally recurrent rectal cancer (LRRC) is used to facilitate preoperative downstaging, to improve the chances of a complete surgical resection, which is currently the strongest predictor of oncological outcome in patients with LRRC.[1–6] Although the use of nCRT is common, many questions still need answering, such as appropriate radiotherapy target volumes. Previously, we defined target volumes based on consensus following a delineation study.[7] It showed that multidisciplinary evaluation of LRRC was indispensable for delineation. Surgical input proved important for determining the clinical target volume (CTV), whereas radiological support proved important in defining the gross tumour volume (GTV) by providing background on the measure of uncertainty in imaging.

We further noticed a large interobserver variation (IOV) amongst radiation oncologists (ROs) in delineations.[7] Especially in fibrotic tumours this might be explained by the challenging differentiation between fibrosis and tumour.[8,9] Efforts to reduce IOV such as adding diffusion-weighted imaging (DWI) to MRI, seem beneficial.[10–13] However, the positive predictive value of MRI in determining involvement of organs can be low.[14,15]

Previous studies have shown that delineation inaccuracy is clinically relevant as it may correlate with clinical outcomes. Non-compliance with radiotherapy protocols in clinical trials has been associated with poorer oncological outcomes, specifically an increased local failure rate and decreased overall survival, e.g., as seen in the HeadSTART trial in head and neck cancer.[16,17] In this trial, up to 25% of reported protocol violations in the non-compliant group could be related to incorrect delineation. Although supporting data are lacking, it is plausible that delineation inconsistencies in LRRC may also influence oncological outcomes.

IOV amongst ROs has been described in several tumour sites.[16,18] High IOV means the likelihood of inaccurate delineations increases. It is therefore important to reduce IOV, thereby hopefully improving accuracy of delineations on a population level. Ideally, delineations would be correlated to pathological specimens to determine accuracy, but obtaining intact specimens and orientating the specimens can be very challenging, especially for LRRC (for example, in the case of multifocal recurrences or when re-resections are performed).[19]

Given the complexities and uncertainties of interpreting radiological images in LRRC, the input of a radiologist on what is deemed macroscopic tumour may reduce IOV. In this exploratory study, it is hypothesized that IOV among ROs will decrease if provided with extra radiological information in the form of a LRRC tumour demarcation by expert radiologists.

MATERIALS AND METHODS

The participants were recruited from PelvEx II trial centres. The PelvEx II trial is a randomized controlled trial investigating the benefit of induction chemotherapy prior to nCRT and surgery for non-metastatic LRRC.[20] Radiologists were all recruited from PelvEx II expert centres, as defined in the protocol, whereas ROs were recruited from all centres providing nCRT.

Fourteen cases of LRRC were selected from a prospectively maintained LRRC database in the Catharina Hospital Eindhoven, according to the following criteria: (1) patients who underwent curative treatment for LRRC; (2) patients who received nCRT after 2016; (3) baseline imaging consisting of at least one MRI and (if applicable) imaging after induction chemotherapy of LRRC was available; (4) Complete DICOM data of nCRT for LRRC was available.

Clinical case summaries consisting of medical history and details of the local recurrence were provided. Original radiology reports were provided to ROs. Rigid registration of planning CT to baseline MRI and, if applicable, MRI after induction chemotherapy and/or FDG-18 PET/CT at baseline and/or after induction chemotherapy was done by an experienced radiotherapy technologist. All available imaging was anonymized and distributed in a DICOM format. A summary of cases can be found in table 1. No delineation guidelines were available, and no observer had insight into delineations performed by other participants.

Expert radiologists in colorectal imaging delineated macroscopic tumour on the planning CT in all 14 cases. A median delineation was constructed using an in-house script developed in RayStation 10B-SP1, incorporating each voxel that was deemed tumour by >50% of the radiologists. Additionally, a total delineation showing each voxel that was deemed tumour by at least one radiologist was provided.
ROs were asked to delineate the GTV on planning CT as in clinical practice. ROs delineated all 14 cases, seven without additional delineations and seven with the previously constructed

radiology delineations. The cases were alternated so that no RO received a case twice and so that the number of ROs delineating without (GTV- group) and with (GTV+ group) the radiology delineation was similar.

Radiological IOV was calculated in reference to their median contour. IOV amongst ROs was also calculated in reference to the median of their respective group. To do so, GTV- and GTV+ median delineations were constructed following the same definition as the radiological median, i.e., incorporating each voxel deemed GTV by >50% of the ROs of their respective group.

The following metrics were used to analyse IOV: Dice Similarity Coefficient (DSC), Surface Dice Similarity Coefficient (SDSC), and Hausdorff Distance at the 98th percentile (HD98).[21,22] As IOV can be described in several metrics that do not necessarily correlate with each other, the described metrics are often used to complement each other.[22] The DSC is defined as twice the intersection of two delineations divided by the sum and is a simple volume-based metric. The SDSC is defined as the agreement of the surface of two delineations within a certain threshold. A threshold of three millimetres was used, as introduced by Nikolov et al.[23] Outliers were evaluated using the Hausdorff distance (HD), defined as the maximum of all smallest distances from each point on the observer's delineation to the median delineation. A lower HD (mm) indicates a lower variation. The HD at 100% level is extremely sensitive to outlying points. To reduce the influence of outlying points, HD was calculated at the 98% level (HD98%). A mean distance to agreement with standard deviation (SD) was calculated for each case and overall, as shown in the supplementary material. All analyses were performed using an in-house research tool developed in RayStation ® (Version 12A-SP1, RaySearch Laboratories AB, Sweden, Released 2022).

To facilitate interpretation of each metric, the following gross cut-off values were chosen; SDSC or DSC<0.6 was categorized as large variation, 0.6 ≤SDSC or DSC<0.8 as average variation and ≥0.8 as little variation. A HD98% of <10mm was classified as little variation, a HD98% ≥20mm was defined as large variation, 10mm≤HD98%<20mm was categorized as average variation. The absolute differences in SDSC, DSC, and HD98% were calculated by subtracting the median GTV- from the median GTV+ values. To determine relevant absolute changes, a threshold of +/- 0.1 was used for DSC and SDSC, and a threshold of +/- 3mm was used for HD98%.

Continuous data were reported as median (with interquartile range (IQR) and/or range). Group comparisons were performed using the Mann-Whitney U test. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0.0.0, IBM Corp. Released 2023. Armonk, NY: IBM Corp. Comparative results were deemed statistically significant if $\alpha \leq 0.05$.

Table 1. Summary of baseline characteristics

#	Radiotherapy	# of lesions	Recurrence type
1	25x2	1	Lateral sidewall
2	15x2	2	Presacral in fibrosis
3	15x2	1	Anastomotic with presacral involvement
4	15x2	>3	Multifocal; along mesorectal TME-planes
5	25x2	2	Multifocal; presacral and central
6	25x2	2	Anastomotic with presacral involvement
7	15x2	1	Lateral nodal
8	15x2	1	Lateral sidewall
9	15x2	1	Anastomotic
10	15x2	1	Lateral nodal
11	15x2	1	Presacral in fibrosis
12	15x2	1	Presacral abscess
13	15x2	2	Multifocal; central and perineal
14	15x2	1	Anastomotic

RESULTS

Eight radiologists and twelve ROs participated in this study. All radiologists returned all 14 cases (112 delineations). ROs returned 157 delineations (n=82 GTV-, n=75 GTV+, range 9-12 per case). The data were screened for structurally outlying observers by assessing each metric for each observer across all cases, but these were not found. Median SDSC, DSC and HD98% of each group (RADs, GTV- and GTV+), with absolute differences in each parameter (GTV+ minus GTV-), are shown in table 2.

Four cases showed a large variation in all parameters amongst radiologists. Of these cases, two cases were anastomotic recurrences, and one was a recurrence located in an abscess. The large variation seen in the lateral nodal recurrence can be explained by a second lesion that was interpreted as GTV by some but considered benign by others.

When disregarding this second lesion, IOV within the recurrence itself seemed little upon visual inspection.
DSC in all cases was lower amongst radiologists compared to radiation oncologists. As GTV volumes are consistently smaller amongst radiologists compared to ROs, as shown in Table S1, and DSC is heavily influenced by volume, direct comparison is not possible. Little variation is seen in seven cases based on SDSC and HD98% alone.

In four cases, an improvement in IOV from GTV- to GTV+ that was consistent along all parameters was seen (Table 2), indicating a potential benefit from exposure to the radiology contours. In one case, a deterioration of all parameters was seen. Here, variation amongst radiologists was also large, possibly introducing uncertainties. In five cases, there were no relevant changes in any parameter used, indicating no benefit from the exposure to radiology contours. Interestingly, three of these cases were lateral recurrences.

In the four remaining cases, differences could only be detected in the median HD98%, ranging from an improvement of 29mm up to a deterioration of 31mm. In one of these cases, a second perineal lesion was missed by all radiologists. All ROs (n=5) in the GTV- group contoured both lesions. In contrast, in the GTV+ group, 4/6 ROs did not contour the perineal lesion, possibly influenced by the radiological miss, causing the median HD98% to increase steeply. Three examples of recurrences in which exposure to the radiology contours decreased IOV, increased IOV and had no influence on IOV are shown in figure 1.

Table 2. Median SDSC, DSC and HD98% for Radiologists (RAD), radiation oncologists not exposed to radiology contours (GTV–), and radiation oncologists that were exposed to the radiology contours (GTV+). Cells with large variation are marked dark blue, with average variation marked light blue, and with little variation marked white. The absolute difference between GTV+ and GTV- contours is categorized as relevant improvement (green), no relevant difference (yellow), and relevant deterioration (red).

#	RADs			ROs GTV-			ROs GTV+			Difference		
	SDSC	DSC	HD98%	SDSC	DSC	HD98%	SDSC	DSC	HD98%	SDSC	DSC	HD98%
1	0.84	0.6	6	0.54	0.54	22	0.91	0.75	5	+0.37	+0.21	-17
2	0.87	0.56	7	0.63	0.58	18	0.95	0.76	6	+0.32	+0.18	-12
3	0.56	0.42	24	0.42	0.49	35	0.63	0.63	25	+0.21	+0.14	-10
4	0.8	0.6	17	0.75	0.69	19	0.88	0.82	15	+0.13	+0.13	-4
5	0.86	0.65	31	0.87	0.74	37	0.91	0.76	8	+0.04	+0.02	-29
6	0.84	0.72	7	0.86	0.8	13	0.89	0.77	7	+0.03	-0.03	-6
7	0.32	0.17	22	0.85	0.71	7	0.92	0.74	6	+0.07	+0.03	-1
8	0.94	0.78	6	0.92	0.84	6	0.94	0.84	5	+0.02	0	-1
9	0.86	0.63	8	0.71	0.64	12	0.71	0.69	12	0	+0.05	0
10	0.99	0.74	3	1	0.81	2	1	0.81	3	0	0	+1
11	0.44	0.32	9	0.63	0.65	11	0.6	0.65	12	-0.03	0	+1
12	0.33	0.4	29	0.75	0.86	9	0.69	0.8	23	-0.06	-0.06	+14
13	0.94	0.75	5	0.91	0.71	6	0.83	0.71	37	-0.08	0	+31
14	0.16	0.04	26	0.82	0.82	18	0.66	0.7	23	-0.16	-0.12	+5

Overall, a mean distance to agreement of 3.86mm was seen amongst all contours by ROs, with an overall SD of 2.27mm, as shown in table S2.

The observed differences were not statistically significant for any single parameter in individual cases, except a significant decrease of median HD98% in case 1 (22mm GTV- to 5mm GTV+, p=0.002). When comparing all GTV- versus all GTV+ contours, only the improvement in SDSC reached statistical significance, as shown in table 3. When excluding cases where radiologists demonstrated large variation (possibly introducing more uncertainties), overall SDSC, DSC and HD98% all significantly improved in the GTV+ group versus the GTV- group, indicating a benefit of the exposure to radiological delineations.

Characteristics and focality of recurrences seem to influence IOV (table 4). The largest IOV is seen in fibrotic recurrences, followed by intraluminal recurrences. The smallest IOV is seen in lateral recurrences, specifically solitary nodal recurrences. The same pattern is seen amongst radiologists (Table S3).

Table 3. Overall median SDSC, DSC and HD98% (mm) of GTV- contours and GTV+ contours. Analyses were performed for all cases and excluding cases with large IOV among radiologists, i.e., cases 3, 7, 12, 14.

		SDSC	**IQR**	**DSC**	**IQR**	**HD98**	**IQR**
All RO contours (n=157)	GTV-	0.84	0.60-0.91	0.72	0.60-0.81	11	6-23
	GTV+	0.88	0.69-0.95	0.76	0.65-0.82	7	5-21
	p-value	**0.019**		**0.116**		**0.075**	
Excluding cases 3, 7, 12, 14 (n=109)	GTV-	0.84	0.65-0.92	0.73	0.62-0.80	11	6-17
	GTV+	0.89	0.80-0.97	0.77	0.68-0.82	6	4-12
	p-value	**0.008**		**0.026**		**0.016**	

Table 4. IOV per group in different recurrence types, categorized as seen in Table 1. The largest IOV is seen in intraluminal and fibrotic recurrences. The smallest IOV is seen in lateral recurrences, specifically in solitary lymph node recurrences. Comparisons are made between median SDSC, DSC and HD98% for GTV- contours and GTV+ contours.

		GTV-		GTV+		p-value
		n=	Median	n=	Median	
Lateral recurrence	SDSC	23	0.85	22	0.95	0.060
4 cases included	DSC		0.72		0.79	0.199
	HD98		7		5	**0.024**
Solitary lymph node recurrence	SDSC	11	0.94	10	0.96	0.756
2 cases included	DSC		0.72		0.79	0.654
	HD98		6		5	0.918
Multifocal recurrence	SDSC	27	0.86	26	0.89	**0.040**
5 cases included	DSC		0.73		0.76	0.072
	HD98		13		7	0.107
Anastomotic recurrence	SDSC	24	0.77	21	0.77	0.741
4 cases included	DSC		0.72		0.75	0.750
	HD98		14		12	0.517
Fibrotic recurrence	SDSC	24	0.58	21	0.69	0.155
4 cases included	DSC		0.59		0.67	0.487
	HD98		14		12	0.495

A: Cases included in the analysis of lateral recurrences: 1, 7, 8, 10
B: Cases included in the analysis of solitary lymph node recurrences: 7, 10
C: Cases included in the analysis of multifocal recurrences: 2, 4, 5, 6, 13
D: Cases included in the analysis of intraluminal recurrences: 3, 6, 9, 14
E: Cases included in the analysis of fibrotic recurrences: 2, 3, 11, 12

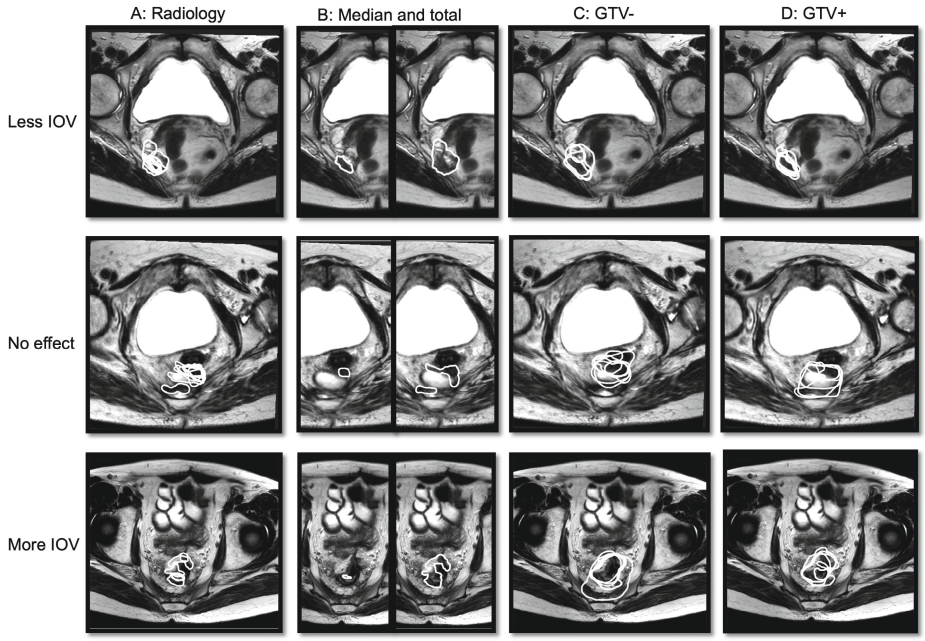


Figure 1. Three examples of recurrences with the constructed radiology contours and its effect on IOV. From left to right, MRI with contours by (a) radiologists, (b) median (left) and total (right) radiology contours, (c) GTV- contours and (d) GTV+ contours are shown for each case. From top to bottom, IOV decreased (case 1), remained the same (case 9) and IOV increased (case 14) from GTV- to GTV+.

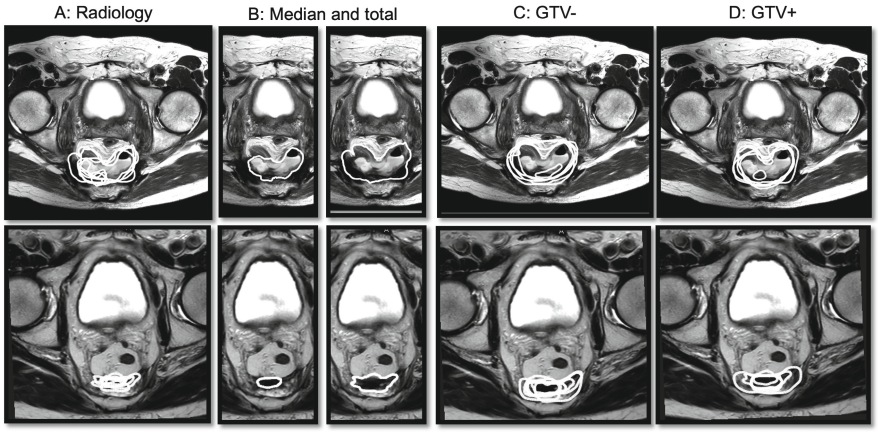


Figure 2. Two examples of recurrence types in which different interpretations of GTV may be explanatory for the observed IOV. From left to right, MRI is shown with (a) delineations by radiologists, (b) constructed median (left) and total (right) radiology contours, (c) delineations by GTV- group and (d) delineations by GTV+ group. The top row shows a recurrence located within a presacral abscess. The bottom row shows a presacral, fibrotic tumour. In both cases, observers either delineated the whole abscess (RADs 4/8; GTV- 5/6; GTV+ 4/5) or fibrosis (RADs 3/8; GTV- 4/6; GTV+ 3/5), or delineated tumour within the abscess (RADs 4/8; GTV- 1/6; GTV+ 1/5) or fibrosis (RADs 5/8; GTV- 2/6; GTV+ 2/5). In both cases, no difference in IOV with or without radiology contours was seen.

DISCUSSION

This study is, to our knowledge, the first to specifically target IOV in LRRC. Our results suggest that providing radiological delineations can reduce IOV, mainly when there is large up-front IOV amongst ROs. No benefit of radiology contours is reported in cases where overall agreement is already high (i.e., little IOV), as seen in solitary nodal recurrences. Certain recurrence types (such as fibrotic recurrences) result in large IOV amongst radiologists and ROs. For these subtypes, a multidisciplinary approach with optimal integration of all available clinical and radiological information seems crucial in optimizing target volume delineation.

Overall, a small but significant improvement of IOV is seen when comparing all GTV- contours with GTV+ contours, when excluding cases with large variation amongst radiologists. This is shown by improved volumetric agreement (DSC), improved surface agreement (SDSC) and decreased outlying boundaries (HD98%) in GTV+ compared to GTV- contours. By reducing IOV, the chance of inaccurate delineations may decrease, although there is no way verify the accuracy (or quality) of the performed contours, as it not feasible to correlate the delineations to pathology. The observed reduction of IOV may however be a sign that a multidisciplinary approach to delineation can aid in target volume delineations for LRRC patients. The effect is, however, only small and varies significantly between individual cases.

In four cases an improvement was seen in all parameters. When visually inspecting these cases, we could see less tumour miss (compared to the radiology contours) (n=2) and significantly smaller GTVs (n=2) in the GTV+ delineations versus the GTV- delineations. In case 4, 4/5 GTV- contours contained tumour miss when comparing them to the radiology contours versus 0/4 in the GTV+ contours. In this study therefore, a reduction in IOV may also translate in a true clinical benefit in 29% of cases. This would be in line with a previous study by Dimigen et al., that reported changes in target volumes in up to 25% of cases when a radiologist is incorporated into the radiation oncology workflow.[24] We would therefore recommend consultation with dedicated radiologists when determining target volumes for LRRC. However, further optimisation of the collaboration and delineation process is needed.

A first step in optimizing the delineation process may be to develop a common language for LRRC. As shown in Figure 2, differences in interpretation of GTV in, for example, fibrotic

tumours and tumours located in an abscess may have hampered IOV results amongst both radiologists and radiation oncologists. The lack of a standard definition of GTV is not a new phenomenon and is seen in several tumour types.[16] In primary rectal cancer, Sluckin et al. detailed several differences in the anatomical interpretation of lateral lymph nodes amongst the disciplines involved, possibly complicating multidisciplinary communication.[25] Given the complexity and heterogeneity of LRRC, due to factors such as differences in recurrence locations and types, differences in previous (neoadjuvant) treatment, altered anatomy after prior surgery, and the loss of normal anatomical boundaries, it is highly likely that interpretation and nomenclature differences are even more substantial in LRRC than in primary rectal cancer.

Ideally, the aim should be to reach consensus on the interpretation of the GTV amongst radiologists and radiation oncologists, to ensure we are 'speaking the same language', and to adjust radiological aid and reporting accordingly. The ESGAR, ESUR and PelvEx collaborative groups are standardizing radiological reporting for patients that are planned to undergo a pelvic exenteration, such as for LRRC.[26] Given the overlap in patient groups, this standardized reporting may also be beneficial for collaboration amongst ROs and radiologists. As of now, we would advise radiologists to detail all (possibly) involved structures and indicate a measure of uncertainty. Demarcations of involved and at-risk areas within the small pelvis may prove helpful in determining tumour extent.

In addition to a standard definition of GTV, a broad consensus on target volumes should be reached. Parallel to the timeframe of this study, a multidisciplinary, consensus-based delineation guideline for LRRC was developed.[7,20] Within the guideline, some differences in GTV interpretation were addressed, such as how to delineate fibrotic tumours, which may have reduced IOV in these cases. However, some observed differences are yet to be specified, such as whether or not to delineate the whole lumen as GTV in anastomotic recurrences. In these instances, the aid of a delineation performed by a radiologist may only be useful after a common interpretation of GTV is established in a delineation guideline.[18] The current study may help in the development of the guideline by highlighting areas of disagreement.

The established guideline combined with prospective peer-review of delineations is currently being evaluated within the PelvEx II trial.[20] In primary rectal cancer, central review of delineations in the PROCARE study led to alterations in up to 74% of cases.[27]

Moreover, the PROCARE study enabled identification of subregions with the least contouring agreement. Subsequent refinement of the consensus guidelines led to higher uniformity in delineations and led to a decrease in the number of alterations to 53%.[28] Quality assurance in the PelvEx II trial will hopefully lead to similar results, by facilitating guideline development and improving uniformity of CRT treatment. Preliminary data from the PelvEx II study have already shown that target volumes are altered in up to 50% of cases after peer-review for LRRC.[29]

Lastly, we would propose working towards agreement on which imaging to use and how to ensure proper visibility and comparability. MRI is the gold-standard modality for locoregional evaluation of LRRC, due to its superior soft tissue visualisation.[8,9,30,31] However, contouring and treatment planning for LRRC is often CT-based. Matching diagnostic MRI to CT is an easy way to facilitate contouring but may lead to setup errors, even more so with angulated images, also complicating comparability. Incorporating an MRI in radiotherapy position into the standard radiotherapy workflow for LRRC patients is a robust way to aid clinicians in delineation by improving image comparability.

Performed subgroup analyses show interesting differences in IOV amongst recurrence types. In solitary nodal recurrences, very little IOV was seen, explaining why no further improvement was seen when comparing GTV- to GTV+, whereas in recurrences located in fibrosis, much larger IOV was seen. Although the groups are small, limiting conclusions, there is a suggestion of an improved IOV from GTV- to GTV+ due to radiological aid, mainly in fibrotic recurrences (SDSC 0.58 to 0.69). Multidisciplinary delineations may therefore still be beneficial, but with more clinical and numerical effect in certain recurrence types than others.

There are several limitations to the current study. As not all ROs returned all cases, the number of contours per group varied, potentially influencing results both for better and for worse. The total number of participants was large, however the number of ROs per group was small, limiting the strength of comparisons. Median and total radiology contours were constructed from 8 delineations performed by expert radiologists. Nevertheless, there is no way to guarantee that these delineations are more accurate than delineations performed by ROs. Moreover, large IOV amongst radiologists is also reported, and this approach can introduce errors such as tumour miss, as reported.

Radiologists mentioned they were hindered by the lack of repeated imaging, complicating recognition. Prior imaging was often unavailable, due to the patient selection from our tertiary referral centre, where patients are discussed after LRRC diagnosis rather than during follow-up, and previous imaging is therefore often not retrieved unless there is clinical doubt.

At the time of the initiation of this study, no formal delineation guidelines or reporting guidelines for LRRC were available. All observers were therefore instructed to delineate primarily on planning CT, as in clinical practice, but without a guideline detailing GTV definition. As discussed earlier, this can lessen the effect of radiological support, as differing interpretations of GTV seemed more influential than spatial disagreement in several cases.

Lastly, IOV is described in metrics, each with their own strengths and weaknesses. By combining three metrics and focussing on differences that were consistent along all three metrics, we have tried to overcome these issues.

CONCLUSION

This study highlights target volume delineation challenges in LRRC. Overall, radiological input reduced interobserver variation amongst radiation oncologists in target volume delineation for LRRC. Large differences do however exist amongst recurrence types. A standard terminology for LRRC and close collaboration between radiologists and radiation oncologists seems necessary to reduce IOV and improve quality of care.

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SUPPLEMENTARY DATA OF CHAPTER 4

Table S1. Median volume (with IQR) amongst radiologists and radiation oncologists per case. For radiation oncologists, median volume of both GTV- and GTV+ group contours are also provided.

#	Radiologists		Radiation Oncologists			
	Median	IQR	Median	IQR	Median GTV-	Median GTV+
1	3.55	2,17-4,45	8.80	5,79-24,68	21.85	5.92
2	2.26	1,23-3,37	5.56	4,50-16,06	12.93	4.50
3	13.93	3,72-22,69	42.61	17,49-91,79	59.53	27.35
4	34.25	21,02-48,73	90.67	58,51-105,21	83.00	91.26
5	5.63	3,92-6,38	10.82	9,96-15,06	10.73	11.57
6	17.09	12,15-21,58	27.77	19,98-32,40	29.82	19.98
7	1.67	1,36-2,44	4.48	2,54-6,14	4.55	4.48
8	6.03	2,05-7,00	9.24	7,39-10,90	9.11	10.20
9	4.18	3,45-4,69	11.96	9,40-21,88	11.02	19.34
10	0.99	0,87-1,26	1.49	1,27-1,85	1.37	1.50
11	1.94	0,54-6,78	15.00	6,85-18,04	15.64	13.58
12	53.11	5,30-100,85	138.42	107,98-204,38	180.26	115.33
13	2.70	2,15-3,30	6.22	4,35-8,94	8.81	5.80
14	2.11	0,99-4,70	34.49	12,59-44,26	34.49	32.18

Table S2. Mean distance to agreement (MDA) and standard deviation (SD) per case of all radiation oncologists in reference to the median GTV of all radiation oncologists. An overall mean and standard deviation of all MDAs is also given.

#	RT	
	MDA (mm)	SD
1	5.39	5.65
2	4.45	4.66
3	8.97	5.64
4	2.97	0.72
5	2.14	1.01
6	1.87	0.73
7	2.56	2.71
8	1.49	0.53
9	3.46	1.39
10	0.88	0.21
11	3.30	1.72
12	7.46	8.61
13	3.53	2.69
14	4.83	4.35
Overall	**3.86**	**2.27**

Table S3. IOV amongst radiologists in different recurrence types, categorized as seen in table 1. Highest IOV is seen in intraluminal and fibrotic recurrences. Lowest IOV is seen in lateral recurrences, but more specifically in solitary lymph node recurrences.

IOV amongst radiologists		**n=**	**Median**
Lateral recurrence	SDSC	32	0.90
4 cases included	DSC		0.67
	HD98		6.0
Solitary lymph node recurrence	SDSC	16	0.82
2 cases included	DSC		0.48
	HD98		5.7
Multifocal recurrence	SDSC	40	0.86
5 cases included	DSC		0.66
	HD98		10.0
Intraluminal recurrence	SDSC	32	0.62
4 cases included	DSC		0.47
	HD98		14.3
Fibrotic recurrence	SDSC	32	0.64
4 cases included	DSC		0.51
	HD98		18.90

Case 1

A 71-year-old female is presenting with a local recurrence located on the right side of the pelvic floor. Patient has a history of T2N0 rectal cancer, for which an APR was performed. Patient has received three cycles of CAPOX induction chemotherapy and has now been referred for nCRT. Patient is planned for surgical resection of the lateral side wall with intraoperative radiotherapy.

Baseline MRI: Suspicion of a local recurrence on the right pelvic side wall.
Baseline PET-CT: Suspicion of a local recurrence as described on MRI. No pathological lymph nodes or distant metastases observed.
PET-CT after induction chemotherapy: Partial metabolic response with a decrease in SUV but a slight increase in size.

Table case 1. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 1	RAD (n=8)		GTV- (n=6)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	3.5	1.5-5.1	21.9	9.6-42.6	5.9	3.3-8.0
SDSC (0-1)	0.84	0.25-0.96	0.54	0.36-0.85	0.91	0.80-0.97
DSC (0-1)	0.60	0.08-0.72	0.54	0.30-0.79	0.75	0.61-0.84
HD98% (mm)	6.3	3.8-22.3	21.8	7.9-38.5	4.6	3.4-6.1

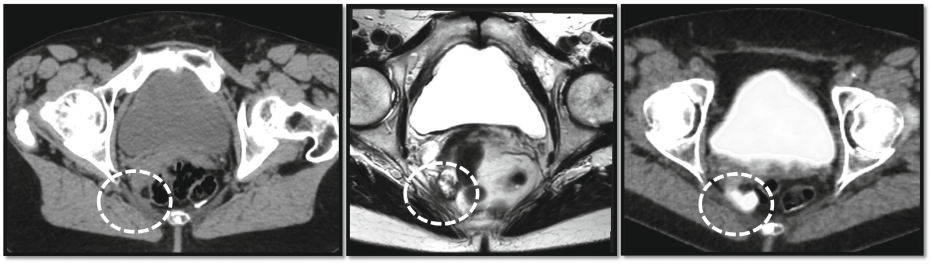


Figure S1a. From left to right, figure showing the planning CT, baseline MRI and baseline PET-CT.

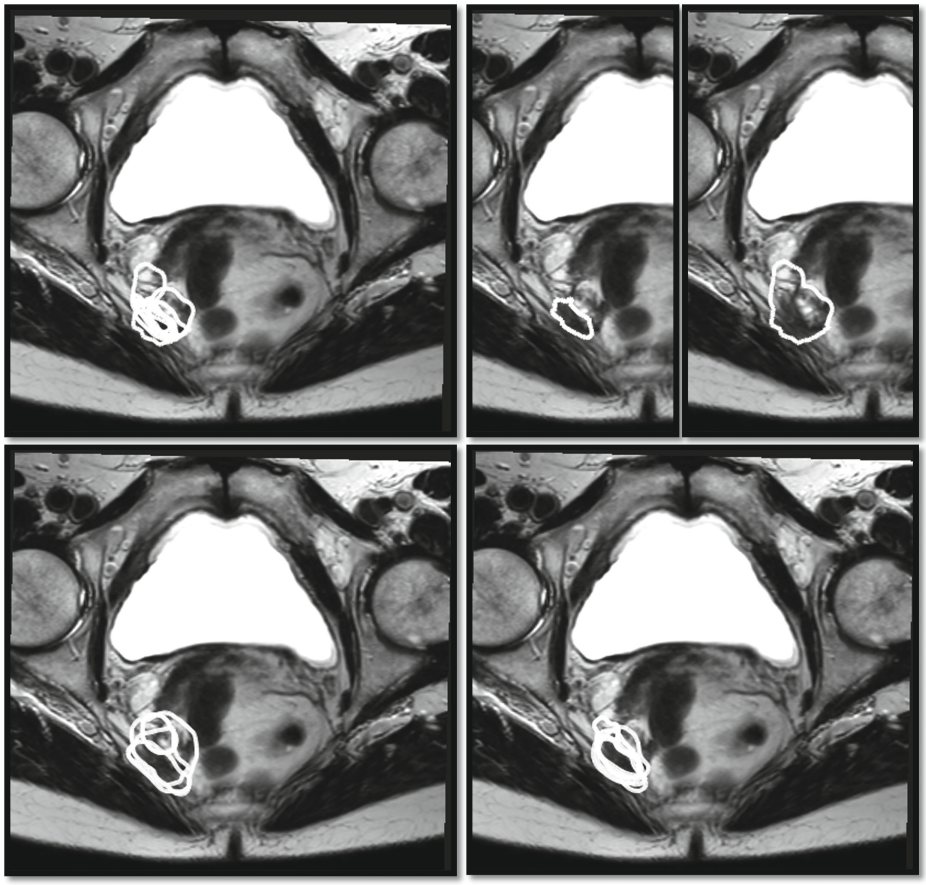


Figure S1b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 2

71-year-old male, with a history of a T3N2M1 rectal cancer (with a solitary liver metastasis). Patient was previously treated with 5x5Gy radiotherapy and 8 cycles of CAPOX, followed by ablation of the liver metastasis and an APR (pT3N2, R0). Patient was referred with a multifocal recurrence and has received 4 cycles of FOLFIRI. Patient is planned for surgical resection and intraoperative radiotherapy following chemo reirradiation.

Baseline MRI: Two locations of local recurrence: nodal recurrence ventral from L5-S1, local recurrence ventral from S4-S5.

Baseline PET-CT: Suspicion of a lymph node metastasis in the trajectory of the inferior mesenteric vessels. Pre-coccygeal FDG-avid mass seen, possibly showing a presacral recurrence.
PET-CT after induction chemotherapy: Good metabolic response of the mesenteric lymph nodes and presacral lesion. No new lesions seen.

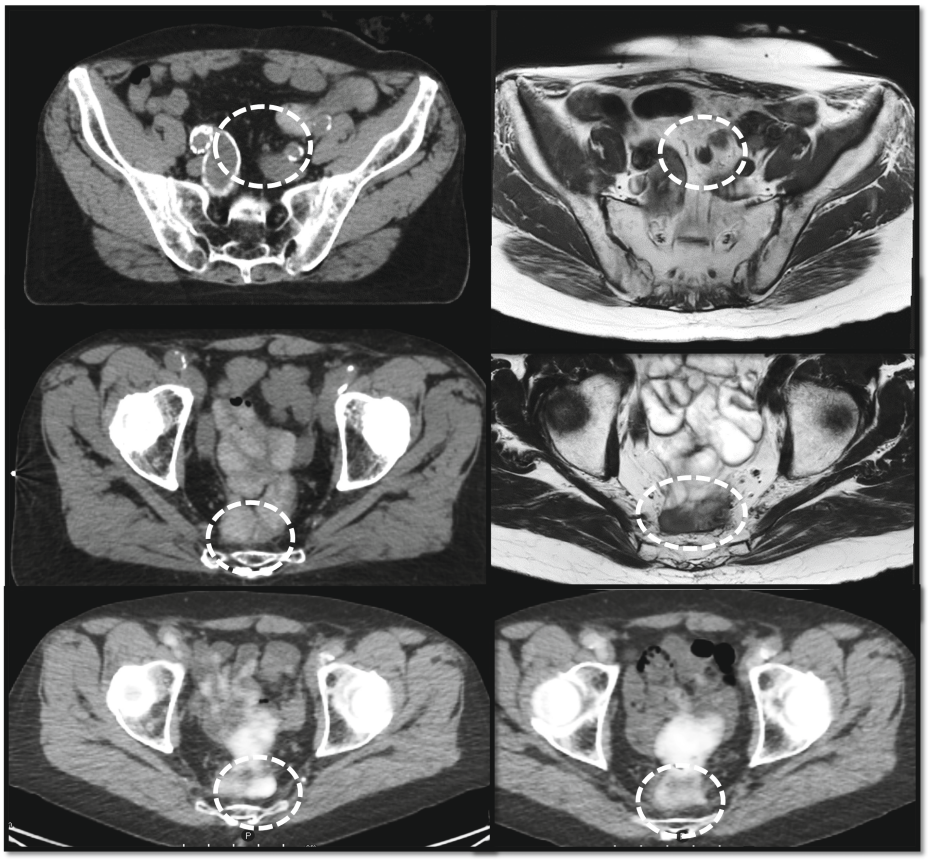


Figure S2a. Figure showing the lymph node recurrence on planning CT (top left) and T1W MRI (top right), as well as the presacral recurrence on planning CT (middle left), MRI (middle right), on PET-CT before induction chemotherapy (bottom left) and after induction chemotherapy (bottom right).

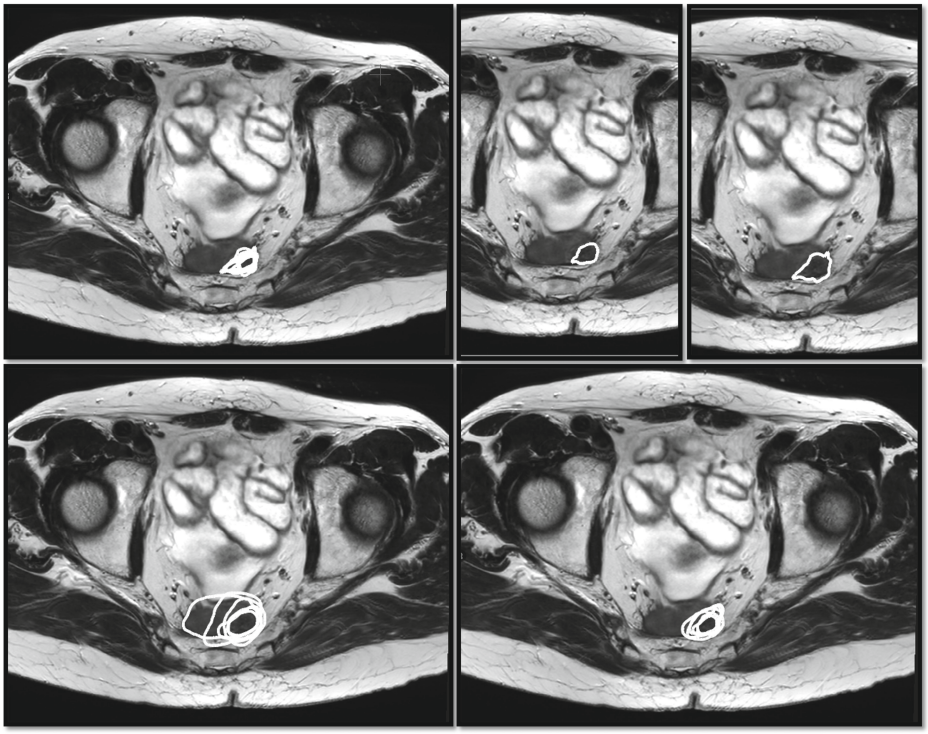


Figure S2b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Table case 2. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 2	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	2.3	0.8-5.3	12.9	5.6-49.2	4.5	2.4-6.1
SDSC (0-1)	0.87	0.70-0.96	0.63	0.39-0.93	0.95	0.81-0.99
DSC (0-1)	0.56	0.47-0.76	0.58	0.37-0.81	0.76	0.63-0.81
HD98% (mm)	6.7	4.2-90.3	18.1	4.6-83.2	5.7	3.0-6.0

Case 3

68-year-old male, with a history of a cT3N0 rectal cancer for which he was treated with 5x5Gy and a LAR (ypT2N1, R1). Patient was diagnosed with LRRC and has received 3 cycles of CAPOX induction chemotherapy. Patient has been referred to you for chemo reirradiation and is planned for an APR with intraoperative radiotherapy.

Sigmoidoscopy at baseline: No mucosal lesions

Baseline MRI: Focal soft tissue at the anastomosis with a direct relationship to the sacrospinous and sacrotuberous ligament and the presacral fascia, maximal diameter of 2.5cm.

Baseline PET/CT: Suspicion of an anastomotic recurrence.

MRI after induction chemotherapy: No clear response to induction chemotherapy on the right side. At the left, it is hard to differentiate between rest fibrosis and malignancy.

PET/CT after induction chemotherapy: Anastomosis is no longer metabolically active.

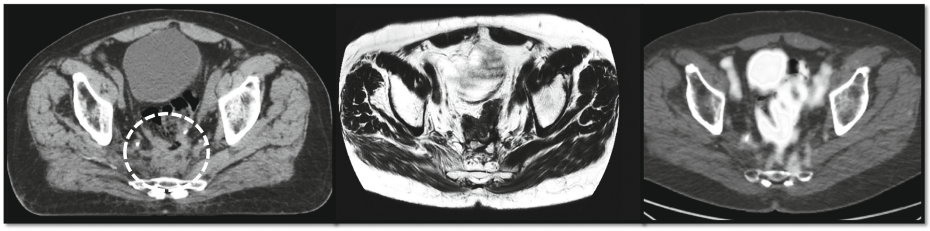


Figure S3a. From left to right, figure showing planning CT, baseline MRI and baseline PET-CT.

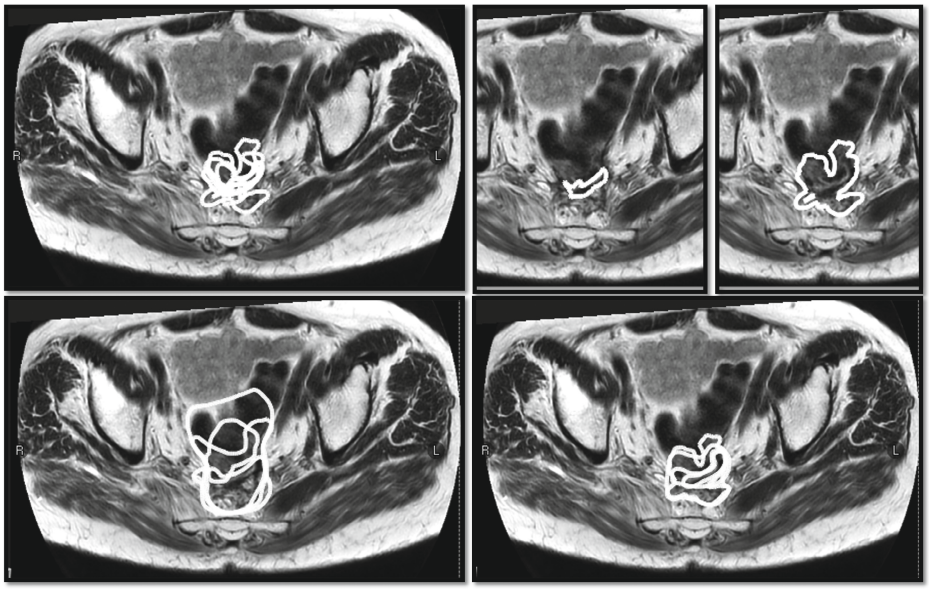


Figure S3b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Table case 3. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 3	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	13.9	1.2-38.7	59.5	11.0-219.2	27.4	3.3-93.4
SDSC (0-1)	0.56	0.21-0.70	0.42	0.26-0.87	0.63	0.25-0.92
DSC (0-1)	0.42	0.09-0.55	0.49	0.17-0.83	0.63	0.15-0.82
HD98% (mm)	24.3	14.1-51.9	34.5	7.5-45.0	27.5	6.0-51.2

Case 4

71-year-old male with a history of a cT3N2M1 (liver) distal rectal cancer, for which he was treated with nCRT, 3 cycles of CAPOX-bevacizumab followed by resection of 5 liver metastases and a LAR (R0). Patient was diagnosed with a multifocal local recurrence for which he was planned to receive 4 cycles of induction chemotherapy (FOLFIRI-Bevacizumab), however due to toxicity only 1 cycle was given. Patient has been referred for chemo reirradiation. Patient will undergo a total pelvic exenteration with intraoperative radiotherapy.

Baseline MRI: Suspicion of a multifocal recurrence in the lesser pelvis. Multiple nodular depositions on the mesorectal fascia, left and right in the lesser pelvis. The largest deposition is +/- 2cm. 2 additional possibly malignant lymph nodes.
Baseline PET/CT: FDG-avid soft tissue in the pelvis, as on MRI, very suspicious for local recurrence. One FDG-avid presacral lymph node (on the right).
MRI after chemotherapy: No response to therapy, stable disease.
PET-CT after chemotherapy: No difference in PET-positive lymph nodes or local multifocal recurrence. No distant metastases.

Table case 4. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 4	RAD (n=8)		GTV- (n=5)		GTV+ (n=4)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	34.2	17.6-63.9	83.0	36.9-121.1	91.3	72.8-114.7
SDSC (0-1)	0.80	0.61-0.87	0.75	0.68-0.86	0.88	0.72-0.91
DSC (0-1)	0.60	0.45-0.71	0.69	0.62-0.82	0.82	0.68-0.85
HD98% (mm)	17.4	7.0-68.5	19.0	9.0-25.5	15.3	7.3-60.3

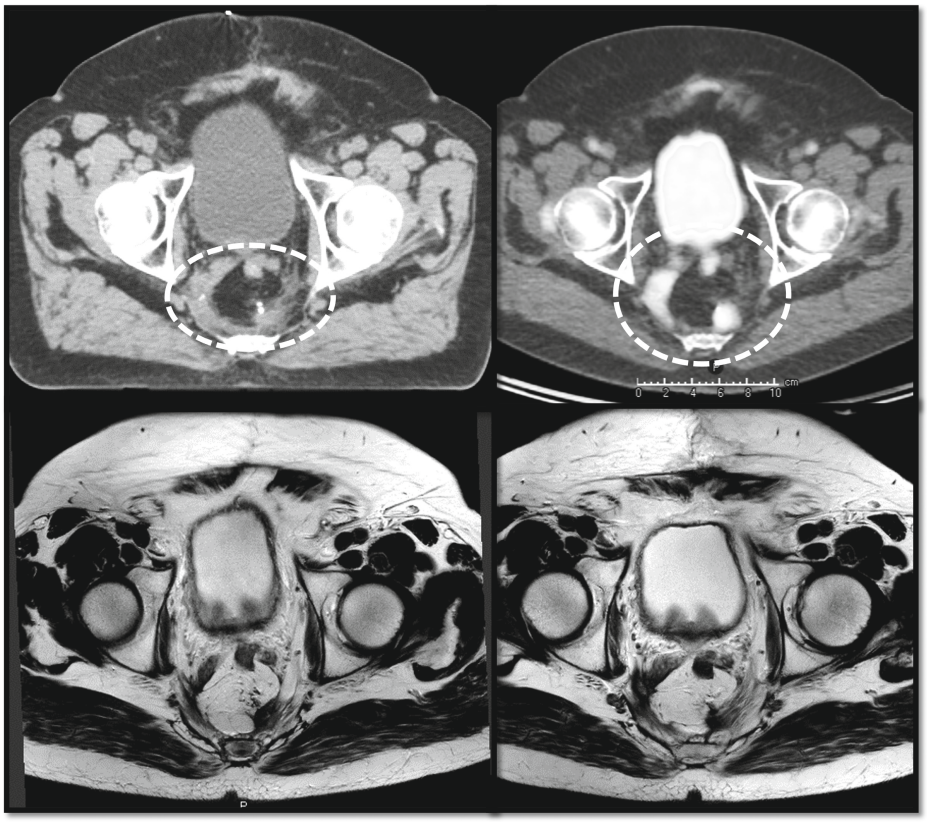


Figure S4a. Figure showing planning CT (top left), baseline PET-CT (top right), baseline MRI (bottom left) and MRI following induction chemotherapy (bottom right).

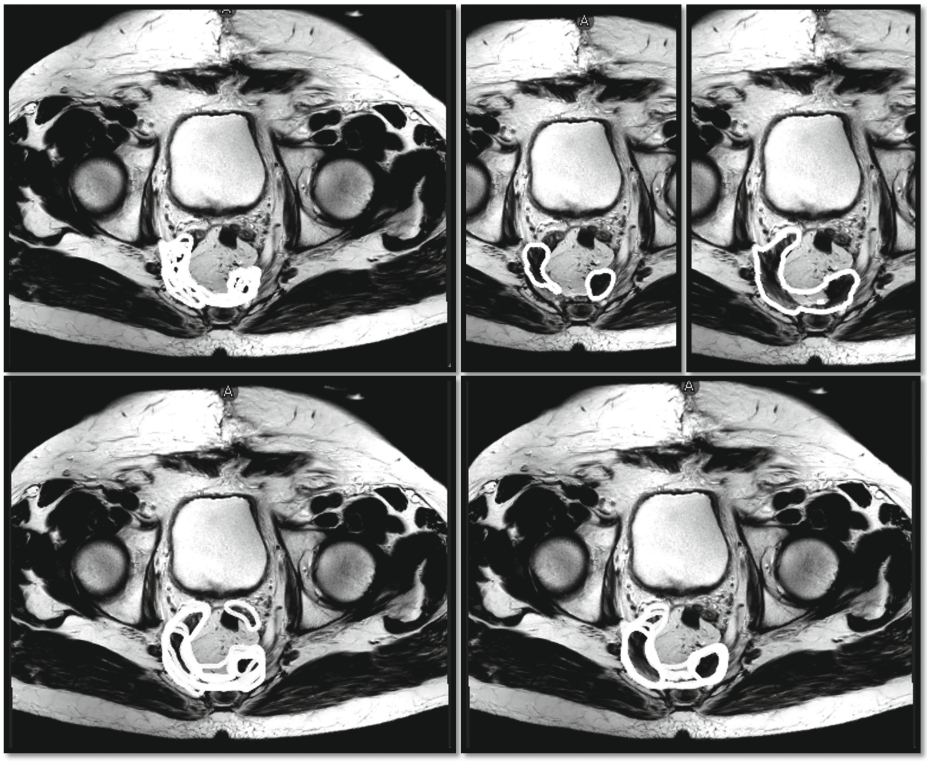


Figure S4b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 5

41-year-old male, with a history of a T3N0 distal rectal cancer for which an APR was performed (pT3N1, R1). Patient presented with a multifocal recurrence and has been referred for nCRT. Patient is planned for surgery with intraoperative radiotherapy.

Baseline MRI: 2 presacral lesions of approximately 8mm, probably pathological lymph nodes.

Baseline PET-CT: PET-positive area left ventrolateral of the coccygeal bone. The second PET-positive lesion is situated dorsally of the prostate. Both are suspicious for a local recurrence. 2 slightly PET-positive presacral lymph nodes, which could be fitting with the MRI findings. No metastases elsewhere.

Table case 5. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 5	RAD (n=8)		GTV- (n=5)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	5.6	3.6-11.6	10.7	6.8-24.2	11.6	7.2-16.8
SDSC (0-1)	0.86	0.65-0.91	0.87	0.65-0.96	0.91	0.77-0.99
DSC (0-1)	0.62	0.55-0.74	0.74	0.56-0.76	0.76	0.61-0.85
HD98% (mm)	31.1	6.1-48.8	36.6	3.5-44.5	7.8	3.0-15.6

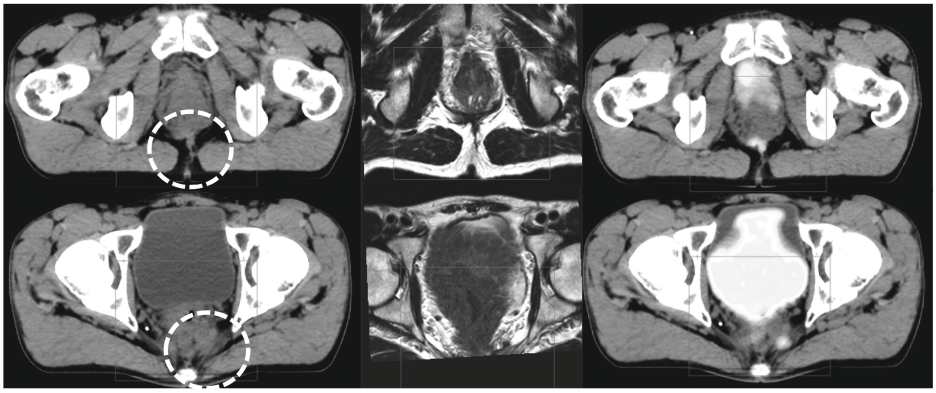


Figure S5a. Figure showing two lesions on planning CT (left), baseline MRI (middle) and baseline PET-CT (right).

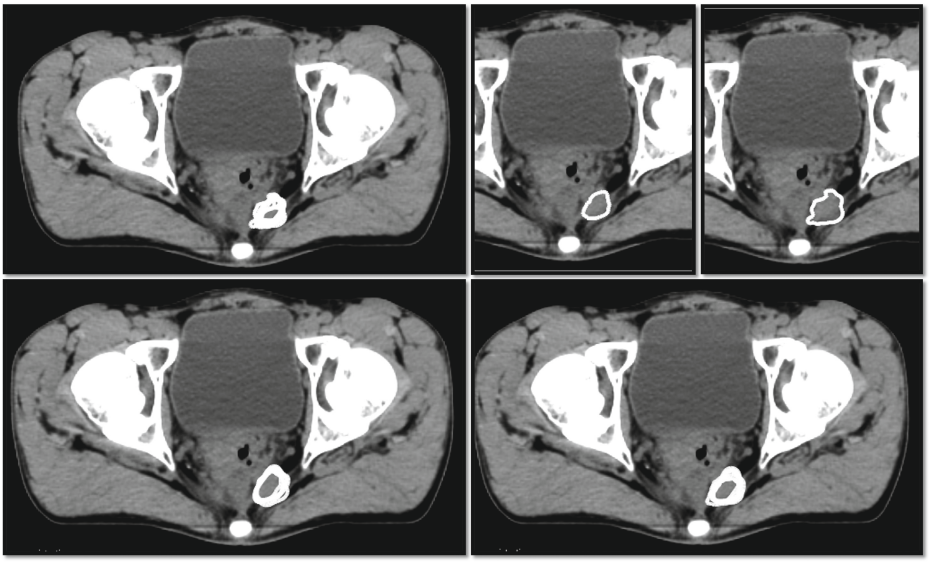


Figure S5b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 6

78-year-old male, with a history of a T3N1 rectal carcinoma for which a LAR was performed. Patient is presenting with an anastomotic recurrence and was referred for full course CRT. Patient is planned for a re-LAR with IORT.

Colonoscopy at baseline: suspicious lesion on the anastomosis in the rectum. PA: adenocarcinoma.
MRI at baseline: Anastomotic recurrence presacral extending towards the sacrum, without evidence of involvement of the sacrum. Also suspicion of a nodal recurrence at the right. Central, right lateral and posterior compartment involved.
PET-CT at baseline: No distant metastases. Prominent local and nodal recurrence (near iliac vessels on the right).

Table case 6. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 6	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	17.1	4.7-22.9	29.8	23.9-45.0	20.0	15.7-32.4
SDSC (0-1)	0.84	0.47-0.98	0.86	0.73-0.95	0.89	0.77-0.99
DSC (0-1)	0.72	0.40-0.84	0.80	0.73-0.82	0.77	0.75-0.91
HD98% (mm)	7.5	3.5-26.8	12.5	4.0-15.3	6.6	3.0-11.4

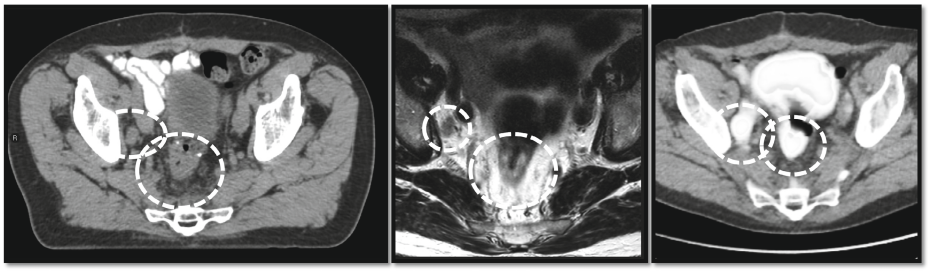


Figure S6a. Figure showing nodal and anastomotic recurrence on planning CT (left), baseline MRI (middle) and baseline PET-CT (right).

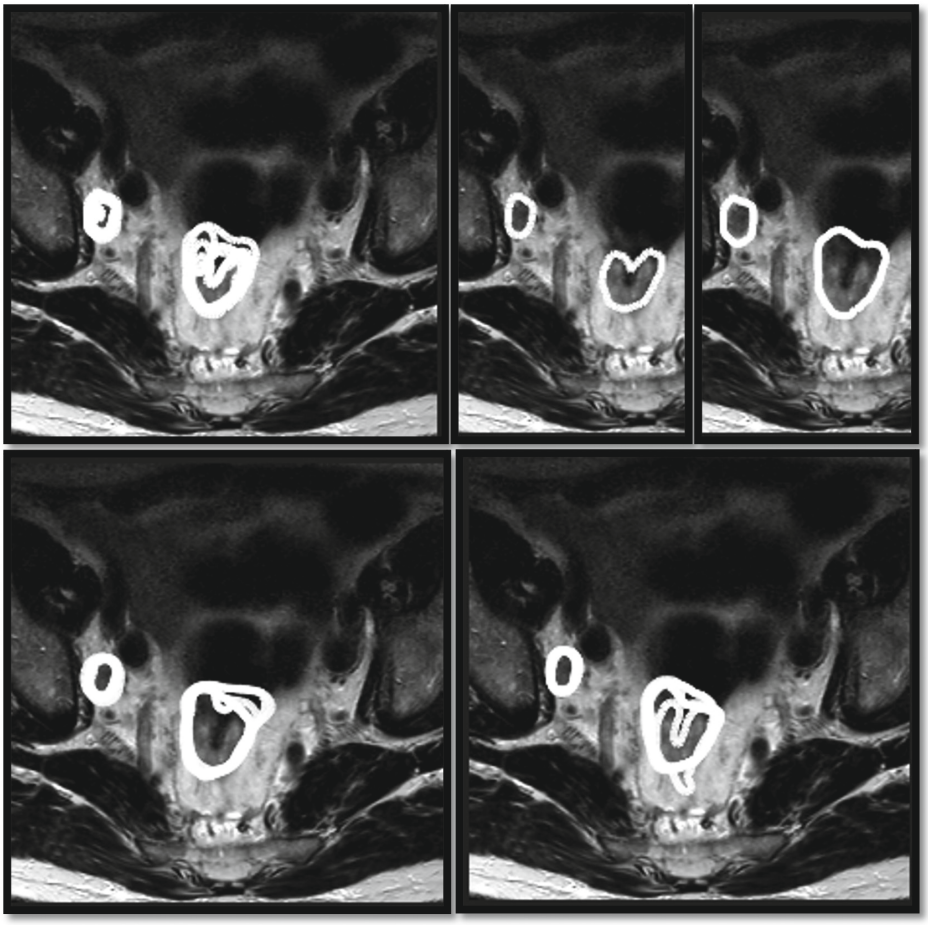


Figure S6b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 7

63-year-old male, with a history of a locally advanced rectal cancer (cTNM stage unknown), treated with CRT and an APR (ypT1N0, R0). Patient was diagnosed with a nodal recurrence and has received 3 cycles of CAPOX induction chemotherapy. Patient has been referred for reirradiation and is planned for surgery with intraoperative radiotherapy.

MRI at baseline: Suspicion of a lateral nodal recurrence (left) with a diameter of 1.7cm, in contact with the internal iliac artery.

PET/CT at baseline: FDG-avid focus laterally against the mesorectal fascia left. No distant metastases.

PET/CT following induction chemotherapy: Strong regression of FDG-uptake in the node against the internal iliac artery left. Only a small amount of activity left. No new lesions.

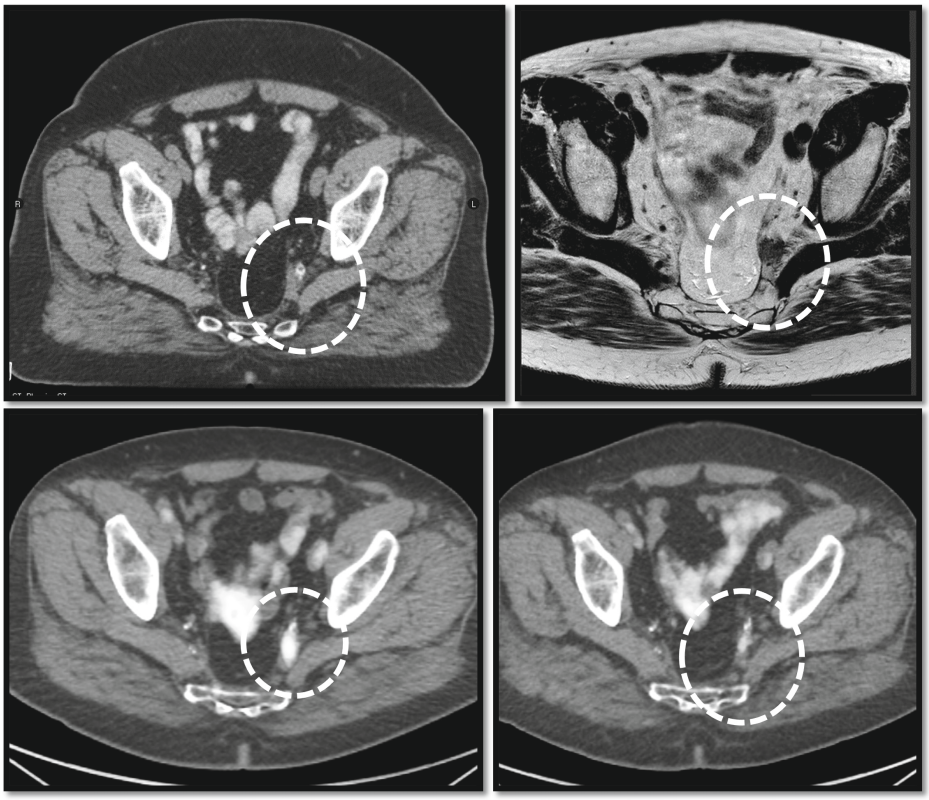


Figure S7a. Figure showing planning CT (top left), baseline MRI (top right), baseline PET-CT (bottom left) and PET-CT following induction chemotherapy (bottom right).

Table case 7. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 7	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	1.7	0.98-39.9	4.6	2.5-10.4	4.5	1.9-7.9
SDSC (0-1)	0.32	0.00-0.81	0.85	0.75-0.94	0.92	0.50-0.95
DSC (0-1)	0.17	0.00-0.48	0.71	0.58-0.80	0.74	0.40-0.84
HD98% (mm)	22.0	6.4-186.5	7.0	6.0-11.7	5.8	4.2-39.0

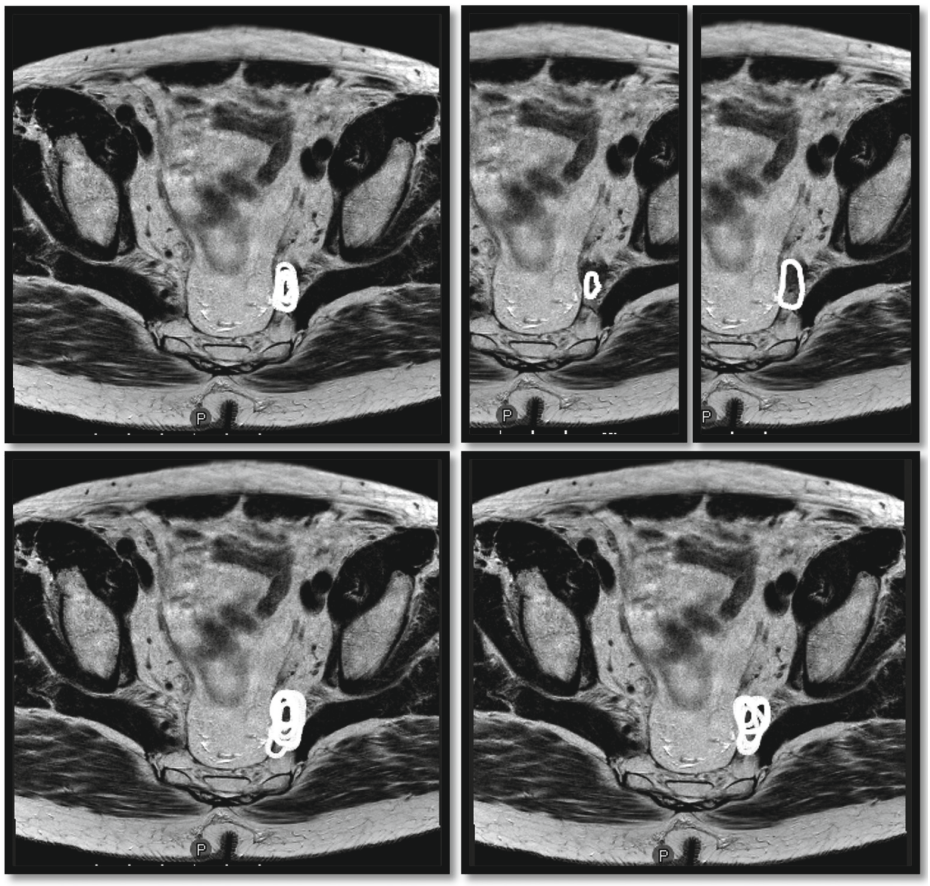


Figure S7b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 8

68-year-old male, presenting with a dorsolateral local recurrence after primary rectal cancer (cTNM stage unknown), which was treated with 5x5Gy and an APR (pT2N1, R0). Patient is referred following 3 cycles of CAPOX induction chemotherapy. Following chemo reirradiation, patient is planned for surgery with intraoperative radiotherapy on the lateral pelvic wall.

Baseline MRI: Suspicion of a unifocal local recurrence against the right pelvic side wall.
Baseline PET-CT: No suspicious lesions outside of the pelvis. Increased FDG uptake can be seen at the right pelvic side wall.

PET-CT following induction chemotherapy: Good metabolic response, possible complete response. No new lesions on PET-CT.

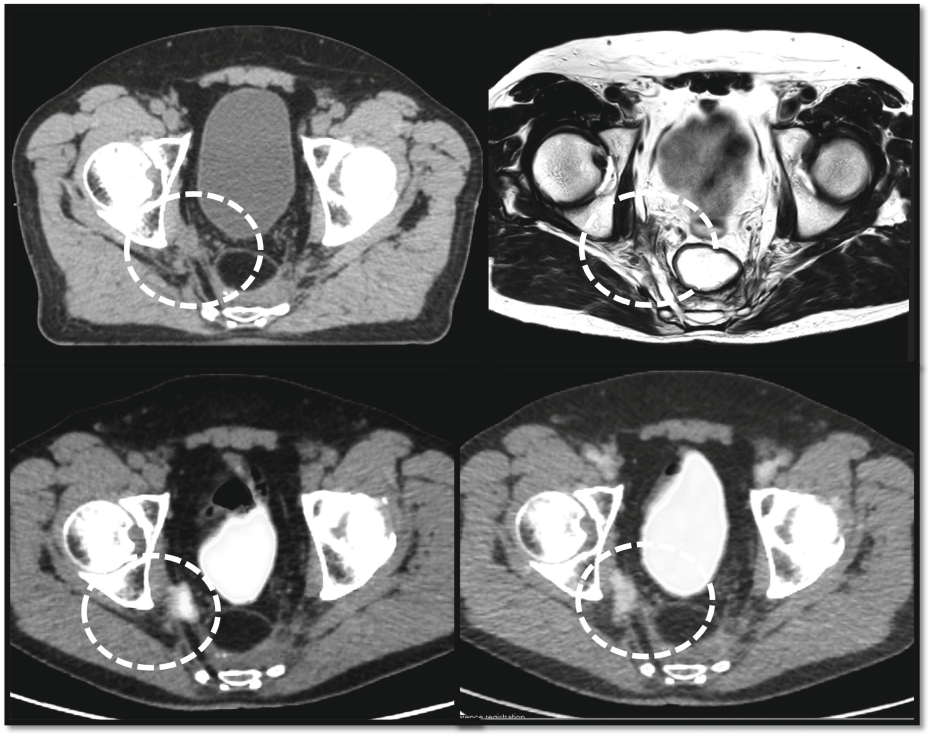


Figure S8a. Figure showing planning CT (top left), baseline MRI (top right), PET-CT at baseline (bottom left) and following induction chemotherapy (bottom right).

Table case 8. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 8	RAD (n=8)		GTV- (n=6)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	6.0	3.8-8.1	9.1	5.1-9.9	10.2	7.0-11.7
SDSC (0-1)	0.94	0.87-0.98	0.92	0.65-0.96	0.94	0.88-0.97
DSC (0-1)	0.78	0.68-0.81	0.84	0.64-0.85	0.84	0.75-0.86
HD98% (mm)	5.8	3.2-8.5	6.1	6.0-9.4	5.1	3.8-6.0

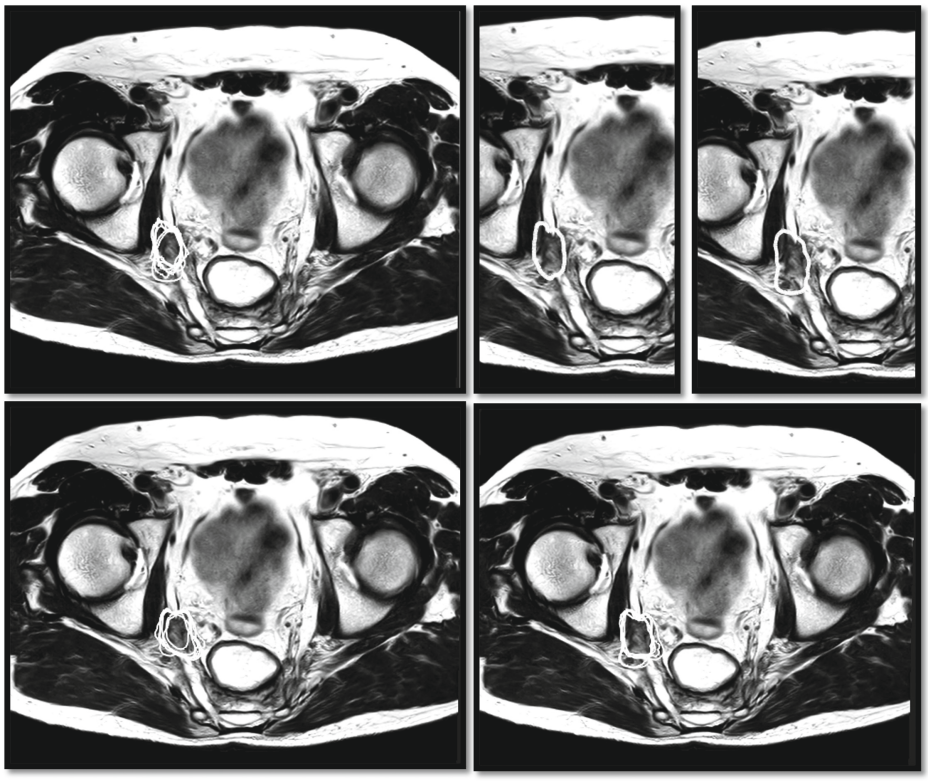


Figure S8b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 9

70-year-old female with a history of a LARC (cTNM stage unknown) for which she received CRT and a LAR (pT2N1). Patient was diagnosed with a distal LRRC. Patient has received 3 cycles of CAPOX induction chemotherapy and has now been referred for chemo reirradiation. Patient will undergo debulking surgery with intraoperative radiotherapy.

Colonoscopy at baseline: Suspicion of a local recurrence distally in the rectum. PA: Adenocarcinoma.
MRI at baseline: Anastomotic recurrence (+/- 2cm) with possible involvement of the cervix.
MRI after induction chemotherapy: The local recurrence in the rectal stump is no longer visible. Fibrosis visible. >75% decrease in volume.

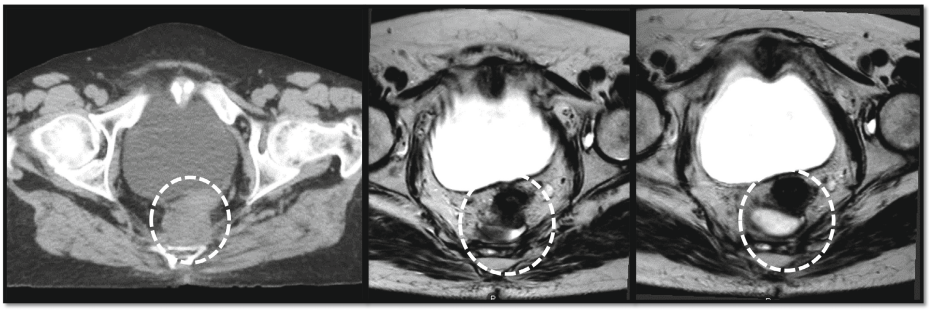


Figure S9a. Figure showing planning CT (left), baseline MRI (middle), and MRI following induction chemotherapy (right).

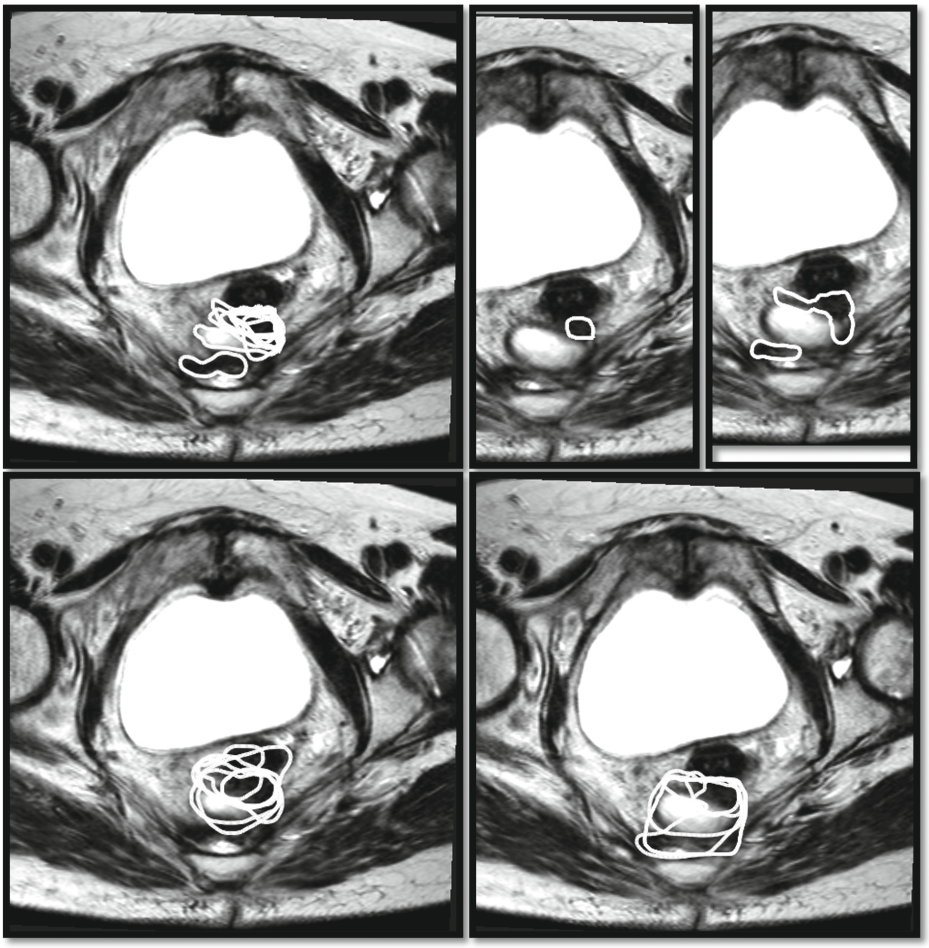


Figure S9b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Table case 9. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 9	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	4.2	1.6-7.1	11	8.5-30.3	19.3	3.7-28.7
SDSC (0-1)	0.86	0.02-0.97	0.71	0.56-0.92	0.71	0.34-0.89
DSC (0-1)	0.63	0.00-0.77	0.64	0.50-0.79	0.69	0.27-0.81
HD98% (mm)	7.5	3.3-26.7	12.1	8.2-14.7	12.0	8.2-21.0

Case 10

65-year-old female, with a history of a cT3N1 (MRF+) rectal cancer for which she was treated with 4 cycles of CAPOX induction chemotherapy, full course CRT and an APR (ypT2N0, R0). Patient presented with a solitary nodal recurrence and has been referred for chemo reirradiation. Patient is planned for a surgical resection with IORT.

Baseline MRI: Solid nodule in the lesser pelvis on the left, approximately 1.2cm, located in the obturator loge.
Baseline PET/CT: Lymph node dorsally in the obturator loge left, suspicious for a solitary lymph node metastasis.

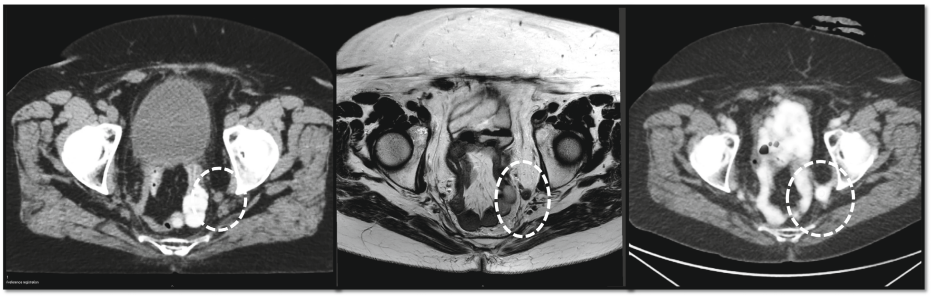


Figure S10a. Figure showing planning CT (left), baseline MRI (middle), and baseline PET-CT (right).

Table case 10. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 10	RAD (n=8)		GTV- (n=5)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	1.0	0.8-1.4	1.4	1.0-2.5	1.5	1.2-2.2
SDSC (0-1)	0.99	0.83-1.00	1.00	0.98-1.00	1.00	0.97-1.00
DSC (0-1)	0.76	0.47-0.85	0.81	0.68-0.84	0.81	0.77-0.82
HD98% (mm)	3.1	3.0-5.0	2.3	2.3-3.2	3.0	3.0-6.0

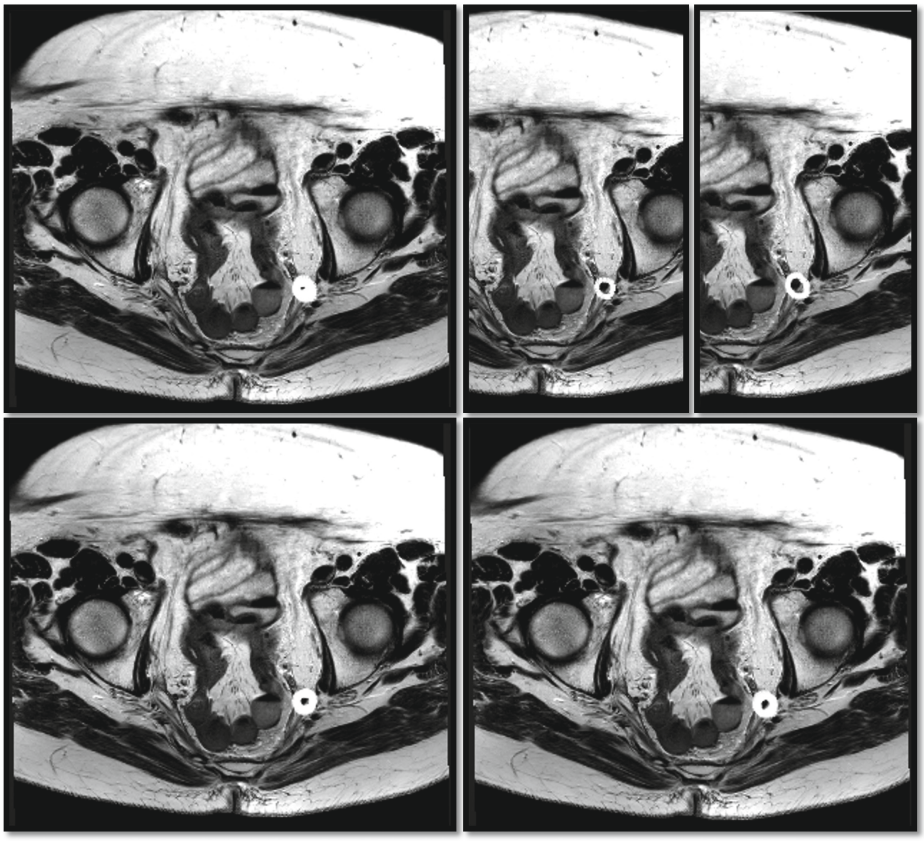


Figure S10b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 11

73-year-old male, with a history of a cT3bN0 (MRF+) distal rectal cancer for which he was treated with CRT and a LAR (TaTME, ypT3N1, R0). Patient presented with a presacral local recurrence and has received 3 cycles of CAPOX induction chemotherapy. He was referred for chemo reirradiation. Patient is planned for resection with intraoperative radiotherapy.

Baseline MRI: suspicion of a unifocal presacral (maximal diameter approximately 26mm).
Baseline PET-CT: High presacral uptake (S4), suspicion of a local recurrence. Two high uptake foci in the prostate, DD prostate carcinoma or focal prostatitis.
Additional prostate MRI: diffuse low T2 signal in the peripheral zone on the right, as fitting for prostatitis. No suspicion of a prostate cancer (PI-RADS 2).

MRI after chemotherapy: Known presacral recurrence with only minimal response. There is still a suspicion of vital tumour.
PET/CT after chemotherapy: clear reduction of metabolic activity in the lesser pelvis at the known local recurrence. No distant metastases.

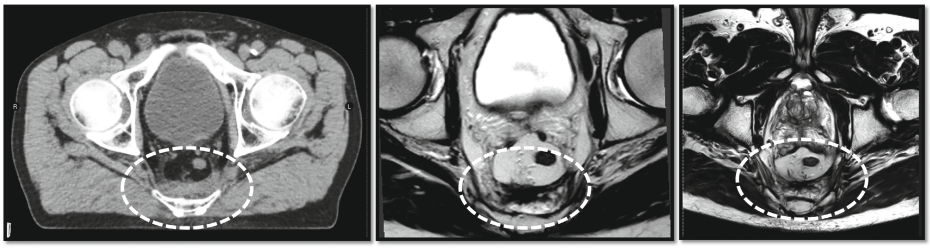


Figure S11a. Figure showing planning CT (left), baseline MRI (middle), and MRI following induction chemotherapy (right).

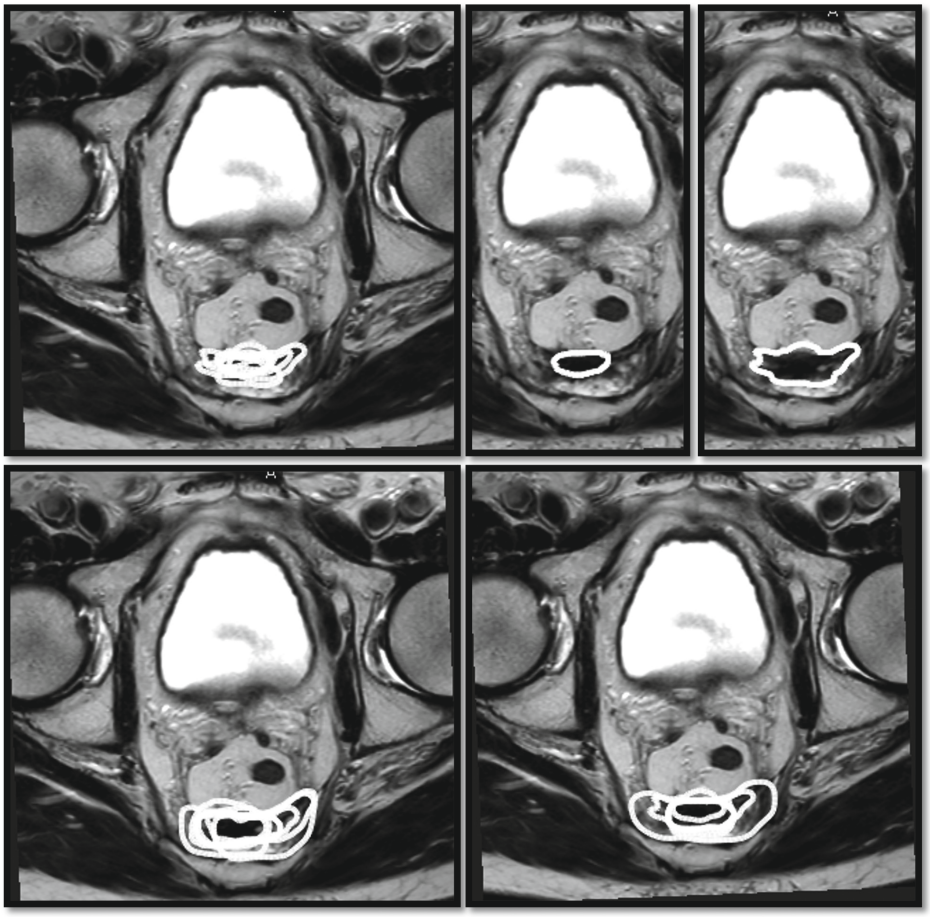


Figure S11b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Table case 11. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 11	RAD (n=8)		GTV- (n=6)		GTV+ (n=5)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	1.9	0.1-7.9	15.6	6.1-43.5	13.6	5.2-49.6
SDSC (0-1)	0.44	0.31-0.84	0.63	0.37-0.92	0.60	0.30-0.96
DSC (0-1)	0.32	0.10-0.69	0.65	0.46-0.84	0.65	0.42-0.87
HD98% (mm)	9.3	4.6-26.7	11.1	4.6-17.3	12.3	4.2-18.9

Case 12

68-year-old male, presenting with a local recurrence within a large presacral abscess after primary rectal cancer nearly 20 years ago, treated with chemoradiotherapy (50.4Gy) and a low anterior resection. Patient has received 4 cycles of FOLFOX-bevacizumab and is now referred for chemo reirradiation. Patient is planned for surgical resection with intraoperative radiotherapy.

Baseline MRI: Known presacral abscess. Inside the abscess is a large soft tissue mass of approximately 10cm up growing until the anus. Possible sacral involvement at S4.
Baseline PET-CT: Intense FDG-uptake presacral. No evidence of distant disease or lymph node involvement.
MRI after induction chemotherapy: Evident response after chemotherapy, possibly residual soft tissue mass at S3-S4.
PET-CT after induction chemotherapy: Partial metabolic response of the local recurrence.

Table case 12. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 12	RAD (n=8)		GTV- (n=6)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	53.1	1.4-155.6	180.3	6.3-307.1	115.3	4.0-259.6
SDSC (0-1)	0.33	0.08-0.79	0.75	0.01-0.91	0.69	0.00-0.98
DSC (0-1)	0.40	0.04-0.82	0.86	0.06-0.92	0.80	0.06-0.94
HD98% (mm)	29.2	17.5-58.2	9.2	4.8-69.4	23.4	3.3-52.2

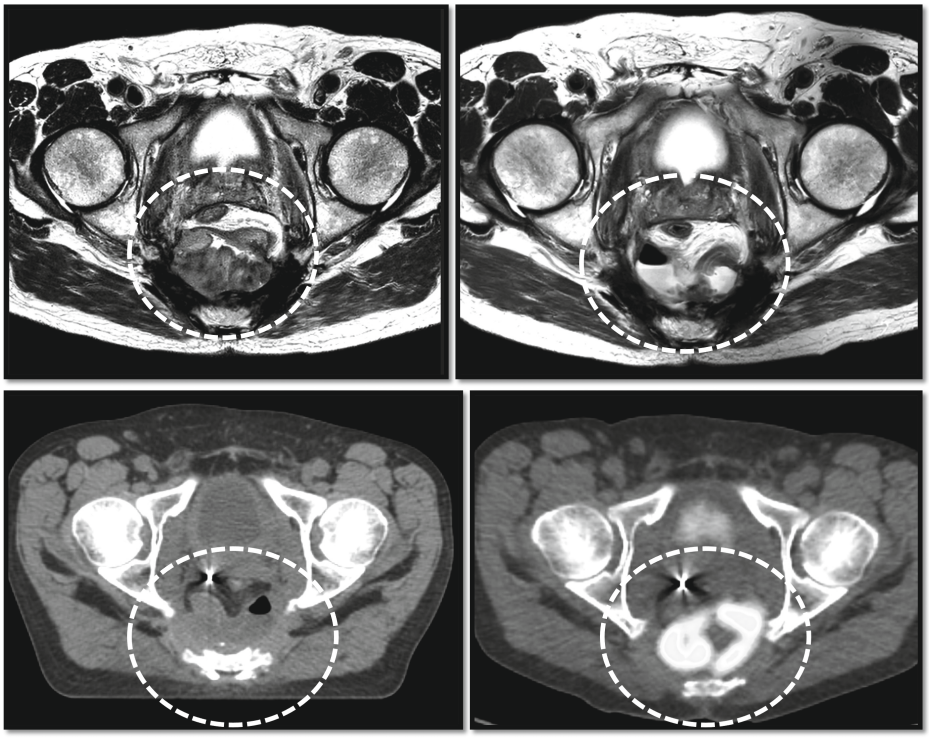


Figure S12a. Figure showing baseline MRI (top left), MRI after induction chemotherapy (top right), planning CT (bottom left) and baseline PET-CT (bottom right).

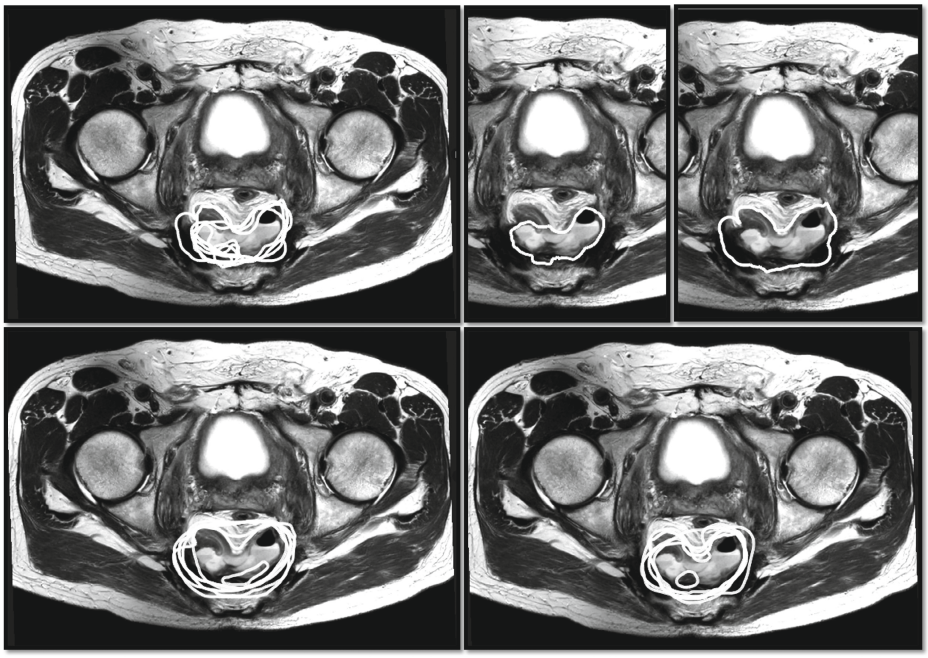


Figure S12b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 13

72-year-old male, with a history of a T1-2N2 rectal cancer for which he received CRT, followed by a TEM due to a good response. The performed TEM was irradical, so it was followed up by an APR (ypT3N0, R0). Patient presented with a local recurrence for which he received four cycles of FOLFOX induction chemotherapy. He has been referred for chemo reirradiation. Patient is planned for a re-APR with intraoperative radiotherapy.

Baseline MRI: Suspicion of a multifocal local recurrence with a solid lesion against the right seminal vesicle (22mm) and a second lesion at the perineum against the base of the penis (13mm).

Baseline PET-CT: Strong suspicion of a local recurrence on the right pelvic floor. Second small focus very caudally at the anus, possibly inflammatory, but recurrence cannot be ruled out. No distant metastases.

MRI after induction chemotherapy: Average response of the multifocal recurrence, with a rest lesion still visible against the seminal vesicles and sacrospinous ligament on the right and between the peritoneum and prostate on the left.

PET-CT after induction chemotherapy: Little response of the recurrence on the mesorectal fascia. There is a complete response of the second lesion at the perineum left. No new lesions.

Table case 13. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 13	RAD (n=8)		GTV- (n=5)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	2.7	2.0-4.0	8.8	4.3-12.6	5.8	4.0-11.1
SDSC (0-1)	0.94	0.75-0.99	0.91	0.80-0.93	0.83	0.67-0.99
DSC (0-1)	0.75	0.58-0.79	0.71	0.71-0.79	0.71	0.55-0.89
HD98% (mm)	4.9	3.2-39.3	5.6	4.2-15.4	37.4	3.0-40.4



Figure S13a. From left to right, figure showing planning CT, baseline MRI and baseline PET-CT.

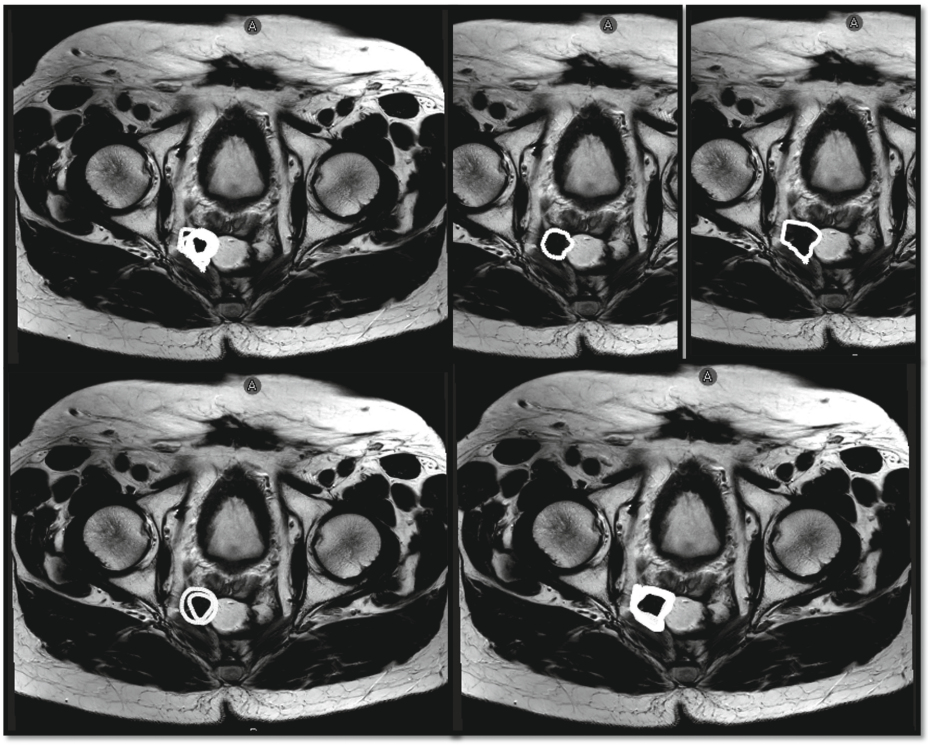


Figure S13b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

Case 14

76-year-old male with a history of a T3N1 mucinous rectal cancer, for which he received 5x5Gy radiotherapy and a LAR (pT2N0, R0). Patient was diagnosed with a recurrence at the anastomosis and has been referred to you following three cycles of CAPOX induction chemotherapy. Following chemo reirradiation, patient is planned for an APR with intraoperative radiotherapy.

Colonoscopy at baseline: At 5cm from the anorectal junction a cancerous lesion is seen (ulcerating). Biopsy: adenocarcinoma.
MRI at baseline: Tumorous soft tissue visible at the anastomosis of approximately 2.6x3.2cm. There is ventral involvement of the seminal vesicles. No involvement dorsally of the mesorectal fascia.

PET-CT at baseline: Known anastomotic recurrence with FDG-PET uptake circumferentially around the anastomosis for approximately 3.8cm. No suspicious local lymph nodes or distant metastases.

MRI after induction chemotherapy: minimal rest lesion at the anastomosis, but still with possible involvement of the posterior side of the seminal vesicles.

PET-CT after induction chemotherapy: Significant reduction of size and metabolic activity of anastomotic recurrence. Small focal metabolic activity fitting with tumorous tissue.

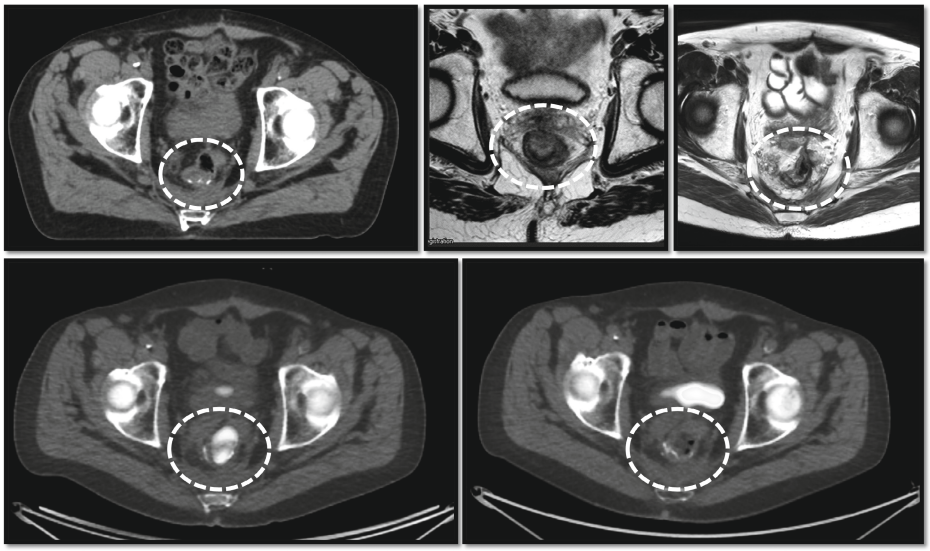


Figure S14a. Figure showing planning CT (top left), baseline MRI (top middle), MRI following induction chemotherapy (top right), baseline PET-CT (bottom left) and PET-CT following induction chemotherapy (bottom right).

Table case 14. Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

Case 14	RAD (n=8)		GTV- (n=6)		GTV+ (n=6)	
	Median	Range	Median	Range	Median	Range
Volume (cc)	2.1	0.9-7.8	34.49	7.4-90.7	32.2	1.7-44.3
SDSC (0-1)	0.16	0.00-0.60	0.82	0.26-0.91	0.66	0.10-0.94
DSC (0-1)	0.04	0.00-0.20	0.82	0.27-0.88	0.70	0.09-0.89
HD98% (mm)	25.6	8.81-45.7	17.5	5.6-26.9	23.3	6.0-26.6

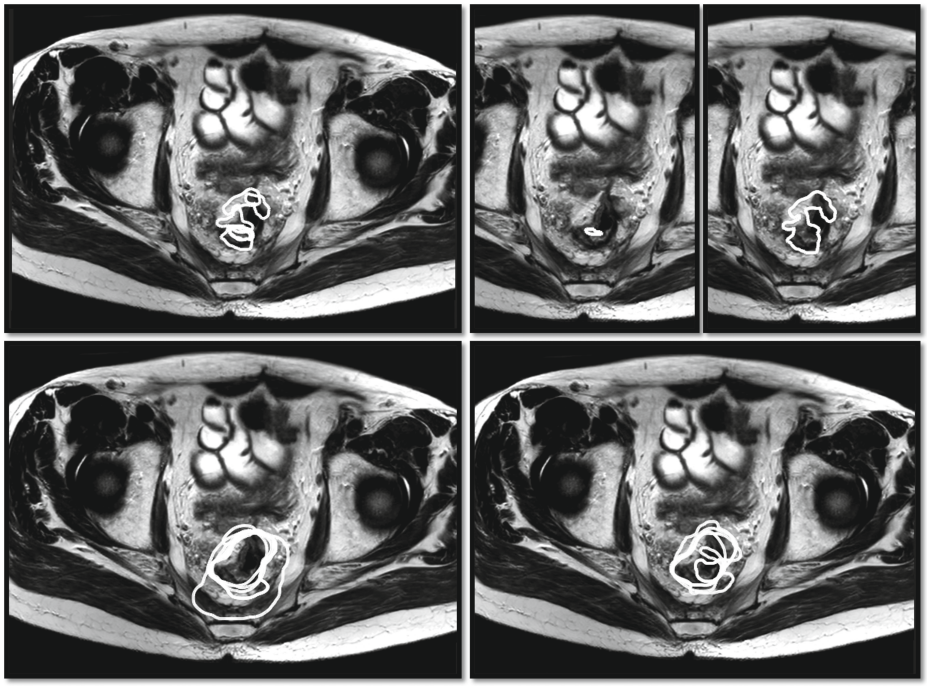


Figure S14b. Figure showing contours performed by radiologists (top left), the constructed median contour (top middle), the constructed total contour (top right), GTV- contours (bottom left) and GTV+ contours (bottom right).

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.

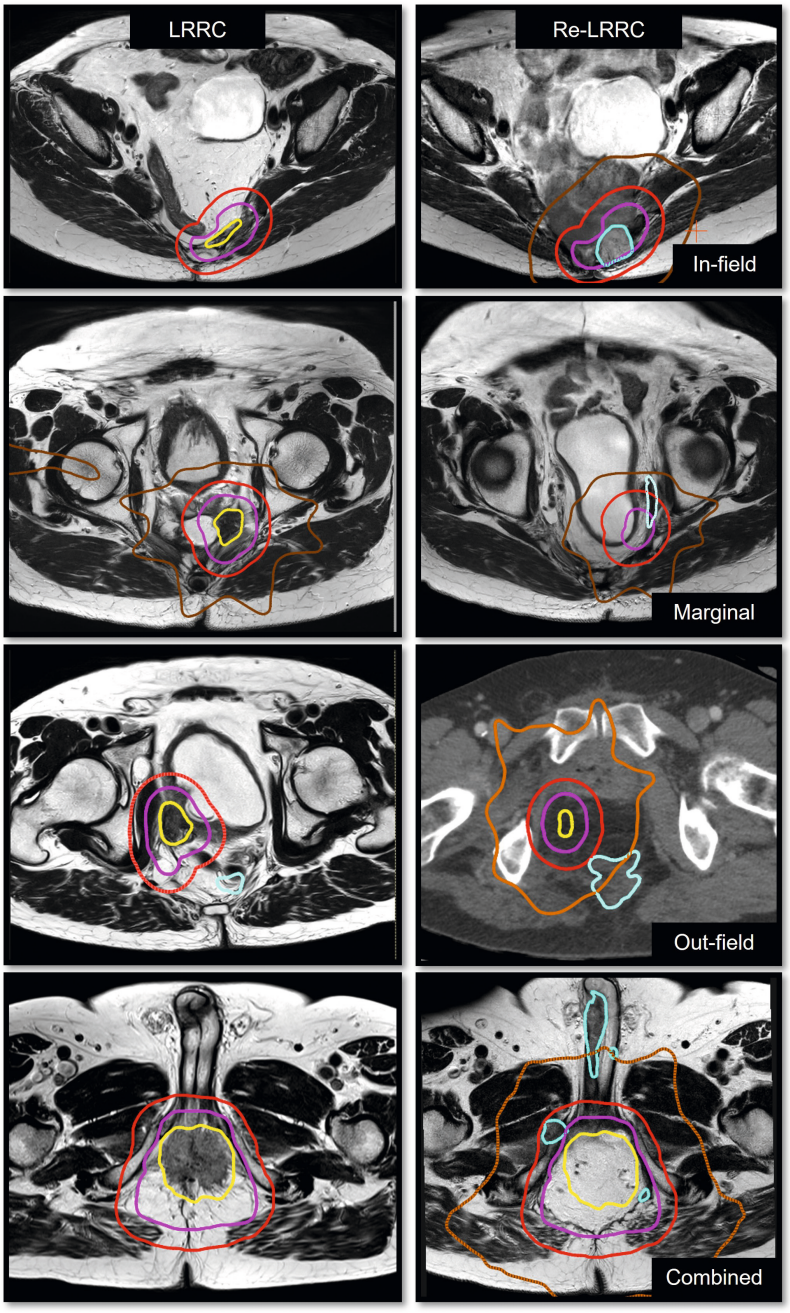


Figure 1. Examples of re-recurrences deemed in-field, marginal, out-field or combined compared to LRRC target volume. MRI or CT of the LRRC is shown on the left, and the re-LRRC on the right. GTV (yellow), CTV (pink), and PTV (red), as well as the 50% isodose line (brown) is shown for the recurrence.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

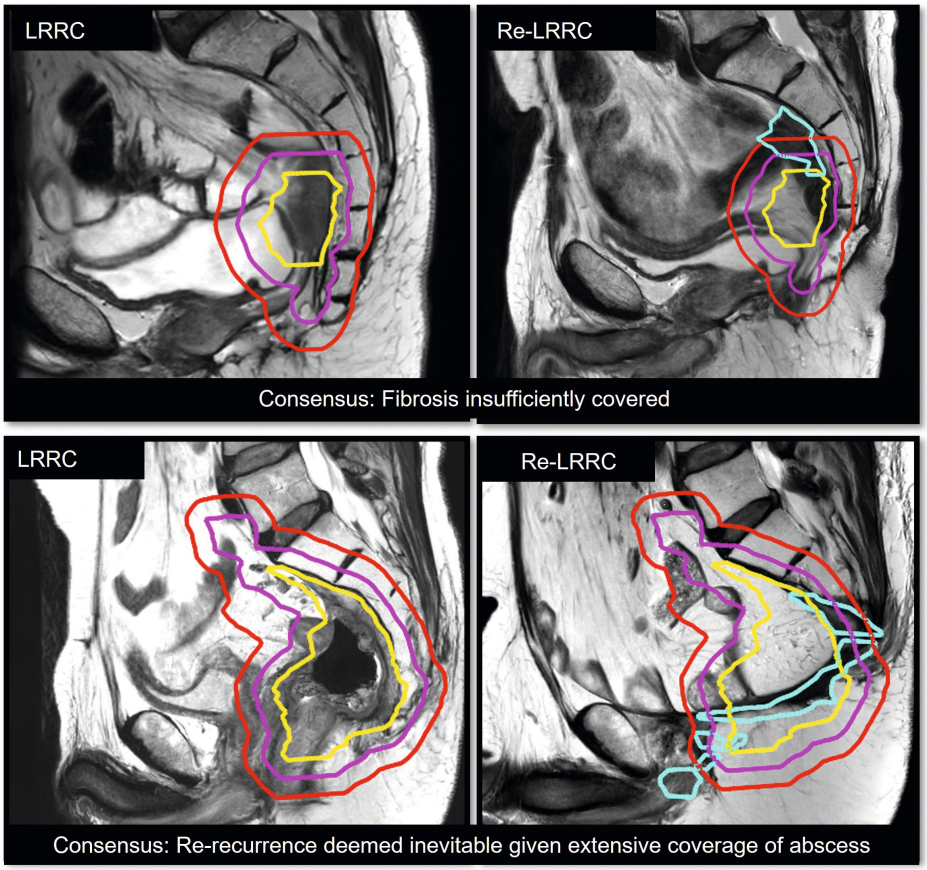


Figure 2. Two examples of discussed cases with different conclusions. For both cases, LRRC imaging is shown on the left, re-LRRC imaging on the right. LRRC target volumes are shown in yellow (GTV), pink (CTV) and red (PTV). The local re-recurrence is delineated in blue. In the top case, the re-recurrence 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%

Chapter 6

Prospective radiotherapy Quality Assurance leads to delineation guideline refinements for recurrent rectal cancer: experience from the PelvEx II study

Piqeur F, Hupkens BJP, Creemers DMJ, Nordkamp S, Berbee M, Buijsen J, Rutten HJT, Marijnen CAM, Burger JWA, Peulen HMU.

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ABSTRACT

Introduction: Target volume delineation in locally recurrent rectal cancer (LRRC) is clinically challenging. To ensure the quality of chemoradiotherapy (CRT) within the PelvEx II trial, a delineation guideline was developed, and prospective quality assurance (QA) was instated for all patients. Guideline adherence, the impact of QA on target volumes, and subsequent guideline refinement are described in this paper.

Methods and materials: All PelvEx II patients starting CRT, either full-course (50-50.4Gy) or reirradiation (30Gy), were eligible for QA. An online meeting with the treating physician and the QA team was planned for each patient prior to treatment, to peer review performed delineations. Adherence to each of the 7 (reirradiation) or 8 (RT naive) guideline recommendations is scored and all suggested adjustments to target volumes as well as any reasons to deviate from protocol are noted. When applicable, target volumes before and after QA are compared. Possible protocol refinements were discussed amongst the trial QA team.

Results: Prospective review of 113 cases of LRRC was performed. All guideline recommendations were followed in 53% of cases. Changes to the GTV and CTV were advised in 21 and 39 cases respectively. A median increase of GTV (+29% ($p<0.001$)) and CTV (+15% ($p<0.001$)) was seen in reirradiation patients, versus a median CTV-increase of +6% ($p=0.002$) in RT naive patients, following proposed changes. Deviations from protocol were accepted in 30 cases (27%). In refining the protocol, 13 adjustments were agreed upon.

Conclusion: Peer-review of LRRC target volumes leads to altered target volumes in up to 48% of cases, resulting in an updated delineation guideline.

INTRODUCTION

The incidence of locally recurrent rectal cancer (LRRC) has decreased in the past decades due to the introduction of total mesorectal excision (TME) surgery and neoadjuvant (chemo) radiotherapy (nCRT) in the primary setting.[1–5] Patients who develop a local recurrence have a poor oncological outcome, with a 5-year overall survival of approximately 30% in patients undergoing treatment with a curative intent.[3,6,7]

Treatment for patients with non-metastatic, (borderline) resectable LRRC in the Netherlands currently consists of nCRT, followed by surgery.[1,3,8–10] Depending on previous radiotherapy, either full course chemoradiotherapy (25x2Gy or 28x1.8Gy) or chemo reirradiation is used (15x2Gy), both with concomitant capecitabine.[11,12] The rationale of nCRT is to downsize tumour volume preoperatively, to facilitate a radical surgical resection (R0). To date, the R0 resection rate is the most well-known and best-described predictor of oncological outcome. Recently however, achieving a pathological complete response (pCR) after neoadjuvant treatment has also been shown to be a strong predictor of oncological outcome.[13,14] The use of induction chemotherapy before nCRT may lead to more patients achieving a pCR.[14–16] Therefore, the randomised PelvEx II trial was initiated, investigating the benefit of induction chemotherapy before nCRT and surgery for LRRC.[17]

Currently there are no international guidelines regarding target volume delineation (TVD) for LRRC, potentially introducing radiotherapy heterogeneity which in turn may even affect the ability to achieve an R0 resection. However, developing such a guideline is complicated due to heterogeneity of the disease. In LRRC, there is a loss of normal anatomical boundaries after surgery (most notably the mesorectal fascia), often leading to an extra-anatomical presentation of LRRC, such as against the pelvic wall or presacral. Moreover, there is a large variation in previous rectal cancer treatment (i.e., no neoadjuvant treatment, previous short-course or long-course (chemo)radiotherapy, use of induction or consolidation chemotherapy) further introducing heterogeneity. Lastly, prospective data that can aid in target volume definition is lacking, as only a handful of prospective trials for LRRC have been performed and data regarding LRRC treatment failure is scarce.

To overcome these issues, the PelvEx II trial aimed to standardize radiotherapy for LRRC. To do so, the first step was to develop a consensus-based delineation guideline, as published previously.[18] Secondly, it is important to monitor guideline adherence and guideline

applicability, to improve the delineation guideline if necessary. A prospective Quality Assurance (QA) programme was therefore instated, consisting of peer-review of TVD.

The aim of this study is to assess the impact of a prospective QA programme within the PelvEx II trial, regarding delineation guideline adherence and guideline applicability, and to refine the current delineation guideline if and where necessary.

MATERIALS AND METHODS

The PelvEx II trial opened in November 2020. The trial includes patients with non-metastatic, (borderline) resectable LRRC after a partial or total mesorectal excision for primary rectal or distal sigmoidal cancer.[17] LRRC staging is performed according to the PelvEx II radiology standard operating procedure, including a description of all (potentially) involved organs and structures. Patients are randomized to either the standard arm, consisting of nCRT followed by surgery, or to the experimental arm, consisting of induction chemotherapy (either 3-4 cycles of CAPOX or 4-6 cycles of FOLFOX or FOLFIRI), followed by nCRT and surgery. All trial patients receive nCRT, either full course (25x2Gy or 28x1.8Gy), or reirradiation (15x2Gy), with concomitant capecitabine, depending on previous primary rectal cancer treatment.

A PelvEx II delineation protocol was established during several multidisciplinary consensus meetings with LRRC experts from the Netherlands and Sweden, as described in a previous publication.[18] In the PelvEx II trial, all radiation oncologists were asked to delineate according to the instated delineation guideline.

Prospective review of all delineations was instated for all randomized in the PelvEx II trial patients from 01-05-2021 onwards, as there was no coordinating investigator available prior to this date. The QA programme consisted of an online peer-review meeting with the treating radiation oncologist, at least one member of the PelvEx II QA team (HP, JB, MB, BH, CM) and the coordinating investigator (FP, DC). A meeting was planned as soon as possible after delineation was performed, to avoid treatment delay. Patients treated in QA centres (i.e., Maastro and Catharina Hospital Eindhoven) were internally reviewed by QA team members.

During the QA meeting, the treating physician presented the case, including information on primary and recurrent disease. GTV and CTV delineations were evaluated. PTV margins

are dependent on local protocol and were therefore not reviewed in QA meetings but should be between 5 and 10mm, as stated in the guideline.

Adherence to each recommendation was scored in a binary fashion (i.e., compliant yes/no). Suggested target volume alterations were noted, and radiation oncologists were asked to save all original target volumes (pre-QA), as well as altered target volumes (post-QA), if applicable. Any agreed upon protocol deviations were noted with the discussed considerations, as were any questions that arose from the instated protocol. Radiotherapy DICOM data were collected after radiotherapy was completed.

All patients randomized by December 31, 2023, were selected for analysis. Patients were excluded in case of withdrawal of informed consent, screening failure, or failure to start nCRT. Median GTV and CTV were calculated and compared before and after QA, when applicable. Categorical data is shown as an absolute number with percentages. Continuous data is either reported as a mean or median, as fit, with a standard deviation (SD) or interquartile range (IQR) respectively. Categorical comparisons are performed using the Chi-Square and Fisher exact test, as applicable. Continuous data are compared by the Mann-Whitney U test and the Wilcoxon Signed Rank test, as applicable. Two-sided p-values of <0.05 were deemed statistically significant for all performed analyses. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0, IBM Corp. Released 2022. Armonk, NY: IBM Corp.

Propositions for guideline refinement were written by the coordinating investigator (FP) following data analysis, incorporating the most common reasons for non-adherence, protocol deviations and questions that arose from QA meetings. Propositions were sent to all members of the QA team and discussed in a guideline meeting. A refined protocol was then written and approved by all members of the PelvEx II QA team.

RESULTS

A total of 168 patients were randomized by December 31, 2023. 12 patients were not eligible for nCRT and therefore excluded from analysis, as shown in figure 1. Overall, 141/156 patients (90%) received (internal or external) peer review. QA was performed in 21 radiotherapy trial centres. The number of QA meetings per centre ranged from 1-12, with a median of 3. The baseline characteristics of all patients eligible for QA are shown in Table 1.

External peer review was performed in 113 patients (72%), of which 64 patients were scheduled for reirradiation (57%), and 49 for full course CRT (43%). In an additional 28 patients, internal QA was performed. In the remaining 15 patients QA was not performed because the QA programme had not yet started (n=5) (i.e., before 01-05-2021), or because QA was not possible due to time constraints or lack of response (n=10).
Internally peer-reviewed cases were excluded from analyses as it was not systematically recorded whether changes to target volumes were made. Of the 113 cases that underwent external peer-review, DICOM data was retrieved for 101 cases (89%). Data could not be retrieved for 12 cases as patients had not yet finished CRT (n=6), or there was no response to the call for data (n=6).

In total, there were seven guideline recommendations for reirradiation, and eight for RT naive patients, as summarized in table 2. All guideline recommendations were followed in a total of 60/113 cases (53%). In reirradiation patients, 58% of cases were completely guideline compliant (7/7 recommendations followed), versus 47% in RT naive patients (8/8 recommendations followed). Nineteen reirradiation cases deviated from one recommendation (30%), seven from two recommendations (11%) and one from three recommendations (1%). Twelve RT naive cases deviated from one recommendation (25%), eleven from two recommendations (22%) and three from three recommendations (6%).

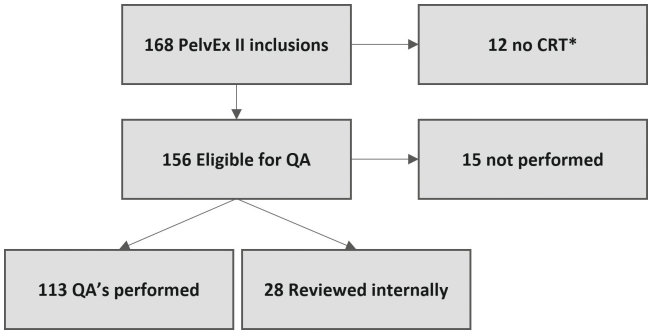


Figure 1. Flowchart of all PelvEx II patients randomized before 31-12-2023 that were eligible for Quality Assurance meetings. An overall QA compliance rate of 90% (141/156) of patients eligible for QA were reviewed. *CRT not performed due to withdrawal of informed consent, screening failures or progressive disease.

Table 1. Baseline characteristics of all patients eligible for QA (n=156).

Baseline characteristics		n	%
Primary tumour			
Gender	Male	113	72.4%
	Female	43	27.6%
cT-stage	cT0-2	29	21.6%
	cT3-T4	105	78.4%
cN-stage	cN0	46	34.8%
	cN1-2	86	65.2%
Neoadjuvant treatment	None	63	40.4%
	CRT	52	33.3%
	Chemotherapy + CRT	10	6.4%
	5x5 Gy	18	11.5%
	Chemotherapy + 5x5 Gy	13	8.3%
Surgical procedure	LAR	71	45.8%
	APR	56	36.1%
	TaTME*	15	9.7%
	Recto sigmoidal resection	13	8.4%
Any metastases before LRRC diagnosis**	Yes	30	19.2%
Local recurrence			
Age at diagnosis	Mean (SD)	64	9.9
Time from surgery to LRRC diagnosis (months)	Median (IQR)	23	12-39
Multifocal recurrence	No	126	80.8%
	Yes	30	19.2%
Type of recurrence	Mucinous	28	19.0%
	Solid	110	74.8%
	Fibrotic	5	3.4%
	Other	4	2.7%
Involved compartments	Anterior	50	32.7%
	Posterior	70	45.8%
	Lateral	86	56.2%
	Central	61	39.9%
Size (largest) lesion (mm)	Median (IQR)	32	20-54

Missing data was excluded from analysis

**TaTME: Transanal total mesorectal excision.*

***Metastases at LRRC diagnosis and/or within 6 months prior to diagnosis is an exclusion criterium. Any metastases before LRRC diagnosis had to be diagnosed and treated at least 6 months prior to diagnosis of the local recurrence for patients to be eligible for the PelvEx II trial.*

The most common reasons for non-compliance were editing towards OAR (n=28), not incorporating all fibrosis into target volumes (n=11) and not delineating all elective target volumes (n=6) or remaining mesorectal fat (n=8) in RT naive patients, despite the fact that the protocol stated all elective target volumes should be delineated as in LARC. An overview of compliance to each guideline recommendation can be found in table 2. Overall, changes to target volumes were made in 54 cases. Pre-QA data was not saved and therefore not retrievable in 8/56 patients.

Changes to the GTV were advised in 21 cases, of which 20 led to an increase in GTV volume. In 11/21 cases, not all fibrosis was incorporated into target volumes, as shown in figure 2 (n=10 reirradiation, n=1 RT naive). Other reasons for proposed GTV editing included but were not exclusively; incorporating the whole lumen in the GTV in an intraluminal recurrence (n=1), expanding the cranio-caudal margins in an intraluminal recurrence (n=1), incorporating an adjacent fistula within the GTV (n=1), incorporating the previous anastomosis into the GTV in an intraluminal recurrence (n=1), and extending the GTV due to uncertainty of image registration (n=2).

A statistically significant increase in median GTV is seen in reirradiation patients where alterations were advised (n=15, +29%, $p<0.001$), but the observed increase does not reach significance in RT naive patients, most likely due to low numbers (n=3, +36%, $p=0.109$) (Table 3). Notably, post-QA GTV was significantly larger in patients undergoing reirradiation (58cc) compared to RT naive patients (33cc) ($p=0.048$).

Changes to the CTV were advised in 39 cases, leading to an increase in CTV volume in 36 cases. The most common advice in regard to CTV was to reverse any editing towards OAR (n=16) (Figure 2), most notably the sacrum, and to adjust delineated elective volumes (n=16). In 7 cases, this adjustment consisted of extending the elective CTV to encompass the obturator nodes (n=7).
CTV was significantly larger in RT naive patients compared to reirradiation patients, due to elective target volumes (Table 3). A statistically significant increase in median CTV is seen in both reirradiation and RT naive patients following QA (reirradiation n=24, +15%, $p<0.001$; RT naive n=14, +6%, $p=0.002$).

Table 2. Summary of recommendations in the PelvEx II delineation guideline. The percentage of peer-reviewed cases adhering to each original recommendation is shown for reirradiation patients (receiving 15x2Gy) and RT naive patients (receiving either 25x2Gy or 28x1.8Gy).

	Guideline recommendation	Reirradiation (n=64)	Full course (n=49)
1	GTV was correctly identified	58 (91%)	48 (98%)
2	All (pre-chemo) GTV was incorporated in the CTV	64 (100%)	47 (96%)
3	Complete fibrosis (when applicable) was covered by GTV or CTV	**54 (84%)**	48 (98%)
4	A correct margin of at least one cm was used to CTV	62 (97%)	43 (90%)
5	All GTV lesions were incorporated in one CTV with correct margins	63 (98%)	47 (96%)
6	CTV was not edited towards organs at risk	**52 (83%)**	**33 (67%)**
7a	No elective target volumes were delineated when performing reirradiation	60 (94%)	n.a.
7b	Elective target volumes were delineated as in LARC	n.a.	43 (88%)
8	All (remaining) mesorectal fat was delineated as in LARC	n.a.	41 (84%)

Protocol deviations were accepted in 30 cases (27%) (Table 3). The most common reasons for accepted protocol deviations were reducing elective target volumes because of potential toxicity (n=11) (such as significant small bowel within the pelvis) and extending the CTV beyond what is currently defined in the protocol (n=12), for example for better coverage of expected resection margins.

In 22 cases, the instated protocol did not give enough guidance on how to delineate. In 6 instances, questions were raised regarding editing towards OAR, mainly towards pelvic bones. Three questions were posed regarding intraluminal recurrences, asking whether or not to delineate the whole lumen as GTV and which cranial-caudal margins should be used (i.e., 1 or 2 cm). The last group of questions was only applicable to RT naive patients, namely, which LARC delineation recommendations should and should not be followed; is it necessary to delineate up to S1 in case of perineal recurrences and is it necessary to delineate all elective fields in case of a high nodal recurrence after PME for distal sigmoidal cancer.

Table 3. Overview of number of changes made, protocol deviations, and median gross target volume (GTV) and clinical target volume (CTV) for reirradiation and RT naive patients.

		Reirradiation (n=64)		RT naive (n=49)		All (n=113)		p-value
		n=	%	n=	%	n=	%	
Any changes made	Yes	30	47	24	49	54	48	0.824
	No	34	53	25	51	59	52	
Number of changes	1	26	87	17	71	43	80	
	2	4	13	6	25	10	19	
	3	0	0	1	4	1	2	
Protocol deviation	Yes	15	23	15	31	30	27	0.394
Volumes (n=101)		Reirradiation (n=60)		RT naive (n=41)		Total (n=101)		p-value
		Median	IQR	Median	IQR	Median	IQR	
GTV	cc	58	16-119	33	16-59	48	16-102	0.048
CTV	cc	275	148-478	464	365-611	374	214-553	<0.001

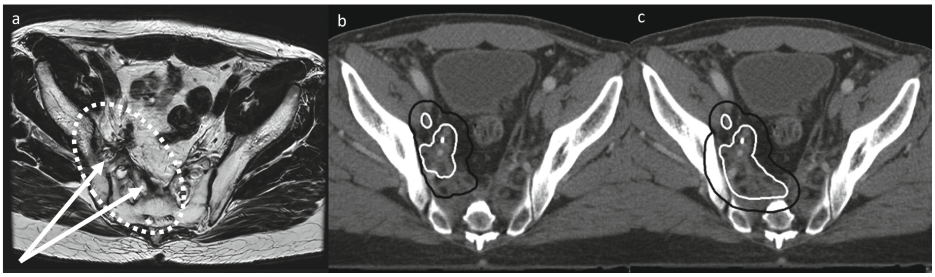


Figure 2. Example of an alteration made during a QA meeting. From left to right, the pre-treatment diagnostic MRI (a), planning CT with pre-QA target volumes (b) and planning CT with post-QA target volumes (c) are shown. The GTV is shown in white, the CTV in black. The original GTV was extended following QA to encompass the complete fibrosis. The CTV was originally edited out of the bone, but it was advised not to do so given the invasive nature of the disease and the risk of an R1-resection at the lateral side wall.

Table 4. Summary of original or new (in bold) GTV and CTV recommendations for LRRC. Exceptions and clarifications are provided in the full delineation guideline in the supplementary material.

GTV	• Delineate all macroscopically visible tumour in primary staging
	• Delineate only visibly involved areas of surrounding organs
	• Consult with a dedicated radiologist to determine the extent of the GTV
	• In case of induction chemotherapy:
	  • If major regression occurs, adjustment towards other non-involved structures is allowed
	  • If a complete response is suspected, GTV should still be defined (i.e., remaining tumour bed or fibrosis)
	• **If the tumour is located in fibrosis, the whole fibrosis should be incorporated**
	• **If the tumour is located within an abscess, the whole abscess should be incorporated**
	• **In case of an intraluminal recurrence, the whole circumference of the lumen should be incorporated**

CTV	• Consult with the treating surgeon to determine surgical resection margins at risk for irradical resection and discuss planned type of surgery
	• CTV = GTV + 1cm margin
	• Combine multifocal recurrences into one CTV using logical anatomical boundaries and staying at least 1 cm beyond the GTV in all directions
	• Do not adjust CTV towards other organs
	• If applicable, all pre chemotherapy GTV must be included in the CTV
	• **In case of an intraluminal recurrence, a cranio-caudal border of 2cm beyond the GTV is advised and a circumferential margin of 1cm is advised**
	• In presacral recurrences, extending the CTV towards the lateral sidewall should be considered, to ensure coverage of surgical resection margins
	• In reirradiation patients, no elective nodal delineation is advised
	• In RT naive patients, elective target volumes should always be delineated
	  • **Remaining mesorectal fat and nodes, presacral nodes, internal iliac nodes and obturator nodes should always be included**
	  • **The cranial border of the CTV is at least the bifurcation of the common iliac arteries into the external and internal iliac artery/sacral promontory, with allowance for national adjustments, or one centimetre above the most cranial GTV if it extends beyond the bifurcation.**
	  • **In case of involvement, delineation of the abdominal presacral lymph nodes and external iliac lymph nodes should be considered**
	  • **The ischiorectal fossa and sphincter complex should be incorporated in case of involvement or a perineal recurrence**

During the guideline meeting, thirteen guideline adjustments were adopted by the QA team. The updated delineation guideline can be found in the supplementary material. A summary of the updated guideline is shown in table 4.

DISCUSSION

In this study, we describe our ongoing experience implementing the first formally published delineation guideline for LRRC, and subsequent prospective peer review of delineations for LRRC within the PelvEx II trial. For trial QA, we use a simple, online approach, minimizing time investment (+/-15 minutes), and omitting the need for data transfers, resulting in a high QA participation (90%). By organizing an online meeting as soon as target volume delineation has been performed and changing target volumes in real time, we avoid treatment delay as much as possible. We further show that target volume alterations are recommended in 48% of cases, clearly highlighting the need for prospective peer review in LRRC. As protocol deviations are reported in 27% of cases, the instated protocol has been tailored to improve guideline adherence.

Based on the presented data, several lessons can be learned. The most common reason for non-compliance in this study was editing towards OAR. We currently advise not to edit the CTV towards OAR, as there is a loss of anatomical boundaries in LRRC after previous surgery, which may lead to more invasion of surrounding structures, potentially hampering surgical resection. Moreover, the positive predictive value of MRI may be limited for tumour invasion into surrounding structures, even though it is the gold standard modality for locoregional staging.[8–10,19–22] One exception previously stated within the guideline was that editing towards pelvic bones is acceptable if it is highly likely that there is no bony invasion (i.e., no invasion of the lateral side wall in case of a presacral recurrence). This was often interpreted as that editing towards bony structures is acceptable when it is not described as invaded on MRI. Consequently, editing towards pelvic bones was seen in numerous cases and recommended against during QA. In the revised guideline, this recommendation has been reformulated.

A common recommendation made during QA is to extend the GTV to encompass all surrounding fibrosis within the GTV. It was previously recommended to delineate all fibrosis as GTV if the difference between tumour and fibrosis was unclear. In cases where the distinction was clear, fibrosis should at least be covered by the CTV. In clinical practice, PET-positive areas within fibrosis were often deemed GTV and therefore surrounding fibrosis was deemed CTV. Although this is guideline compliant, the potential risk of false negativity of the PET-CT is often underestimated.[21] Although no data specifying the true risk of false negativity in fibrotic LRRC is currently available, underestimation of GTV

should be avoided. Therefore, it was agreed that all fibrosis should always be incorporated within the GTV, regardless of the PET-CT, leading to a protocol adaptation.

The protocol stated that RT naive LRRC cases should be delineated as if they were a locally advanced primary tumour. However, a lot of protocol deviations in regard to elective target volumes in RT naive patients were reported, implying this recommendation was not sufficiently detailed. It was therefore proposed to explicitly specify which elective volumes should be irradiated. Each LRRC should be deemed at very high risk for locoregional failure due to the loss of anatomical boundaries and the poor LRFS.[23] Therefore, all remaining mesorectal fat, all (remaining) mesorectal nodes, presacral nodes, internal iliac nodes and obturator nodes should be irradiated. Other elective volumes should only be delineated in specific cases, as stated within the full guideline in the supplementary material.

Lastly, tailoring the protocol to different recurrence types seen within the trial seemed necessary, based on reoccurring questions during QA. These questions led to additional recommendations for tumours located intraluminal, tumours located in an abscess, very high recurrences (completely above S2/S3) and very distal recurrences.

As of now, the updated and approved delineation guideline has been distributed amongst PelvEx II trial centres. Ideally, the updated guideline would lead to more homogeneity of performed delineations within the trial population. Refining the guideline may have the added benefit of decreasing the number of modifications needed, as seen in primary rectal cancer, where two central review platform studies by Joye et al. showed that refinement of delineation recommendations led to a significant decrease in the number of CTV modifications.[24,25]

Interestingly, the study group of Joye et al. was also able to show a learning effect after ten performed reviews, albeit in primary cancer.[25] A learning effect cannot be discerned yet based on the current QA data, which may be explained by the heterogeneity and complexity of LRRC, or by the fact that exposure to LRRC is often limited for individual physicians.

A recent review by Brooks et al. proposes prospective review for all trial patients, given that on-trial protocol deviations are found continuously, even after benchmark accreditation across several tumour types.[26] It is therefore reasonable to assume that even if a learning

effect did occur, this may not be sustained in LRRC delineations. They further advocate a risk-adjusted approach, tailoring the intensity of QA to trial-specific factors. Although planning is relatively simple for LRRC given there are no formal dose constraints, TVD is highly complex. Therefore, it is the ambition to continue the QA programme until all PelvEx II patients have undergone nCRT. Based on accrual so far, this would be expected in 2027. A potential learning effect could then be re-evaluated based on available data.

Given the number of alterations made within the trial, it is likely that a peer review process for all patients with LRRC would be beneficial, as seen in previous studies investigating the benefit of peer review in non-trial populations.[27] By doing so, non-trial patients may benefit from research developments and quality control in real time. An additional benefit would be that the current guideline can be tested for applicability in a palliative population, as up to 50% of patients with LRRC present with either metastatic or local irresectable disease.[6,7,28] The guideline was initially developed with cases of LRRC in a curative setting and is now also ongoingly tested within a curative population. For a palliative population, other outcomes such as quality of life and local control may be more important than sufficient downstaging of tumour volume. Therefore, prospective peer-review of all LRRC cases may help answer questions in regard to target volumes for a palliative population.

To summarize, prospective peer review of LRRC target volumes leads to changes in up to 48% of cases, highlighting the need for collaboration in this complex tumour type. Based on the current data, the protocol was further refined by incorporating commonly recommended alterations, tailoring recommendations to different tumour types and incorporating frequent protocol deviations.

Several limitations do however apply to our study. Although the use of this first delineation guideline will likely result in more consistent TVD throughout the trial, there is no gold standard to determine the accuracy of delineations. The guideline was developed based on consensus with several experts from different specialities in the Netherlands and Sweden, but prospective data to substantiate the validity of the protocol is still lacking. Lastly, no information on response to chemotherapy can be disclosed as the trial is still ongoing, but it may have a significant effect on how delineations are performed.

CONCLUSION

Peer review of target volumes after guideline implementation for LRRC led to alterations in target volumes in up to 48% of cases, highlighting the need for real-time quality assurance of LRRC delineations. Based on advised alterations, noted protocol deviations, and reoccurring questions, the guideline was updated. By continuing trial quality assurance, development of an evidence-based delineation guideline will be possible.

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SUPPLEMENTARY DATA OF CHAPTER 6 - PELVEX II CHEMORADIOTHERAPY MANUAL

Purpose and scope

This document has been developed for and applies to the PelvEx II study and serves as a guideline for the process of planning and delivering (chemo)radiotherapy treatment in radiotherapy naive and previously irradiated patients with locally recurrent rectal cancer enrolled in the study. The aim of this document is to ensure uniform delivery of radiotherapy and the collection of high-quality data for study analysis.

As recognized in the first version of this SOP, variability in target volumes can occur. Four multidisciplinary delineation workshops with PelvEx II trial centres in the Netherlands and Sweden were organized to overcome this issue. In these workshops, consensus was reached by participating radiation oncologists, but also surgeons and an expert radiologist, on how to define target volumes for our trial population. The development of the delineation guideline has been published by Piqeur and Hupkens et al.[1] Following the development of the delineation guideline, a real-time quality assurance (QA) programme has been instated, as large inter-observer variation was reported.

The initial proposal was to perform a central review of the first 5 patients per centre. Based on preliminary data from the QA programme, of the first 168 trial patients, changes are made in up to 48% of cases after peer-review.[2] Therefore, the QA programme will be continued for all patients included in the PelvEx II study.

Preliminary data further showed that consensus was reached to deviate from protocol in up to 30% of cases, and the protocol was deemed unclear in up to 22% of cases, when using SOP version 1.1 and 1.2.[2] Therefore, recommendations in this SOP (version 2) have been refined and updated based on the observations made within the QA programme so far.

It is recognised that during the conduct of the trial, it may be necessary to further modify the defined protocol either because of the publication of new data regarding target volume definition, consensus views derived from radiotherapy planning workshops or observations during trial QA (see below). It is likely that any changes will be minor and can be introduced through modification of this radiotherapy planning document as they will not interfere

with the key primary and secondary end points of the study. In the event of the need for a major change requiring alteration of the main protocol, a formal protocol amendment will be initiated.

To evaluate late effects of reirradiation, information on the previously given radiotherapy is essential. However, this may not be easy to retrieve. When available, the DICOM data of the previous treatment plan should be uploaded together with the reirradiation. If this is not available, the same volume parameters as for the re-irradiation plan should preferably be reported.

1 QA Meeting

Participating physicians are asked to join a QA meeting before starting neoadjuvant chemoradiotherapy for their patient. The QA meeting is planned online via MS-teams by the trial coordinator. Ideally, the QA meeting is planned after the delineation has been made, but before any treatment planning is performed. The treating physician is asked to give a short introduction on the case, including information of primary rectal cancer presentation and treatment, and recurrent rectal cancer presentation. The physician is then asked to share their screen and show the performed delineations. Only target volumes are discussed. Delineation of OAR and treatment planning are not discussed. Radiation oncologists are asked to save all RT-structures. If any alterations are advised, this means old and new versions of the target volumes should be saved (for example: GTV_old and GTV_new).

Once patients have finished nCRT, all information on delineation and treatment planning is retrieved by the coordinating investigator. This information consists of the DICOM files of the planning CT, RT-structure, RT-dose, and RT-plan. The retained information is used to aid in further development of a delineation guideline for locally recurrent rectal cancer.

2 Radiotherapy treatment planning

The use of a planning CT scan with target volumes delineated on each slice and pixel-based inhomogeneity correction is considered standard practice and is a mandatory requirement. Matching with the pre-treatment MRI is strongly recommended. Alternatively, delineation and planning on an MRI is allowed.

3 Patient set-up

It is recommended that appropriate immobilisation and a scan/treatment position is used with which the site is familiar with. The supine position is recommended to improve reproducibility of the treatment position, but it is not mandated. A belly board may be used for treatments in the prone position, but it is not a requirement.

4 Patient data acquisition

The scan limits are the superior aspect of L5 superiorly to 4 cm below the anal verge. The recommended slice thickness is 3 mm.

5 Use of contrast

The use of intravenous and oral contrast is optional and should align with local centre policy.

6 Target volumes

The target volume definition process requires the delineation of gross, clinical and planning target volumes. These are defined below.

6.1 Gross tumour volume (GTV)

All macroscopic visible must be delineated. This information is derived from the diagnostic imaging (at least a pelvic MRI, if available a PET-CT) and supplemented by clinical examination and possible endoscopic findings. Only involved areas of any organ will be included (i.e., it is not necessary to encompass the full bladder or vagina at involved levels).

If patients have received induction chemotherapy, all pre-chemotherapy macroscopic tumour should be delineated. Adjustment towards other structures is allowed in case of regression. In case of a complete response there will still be a GTV (the tumour bed/fibrosis after induction chemotherapy).

If the tumour is located in **fibrosis**, all adjacent fibrosis should be incorporated in the GTV.

Reasoning: Interpretation of radiological imaging of tumours in fibrosis can vary significantly, as shown in figure 1. Even if PET-positive areas within fibrosis seem to be distinguishable as tumour compared to surrounding fibrosis, it is advised to encompass all fibrosis in GTV, as shown in figure 2, given the risk of false negativity of the MRI and the PET-CT.[3]

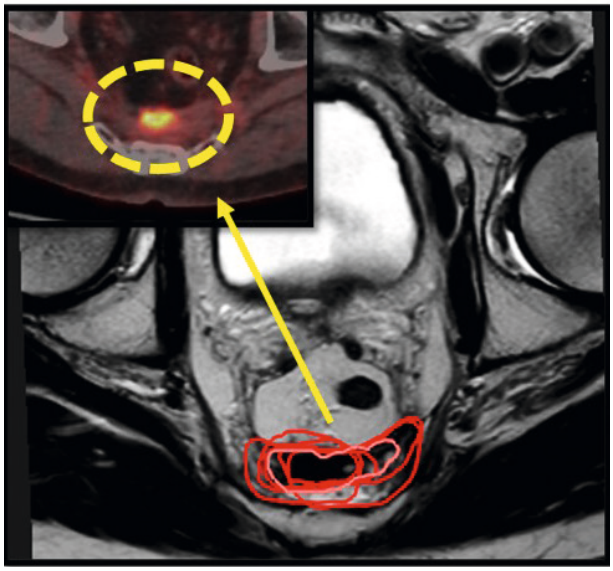


Figure 1. Delineation of a PET-positive tumour located in fibrosis. A (not yet published) delineation study showed differences in GTV interpretation in tumours located in fibrosis. 3/8 radiologists and 7/11 radiation oncologists delineated all fibrosis as tumour, whereas 5/8 radiologists and 4/11 radiation oncologists only delineated the PET-positive area within fibrosis as tumour. Consensus has been reached that all surrounding fibrosis should be deemed GTV, as shown in figure 2.

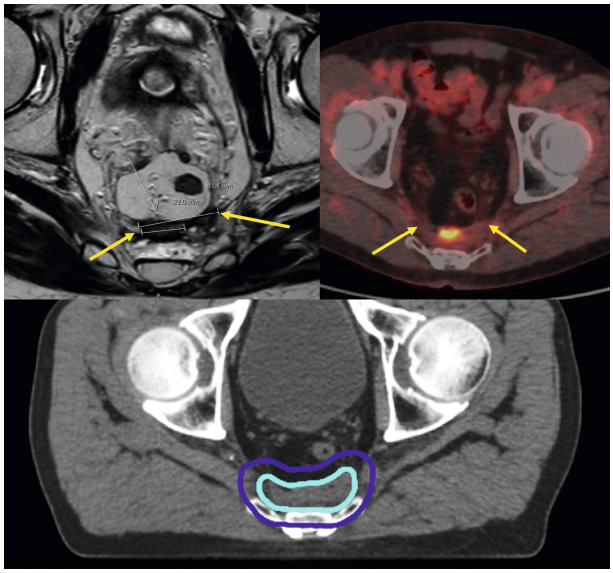


Figure 2. Example of how to delineate a presacral, fibrotic tumour. The GTV (light blue) should include all surrounding fibrosis. The CTV (dark blue) can then be extended towards the lateral sidewalls to guarantee that surgical resection margins are completely incorporated in the CTV. The CTV should not be edited towards the sacrum, as this area would be where a potential irradical resection may occur.

If the tumour is located within an **abscess**, the whole abscess should be incorporated in the GTV.

Reasoning: In tumours located within an abscess, it is intuitive to account for potential tumour spread within circulating fluids by including the whole abscess within the GTV.

In case of an **intraluminal** recurrence (for example at the previous anastomosis), the whole circumference of the lumen should be deemed GTV.

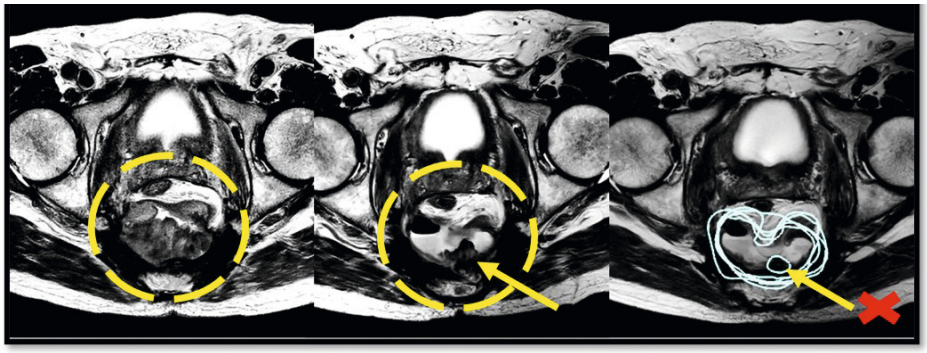


Figure 3. Example of a recurrence located in an abscess, before (left) and after (middle) induction chemotherapy. The whole remaining abscess should be delineated as GTV as shown on the right, instead of delineating only remnant solid tumour as GTV.

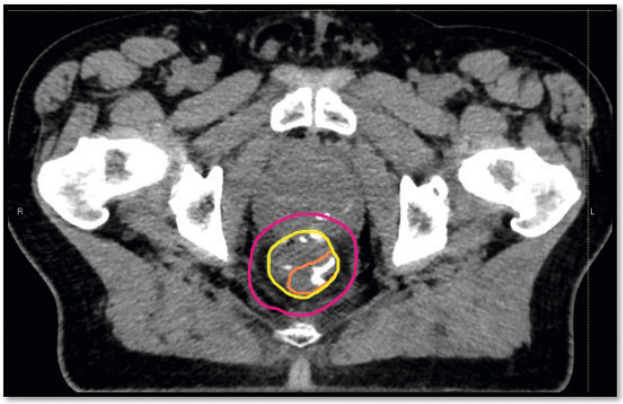


Figure 4. An example of an anastomotic recurrence previously reviewed during Quality Assurance. Consensus was reached to extend the original GTV (orange) to encompass the whole lumen (yellow).

6.2 Clinical target volume (CTV)

The CTV should always encompass the GTV with at least a 1cm margin in all directions, irrespective of any additional elective volumes.

In case of **multifocal** recurrences, all localizations should be combined in one CTV, with logical anatomic boundaries. Small separate islands are not allowed. The limit of the CTV should be at least one centimeter beyond each GTV in every direction.

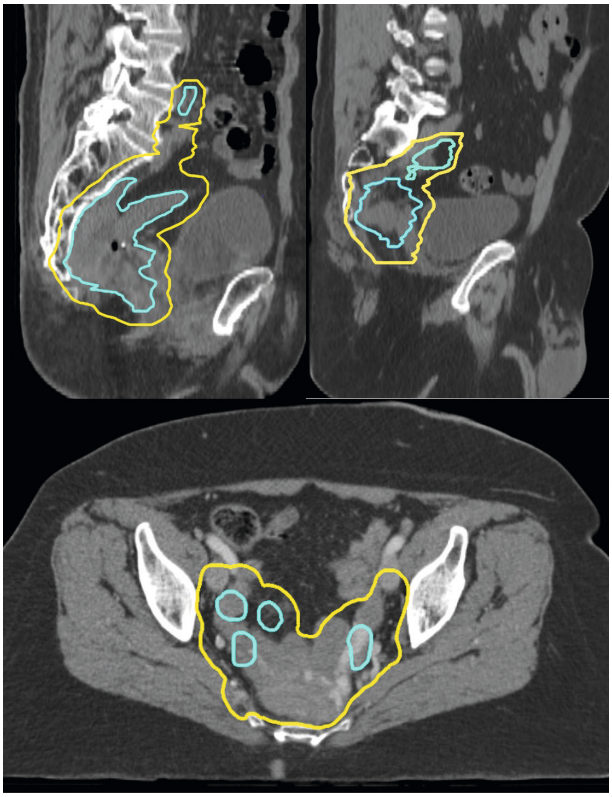


Figure 5. Three examples of multifocal recurrences. All GTV lesions (light blue) should be incorporated into one CTV with logical anatomical boundaries, irrespective of additional elective target volumes.

In case of **intraluminal** recurrences, a cranio-caudal border of 2 cm beyond the GTV is advised. Circumferentially, a one-centimeter margin is recommended, as in other recurrence types.

In case of a recurrence located in a **rectal stump**, delineation of the remaining rectal stump as CTV can be considered. A cranial border extending beyond the rectal stump can be adjusted to a minimum of 1 cm instead of 2 cm.

In case of **presacral** recurrences, extending the CTV margins towards the lateral sidewall to encompass complete surgical resection margins should be considered (figure 2, 6). In general, the advice is to rather be too extensive than too conservative when incorporating surgical resection margins within the CTV.

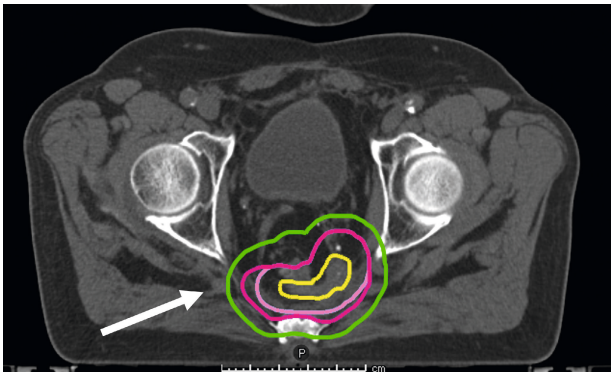


Figure 6. QA example in which the original CTV (light pink) was extended beyond the prescribed 1 cm margin, to ensure that surgical resection margins near the lateral side wall were adequately incorporated within the CTV (dark pink).

Adjustment of the CTV towards other organs is not allowed. This means the CTV often extends into surrounding organs and structures (such as bone, bladder, prostate, uterus).

In cases where it is beyond any clinical doubt whether or not surrounding organs are involved (for example when there are several non-involved structures laying between the OAR and the tumour), adjusting towards OAR can be considered.

Reasoning: Given the recurrent nature of the tumour and the loss of anatomical boundaries due to previous surgery, it is often at the border of structures and organs near the recurrence that surgeons are afraid an R1-resection may occur (figure 7). Adequate target coverage should therefore outweigh toxicity concerns in these areas.

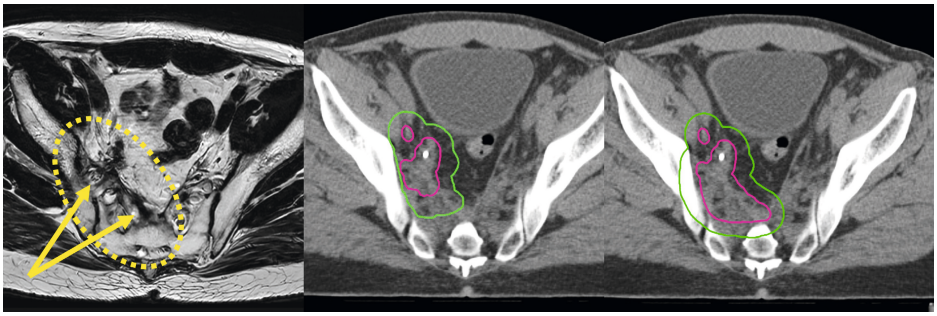


Figure 7. Example of a lateral recurrence in which GTV (pink) was extended from before to after QA (middle and right respectively) to encompass complete fibrosis. Subsequently, the CTV (green) was extended and performed editing towards the lateral sidewall was reversed, as there is a risk of undertreatment of surgical resection margins.

Further recommendations in regard to CTV are tailored to patients who are radiotherapy-naïve and to patients undergoing reirradiation.

6.2.1 Patients undergoing reirradiation

For patients undergoing reirradiation, no elective volumes should be included within the CTV.

In **lateral recurrences**, elective reirradiation of the complete lateral compartment can be considered.

Reasoning: In a (not yet published) retrospective analysis of re-recurrences after LRRC treatment with curative intent, several lateral recurrences re-recurred within the lateral compartment, as shown in figure 8. As the potential toxicity of lateral compartment reirradiation seems less significant than complications arising from surgical resection of the lateral compartment, consensus was reached that elective reirradiation of the lateral compartment can be considered in lateral recurrences.

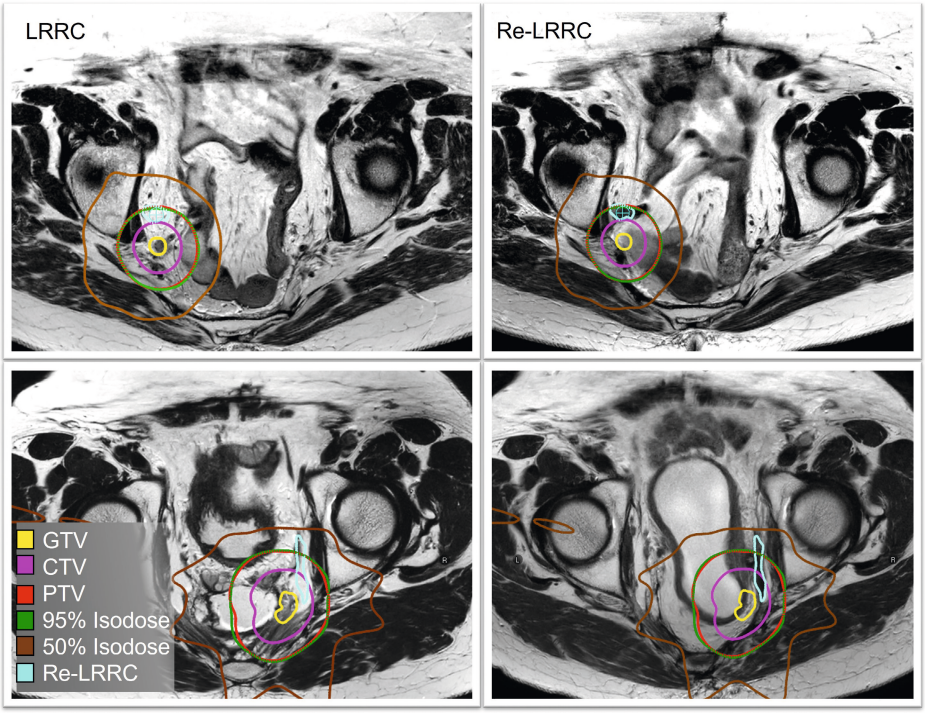


Figure 8. First (left) and second recurrence (right) shown on MRI of two individual cases (above and below). First and second recurrence MRIs have been matched to the LRRC planning CT, to be able to visualise the recurrence in the anatomy of the re-recurrence, and vice versa. The re-recurrence is shown in light blue. LRRC with target volumes (GTV yellow, CTV pink, PTV red) and isodose lines (95% green, 50% brown) are also shown. In both cases, re-recurrences developed in the lateral compartment, at the margins of the original PTV.

6.2.2 RT naive patients

In general, RT naive patients should be handled according to the guidelines of Valentini et al.[4] This leads to the following recommendations:

(1) Any remaining mesorectal fat should be included in the CTV, even though exact delineation of the mesorectum may not be possible due to prior surgery.

(2) The cranial border of the CTV is the bifurcation of the common iliac arteries into the external and internal iliac artery/sacral promontory, with allowance for national adjustments. The CTV should be extended in the cranial direction if there is a suspicion of the local recurrence, or any (possibly) involved lymph nodes extending beyond this upper limit. In that case, the cranial border should be at least one centimetre above the most cranial GTV.

(3) The following lymph nodes should always be included in the CTV.

a. Mesorectal nodes
b. Presacral nodes
c. Internal iliac nodes
d. Obturator nodes

(4) Incorporating the following lymph nodes in the CTV should be considered in case of involvement:
   a. Abdominal presacral lymph nodes
   b. External iliac lymph nodes (in case of **unmistakeable** involvement).

(5) The ischiorectal fossa should be incorporated in the CTV in case of ischiorectal fossa infiltration, or external anal sphincter involvement, or a perineal recurrence.

(6) The sphincter complex (if applicable) should be incorporated in the CTV in case of tumour infiltration or perineal recurrences.

(7) Incorporating the inguinal lymph nodes in the CTV is not recommended, given the high risk of toxicity and the high risk of morbidity due to surgical resection of inguinal lymph nodes. In case of clear involvement of inguinal lymph nodes, the risk of complications due to additional radiotherapy prior to surgical resection should be weighed appropriately.

Some exceptions do apply:

– In case of **distal recurrences** and extensive small bowel within the pelvis, decreasing the cranial border to S2/S3 instead of the bifurcation of the common iliac arteries into the external and internal iliac artery/sacral promontory can be considered.
– In case of isolated lymph node recurrences or intraluminal recurrences **above S2/S3**, it can be considered to not perform irradiation of elective target volumes as described above. It is however recommended to incorporate at least the internal iliac lymph nodes in the CTV until at least two centimeters beyond the GTV caudally.

7.3 Planning target volume (PTV)

This volume ensures coverage of the CTV considering the systematic and random set-up errors, changes over time in the patient geometry and internal organ movement that may occur when delivering a radical course of radiation. Since the required margin is dependent on the local image guidance protocols, the extent of this margin should be determined according to the local policy (between 5mm and 10mm).

7 Dose and volume guidelines

All doses are prescribed as target absorbed doses according to International Commission on Radiation Units (ICRU) guidelines.

7.1 Radiotherapy naive patients

A total dose of 50 Gy in 25 daily fractions of 2.0 Gy per fraction should be delivered. Alternatively, a total dose of 50.4 Gy in 28 fractions can be given.

7.2 Previously irradiated patients

A total dose of 30 Gy in 15 daily fractions of 2.0 Gy per fraction should be delivered.

In patients undergoing reirradiation, it can occur that the PTV is partially located in previously irradiated tissue, whilst the PTV is also partially located within RT naive tissue. For example, a patient can present with a distal recurrence, and involved lymph nodes above S1/S2 that have not been previously irradiated. In these cases, it **can be considered** to give a higher dose (50Gy) to the PTV within RT naive tissue. In that case, the distal recurrence would be prescribed 30Gy, and the involved lymph nodes would be prescribed 50Gy.

7.3 Target dose constraints

All fields or treatment arcs must be treated during each treatment session. It is conventional to report the dose to the ICRU reference point, the maximum dose to the PTV and the minimum dose to the PTV. The isocentric treatment plan is usually specified to receive 100% with the 95% isodose line encompassing the PTV and no more than +7% and -5% inhomogeneity within the target volume. It is also advised to examine the dose distribution in both coronal and sagittal views to ensure the optimal anatomical arrangement of isodoses around the target volume.

7.4 Organs at risk

The anus, femoral heads, bladder, and small bowel are considered organs at risk (OAR). Delineation of these OARs is mandatory. Further detailed delineation of the anus (i.e., inner and outer sphincter) is strongly recommended but not mandated. OAR contours are defined as below.

- Anus: Inner and outer sphincter, from the level of the anorectal junction. The anorectal junction is easiest recognised on coronal images, at the insertion of the levator ani into the puborectalis (continuous with the external sphincter).
- Small bowel: Small bowel according to hospital specific guidelines, either RTOG, small bowel bag or EMBRACE)
- Bladder: Entire bladder including bladder wall.
- Femoral heads: Contoured to the most inferior extent including the lesser trochanter.

Reliable data on constraints are lacking and highly dependent on the volume and location of the recurrence. Therefore, optimization objectives cannot be given.

For intensity modulated radiotherapy (IMRT) treatment plans, there are no mandated OAR dose-constraints with the priority being target coverage. The order of priority for optimisation in decreasing priority is CTV > PTV > Small bowel > Bladder > Other OAR.

To allow for reliable plan comparisons, the following volume parameters should be reported:

- Volume CTV
- Volume PTV
- Whole body: V5/10/15/20/30/45 Gy
- Bladder: V5/10/15/35/50 Gy

8 Treatment planning

Radiation therapy should be delivered with photon energies ≥ 6 MV using a linear accelerator. Equipment of 10 MV or higher is recommended. The use of IMRT or dynamic arc radiotherapy is mandated.

9 On treatment verification

Movement of the CTV is known during the course of radiotherapy and is most marked in the upper rectum. The best available positional verification methods should hence be used which may include electronic portal images compared to digitally reconstructed radiographs (DRRs), or cone-beam CT matching using the planning scan. Adaptive treatment on a MR-Linac is allowed.

Treatment verification should be performed according to local protocol. Acceptable deviations should be assessed according to local policies and the isocentre moved if disagreement is seen in excess of agreed local tolerance levels – usually 5 mm.

10 Concomitant chemotherapy

Radiotherapy for radiotherapy-naïve and previously irradiated patients will be combined with capecitabine administered orally in a dose of 825 mg/m2 twice daily on radiotherapy treatment days. In case of unacceptable toxicity of capecitabine during induction chemotherapy (physician's discretion) Teysuno may be administered orally in a dose of 25mg/m^2 twice daily on radiotherapy days.

11 Minimal requirements for chemoradiotherapy reporting

To enable correct data extraction from the patient file into the electronic case report form, the following issues need to be clearly stated in the patient file:

- Total amount of Gray delivered
- Concomitant chemotherapy agent
- Were any dose reductions necessary?
    - o If yes, please state why (i.e., type of toxicity) and specify dose reduction (e.g. stop concomitant chemotherapy)
- Where there any reportable adverse events (AE) during chemoradiotherapy treatment?
    - o If yes, please note the severity of the AE according to the National Cancer Institute – Common Terminology Criteria for Adverse Events v5.0
      (For the purpose of the PelvEx II study, only AE's grade ≥3 will be recorded)

12 References

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Chapter 7

Postoperative complications following dose adaptation of Intraoperative Electron Beam Radiation Therapy (IOERT) for Locally Advanced or Recurrent Rectal Cancer

Piqeur F, Peulen HMU, Cnossen JS, Huibregtse Bimmel-Nagel CCA, Rutten HJT, Burger JWA, Verrijssen AE.

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ABSTRACT

Purpose: The benefit of intraoperative radiotherapy (IORT) in the treatment of locally advanced (LARC) or recurrent rectal cancer (LRRC) lies in its ability to provide a high radiation dose to a limited at-risk volume, thereby eliminating microscopic disease, whilst limiting toxicity concerns. A comparative study between high-dose-rate brachytherapy (IOBT) and intraoperative electron radiotherapy (IOERT) was performed, showing favourable LRFS after IOBT, possibly due to a higher surface dose that is inherent to the IOBT technique. The IOERT technique in CHE was adapted to increase the surface dose, aiming to improve local control. Postoperative complications due to an increased radiation dose remain of concern. This retrospective study compares complication rates before and after adapted IOERT dose.

Materials and methods: All patients undergoing surgery with IOERT for LARC or LRRC from September 2019 until July 2023 were selected. Patients selected until August 31, 2021, were included in the control cohort (n=108), from September 1, 2021, onwards were included in the intervention cohort (n=92). Perioperative and (major) postoperative complications were classified retrospectively; during admission, at 30 days and at 90 days.

Results: In LARC, a decrease in postoperative complications was seen (p=0.009). 19% of LARC patients experienced major postoperative surgical complications, i.e., Clavien-Dindo Grade 3b-5, regardless of treatment group. No difference in major 90-day complications was seen (p=0.142). In LRRC patients, use of induction chemotherapy dropped from 78% to 29% (p<0.001), complicating comparison. However, no difference in major postoperative complications was seen at 30 days (p=0.222) or 90 days (p=0.977) after surgery.

Conclusion: Increased surface dose of IOERT does not seem to lead to an increase in postoperative complications. Further research is needed to evaluate the efficacy of dose adaptation in IOERT to improve local oncological control rates. Routine evaluation of CTCAE scores in follow-up will help uncover possible long-term radiation-induced toxicity.

PURPOSE

In the field of rectal cancer, the risk of locoregional recurrence has been reduced by the introduction of Total Mesorectal Excision (TME) surgery, that has significantly improved locoregional control.[1–4] Neoadjuvant (chemo)radiotherapy has further reduced the chance of locoregional recurrence in patients with locally advanced rectal cancer (LARC).[5–8] Nevertheless, recurrences still occur and prove difficult to treat. In both primary and locally recurrent rectal cancer (LRRC), a microscopically radical (R0) resection margin has shown to be extremely important in improving local control.[4,7,9–11]

Intraoperative radiotherapy (IORT) can further improve local control in patients with locally advanced or recurrent rectal cancer (LARRC) by delivering a high dose of radiation to a limited at-risk volume, thus reducing excessive toxicity. By applying IORT to the at-risk resection margin, remaining microscopic disease may be treated intraoperatively.[12,13] IORT is mainly performed with electrons (IOERT), high-dose-rate (HDR) brachytherapy (IOBT), or low-kV X-rays (orthovoltage).

A recent article compared the results of IOERT versus IOBT for microscopically irradical (R1) resections in patients with LARRC.[14] An improvement in local recurrence-free survival (LRFS) was seen favouring IOBT. Not only does this suggest that IORT affects LRFS in general, but the difference in favour of IOBT raises the question of why this might be. Although many factors may have contributed, such as different patient populations, larger irradiated volumes, differences in operating times and various applicator types, one striking difference is the higher surface dose of IOBT compared to IOERT.[15] Since the surgical resection surface is the site where potential microscopic disease remains, it has been suggested that the different surface doses may have contributed strongly to the results. In a second article, the two techniques were compared and the IOERT technique was adapted to increase the surface dose to approximate that of IOBT (Figure 1).[16] First, a bolus of tissue equivalent Polymethyl methacrylate (PMMA) was added to the IOERT applicator exit to move the maximum dose to the tissue surface (Figure 2).The dose was then rescaled to increase the surface dose to approximate that of IOBT. The prescribed dose (10Gy) of the adjusted dose curve is still at 9mm, as in the original dose curve of IOERT. In this way, the dosimetric difference between IOERT and IOBT is reduced at the surface. One point of concern, however, is the potential additional toxicity caused by the higher surface dose. As described in Verrijssen et al, this was not expected, as the published literature on IOBT, which is characterized by a higher surface dose, does not show this increase in toxicity.[16] The present work aims to confirm this hypothesis.

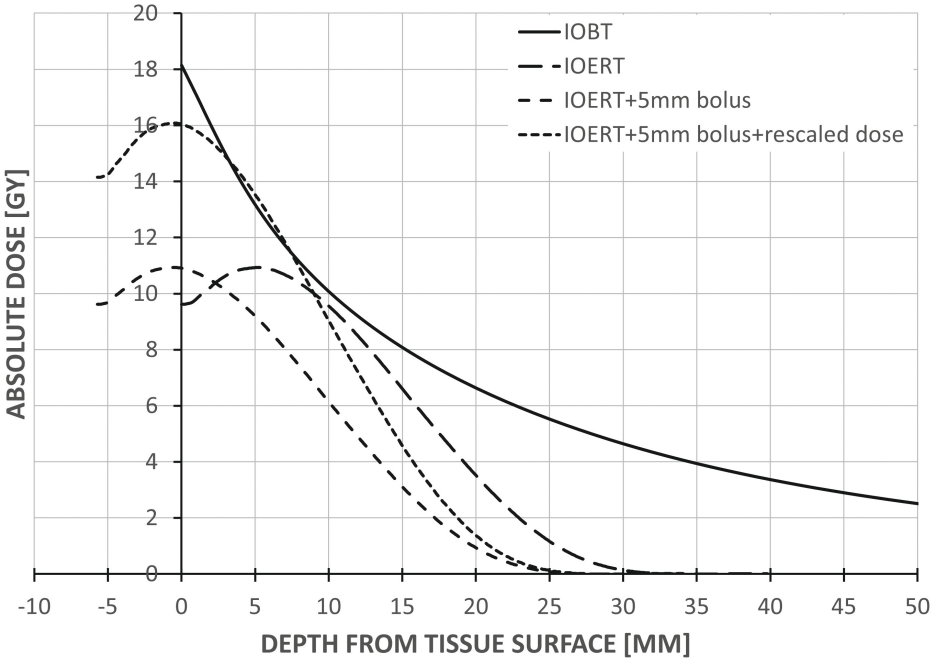


Figure 1. Graph showing the current situation for IOERT and IOBT in absolute dose at depth for IOBT (solid line) and IOERT (long dashed line). The short, dashed line illustrates the IOERT curve after applying a bolus, but before rescaling. The dotted line shows the IOERT curve with bolus and rescaling to deliver 10 Gy at 9 mm.

MATERIALS AND METHODS

Patient selection

All patients who underwent surgery in combination with IOERT for LARRC at Catharina Hospital Eindhoven (CHE) from September 1, 2019, to July 31, 2023, were selected. Patients treated until August 31, 2021, were included in the control cohort. Patients treated from September 1, 2021, onwards were included in the intervention cohort, after the adapted technique was introduced. Patients with a re-recurrence were excluded. Data of LRRC patients were extracted from a prospectively maintained database and were updated from electronic patient records as necessary. Data of LARC patients were retrieved from medical records. Information recorded consisted of baseline characteristics, neoadjuvant treatment, surgery, outcome, and follow-up. Follow-up was completed until August 29, 2023. The study was approved by the local medical ethics committee (nWMO-2022.130).

(Neoadjuvant) treatment

All patients received neoadjuvant (chemo)radiotherapy. For LARC, treatment regimens consisted of either short course radiotherapy (5x5Gy) or full course chemoradiotherapy (CRT) (25x2Gy), with concomitant capecitabine. LRRC patients received either full course CRT or chemo reirradiation (15x2Gy), with concomitant capecitabine. Selected LARRC patients received induction chemotherapy prior to (chemo)radiotherapy, which generally consisted of either 3-4 courses of CAPOX (capecitabine and oxaliplatin) or 4-6 courses of FOLFOX (5-FU, leucovorin and oxaliplatin).

Surgery was categorized as follows; abdominoperineal resection (APR); low anterior resection (LAR); total exenteration (TE) (consisting of a resection of the rectum, bladder, prostate and vesicles in male patients or ovaries, vagina, and uterus in female patients); and a tumour resection not otherwise specified (n.o.s.), i.e., tumour resection without formal bowel resection. All resections performed in addition to a formal bowel resection were documented separately (i.e., in the case of a TE, resections of the bladder, prostate and vesicles were also noted separately).

IOERT

A preliminary assessment of IOERT indication is performed for all patients undergoing either curative surgery or surgery in a palliative setting for maximal local control of LARRC. This is done during an expert multidisciplinary tumour board, consisting of at least an oncologic surgeon, a medical oncologist, a radiation oncologist and a radiologist, where staging at baseline and after neoadjuvant treatment is discussed. Perioperatively, the IOERT indication is reestablished by the surgeon and the radiation oncologist. In both instances, a clinical suspicion of either narrow or involved resection margins is considered an IOERT indication. Additional frozen sections of excised tissue can be used perioperatively to aid decision-making but are not required. The IOERT dose and irradiation site are also determined perioperatively, targeting the area at-risk for R1 resection. IOERT is administered via a Mobetron 2000 linear accelerator (IntraOp Medical, Sunnyvale California, USA), with energy of either 6, 9 or 12 MeV. Applicators with a diameter of five to ten centimetres can be used, with bevel angles of 0, 30 or 45 degrees. The dose rate is set at around 10 Gy/min. The IOERT dose previously depended on the depth of tissue considered at-risk for R1 resection, and was prescribed (at depth) at 10Gy, 12.5Gy or 14.4Gy to the 90% isodose surface. From September 1, 2021, onwards, all patients received a dose of 10Gy at the target depth, which corresponds to a dose between 15.5Gy and 16.5Gy at the tissue surface

(Figure 1).[16] The following IOERT variables are reported for each patient: Dose at target depth, dose at the surface (i.e., at 1mm tissue depth), and irradiated surface (cm^2).

Complications

Follow-up was performed according to the Dutch national guidelines for colorectal cancer.[17] Endpoints included all complications and readmissions within 30 days after surgery, as well as all major postoperative complications 90 days after surgery. Analyses were performed separately for LARC and LRRC. Perioperative and postoperative complications were retrospectively classified via the Clavien-Dindo classification.[18] The highest Clavien-Dindo grade was noted for each patient up to 30 days after surgery. Major postoperative complications (Clavien-Dindo grade 3b-5) were additionally classified at 90 days postoperatively. From September 1, 2021, adverse events were routinely assessed by the radiation oncologist, using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) at 3- and 12-months after IOERT.[19] These data were used to assess any long-term postoperative neuropathy. If not available, patient records were reviewed for evidence of peripheral neuropathy. No neuropathy was only classified as such if it was explicitly stated that no peripheral neuropathy was present.



Figure 2. Picture of the tissue-equivalent polymethyl methacrylate (PMMA) bolus attached to the IOERT applicator exit to move the maximum dose to the tissue surface.

Table 1. Baseline, tumour, and neoadjuvant treatment characteristics of patients with LARC and LRRC.

Patients with LARC		**Control n=54 (%)**	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**
Gender	Male	35 (65)	28 (60)	63 (62)	0,588
	Female	19 (35)	19 (40)	38 (38)	
Age at diagnosis	Mean (SD)	62 (10,1)	60 (11,9)	61 (11,0)	0,180
T stage	T3	23 (43)	13 (28)	36 (36)	0,137
	T4	31 (57)	33 (72)	64 (64)	
N stage	N0	9 (17)	7 (15)	16 (16)	0,844
	N+	45 (83)	39 (85)	84 (84)	
M stage	M0	45 (83)	36 (77)	81 (80)	0.458
	M1	9 (17)	11 (23)	20 (20)	
MRF involved	Yes	44 (90)	39 (89)	83 (89)	0,857
Induction chemotherapy	No	30 (56)	19 (40)	49 (49)	0,129
	Yes	24 (44)	28 (60)	52 (52)	
Neoadjuvant RT	25x2Gy	47 (87)	41 (87)	88 (87)	0,722
	5x5Gy	6 (11)	4 (9)	10 (10)	
	Other	1 (2)	2 (4)	3 (3)	
Interval RT to surgery (weeks)	Median (IQR)	13 (12-15)	14 (12-18)	13 (12-16)	0,134
Patients with LRRC		**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Gender	Male	37 (69)	32 (71)	69 (70)	0,780
	Female	17 (32)	13 (29)	30 (30)	
Age at diagnosis	Mean (SD)	65 (9,0)	67 (8,5)	66 (8,8)	0,278
Multifocal recurrence	No	40 (76)	35 (78)	75 (77)	0,788
	Yes	13 (25)	10 (22)	23 (24)	
Induction chemotherapy	No	12 (22)	32 (71)	55 (44)	<0,001
	Yes	42 (78)	13 (29)	55 (56)	
Neoadjuvant RT	Full course	22 (41)	14 (31)	36 (36)	0,392
	Reirradiation	31 (57)	30 (67)	61 (62)	
	Other	1 (2)	1 (2)	2 (2)	
Metastases at diagnosis	No	48 (89)	43 (96)	91 (92)	0.286
	Yes	6 (11)	2 (4)	8 (8)	
Interval RT to surgery (weeks)	Median (IQR)	13 (11-14)	13 (11-14)	13 (11-14)	0,673

*MRF = mesorectal fascia, RT = radiation therapy. *Missing data were excluded from group comparisons **Due to rounding, not all percentages add up to 100%.*

Statistical analysis

Continuous data were expressed as a median (interquartile range (IQR)) or mean (standard deviation (SD)), as appropriate. Categorical data was presented as absolute numbers with percentages. Comparisons of continuous data were performed using independent T-tests, Wilcoxon sign rank test and Mann-Whitney U test, as appropriate. Comparisons of categorical data were performed using the Chi-Square test and Fisher-exact test, as appropriate. Two-sided p-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 29.0, IBM Corp. Released 2022. Armonk, NY: IBM Corp.

RESULTS

Locally advanced rectal cancer

Between January 1, 2019, and July 31, 2023, 101 patients underwent surgery, of whom 54 (53%) were treated in the control group, and 47 (47%) in the (dose-escalated) intervention group. There were no significant differences in baseline characteristics, as summarized in Table 1. Surgeries performed were similar amongst treatment groups (p=0.248), as summarized in Table 2. Additional treatment characteristics of LARRC patients with metastatic disease can be found in the Supplementary Material. Overall, patients in the intervention group underwent fewer additional resections (13% vs 32%, p=0.025) than patients in the control group, with the exception that significantly more pelvic sidewall resections were performed in the intervention group (40% vs 19%, p=0.015). Of the 54 patients in the control cohort, 34 (63%) received 10Gy, 9 (17%) received 11.5Gy, 7 received 12.5Gy (13%) and 4 received 14.4Gy (7%), both at the surface and at depth. All patients in the intervention group received 10Gy at depth but obtained significantly higher IOERT dose at tissue surface (15.0Gy (n=1; 2%), 15.5Gy (n=20; 43%), 16.0Gy (n=26; 55%)), with a median of 16Gy (IQR 15.5-16) versus 10Gy (IQR 10-12) in the historical cohort (p<0.001). The irradiated surface was similar (p=0.13).

Table 3 shows comparisons of complications and readmissions for all patients. In LARC patients, the length of stay was shorter in the intervention group (7 days vs. 10 days, p=0.010). There were significantly fewer 30-day postoperative complications in the intervention group (80% vs. 55%, p=0.009), but the type of complications did not differ. Importantly, there was no increase in infectious gastrointestinal complications (p=0.267) or wound complications (p=0.748). Major postoperative complications were reported in

19% of patients, with no difference between treatment groups (20% vs 17%, p=0.761). There was no difference in complications at 90 days postoperatively (11% vs 23%, p=0.142), although data were missing in 24% of patients, mainly in the control group (30% vs 17%).

Locally recurrent rectal cancer

Between January 1, 2019, and July 31, 2023, 99 patients with LRRC underwent surgery, of which 45 (45%) were treated in the intervention group. The baseline characteristics of LRRC can be found in table 1. Primary tumour characteristics can be found in the supplementary material. No differences in baseline characteristics were observed. However, patients in the intervention cohort received significantly less induction chemotherapy (78% vs. 29%, p<0.001), but neoadjuvant CRT was similar (p=0.392).
Full details of the operation and IOERT are given in Table 2. Forty-nine percent of patients in the intervention group underwent a TE, compared to 19% in the control group (p=0.006). Significantly more bladder (53% vs 17%, p<0.001) and prostate resections (63% vs 27%, p=0.003) were performed in the intervention group, partly due to the higher number of TEs performed. Although the operations were more extensive, there was no difference in the duration of surgery (p=0.674).

Thirty-seven (67%) patients in the control group received 10Gy IOERT, 6 (11%) received 11.5Gy, 7 received 12.5Gy (13%) and 5 received 14.4Gy (9%), both at the surface and at the specification depth. The dose at depth was 10Gy for all patients in the intervention group, but the dose at the surface was significantly higher (15.5Gy (n=26; 58%), 16.0Gy (n=19; 42%)), with a median of 15.5Gy versus 10Gy (p<0.001). The irradiated surface was larger in the intervention group (40cm^2) than in the control group (28cm^2) (p=0.009). The overview of the applicator diameter and bevel used is presented in the Supplementary Material.

Postoperative complications were common but similar, occurring in 74% and 76% of patients, before and after dose adjustment, respectively (p=0.866). Major postoperative complications occurred in 18 patients before (33%) and in 11 patients after (24%) dose adjustment (p=0.624) at 30 days. There was no difference in the type of complications. No difference was found in major complications at 90 days (p=0.977), but data was missing in 32% and 22% of patients from the control and intervention group, respectively.

Table 2. Surgical and intraoperative radiation therapy characteristics of patients with LARC and LRRC.

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Surgical procedure	LAR	18 (33)	23 (49)	41 (41)	0,248	9 (17)	3 (7)	12 (12)	0,006
	APR	29 (54)	18 (38)	47 (47)		18 (33)	14 (31)	32 (32)	
	Total exenteration	7 (13)	6 (13)	13 (13)		10 (19)	22 (49)	32 (32)	
	Resection N.O.S.	0 (0)	0 (0)	0 (0)		17 (32)	6 (13)	23 (23)	
Blood loss (litre)	Median (IQR)	1,4 (0,8-2,0)	0,9 (0,5-1,6)	1,1 (0,7-1,8)	0,062	2,0 (1,1-2,9)	2,5 (1,4-4,0)	2,2 (1,1-3,5)	0,069
Time surgery (hours)	Median (IQR)	4 (3-4)	4 (3-5)	4 (3-5)		5 (4-6)	5 (4-6)	5 (4-6)	0,674
Additional resection performed?	Yes	17 (32)	6 (13)	23 (23)	0,025	44 (82)	42 (93)	86 (87)	0,082
IOERT dose (Gy)	*Bladder*	7 (13)	6 (13)	13 (13)	0,990	9 (17)	24 (53)	33 (33)	<0,001
	Pelvic side wall	10 (19)	19 (40)	29 (29)	0,015	10 (19)	17 (38)	27 (27)	0,032
	Prostate	8 (23)	9 (32)	17 (27)	0,409	10 (27)	20 (63)	30 (44)	0,003
	Vesicles	15 (43)	17 (61)	32 (51)	0,159	18 (49)	22 (69)	40 (58)	0,092
At depth	Median (IQR)	10 (10-12)	10 (10-10)	10 (10-10)	<0,001	10 (10-12)	10 (10-10)	10 (10-13)	<0,001
At surface	Median (IQR)	10 (10-12)	16 (16-16)	14 (10-16)	<0,001	10 (10-12)	16 (16-16)	13 (10-16)	<0,001
Cumulative (EQD2)	Median (IQR)	n.a.	n.a.	n.a.	n.a.	78 (67-97)	94 (83-113)	94 (73-103)	0,002
Cumulative (EQD2 current tumour)	Median (IQR)	67 (67-71)	83 (83-85)	71 (67-83)	<0,001	53 (47-67)	65 (63-83)	63 (53-67)	<0,001
IOERT surface (cm2)	Median (IQR)	28 (28-40)	40 (28-40)	28 (28-40)	0,13	28 (28-40)	40 (28-40)	40 (28-40)	0,009

** Missing data were excluded from group comparisons.*

*** Due to rounding, not all percentages add up to 100%.*

**** Only men are included in group analysis of prostate and vesicle resections. No significant differences were reported in resections of the ureter, sacrum, lymph nodes, uterus, ovaries or vagina.*

Table 3. Group comparison of postoperative complications and readmission rates.

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Admission (days)	Median (IQR)	10 (7-14)	7 (5-12)	9 (7-14)	0.010	11 (8-16)	11 (8-15)	11 (8-16)	0.894
Any complication (30d)	Any grade	43 (80)	26 (55)	69 (68)	0.009	40 (74)	34 (76)	74 (75)	0.866
Urogenital complications	Any grade	13 (24)	11 (23)	24 (24)	0.937	13 (24)	6 (13)	19 (19)	0.177
	Grade 1-2	13	10	23		11	5	16	
	Grade 3a-5	0	1	1		2	1	3	
Cardiopulmonary complications	Any grade	8 (15)	2 (4)	10 (10)	0.100	6 (11)	10 (22)	16 (16)	0.135
	Grade 1-2	7	2	9		5	8	13	
	Grade 3a-5	1	0	1		1	2	3	
Wound complications	Any grade	6 (11)	4 (9)	10 (10)	0.748	4 (7)	5 (11)	9 (9)	0.728
	Grade 1-2	1	0	1		2	4	6	
	Grade 3a-5	5	4	9		2	1	3	
Gastro-intestinal complications	Any grade	24 (44)	19 (40)	43 (43)	0.684	29 (54)	21 (47)	50 (51)	0.486
	Grade 1-2	13	12	25		15	15	30	
	Grade 3a-5	11	7	18		14	6	20	
GI: Ileus/Gastroparesis	Any grade	13 (24)	10 (21)	23 (23)	0.738	19 (35)	14 (31)	33 (33)	0.669
	Grade 1-2	11	8	19		14	12	26	
	Grade 3a-5	2	2	4		5	2	7	
GI: Infectious (including abscess)	Any grade	10 (19)	5 (11)	15 (15)	0.267	14 (26)	10 (22)	24 (24)	0.669
	Grade 1-2	2	2	4		4	5	9	
	Grade 3a-5	8	3	11		10	5	15	

Table 3. Continued

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Other complications	Any grade	11 (20)	5 (11)	16 (16)	0.182	16 (30)	15 (33)	31 (31)	0.692
	Grade 1-2	10	4	14		11	8	19	
	Grade 3a-5	1	1	2		5	7	12	
Highest Clavien-Dindo (30d)	Grade 0-2	38 (70)	36 (77)	74 (73)	0.761	33 (61)	31 (69)	64 (65)	0.624
	Grade 3a	5 (9)	3 (6)	8 (8)		3 (6)	3 (7)	6 (6)	
	Grade 3b-5	11 (20)	8 (17)	19 (19)		18 (33)	11 (24)	29 (29)	
Readmission (30d)	Yes	4 (7)	5 (11)	9 (9)	0.730	15 (28)	6 (14)	21 (22)	0.101
Late major complications (31-90d) Grade 3b-5	No	4 (11)	9 (23)	13 (17)	0.142	14 (38)	12 (38)	26 (38)	0.977

** Missing data were excluded from group comparisons.*

*** Due to rounding, not all percentages add up to 100%.*

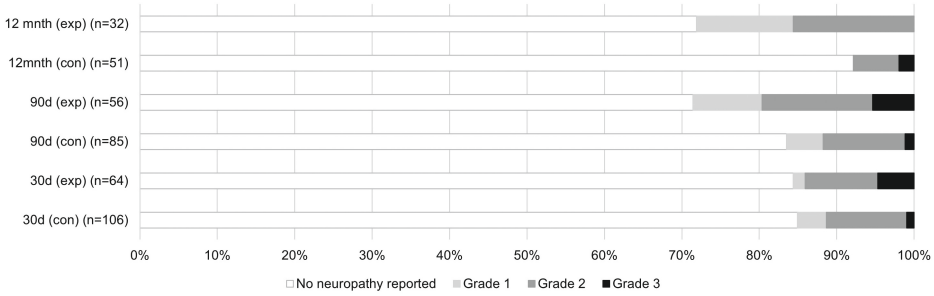


Figure 3. Physician-reported peripheral neuropathy relatively displayed. Missing data were excluded from analysis. Peripheral neuropathy was analysed for all patients, to account for the low number of events.

Peripheral neuropathy

Peripheral neuropathy was reported in 26 patients (15%) within 30 days and in 30 patients (21%) within 90 days of surgery, as shown in Table 4 and Figure 3. An increase in reported neuropathy was seen at 12 months postoperatively in the intervention group (28%), compared to the control group (8%) (p=0.019), but not at 30 or 90 days postoperatively. Data were missing in 15% at 30 days, in 30% at 90 days and in 59% at 12 months postoperatively. No CTCAE grade 4 or 5 neuropathy was observed. Operation reports were reviewed to investigate possible effects of surgery. In 12 patients (48%), neuropathy can be explained (in part) by the explicitly mentioned surgical resection of nerves or plexuses. Ten patients reported peripheral neuropathy at baseline that was due to chemotherapy or previous surgery. Peripheral neuropathy over time is shown in the Supplementary Material.

Table 4. Physician reported peripheral neuropathy.

Characteristic		Control n=108 (%)	Intervention n=92 (%)	Total n=200 (%)	p-value
Physician reported neuropathy	30 days (n=170)	16 (15)	10 (11)	26 (15)	0,379
	90 days (n=141)	14 (17)	16 (29)	30 (21)	0,258
	12 months (n=83)	4 (8)	9 (28)	13 (16)	0,019

DISCUSSION

This study suggests that increasing the IOERT surface dose in LARRC patients does not lead to an increase in postoperative complications. These results are in line with expectations expressed when the technique adaptation was introduced.[16] In Voogt et al., significantly more major complications occurred in LRRC patients treated with IOBT than with IOERT.[14]

These complications were presacral abscesses (26%), abdominal wound dehiscence with evisceration (8%), and intra-abdominal abscesses (6%). Several possible explanations have been mentioned, such as a larger irradiated area with IOBT, and a slower dose fall-off of IOBT, meaning that a larger volume of tissue receives a higher dose. Operating times are also generally longer as more time is required for applicator modulation and treatment planning. Another reason could be the higher surface dose of IOBT, with more heterogeneity within the surface dose and more hotspots. However, in this study, no increase in postoperative complications was observed despite an increase in the surface dose. This may indicate that the increased toxicity was caused by the other reasons mentioned.

In this study, there was a visible trend towards a larger irradiated area in the intervention group. However, the IOERT-irradiated volume was still smaller than that of IOBT. Previous studies have shown IOBT volumes are on average 2-3 times larger than IOERT with an upper limit exceeding 200 cm^2.[14,20–22] Therefore, the relatively small irradiated volume in IOERT may explain why no increase in complications was observed. An alternative hypothesis may be that although the surface dose was increased, the dose fall-off was steeper because of the dose build-up within the PMMA bolus (Figure 1). Moreover, the IOERT dose in the historical cohort was scaled up to 14.4 Gy to increase the surface dose; however, owing to the physical properties, this also leads to an increased dose beyond one centimetre depth. Therefore, with the PMMA bolus applied, theoretically, the dose at depth was less than that in the historical cohort.

Several factors complicated comparisons in this analysis. Due to the initiation of the PelvEx II trial in LRRC, the proportion of patients receiving induction chemotherapy decreased, as induction chemotherapy was standard of care for LRRC prior to the PelvEx II study in the CHE.[23] This may have decreased the perioperative morbidity, concealing the possible increase in toxicity due to IOERT. Although data on toxicity due to preoperative chemotherapy is lacking in LRRC, the RAPIDO trial in LARC patients saw no increase in postoperative complications after 6 cycles of CAPOX.[7] Moreover, in the current study, the proportion of patients treated with induction chemotherapy in LARC showed an increasing trend (44% versus 60%, p=0.129), in part due to the MEND-IT trial investigating the benefit of FOLFOXIRI induction chemotherapy in LARC.[24] Even so, in patients with LARC, no increase in toxicity was observed. Therefore, the confounding effect of induction chemotherapy on perioperative and postoperative complications may be minimal. Prospective data generated from both trials will provide more insight on induction chemotherapy-related complications.

The differences in surgical techniques further complicate the comparison. In patients with LARC, the proportion of LAR vs. APR vs. TE was consistent. In LRRC, resections were significantly more extensive in the intervention cohort, due to an increase in TEs (19% vs. 49%). This increase may be related to a cohort study comparing LRRC management between the Karolinska Institute (KAR) and CHE, revealing more R0 resections at KAR (76% R0 vs 61%), hypothesized to be due to more TEs (KAR 25% vs CHE 16%, p=0.02), with no difference in major complications (KAR 32% vs CHE 30%, p=0.742).[25] On the one hand, more extensive resections could lead to an increase in complications and length of surgery. On the other hand, a TE is an en-bloc resection, whereas operating more conservatively may result in additional partial resections, possibly leading to more tissue-healing complications. Nevertheless, no difference in complications was observed when stratifying for IOERT technique in either LARC or LRRC patients, despite varying operative management, supporting the idea that IOERT dose adaptation did not influence complications.

Peripheral neuropathy is an area of concern. The literature states that 3-23% of patients suffer from peripheral neuropathy due to extensive surgery and radiation within the pelvis.[26,27] Clinically, there seems to be underreporting of peripheral neuropathy, and it should be expected that this is also true in the current study. Although the data were limited, there was an increase in peripheral neuropathy in the intervention group at 12 months. However, shortly prior to introducing the dose-adaptation, a routine evaluation of peripheral neuropathy via CTCAE scoring at three months and one year postoperatively was introduced. Therefore, it is possible that the increase in peripheral neuropathy is merely due to improved reporting rather than due to the increased surface dose. Other factors influencing neuropathy are the surgery itself and chemotherapy.[28] As reported, neuropathy may also be explained by the performed surgery in several patients, as damage to the nerves or plexus within the pelvis was specifically mentioned in the surgical report. However, in reality, this percentage may be higher. When combining these factors, drawing conclusions, even on the extent of peripheral neuropathy, as well as the difference in neuropathy between IOERT techniques, is challenging. Standardized CTCAE scoring of peripheral neuropathies will help improve our understanding of this potentially invalidating toxicity following IOERT. Neuropathy should remain an area of caution, as it can lead to severe decrease in quality of life.[28–30]

One potential drawback of the new technique is the compromised view of the target volume due to the PMMA bolus attached at the applicator exit. Adequate inspection of the at-risk volume and the surrounding healthy tissue is necessary, with thorough multidisciplinary communication to deliver IOERT accurately and safely. Target volume reproducibility is also challenging and may impede future treatment planning or the understanding of IOERT-related complications. Intraoperative navigation may be able to provide a solution, by facilitating preoperative planning on MRI, intraoperative target volume definition and postoperative dose reconstruction.[31–34]

Ultimately, the goal is to improve the LRFS. In Voogt et al., a significantly higher LRFS was seen after IOBT versus IOERT.[14] There are many differences between IOERT and IOBT that may have influenced these results, such as the larger irradiated volumes or the flexible applicator in IOBT allowing for closer coverage of the at-risk area.[16] However, the fact remains that the at-risk area is generally at the tissue surface, at the resection margin Therefore, it was hypothesized that the higher surface dose for IOBT could have contributed largely to these results. Several papers, including that of Appelt et al., allude to a dose-response relationship for tumour regression in rectal cancer.[35] A higher surface dose could translate to a more effective eradication of the remaining microscopic disease. A longer follow-up is needed to evaluate oncological outcomes.

This study has several limitations. Due to the recent introduction of the new technique and the fact that patients are often referred to their own hospital after surgery, follow-up is often short, limiting conclusions. As follow-up data were mainly missing in the control group, there was a risk of bias and underreporting of complications in the control group, although there is no reason to believe that the missing data will significantly influence the results. The introduction of the PelvEx II trial, as well as a shift in the surgical approach, caused a significant difference in the characteristics of patients with LRRC. Nevertheless, it is unlikely that a clinically relevant, severe increase in toxicity due to IOERT dose adaptation would be missed because of the mentioned biases.
Although some conclusions can be drawn regarding the safety of dose adaptation, no conclusions can be drawn regarding oncological effects. A longer follow-up period in a larger cohort is necessary. Additionally, a larger cohort will be needed to draw conclusions on more subtle complications, such as peripheral neuropathy, which can be detrimental to quality of life, but are notoriously difficult to evaluate retrospectively. Standardized CTCAE scores during the follow-up will facilitate future toxicity comparisons. Future work

will also consist of analyses of oncological outcomes, especially of (in-field) LRFS, providing more information on the efficacy of dose adaption.

CONCLUSION

An increased surface dose of IOERT did not appear to increase postoperative complications. Further research is needed to evaluate the efficacy of dose adaptation of IOERT in improving the local oncological control rates. Routine evaluation of CTCAE scores during follow-up will help uncover possible long-term radiation-induced toxicities.

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SUPPLEMENTARY DATA OF CHAPTER 7

Table S1. Additional treatment characteristics of patients with distant metastases.

		LARC (n=20)	LRRC (n=8)
Group	Control	9 (45%)	6 (75%)
	Intervention	11 (55%)	2 (25%)
Diagnosis of metastases	Synchronous	20 (100%)	8 (100%)
Number of metastases	1	13 (65%)	4 (50%)
	2	3 (15%)	3 (38%)
	≥3	4 (20%)	1 (13%)
Intent of treatment	Curative*	18 (90%)	4 (50%)
	Palliative/not mentioned**	2 (10%)	4 (50%)
Location of metastases	Liver	11 (55%)	2 (25%)
	Lung	3 (15%)	5 (63%)
	Liver and Lung	1 (5%)	0 (0%)
	Supra-regional nodes	3 (15%)	0 (0%)
	Cerebral	1 (5%)	0 (0%)
	Peritoneal	1 (5%)	1 (13%)

** All patients treated with curative intent had oligometastatic disease. All metastases were treated radically, with SBRT and/or surgical resection and/or RFA.*

*** In two patients with LARC, intent of treatment was not explicitly mentioned and therefore scored palliatively. One patient presented with peritoneal metastases which were treated with HIPEC and IORT. One patient had a solitary cerebral metastasis for which a surgical resection was performed.*

*** In four patients with LRRC, intent of treatment was not explicitly mentioned and therefore scored palliatively. Two patients presented with lung metastases, that were treated with SBRT. One patient had peritoneal tumour depositions that were treated with HIPEC and IORT. One patient presented with a solitary liver metastasis, that was treated postoperatively at a referring hospital.*

Table S2. Primary tumour characteristics of patients presenting with LRRC.

Characteristic (LRRC)		Control n=54 (%)	Intervention n=45 (%)	Total n=99 (%)	p-value
Primary tumour					
Gender	Male	37 (69)	32 (71)	69 (70)	0,78
	Female	17 (32)	13 (29)	30 (30)	
T-stage	T0-2	4 (11)	9 (24)	13 (17)	0,128
	T3-T4	34 (90)	29 (76)	63 (83)	
N-stage	N0	14 (37)	16 (41)	30 (39)	0,707
	N1-2	24 (63)	23 (59)	47 (61)	
M-stage	M0	48 (91)	39 (89)	87 (89)	0,756
	M1	5 (9)	5 (11)	10 (10)	
Neoadjuvant treatment	None	23 (43)	15 (34)	38 (39)	0,365
	(C)RT	27 (50)	22 (50)	49 (50)	
	IC+CRT	4 (7)	7 (16)	11 (11)	
Neoadjuvant RT	Full-course CRT	22 (71)	16 (57)	38 (64)	0,508
If applicable	5x5Gy	8 (26)	10 (36)	18 (31)	
	Other	1 (2)	2 (7)	3 (5)	
Surgical procedure	LAR	34 (63)	28 (62)	62 (63)	0,814
	APR	15 (28)	14 (31)	29 (29)	
	Total exenteration	1 (2)	0 (0)	1 (1)	
	Other	4 (7)	3 (7)	7 (7)	
History of metastases?	No	40 (74)	39 (87)	79 (80)	0,106
	Yes	25 (26)	5 (11)	19 (19)	

Table S3. Surface area of IOERT determined by bevel and diameter.

Surface area IOERT (cm2)	Bevel (degrees)	Diameter (cm)	LARC		LRRC	
			Control n=54 (%)	Intervention n=47 (%)	Control n=54 (%)	Intervention n=45 (%)
27,8	**45**	**5**	30 (56)	22 (47)	25 (46)	11 (24)
40	**45**	**6**	15 (28)	21 (45)	18 (33)	26 (58)
54,4	**45**	**7**	3 (6)	3 (6)	4 (7)	7 (16)
22,7	**30**	**5**	3 (6)	0	3 (6)	1 (2)
40	**30**	**6**	3 (6)	0	2 (4)	0
54,4	**30**	**7**	0	0	1 (2)	0
19,6	**0**	**5**	0	0	1 (2)	0
28,3	**0**	**6**	0	0	0	0
38,5	**0**	**7**	0	1 (2)	0	0

**Due to rounding, not all percentages add up to 100%.*

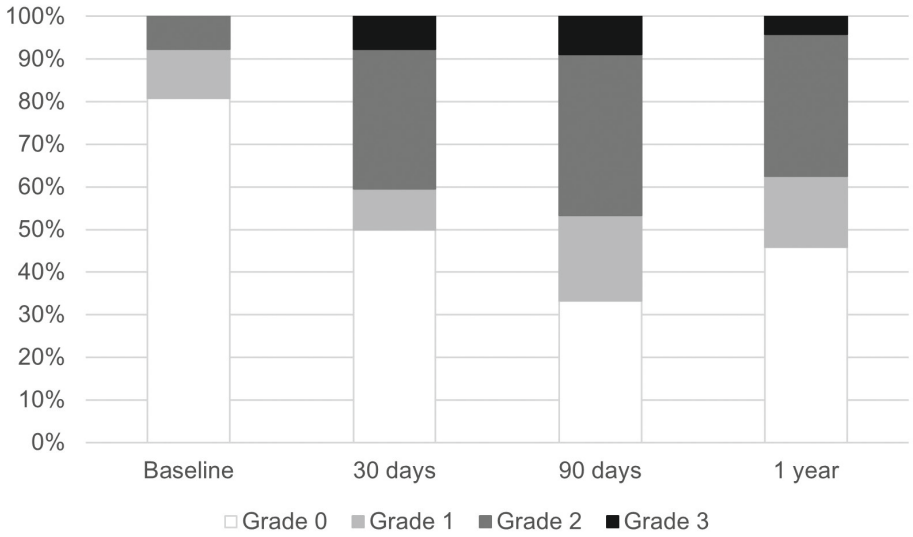
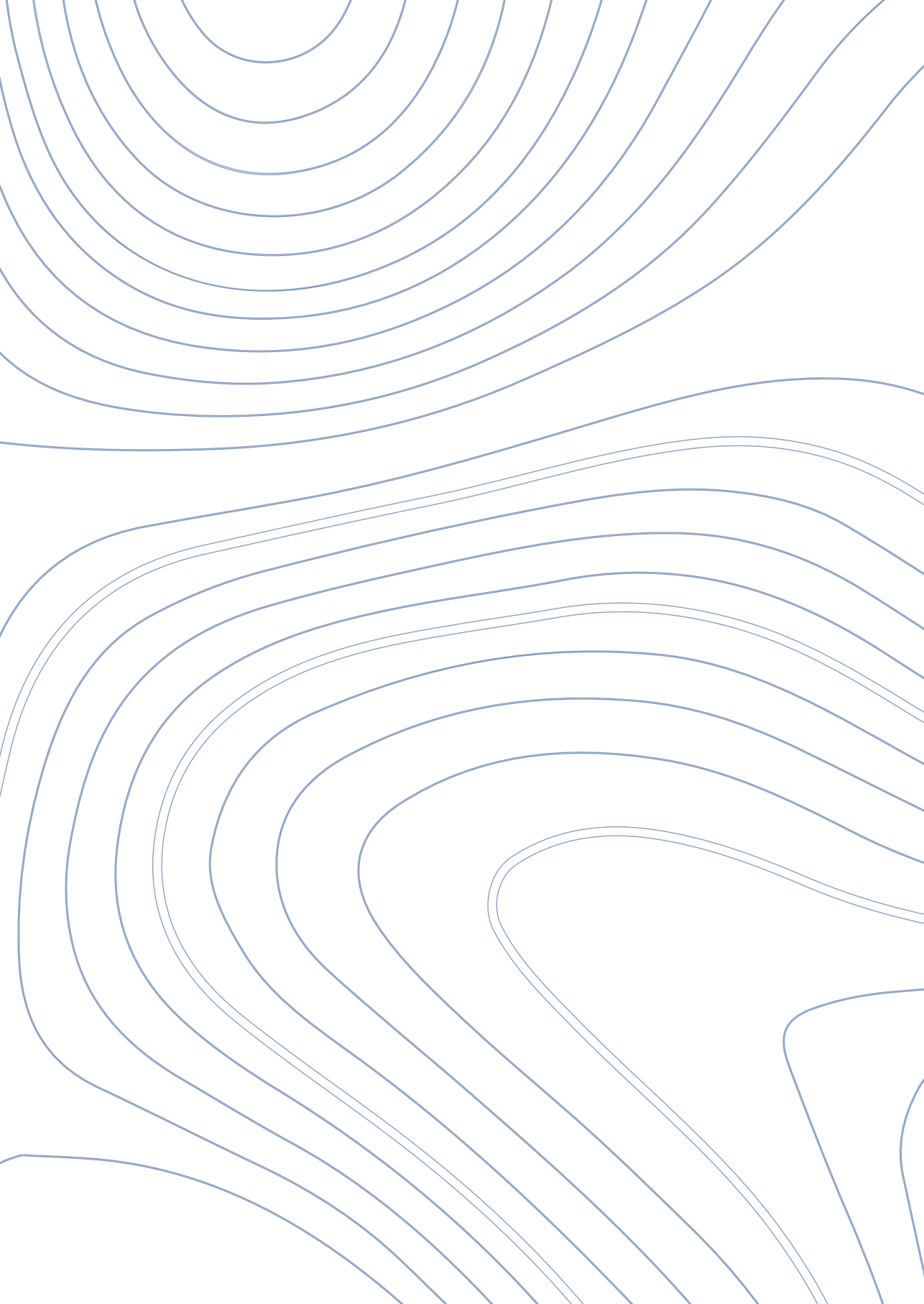


Figure S1. Peripheral neuropathy over time (n=52). Patients in whom no peripheral neuropathy was reported at any time point (n=148), were excluded. Missing data consisted of 0% at baseline, 0% at 30 days, 13% at 90 days, 54% at 12 months.

Part III

Oncological outcome of (re-)recurrent rectal cancer



Chapter 8

Locally recurrent rectal cancer: Oncological outcomes for patients with a pathological complete response after neoadjuvant therapy

Nordkamp S, Piqeur F, van den Berg K, Tolenaar J, van Hellemond IEG, Creemers GJ, Roef M, van Lijnschoten G, Cnossen JS, Nieuwenhuijzen GAP, Bloemen JG, Coolen L, Nederend J, Peulen HMU, Rutten HJT, Burger JWA

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ABSTRACT

Background: For patients with locally recurrent rectal cancer (LRRC), it is an ongoing pursuit to establish factors predicting or improving oncological outcomes. In locally advanced rectal cancer, pathological complete response (pCR) appears to be associated with improved outcomes. The aim of this retrospective cohort study was to compare the oncological outcomes of LRRC patients with and without pCR.

Method: Patients who underwent neoadjuvant treatment and surgery for LRRC with curative intent between January 2004 and June 2020 at a tertiary referral hospital were analysed. Primary outcomes include overall survival, disease-free survival, metastasis-free survival, and local re-recurrence-free survival, stratified for patients with and without pCR.

Results: Of the 345 patients, 51 patients had a pCR (14.8%). Median follow-up was 36 months (IQR 16-60). The 3-year overall survival was 77.4% for patients with pCR and 51.1% for those without pCR (log-rank test; $p<0.001$). The 3-year disease-free survival was 55.6% for patients with pCR and 26.1% for those without pCR (log-rank test; $p<0.001$). The 3-year local re-recurrence-free survival was 81.6% for patients with pCR and 44.4% for those without pCR (log-rank test; $p<0.001$). Surgical procedures, including soft tissue, sacrum and urogenital organ resections, and postoperative complications were comparable between patients with and without pCR.

Conclusion: This study showed that patients with pCR have superior oncological outcomes compared to patients without pCR. It may therefore be safe to consider a watch-and-wait approach in highly selected patients, potentially improving quality of life by omitting extensive surgical procedures without compromising oncological outcomes.

INTRODUCTION

Despite substantial treatment improvements in recent decades, oncological outcomes for patients with locally recurrent rectal cancer (LRRC) remain poor.[1–5] The debate regarding the most appropriate treatment strategy is still ongoing. The achievement of an R0 resection is considered the most important prognostic factor for survival. This knowledge has led to extensive surgical approaches aiming to achieve an R0 resection, with or without prior downstaging by neoadjuvant treatment.[4,6–10]

Although the value of neoadjuvant downstaging in LRRC has yet to be determined, in locally advanced rectal cancer (LARC), neoadjuvant treatment has led to an increase in pathological complete responses (pCR).[11,12] Oncological outcomes of patients with a pCR in LARC are significantly better than in patients without a pCR.[13] These beneficial outcomes have resulted in less extensive surgical procedures allowing the development of watch and wait strategies.[14,15]

The correlation between pCR and long-term oncological outcomes is unclear in patients with LRRC. It has been postulated that a similar correlation to LARC exists between outcome and pCR in patients with LRRC.[10,16] However, as most patients with LRRC have received neoadjuvant treatment for their primary tumour, neoadjuvant treatment options for LRRC are limited, thereby potentially decreasing the chance of achieving a pCR and any associated beneficial oncological outcomes.

This study aimed to evaluate oncological outcomes of patients with LRRC and a pCR to neoadjuvant treatment.

METHODS

The outcomes of all patients who underwent surgical resection with curative intent for LRRC at Catharina Hospital Eindhoven between January 2004 and June 2020 were retrospectively studied. LRRC diagnosis was based on an MRI of the pelvis and a thoracoabdominal CT, after which all patients were discussed by a dedicated LRRC multidisciplinary team. LRRC was defined as recurrent rectal cancer in the pelvis after a total or partial mesorectal excision. Patients were excluded from analyses in case of a second or third recurrence, metastases at the time of recurrence, a recurrence after local endoscopic excision of the primary tumour, or failure of a watch and wait approach for a primary rectal cancer. Follow-up was completed until 22 February 2022.

In radiotherapy naive patients, long course chemoradiotherapy was delivered with a cumulative dose of 50-50.4Gy, usually with concomitant capecitabine (825mg/m^2 twice

daily on radiotherapy days). In patients who previously received pelvic radiotherapy by means of long course chemoradiotherapy (50-50.4Gy) or short course radiotherapy (25Gy) for the primary tumour, chemoradiotherapy was delivered with a cumulative dose of 30-30.6Gy, again usually with concomitant capecitabine. From 2012 onwards, selected patients with extensive disease (i.e. invasion of adjacent organs, pelvic sidewall, sacral bone and/or vascular invasion) received induction chemotherapy (ICT) preceding chemoradiotherapy (CRT), From 2016 onwards, ICT became standard of care until the end of the study period. ICT generally consisted of three to four cycles of CAPOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin). Patients were restaged after three to four cycles of induction chemotherapy; in case of successful downstaging and good chemotherapy tolerance, one or two additional cycles were given. Adjuvant chemotherapy was not standard of care and was not offered to any patient.

Surgery was performed 8–14 weeks after the final cycle of chemoradiotherapy, generally consisting of an en-bloc resection of the tumour including involved pelvic organs and structures to achieve clear surgical margins. The procedures were categorised as followed: restorative rectal resection with re-anastomosis; abdominoperineal resection (APR); total pelvic exenteration, defined as resection of the rectum, bladder, and prostate with seminal vesicles or uterus with adnexa; and tumour resection "not otherwise specified" (n.o.s.), defined as an extra-anatomical, soft tissue and/or bone resection. Specific organs that were resected were identified separately as sacrum, bladder, seminal vesicles, prostate, uterus, adnexa, and vagina. Procedures could be combined with intraoperative radiotherapy (IORT) with a dose of 10–15Gy at the at-risk area (i.e. a location where the chance of a positive resection margin was deemed high by the surgeon and radiation oncologist, based on the combination of preoperative imaging and perioperative findings).

Standard pathological assessment was performed by experienced gastrointestinal pathologists with expertise in LRRC. The specimen was fixed with formalin and sampled in at least one section per centimetre of the tumour bed. In the pathology report, pCR was defined as the absence of any residual tumour in the complete specimen.

Endpoints were overall survival (OS), local re-recurrence-free survival (LRFS), distant metastasis free survival (MFS) and disease-free survival (DFS). OS was calculated from the date of surgery until the date of death from any cause or was censored at the date of last follow-up. LRFS, MFS and DFS were calculated from the date of surgery until the date

an event occurred or were censored at the date of last follow-up or death. Continuous data were reported as median or mean (interquartile range or 95% confidence interval respectively) and categorical data as counts and percentages. Group comparisons were performed using the Chi-square test, Fisher exact tests or the Mann–Whitney U test, as appropriate. Survival rates were calculated using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. As patients with pCR will have an R0 resection by definition, these variables are statistically completely dependent. A new combined variable of pCR status and R status was created, resulting in three different patient categories: R0 resection with pCR, R0 resection without pCR, and R1/2 resection. A Cox regression analysis was performed of this variable to calculate the hazard ratios (HR). A Cox proportional hazards model was used to examine the influence of pCR on oncological outcome. Multivariable logistic regression analysis was performed to find predictors for pCR, using associated factors in univariable logistic regression (p<0.10). Potential confounders for pCR were tested for each variable separately. Two-sided p-values p<0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 29.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

A total of 345 patients underwent surgery with curative intent for LRRC, of whom 51 had a pCR (14.8%). Patient and tumour characteristics for patients with and without pCR were comparable, as shown in *Table 1* and *Supplementary Table 1*. The median follow-up period was 36 months (IQR 16-60).

Most patients received neoadjuvant CRT (35.5% long course, 61.6% re-irradiation). One hundred and twenty-nine patients also received ICT (37.4%), of whom 30 patients received ICT in combination with long course CRT, and 99 received ICT in combination with reirradiation. The median time between the last radiotherapy fraction and surgery was 11.0 weeks (IQR 9.0-13.0) for patients undergoing long course chemoradiotherapy, and 11.0 weeks (IQR 9.0-13.5) for patients undergoing reirradiation (p=0.124).
Of the 30 patients who received ICT preceding long course CRT, nine patients had a pCR (30.0%). Out of the 99 patients who received ICT followed by reirradiation, 17 patients had a pCR (17.2%). Of the 90 patients receiving only long course CRT, 15 patients had a pCR (16.7%). Of the 111 patients receiving only chemo reirradiation, 10 patients had a pCR (9.0%) (Table 2). In the univariable logistic regression analysis, ICT and long course chemoradiotherapy were significantly associated with a pCR (Table 3).

The three-year OS was 77.4% in patients with a pCR, compared to 51.1% in patients without a pCR (HR 0.41, 95% CI 0.26-0.63; *p*<0.001). The one- and three-year DFS were 78.0% and 55.6% respectively in patients with a pCR, compared to 55.9% and 26.1% in patients without a pCR (HR 0.39, 95% CI 0.24-0.61; *p*<0.001). The one- and three-year LRFS were 95.4% and 81.6% respectively in patients with a pCR, compared to 71.9% and 44.4% in patients without a pCR (HR 0.21, 95% CI 0.10-0.43; *p*<0.001). Within 3 years, 36.7% of patients with a pCR developed distant metastases, compared to 54.3% in patients without pCR (HR 0.50, 95% CI 0.30-0.85; *p*<0.001). The oncological outcomes of patients with a pCR compared to patients without a pCR are shown in *Figure 1*.

Table 1a. Patient and tumour characteristics, stratified for patients with and without a pCR

Patient characteristics		**pCR n=51 (%)**	**No pCR n=294 (%)**	**Total n=345 (%)**	***p*-value**
Age	Mean (SD)	64.5 (59-70)	64.6 (58-72)	64.6 (59-72)	0.957
Gender ratio	M:F	36:15	194:100	36:15	0.520
ASA class	1	3 (6.3)	25 (9.1)	28 (8.6)	0.031
	2	31 (64.6)	215 (77.9)	246 (75.9)	
	3	14 (29.2)	35 (12.7)	49 (15.1)	
	4	0	1 (0.4)	1 (0.3)	
Primary origin	Sigmoid	5 (9.8)	31 (10.5)	36 (10.4)	0.873
	Rectum	46 (90.2)	263 (89.5)	309 (89.6)	
Primary tumour stage	T0-T2	12 (26.7)	53 (21.1)	65 (22.0)	0.407
In pathology	T3-T4	33 (73.3)	198 (78.9)	231 (78.0)	
Primary nodal stage	N0	17 (37.8)	123 (49.8)	104 (47.9)	0.138
In pathology	N+	28 (62.2)	124 (50.2)	152 (52.1)	
Treatment characteristics of local recurrence					
Number of lesions	1	36 (83.7)	234 (88.3)	270 (87.7)	0.535
	2	5 (11.6)	18 (6.8)	23 (7.5)	
	≥3	2 (4.7)	13 (4.9)	15 (4.9)	
Size of the largest lesion	Median (IQR) mm	40.0 (21-57)	42.0 (30-61)	42.0 (29-60.8)	0.321
Interval RT-surgery	Median (IQR) weeks	11.0 (9.0-13.0)	11.0 (9.0-13.0)	11.0 (9.0-13.0)	0.456
Surgery	LAR	18 (35.3)	56 (19.0)	74 (21.4)	0.068
	APR	19 (37.3)	119 (40.5)	138 (40.0)	
	Tumour resection n.o.s.*	6 (11.8)	44 (15.0)	50 (14.5)	

Table 1a. Continued

Patient characteristics		pCR n=51 (%)	No pCR n=294 (%)	Total n=345 (%)	*p*-value
	Total pelvic exenteration	8 (15.7)	71 (24.1)	79 (22.9)	
Sacral resection	Partial or complete	12 (33.3)	89 (37.4)	101 (36.9)	0.692
Bladder resection	Complete	6 (11.8)	45 (15.3)	51 (14.8)	0.777
	Partial	10 (19.6)	51 (17.3)	61 (17.7)	
Uterus resection	Uterus	0	9 (10.0)	8 (8.7)	0.366
Female only	Uterus with adnexa	5 (38.5)	23 (25.6)	28 (27.2)	
Vagina resection	Partial w/o reconstruction	3 (23.1)	24 (26.4)	27 (26.0)	0.837
Female only	Resection w reconstruction	3 (23.1)	15 (16.5)	18 (17.3)	
Prostate resection	Partial	1 (3.7)	16 (9.2)	17 (8.5)	0.483
Male only	Complete	2 (7.4)	20 (11.5)	22 (10.9)	
Vesicle resection	Unilateral	5 (18.5)	26 (14.9)	31 (15.4)	0.834
Male only	Bilateral	6 (22.2)	35 (20.1)	41 (20.4)	
IORT	Yes	44 (86.3)	257 (87.4)	301 (87.2)	0.822
Complications	None	14 (27.5)	86 (29.4)	100 (29.1)	0.872
Clavien-Dindo	I-II	22 (43.1)	115 (39.2)	137 (39.8)	
	III-V	15 (29.4)	92 (31.4)	107 (31.1)	

**Tumour resection not otherwise specified, i.e., a tumour resection with formal bowel resection.*
**LAR: low-anterior resection or resection with re-anastomosis*

Table 2. Patients with and without a pathological complete response stratified by type of neoadjuvant treatment [ICT: induction chemotherapy; CRT: chemoradiotherapy]

	ICT + CRT n=30 (%)	ICT + reirradiation n=99 (%)	CRT n=90 (%)	Reirradiation n=111 (%)
pCR (n=51)	9 (30.0)	17 (17.2)	15 (16.7)	10 (9.0)
No pCR (n=294*)	21 (70.0)	82 (82.8)	75 (83.3)	101 (91.0)
Median follow up (IQR)**	37.0 (23.5-49.2)	29.6 (15.0-50.1)	44.2 (22.4-85.5)	37.9 (14.9-63.1)

**15 patients received no radiotherapy*
***In months*

Table 3. Logistic regression analysis of factors correlated with a pathological complete response

		Univariable regression			Multivariable regression		
		HR	**CI**	**p-value**	**HR**	**CI**	**p-value**
Number of lesions	1	1	ref				
	>1	1.468	0.601-3.582	0.399			
Induction chemotherapy	No	1	ref		1	ref	
	Yes	1.743	0.958-3.171	0.069	2.115	1.127-3.968	0.02
Chemoradiotherapy	30Gy	1	ref		1	ref	
	45-50Gy	1.678	0.919-3.063	0.092	2.041	1.084-3.842	0.027
Consolidation chemotherapy	No	1	ref				
	Yes	1.059	0.297-3.772	0.93			

30Gy: reirradiation; 45-50Gy: Long-course chemoradiotherapy

When looking specifically at local control during the follow-up period in this cohort, 20 of the 51 patients with a pCR (39.2%) developed recurrent disease, of whom only four patients had a solitary local re-recurrence (7.8%) without distant metastasis. Of these four patients, two developed a re-recurrence in the same field as the recurrent tumour, and two patients developed a multifocal re-recurrence. Of the 16 patients that developed distant metastases, most presented with pulmonary metastases (n=7, 44.0%) or hepatic metastases (n=4, 26.0%).

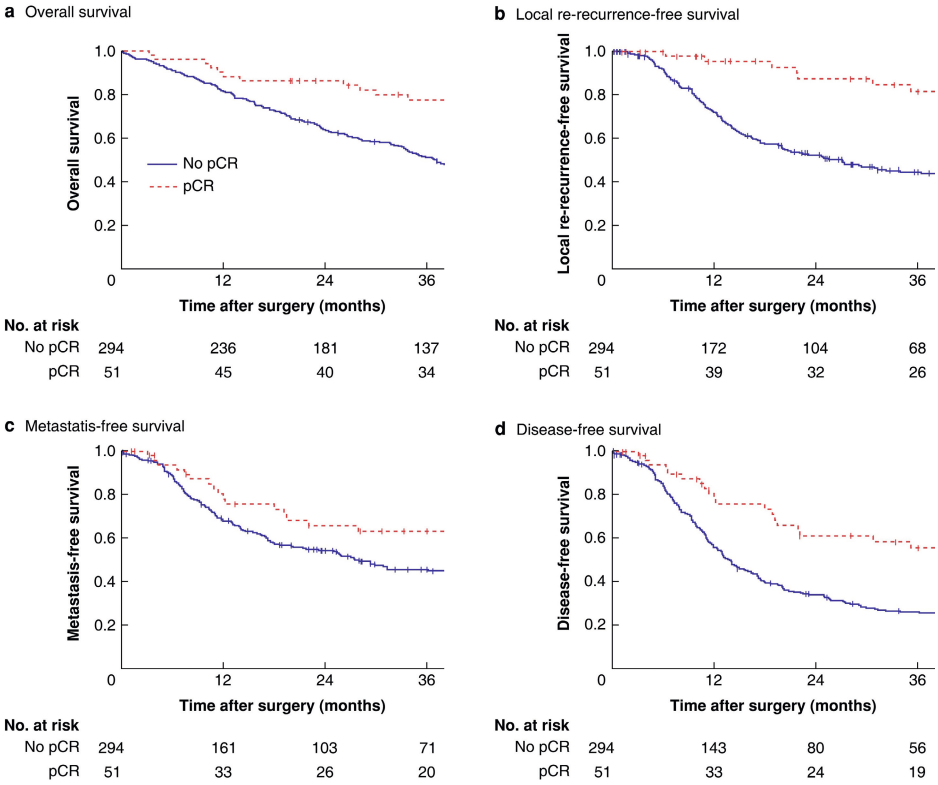


Figure 1a-d. Kaplan-Meier analysis of oncological outcomes in patients with and without a pathological complete response.

1a. Overall survival in patients with a pCR (red) and without a pCR (blue)
1b. Local re-recurrence free survival in patients with a pCR (red) and without a pCR (blue)
1c. Metastasis free survival in patients with a pCR (red) and without a pCR (blue)
1d. Disease free survival in patients with a pCR (red) and without a pCR (blue)

A radical resection with microscopically clear margins (R0 resection) was achieved in 226 patients (65.5%), of whom 51 patients had a pCR (22.6%). The 3-year OS, LRFS and MFS of patients with an R0 resection were significantly better than in patients with an irradical (R1/2) resection (61.9% vs 41.3% p<0.001, 63.7% vs 23.1% p<0.001 and 57.8% vs 30.7% p<0.001 respectively). The hazard ratio for OS in patients with an R0 resection was 0.49 (95% CI 0.38-0.63; p<0.001) compared to an R1/2 resection. In this study cohort, the 3-year OS of patients with a pCR (and R0 by definition) was higher than that of the total group of patients with an R0 resection, with or without pCR (77.4% vs. 61.9%). The same applies for LRFS (81.6% vs. 63.7%) and MFS (63.3% vs. 57.8%). In Cox regression analysis, a variable of three groups was analysed: R1/2 resection, R0 with pCR, and R0 without pCR. This

showed a hazard ratio for OS of 0.56 (95% CI 0.43-0.74; p<0.001) in patients with an R0 resection without a pCR compared to patients with an R1/2 resection. Patients with an R0 resection with pCR had a hazard ratio of 0.29 (95% CI 0.18-0.45; p<0.001) for OS compared to patients with an R1/2 resection (Figure 2).

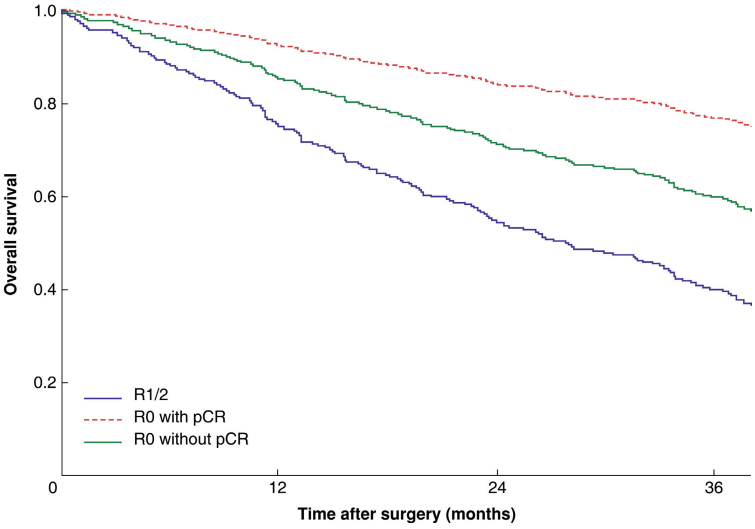


Figure 2. Cox regression analysis of overall survival, showing the curves of the combined variables; R0 resection with pathological complete response, R0 resection without pathological complete response and R1/2 resection

DISCUSSION

This study shows that patients with LRRC who achieved a pCR after neoadjuvant treatment had a superior OS, DFS, LRFS and MFS compared to patients without a pCR. The OS of patients with a pCR is also higher than that of patients with an R0 resection, where the latter group consists of both patients with and without pCR.

Achieving an R0 resection is currently the main goal in curative treatment for LRRC, as this has consistently been identified as the strongest predictor for survival.[17] The pursuit of an R0 resection, however, leads to extensive surgical procedures being performed, such as large multi-visceral "beyond TME" resections, en-bloc sacrectomy, total pelvic exenteration and hemipelvectomy. These major surgical procedures are associated with postoperative complications, functional impairment and impaired quality of life.[7,8,18–21] Furthermore, an R0 resection is only achieved in 30-65% of these patients, and the OS of patients treated curatively for LRRC remains disappointing with a 5-year OS of 30%

regardless of treatment strategy.[22,23] Moreover, even in the case of an increasing R0 resection rate, it is doubtful the overall survival will continue to improve.[23]

In search of ways to improve the R0 resection rate, an important prognostic factor for oncological outcomes seems to be disregarded: the biological behaviour of the tumour.[24] It remains questionable whether important improvements in oncological outcome in tumours with poor biology can be achieved by pushing surgical boundaries. Tumours with poor biological behaviour tend to recur and metastasise despite local treatment.[24] It seems unlikely that escalating surgical treatment would change that course. It should also be considered that patients with LRRC most often succumb to distant metastases, rather than to an overwhelming local re-recurrence.[15,25,26]

The OS, LRFS and MFS of patients with a pCR were superior to that of patients with an R0 resection in this study. A statistical comparison of patients with a pCR versus patients with an R0 resection was not suitable however, as patients with pCR have an R0 resection by default. When looking at survival data of pCR patients versus survival data of all patients with a R0 resection, patients with pCR appear to have a superior prognosis. Over time, the relatively good prognosis after an R0 resection resulted in R0 being labelled as the main goal of LRRC treatment. A favourable tumour biology and the quality of surgery enable an R0 resection. There is a certain turning point at which the extent of surgery will not make a difference anymore and only result in more morbidity while not improving survival. Based on the results of this study, it can be debated whether striving for a pCR is an alternative, legitimate goal. Increasing the pCR rate may not result in survival benefits for the entire group of patients with LRRC, but there may be other advantages to this approach.[10,16,27]

Tumour downstaging may result in less extensive surgical procedures in order to achieve an R0 resection. Surgical procedures could be postponed, thereby allowing time for observation of the natural behaviour of the tumour and thus preventing upfront debilitating surgical procedures in patients that will present with metastases shortly after.[23,26] Although a pCR is still relatively rare in patients who underwent radiotherapy for their primary tumour, pCR rates do seem to increase due to intensification of neoadjuvant treatment, and may become a significant factor in treatment decisions in the future. Ultimately, since local re-recurrences were very rare in patients with pCR, a watch and wait strategy in patients with a clinical complete response may be an appealing treatment option. In LARC,

watch and wait approaches have proven to be safe and result in similar oncological outcomes as surgical resection.[14,28,29] These findings are difficult to be translated directly from LARC to LRRC, as differences in tumour biology are to be expected. Moreover, in case of a suspected clinical complete response in LRRC, surveillance in a watch and wait approach will be less straightforward due to altered anatomy and often the inability to perform endoscopic follow-up. Therefore, the comparison of repeated high-quality imaging would be the way to move forward. In two recently published studies from our centre, response after neoadjuvant treatment on imaging was analysed and compared to pathological response.[30,31] These studies showed that response evaluation was indeed more challenging in LRRC than in LARC. For radiological assessment with MRI, a fair to moderate agreement between a good clinical response and good pathological response was observed. With a sensitivity of 46% and a specificity of 99%, these results seem comparable to literature on response evaluation in locally advanced rectal cancer.[30] This implies that in the case of a clinical complete response on MRI, it could be safe to explore watch and wait strategies in selected patients in centres with dedicated radiologists specialising in LRRC. Future developments, such as the combined interpretation of MRI with PET, the use of artificial intelligence, and possibly circulating tumour DNA may improve our ability to predict pCR and therefore aid in appropriate patient selection.[32,33]

The retrospective nature of our study means that only patients that finished curative treatment were included. There may have been patients whose disease progressed during neoadjuvant therapy, or in whom toxicity prevented further treatment. These patients are missing from our analysis, which results in selection bias. Determining correlations between specific baseline and treatment characteristics and pCR may not have been possible due to the relatively small number of patients with pCR, even though it is by far the largest cohort of patients reported in the literature.[10,16,27]

In this study, treatment with ICT and long course CRT was significantly associated with the achievement of a pCR. This could insinuate two things. It may be true that patients able to receive both options may have a more favourable tumour biology, due to the fact that no neoadjuvant treatment was given to the primary rectal cancer and selection of therapy resistant clones did not occur. It could however also be hypothesised that these tumours have a better outcome as they are treated more aggressively. Due to the small group numbers and retrospective design of the study, this cannot be investigated further.

High quality data on the efficacy of neoadjuvant treatment strategies will be generated by two randomized controlled trials that are currently recruiting, the PelvEx II and GRECCAR15 trials.[34,35] These trials will provide prospective data on the efficacy of neoadjuvant treatment in regard to the achievement of an R0 resection, but also with regard to the achievement of pCR, compliance to therapy and toxicity due to different treatment regimens, and oncological outcomes.

CONCLUSION

This study showed that patients who developed a pCR after neoadjuvant treatment for LRRC had an excellent overall survival and a very low re-recurrence rate compared to patients without a pCR. Based on these results, achieving a complete response could be a legitimate goal of treatment in patients with LRRC.

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SUPPLEMENTARY DATA OF CHAPTER 8

Table S1. Treatment details for primary rectal tumour

		pCR n=51 (%)	No pCR n=294 (%)	Total n=345 (%)	*p*-value
Neoadjuvant chemotherapy	Yes	3 (5.9)	9 (3.1)	12 (3.5)	0.326
Administered radiotherapy	No	24 (47.1)	104 (35.9)	128 (37.5)	0.045
	Short course (25Gy)	19 (37.3)	83 (28.6)	102 (29.9)	
	Long course (45-50Gy)	8 (15.7)	97 (33.4)	105 (30.8)	
	Adjuvant radiotherapy	0	6 (2.1)	6 (1.8)	
Primary surgery*	Sigmoidal resection	11 (21.6)	30 (10.2)	41 (11.9)	0.136
	Subtotal colectomy	0	3 (1.0)	3 (0.9)	
	Hartmann resection	1 (2.0)	11 (3.7)	12 (3.5)	
	Low anterior resection	30 (58.8)	152 (51.7)	182 (52.8)	
	APR	9 (17.6)	94 (32.0)	103 (29.9)	
	Posterior pelvic exenteration	0	1 (0.3)	1 (0.3)	
	Total pelvic exenteration	0	3 (1.0)	3 (0.9)	
Intra-operative radiotherapy	Yes	2 (3.9)	22 (7.5)	24 (7.0)	0.356
HIPEC**	Yes	0	2 (0.7)	2 (0.6)	0.555
Resection margin	R0	9 (17.6)	57 (19.4)	66 (19.1)	0.273
	R1	0	17 (5.8)	17 (4.9)	
	Unknown	42 (82.4)	220 (74.8)	262 (75.9)	
Adjuvant chemotherapy	Yes	4 (8.0)	53 (18.2)	57 (16.7)	0.095

**In which at least a partial mesorectal excision was performed*

***For concurrent peritoneal metastases*

Chapter 9

Locally recurrent rectal cancer: Treatment of a second local re-recurrence

S Nordkamp, F Piqeur, E Banken, SHJ Ketelaers, JL Tolenaar, IEG van Hellemond, GJ Creemers, GAP Nieuwenhuijzen, JG Bloemen, J Nederend, AE Verrijssen, HMU Peulen, HJT Rutten, JWA Burger.

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ABSTRACT

Introduction: Little is known about the outcomes of patients with rLRRC. Understanding the impact of patient and tumour characteristics on survival and treatment success can guide therapeutic strategies. This study provides insights into the outcomes of curative versus palliative treatment for rLRRC.

Methods: A retrospective review of patients who underwent surgery for locally recurrent rectal cancer (LRRC) between 1994 and 2022 was conducted. Data were collected regarding patient demographics, primary tumour, LRRC, and rLRRC characteristics. Oncological outcomes and treatment details were compared between patients treated with curative and palliative intent.

Results: Among 512 LRRC patients, 182 developed rLRRC. Of these, 66 (36.3%) were treated with curative intent, and 116 (63.7%) with palliative intent. Surgery for rLRRC was performed in 60/66 patients, achieving a negative surgical margin (R0) in 40 cases. Three-year overall survival was 57.5% for the curative group versus 28.5% for the palliative group ($p<0.001$). For R0 resections, three-year overall survival was 76.3%, compared to 26.8% with involved margins ($p<0.001$). An interval from LRRC to rLRRC of less than 12 months, synchronous metastases, and multifocality were all factors associated with poor oncological outcome.

Conclusions: Selected rLRRC patients can be treated with curative intent. Multidisciplinary teams should carefully evaluate patient and tumour characteristics, including the likelihood of R0 resection, presence of synchronous metastases, multifocality, and interval between LRRC and rLRRC, to determine eligibility for curative treatment.

INTRODUCTION

Locally recurrent rectal cancer (LRRC) is associated with a poor prognosis. In patients eligible for curative treatment, five-year overall survival rates are approximately 30-40%.[1] At diagnosis, only 35-45% of patients with LRRC are considered eligible for treatment with curative intent. In the remaining majority, the presence of distant metastases, irresectability of the tumour or other patient related factors limit curative options.[2–5] In 22-63% of LRRC patients who underwent surgical treatment with curative intent, a local re-recurrence develops within five years, posing a difficult challenge for clinicians as re-treatment options are limited.[6–8]

It is questionable whether the potential oncological benefits of treating rLRRC with curative intent balances the impact of treatment on morbidity and quality of life.[6,9] A substantial number of patients with rLRRC already underwent extensive neoadjuvant treatment for the primary and recurrent rectal tumour, including (chemo)radiotherapy, (chemo)reirradiation and/or systemic therapy. Additionally, due to previous surgical resections and radiation-induced fibrosis, the surgical resection of local re-recurrences is considered complex.

Little is known about the management and outcomes of rLRRC patients, and it is unclear whether curative intended treatment, as opposed to palliative treatment, is beneficial in terms of oncological outcome.[10,11] Establishing the outcome of different treatment modalities, and determining factors associated with the intention of treatment and outcomes are warranted to improve patient selection in rLRRC.

This study presents a large cohort of patients with LRRC who developed rLRRC. This study assessed the oncological outcomes of patients with rLRRC based on treatment intention, and on tumour and treatment characteristics of the primary, local recurrent and local re-recurrent rectal cancer, to identify factors which may help in the selection of patients for either curative or palliative treatment.

METHODS

Patients who underwent surgical treatment for LRRC from March 1994 to June 2022 (n=512) were included in a prospectively maintained registry. All patients were followed and all details on local or distant re-recurrence were recorded. Patients who developed a local re-recurrence (rLRRC) were identified and additional characteristics of patients and treatment were retrieved. Diagnosis of rLRRC was based on thoracoabdominal CT and/or MRI of the pelvis and was defined as local re-recurrence in the lesser pelvis when it occurred after a primary resection of LRRC. Patient and treatment characteristics were

collected, including data on the primary tumour, LRRC, and rLRRC, as well as data on oncological outcomes. Follow up was completed up to 5 January 2023.

For each patient with rLRRC, the preferred treatment strategy was decided by a dedicated multidisciplinary LRRC team. If patients were considered eligible for curative treatment, neoadjuvant treatment with induction chemotherapy and/or chemoradiotherapy was considered, followed by surgical resection. When curative treatment was deemed impossible, treatment modalities with palliative intent were offered, for example best supportive care, chemotherapy, radiotherapy or a combination of these, aiming for disease and symptom control.

Overall survival (OS) was compared in patients treated with curative versus palliative intent. In rLRRC patients treated with curative intent, a comparison of characteristics of patients with an R0 resection versus those with a non-radical (R1) resection was performed. The characteristics of patients treated with curative intent who were alive three years after resection of rLRRC, were compared to patients who were not. In all patients treated with curative intent, the disease-free survival (DFS), local re-re-recurrence free survival (LrrRFS), and metastasis-free survival (MFS) were determined.
OS was calculated from the date of diagnosis of LRRC and rLRRC until the date of death or was censored at the date of last follow-up. DFS, LrrRFS and MFS were calculated from the date of diagnosis of rLRRC until the event occurred or were censored at last follow-up. Continuous data were reported as median or mean (with interquartile range or 95% confidence interval respectively), depending on parameter distribution, and categorical data as counts and percentages. Group comparisons were performed using Chi-square test, Fisher exact tests or the Mann–Whitney U test, when appropriate. Survival rates were calculated using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. All tests were two-sided. P-values $p<0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 29.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

A total of 512 patients with LRRC were included, of whom 182 patients developed a rLRRC. The median follow-up period of these patients following LRRC surgery was 35.9 months (IQR 15.2-70.9). Of the 182 rLRRC patients, 66 (36.3%) were treated with curative intent and 116 (63.7%) with palliative intent. (*Supplementary Figure S1*).

In rLRRC patients treated with curative intent, neoadjuvant therapy was administered in 59 patients (89.4%). Induction chemotherapy was administered in 37 patients (56.1%), which was followed by neoadjuvant chemoradiotherapy in 16 patients. In total, 36 patients (54.5%) received neoadjuvant radiotherapy, consisting of chemo reirradiation in 18 patients (27.3%) and full course chemoradiotherapy in 15 patients (22.7%). Sixty patients (90.9%) were deemed eligible for surgical resection of the rLRRC after neoadjuvant treatment. Six patients (9.1%) were considered ineligible for resection due to disease progression or patient preferences. A radical resection (R0) was achieved in 40 patients (66.7%). (*Table 1)*

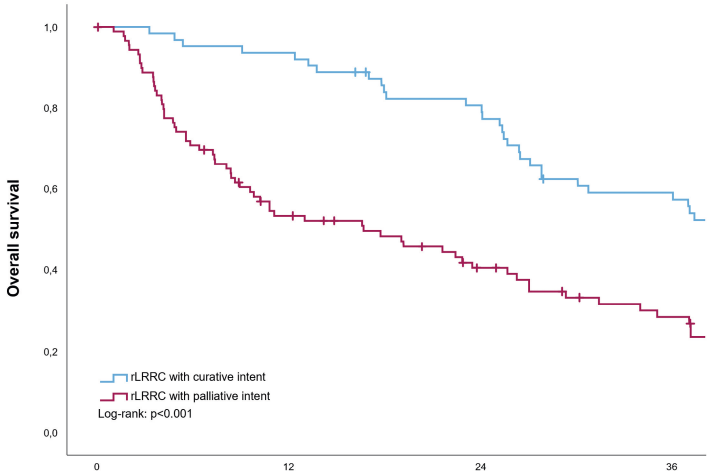
The three-year OS of 512 patients treated with curative intent for LRRC was 42.8% following surgery. Median OS after diagnosis of rLRRC of all 182 patients with rLRRC was 37.5 months (95% CI 24.0-57.3), and the three-year OS was 40.9%. In patients treated with curative intent for rLRRC, median OS was 41.6 months (95% CI 33.8-49.3) and three-year OS was 57.5%. In comparison, in patients treated with palliative intent, median OS was 16.6 months (95% CI 6.97-26.3), and three-year OS was 28.5% ($p<0.001$). (*Figure 1*) Of the patients treated with palliative intent, 47 had distant metastases at the time of diagnosis of rLRRC, while 49 patients had no distant metastases. Palliative patients without distant metastases had a median survival of 27.0 months (95% CI 14.1-39.8) and a three-year overall survival of 32.4%, while patients with distant metastases had a median survival of 12.9 months (95% CI 3.09-22.8) and a three-year overall survival of 24.4% ($p=0.235$).

Table 1. Treatment characteristics of patients treated with curative intent for rLRRC

Re-recurrence	**Curative rLRRC** *n=66 (%)*
Neoadjuvant treatment	37 (56.1)
- Induction chemotherapy	36 (54.5)
- (Chemo)radiotherapy	15 (37.8)
• Full course (50-50.4Gy)	1 (2.7)
• 5x5Gy	18 (48.6)
• Reirradiation (30-30.6Gy)	2 (8.1)
• Other	
Treatment synchronous metastases	3 (4.5)
Underwent surgical resection	60 (90.9)
Type of surgery	1 (1.5)
- Re-resection with anastomosis	15 (22.7)
- APR	2 (3.0)
- Posterior exenteration	10 (15.2)
- Total exenteration	31 (47.0)
- Tumour resection n.o.s.	
Additional resection	54 (81.8)
Intra-operative radiotherapy	31 (47.0)
HIPEC	3 (4.5)
R-status[1]	40 (60.6)
- R0	18 (27.3)
- R1/2	
Pathological complete response	4 (6.1)

[1] *missing/unknown in 2 patients*

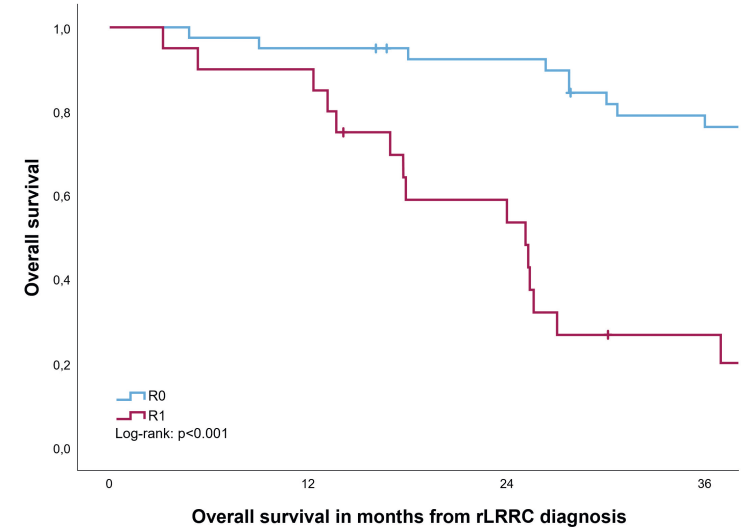
Median DFS in all patients treated with curative intent was 12.9 months (95% CI 10.7-15.2). Three-year DFS, MFS and LrrFS were 17.2%, 26.7%, and 38.1%, respectively. (*Figure 2*) In patients that had an R0 resection, three-year OS was 76.3%, versus 26.8% in case of an irradical resection (p<0.001), three-year DFS was 20.3% versus 7.5% (p=0.002), three-year MFS was 47.3% versus 26.8% (p=0.017) and three-year LrrFS was 32.3% versus 8.2% (p<0.001).



Number at risk				
Curative intent	66	64	61	53
Palliative intent	116	97	61	49

Figure 1. Kaplan-Meier analysis of OS in rLRRC patients treated with curative or palliative intent

Patients who were alive three years after resection of rLRRC had a longer interval between surgery for the first recurrence and the diagnosis of rLRRC than patients who died within three years: 19.3 months (IQR 12.4-31.4) versus 6.9 months (IQR 4.2-8.8) (p=0.004). Patients who developed a rLRRC within 12 months after the diagnosis of LRRC had inferior three-year overall survival (29.5%) compared to patients who developed a rLRRC after more than 12 months (52.2%) after the diagnosis of LRRC (OR 0.511; 95% CI 0.257-1.016, p=0.055).



Number at risk				
R0	42	42	41	38
R1	20	18	15	10

Figure 2. Kaplan-Meier analysis of OS in rLRRC patients treated with curative intent, resulting in an R0 resection versus R1 resection

rLRRC patients treated with curative intent less often received neoadjuvant chemoradiotherapy for the primary tumour compared to rLRRC patients treated with palliative intent (53.0% versus 73.3%, p=0.006). (Neo-)adjuvant chemotherapy is rarely administered in rectal cancer in the Netherlands and there was no difference in the number between patients treated with curative and palliative intent. In rLRRC patients treated with curative intent, induction chemotherapy for the primary tumour was administered in 2 patients (3.0%), versus in 6 patients (5.2%) in the palliative rLRRC group (p=0.498). In rLRRC patients treated with curative intent, patients received significant different surgical procedures (p=0.002); a sigmoidal resection was performed in 21.2% of the primary tumours compared to 3.4% in patients treated with palliative intent. A low anterior resection (LAR) was performed in 57.6% of rLRRC patients treated with curative intent and in 64.7% of rLRRC patients treated with palliative intent. (*Table 2*)

Patients treated with curative intent for rLRRC less often had a multifocal LRRC (3.0% versus 21.6%, p<0.001). In addition, rLRRC patients treated with curative intent less often underwent induction chemotherapy (18.2% versus 55.2%, p<0.001) and (chemo)radiotherapy (59.1% versus 94.0%, p<0.001) for their LRRC. In the rLRRC group treated with curative

intent, none of the patients underwent a total pelvic exenteration for their LRRC, versus 20 (17.2%) patients in the palliatively treated rLRRC group. An R0 resection of the LRRC was performed in 63.6% of rLRRC patients treated with curative intent, compared to 48.2% of rLRRC patients treated with palliative intent (p=0.060). (*Table 2*).

The median interval between treatment of LRRC and diagnosis of rLRRC was 16.1 months in rLRRC patients treated with curative intent (IQR 7.4-29.0) versus 11.3 months (IQR 5.6-22.1) in case of a palliative intent (p=0.054). rLRRC patients treated with curative intent less often had distant metastases at the time of rLRRC diagnosis when compared to rLRRC patients treated with palliative intent (6.2% versus 49.0%, p<0.001). (*Table 3)*

Table 2. Treatment history of curative treated patients with rLRRC versus palliative treated rLRRC

Primary tumour	**Curative rLRRC** ***n=66 (%)***	**Palliative rLRRC** ***n=116 (%)***	**p-value**
Male	36 (54.5)	83 (71.6)	0.020
Female	30 (45.5)	33 (28.4)	
Tumour location	51 (77.3)	110 (94.8)	<0.001
- Rectum	15 (22.7)	6 (5.2)	
- Sigmoid			
cM-stage	63 (95.5)	104 (89.7)	0.171
- cM0	3 (4.5)	12 (10.3)	
- cM1			0.498
Neoadjuvant treatment	2 (3.0)	6 (5.2)	0.006
- Induction chemotherapy	35 (53.0)	85 (73.3)	
- (Chemo)radiotherapy			
Initial surgery	38 (57.6)	75 (64.7)	0.002
- LAR/Hartmann	14 (21.2)	34 (29.3)	
- Abdominoperineal resection	14 (21.2)	4 (3.4)	
- Sigmoidal resection	0	1 (0.9)	
- Total exenteration	0	2 (1.7)	
- Other			
Intra-operative radiotherapy	4 (6.1)	11 (9.6)	0.445
R-status[1]	28 (84.8)	42 (82.4)	0.764
- R0	5 (15.2)	9 (17.6)	
- R1/2			
Metachronous metastases	5 (7.8)	15 (12.9)	0.296
Adjuvant treatment	21 (35.6)	24 (24.2)	0.126

Table 2. Continued

Primary tumour	Curative rLRRC *n=66 (%)*	Palliative rLRRC *n=116 (%)*	p-value
First Recurrence (LRRC)			
Months between primary and LRRC surgery (SD)	25.8 (34.0)	37.6 (29.4)	0.391
Multifocal recurrence	2 (3.0)	25 (21.6)	<0.001
Size of the tumour in mm, median (IQR)	31.0 (20.1-54.0)	38.0 (27.0-64.5)	0.243
cM-stage[2]			0.296
- cM0	52 (85.2)	81 (78.6)	
- cM1	9 (14.8)	22 (21.4)	
Neoadjuvant treatment	12 (18.2)	64 (55.2)	<0.001
- Induction chemotherapy	39 (59.1)	109 (94.0)	<0.001
- (Chemo)radiotherapy	11 (28.2)	23 (21.1)	0.020
• Full course (50-50.4Gy)	3 (7.7)	0	
• 5x5Gy	24 (61.5)	83 (76.1)	
• Re-irradiation (30-30.6Gy)	1 (2.6)	3 (2.8)	
• Other			
Surgery	15 (22.7)	18 (15.5)	0.004
- LAR	28 (42.4)	37 (31.9)	
- APR	2 (3.0)	8 (6.9)	
- ASR/Posterior exenteration	0	20 (17.2)	
- Total exenteration	21 (31.8)	33 (28.4)	
- Tumour resection n.o.s.			
Additional resections	55 (83.3)	115 (99.1)	<0.001
Intra-operative radiotherapy	31 (47.0)	95 (81.9)	<0.001
HIPEC	2 (3.0)	6 (5.2)	0.713
R-status[3]	35 (63.6)	55 (48.2)	0.060
- R0	20 (36.4)	59 (51.8)	
- R1/2			
Complications	7 (22.6)	14 (15.6)	0.395
- No complications at all			
- Clavien-Dindo I-IIIa	21 (67.7)	59 (65.6)	
- Clavien-Dindo IIIb-IV	3 (9.7)	17 (18.9)	

[1] missing/unknown in 89 patients, [2] missing/unknown in 18 patients, [3] missing/unknown in 13 patients

Table 3. Patient characteristics of rLRRC patients, stratified for treatment intent

Re-recurrence (rLRRC)	Curative rLRRC *n=66 (%)*	Palliative rLRRC *n=116 (%)*	p-value
Age at diagnosis rLRRC in years, mean (SD)	63.5 (9.3)	64.7 (10.1)	0.466
Months between LRRC and rLRRC, median (IQR)	16.1 (7.4-29.0)	11.3 (5.6-22.1)	0.054
Complains of rLRRC at diagnosis	16 (24.2)	34 (29.3)	0.462
Multifocality of the rLRRC[1]			
- No	44 (80.0)	44 (68.8)	0.163
- Yes	11 (20.0)	20 (31.3)	
Size of the tumour in mm, median (IQR)	37.0 (23.0-48.5)	42.0 (27.8-84.5)	0.570
cM-stage[2]	60 (93.8)	49 (51.0)	<0.001
- cM0	4 (6.2)	47 (49.0)	
- cM1			

[1] missing/unknown in 63 patients, [2] missing/unknown in 22 patients

DISCUSSION

This study shows that a select group of patients with rLRRC can be treated with curative intent. Prolonged OS may be achieved in these patients with 3-year OS rates of 57.5%. An R0 resection and an interval between diagnosis of rLRRC and treatment of LRRC of more than 12 months were associated with better oncological outcome.

Patients who were selected for treatment with curative intent were less often treated with neoadjuvant (chemo)radiotherapy for their primary tumour and LRRC, and less often underwent extensive surgical resections such as a total pelvic exenteration for their previous tumours. The absence of earlier neoadjuvant chemotherapy and radiotherapy and extensive surgical resections broaden the possibilities for neoadjuvant therapy and downstaging of the rLRRC and increase the possibilities for the surgeon to perform multivisceral resections with a chance of achieving clear resection margins.

On the other hand, patients were more often selected for palliative treatment if they had multifocal disease and/or synchronous metastases at diagnosis of rLRRC. If the presentation of the primary LRRC was multifocal, the chance for a second curative treatment was very limited. Although evidence is limited, physicians often correlate a multifocal recurrence to poor prognosis, since achieving an R0 resection is more challenging, and multifocality may be a sign of poor tumour biology. A history of a multifocal LRRC may be a reason to steer away from curative treatment.[12–14] Another factor that prompted palliative treatment of rLRRC was the presence of distant metastases, also reflecting poor tumour biology.[11,15]

Patients who were selected for palliative treatment also had shorter intervals between treatment of LRRC and the diagnosis of rLRRC. In those selected for palliative treatment, the median interval was shorter (11.3 months) than in patients treated with curative intent (16.1 months) (p=0.054).
A short interval is probably the result of poor tumour biology, which is supported by the finding that an interval between LRRC and rLRRC of less than 12 months was associated with inferior three-year OS. These factors, suggesting poor tumour biology and thereby poor oncological outcome, probably steer the patient and the multidisciplinary team away from extensive and invasive treatment strategies.

In our cohort of 182 patients diagnosed with rLRRC, 36% of patients were selected for treatment with curative intent. With adequate patient selection, the OS of these patients was found to be at least as good as in patients treated with curative intent for a first LRRC. While literature on rLRRC is scarce, Harji et al[10] previously described 30 patients that underwent resection of rLRRC. In line with our findings, an R0 resection resulted in far better survival rates than R1/R2 resections. If obtaining an R0 resection for rLRRC is not likely, an attempt for surgical resection is probably not warranted, since it is associated with poor survival. While in our cohort both median survival and OS rates were higher, it should be noted that both studies describe very heterogeneous patient groups. Any differences in these outcomes may well be explained by differences in national practice, previous treatment and patient selection.

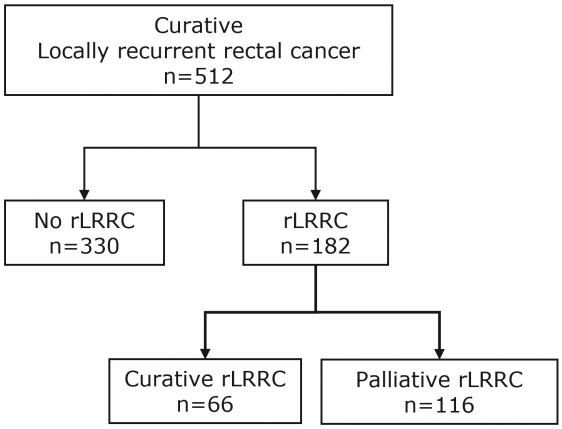
This study is the second to describe a cohort of patients with rLRRC and represents the largest cohort described so in the literature. In addition, a major strength of our study is that all patients with rLRRC were retrieved from a prospective database of LRRC patients who were treated curatively. Therefore, we were able to identify both patients treated with curative intent and with palliative intent. A limitation of our study is the relative lack of data on the palliative treatment that patients received. This is caused by the fact that patients were often referred back to referring hospitals or their general practitioner for palliative treatment or best supportive care.
The results of this study have led us to put forward the following statements regarding the treatment of rLRRC.
(1) When patients cannot receive further neoadjuvant treatment or when previous surgery for LRRC was extensive, a radical resection (R0) of rLRRC becomes increasingly difficult, while perioperative morbidity and mortality more likely will increase. Since an irradical

resection is associated with poor survival outcomes, we advise caution in treating rLRRC patients with curative intent who already received extensive treatment for the LRRC.
(2) We consider synchronous distant metastases and a multifocal rLRRC as warning signs of poor tumour biology: extensive resections may not be warranted.
(3) In case of a short interval between treatment of the LRRC and diagnosis of the rLRRC, long term survival is unlikely. An interval of at least 12 months seems a reasonable threshold for considering treatment with curative intent.

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SUPPLEMENTARY DATA OF CHAPTER 9

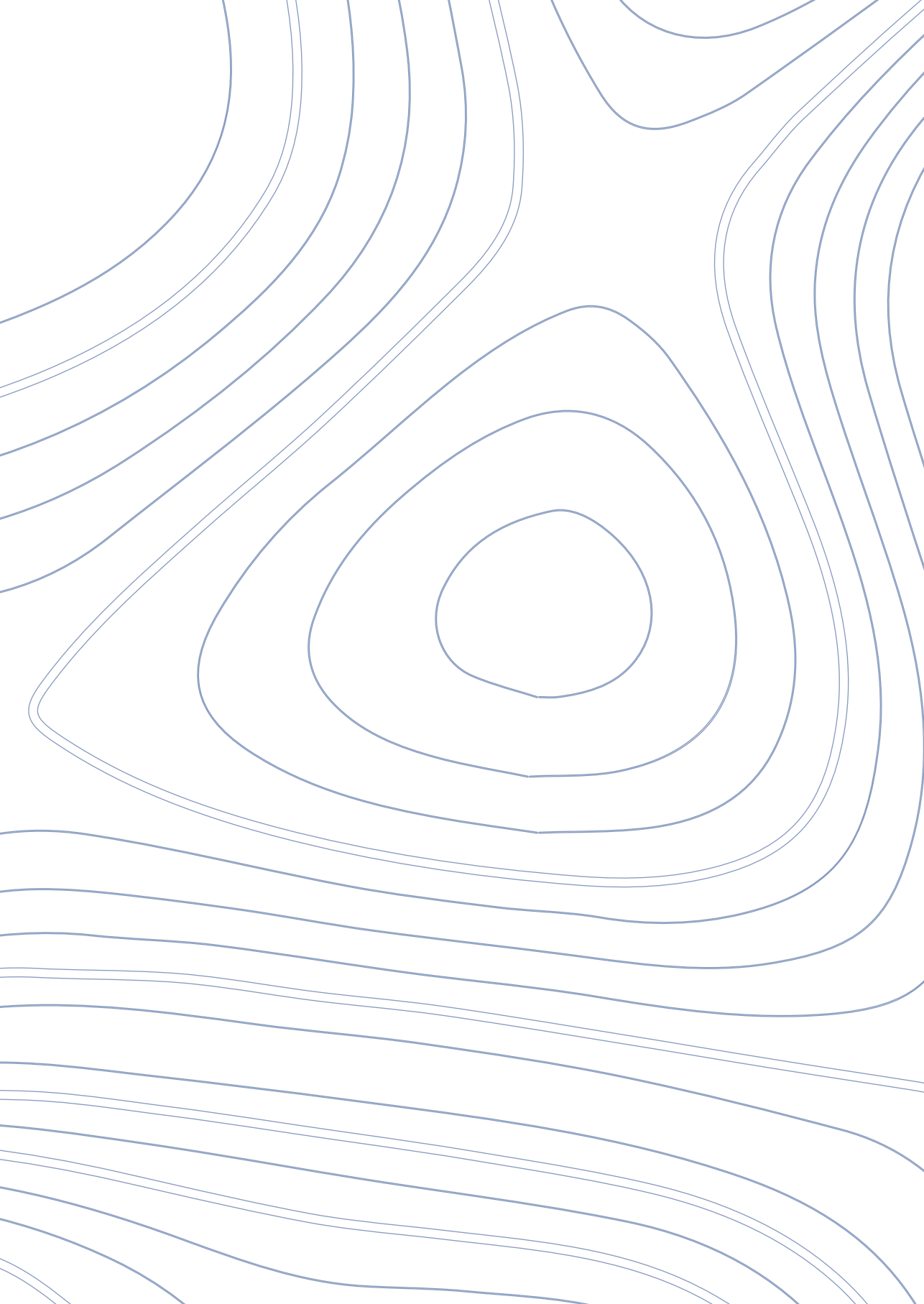


Supplementary Figure S1. Flowchart of included patients within the study

Part IV

Summary, general discussion,
future perspectives and appendices





Chapter 10

General discussion and future perspectives

GENERAL DISCUSSION

The treatment of locally recurrent rectal cancer (LRRC) remains a clinical challenge. The heterogeneous patient presentation, the invasive nature of disease and the differences in previous treatments amongst patients all complicate management significantly. The low incidence of LRRC also hampers collection of high-quality, prospective data. Hence, treatment is often based on low-grade retrospective evidence, local practice, or consensus statements.[1–3]

In the Netherlands, radiotherapy is often used as a neoadjuvant modality in the curative setting, in order to downstage tumour volume preoperatively, increase the chance of a radical (R0) surgical resection and improve local re-recurrence free survival (LrRFS).[4–6] For RT naive LRRC patients, full course CRT may improve overall survival (OS), but an OS benefit following reirradiation has not been reported.[6–8]

Despite the lack of an OS benefit, improving LrRFS remains an important goal of LRRC management. Complaints such as pain, fistulation and tumour mass effect due to local disease are common and detrimental to quality of life in LRRC patients.[9–11] Therefore, achieving local control in the palliative setting and preventing a re-recurrence in the curative setting is equally important as improving OS, warranting the use of reirradiation. However, many questions still remain unanswered regarding radiotherapy, and data to answer these questions is scarce. Questions such as optimal dose constraints, the potential for reirradiation beyond 30Gy, indications of radiotherapy for LRRC outside of the neoadjuvant or palliative setting, and the benefit of novel radiotherapy techniques remain. Given the lack of robust data and evidence-based guidelines steering clinical decision making for LRRC, this thesis aimed to benchmark the current treatment of LRRC, as well as improve radiotherapy for LRRC. The need for further research regarding radiotherapy in LRRC is evident, as well as the need for strong multidisciplinary collaboration in expert centres, working with and towards a common standard of care.

Advancing radiotherapy

Target volume delineation

The development of the first delineation guideline for LRRC with leading LRRC experts was important in standardizing radiotherapy for all patients included in the PelvEx II trial, which is investigating the benefit of induction chemotherapy prior to chemoradiotherapy and surgery for LRRC. To guarantee the validity of the trial, it is crucial that patients in both arms receive radiotherapy that adheres to a uniform standard of care, as the primary

outcome is the R0 resection rate, which is influenced by chemoradiotherapy. Guideline development was not only important in raising awareness for LRRC-specific delineation challenges, but also highlighted the lack of substantiating data to corroborate any recommendations made.

Substantial interobserver variation (IOV) in target volume delineation amongst radiation oncologists was found. While large IOV does not necessarily reflect the accuracy or quality of individual delineations, it does indicate a lack of consensus regarding appropriate target volumes. The observed IOV was hypothesized to stem from challenges in interpreting diagnostic imaging, complicating GTV delineation. Incorporating a dedicated radiologist in a multidisciplinary approach to delineation was therefore seen as a logical step in improving care.

Overall, improvement in IOV when delineating with radiologists' input was modest, although the effect varied considerably across cases. In some recurrences, such as solitary lymph node recurrences, there was little IOV amongst all participating radiologists and radiation oncologists. In cases with low up-front IOV, an improvement was not expected or necessary.
However, the varying effect in more complex recurrences was not expected. This could be attributed to the lack of a common definition for GTV, such as in tumours in fibrosis. IOV in these cases was high amongst both radiation oncologists and radiologists, as the IOV could largely be explained by either delineating the whole fibrosis as GTV, or only apparent tumour within fibrosis as GTV. IOV can then only be reduced if either approach is assigned based on consensus. In the literature, this consensus does not exist. In primary rectal cancer, substantial differences are found in something as seemingly simple as defining lateral lymph nodes.[12] In LRRC, where the complexity is much higher due to altered anatomy and heterogeneity of disease, it is inevitable that the definition of GTV also varies amongst clinicians. For radiation oncologists, the delineation guideline can help reduce these variations. For radiologists, no common staging or reporting system currently exists.[13]

The lack of substantiating data to support the delineation guideline was apparent. To address this, multidisciplinary case discussions were held, debating patients who suffered re-recurrences after intended curative treatment for LRRC. In over half of the discussed cases, at least one point of improvement to treatment could be noted. In the majority of

cases, this included adapting target volumes. Often, proposed adaptations fell in line with current delineation guideline recommendations; however, some new recommendations were proposed, as in recurrences located in an abscess. In some cases, an abscess around a local recurrence was not completely irradiated during LRRC treatment. Re-recurrences subsequently developed along the border of the previous abscess. This may indicate that this area was insufficiently treated, especially considering the potentially tumour-conducive micro-environment of an abscess and the circulating fluids within.[14,15] By discussing cases in which treatment failed, target volume recommendations can be improved. Of course, prospective validation of these hypotheses should be sought, but until then, these observations are used for further guideline development.

Inevitably, the guideline that was established will not be applicable to all LRRC, as the limited number of cases used can never completely reflect a heterogeneous disease as LRRC. To address this, the PelvEx II trial quality assurance (QA) programme was implemented. QA goals included ensuring homogeneous treatment within the PelvEx II trial and assessing guideline applicability in several types of local recurrences. This programme has provided valuable insights on how to improve target volume recommendations. It also highlighted some recurrence types that were not properly discussed in the first delineation guideline, such as high (nodal) recurrences after a partial mesorectal excision.

Ultimately, the goal of guideline development is to determine a standard of care and simplify delineation for radiation oncologists, especially those who do not often encounter LRRC. Based on the results in this thesis, it is pivotal that radiologists and radiation oncologists, but also surgeons agree on how to report, define and target LRRC in order to further improve. Radiologists are important in evaluating the extent of the tumour and their input can improve GTV delineations in up to a third of cases. This effect could however be larger if consensus on GTV definition is reached. For now, radiologists could facilitate target volume delineation by demarcating the extent of the tumour on MRI as clearly as possible, for example with arrows pointing to the tumour border in several plains and directions, and by detailing all involved or potentially involved organs and structures as clearly as possible. Surgeons provide important information on where surgical resection margins will be. These margins should always be incorporated within the CTV, as this is where an irradical resection may occur, which neoadjuvant therapy aims to prevent.[4,5,16]

Surgeons could therefore improve target volume delineation by discussing the surgical plan prior to radiotherapy treatment.

The overall effect of introducing a delineation guideline on quality of care should not be underestimated and guideline improvements have already been made based on results from several successive studies. In the future, many more questions regarding target volume delineation will likely arise. Target volume delineation in LRRC should therefore remain an area of research and guideline development should continue using PelvEx II data.

Dose escalation

One of the most prominent questions in LRRC radiotherapy is in regard to the dose of reirradiation. Reirradiation is used as a neoadjuvant treatment, to improve the chance of an R0 resection and improve LrRFS, but its effect is less than that of full course CRT.[4,6] This difference in efficacy may be caused by a lower and thus suboptimal reirradiation dose, by a higher incidence of radiation-insensitive tumours, or a combination of both. Either way, the key question in the neoadjuvant setting is whether further dose escalation could enhance oncological outcome.

Toxicity concerns have previously limited dose escalation of neoadjuvant reirradiation after the benchmark trial by Valentini et al., which employed hyperfractionated reirradiation up to 40Gy.[17] Fortunately, recent cohorts report low acute toxicity rates using conventional fractionation schedules.[7,18–22] Moreover, no difference in postoperative complications is seen when comparing patients irradiated prior to surgery to patients treated with up-front surgery.[23] Furthermore, advances in radiotherapy have enabled better sparing of organs at risk (OAR), suggesting that higher reirradiation doses can be explored. As of yet, dose-escalation in the neoadjuvant setting has not been researched in the Netherlands. This is because intraoperative radiotherapy is often used as an adjunct modality, adding a single-fraction boost of 10-16Gy to the at-risk margins during surgery, resulting in an EQD2 of over 40Gy (α/β=10), albeit to a small at-risk volume.[24,25] Hyperfractionated radiotherapy may aid in dose-escalation but is not the most patient-friendly option and it places a substantial burden on resources due to the twice-daily schedule. Dose-escalation with conventional fractionation to at least 40Gy may however be a feasible starting point for clinical trials, given the low acute radiotherapy toxicity reported following 30Gy.

In patients not eligible for surgery, due to frailty, tumour characteristics or preference, reirradiation may be used for palliation, local control, or even as an alternative to surgery. Chung et al. performed reirradiation up to 50Gy, showing an in-field progression-free survival of 49% and OS of 55% at 2-years without surgery.[26] However, a relatively high late severe toxicity rate of 41% was reported, compared to 25% reported in a reirradiation meta-analysis.[22] Achieving dose-escalation without increasing toxicity is therefore key. In the United Kingdom, a hypofractionated approach with Stereotactic Ablative Radiotherapy (SABR) is being studied for selected cases within this population. SABR is characterized by a high biological effective dose (BED) and a steep dose fall of towards surrounding (healthy) tissues. In general, smaller tumours (<5cm) with enough distance to surrounding (critical) OAR are eligible for SABR. Relatively small margins are used, adding only a 5mm margin to the GTV, thereby minimizing the target volume. Dose-escalation is performed in an isotoxic manner, meaning the radiation dose is tailored to the tolerance of surrounding OAR rather than the target volume.[27,28] By doing so, it is hoped that dose-escalation can be achieved, without exceeding a pre-defined OAR tolerance threshold. In a planning study, median EQD2 increased from 43 to 61Gy, which could have a significant effect on oncological outcome.[28] Toxicity data and oncological outcomes of this approach are awaited, as this may become a valid alternative to conventional reirradiation in patients opting out of surgery.

Although dose-escalation in reirradiation seems feasible based on recent cohorts and technical advances, it is possible that no oncological benefit will be found. Patients undergoing reirradiation have already demonstrated poor tumour biology and some degree of radiotherapy resistance. Future research should therefore focus on understanding the dose-response relationship in reirradiation and uncovering the underlying mechanisms of potential radiation resistance, as well as researching the safety of dose-escalation in both neoadjuvant and non-operative settings.

Implementation of novel modalities

Another point of discussion is the use of novel radiotherapy modalities in LRRC irradiation, such as the MR-linac, which may reduce side effects and facilitate dose escalation. The MR-linac enables more precise target volume delineation due to the MRI's superior soft-tissue visualization.[29–31] The MR-linac could prove valuable in reducing toxicity or escalating radiotherapy dose, by reducing planning target volume (PTV) margins and facilitating a boost to the GTV. In primary rectal cancer, such an approach has been studied.[32] The

MR-linac allows for compensation of inter- and intrafraction variation and a reduction of delineation uncertainty, which is accounted for in the PTV.[33–35] By reducing PTV margins, toxicity is reduced.[36–39] This could facilitate dose-escalation, for example by a boost to the GTV, which results in more pathologic tumour response in primary rectal cancer.[40,41] It is highly likely that a similar effect can be achieved in LRRC. An increased pathologic tumour response correlates to a superior oncological outcome in LRRC.[42–45]
The benefit of an MR-linac may however not be as large as in primary rectal cancer, as recurrences are often fixated within the small pelvis.[46,47] Therefore, accounting for tumour motion may only result in a minimal PTV reduction. Moreover, more precise target volume delineation may also be facilitated by implementing a diagnostic MRI in radiotherapy treatment position for each patient. This approach already improves image comparability and reduces registration errors that may occur when using a standard diagnostic MRI.[48] Additionally, the workflow of an MR-linac can consume up to an hour per fraction compared to ten minutes per fraction on a conventional linac.[49] Lastly, the availability of the MR-linac is limited and its use may therefore be more justified in other tumour sites. Although an MR-linac workflow for LRRC holds potential, this approach may not be warranted just yet, and should be studied prospectively.

Other potentially beneficial modalities include proton and carbon-ion radiotherapy. Proton radiotherapy's unique dose distribution properties allow for more precise radiotherapy, enabling higher doses while better sparing OAR.[50–53] Similarly, carbon-ion radiotherapy's steep Bragg peak and higher linear energy transfer may provide the benefit of better targeting relatively radiotherapy-resistant tumours, such as in LRRC reirradiation.[54–58] However, the significantly higher costs and limited availability of these advanced modalities may restrict their widespread adoption. Additionally, the low toxicity rates currently reported with chemo reirradiation for LRRC suggest that the boundaries of conventional radiotherapy have not yet been fully explored, making the immediate use of more expensive and less accessible techniques questionable. A Danish reirradiation trial for LRRC is currently investigating the feasibility and efficacy of dose-escalation up to 60 Gy using proton radiotherapy in patients with irresectable local disease. Its results will provide necessary information on whether or not proton radiotherapy could be of additional benefit, and whether steep dose-escalation could be feasible and beneficial for palliative patients.

Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) is used in LRRC to improve LrRFS, although the evidence is limited and often confounded by different nCRT schedules and mixed locally advanced and recurrent rectal cancer cohorts.[24,59,60] Nevertheless, IORT is frequently considered as an additional modality to improve local control given the significant morbidity associated with local failure.[9–11,24] Inaccurate IORT dose-reconstruction after surgery may have previously hindered proper data collection and research. This is partly due to the ad-hoc placement of IORT, which is based on the surgeon's assessment of where an incomplete resection may have occurred. Another reason is the substantial anatomical change that occurs between the preoperative and postoperative setting, which can lead to a mismatch between the planned and delivered IORT location. As a result, it can be challenging to determine whether a subsequent tumour re-recurrence develops within the area treated by IORT. The introduction of intraoperative navigation may offer a potential solution to these issues, by facilitating IORT dose reconstruction during or following surgery.[61–64] This combination of IORT and intraoperative navigation may facilitate and accelerate research in the field of IORT.

Overall, many questions still stand in regard to radiotherapy for LRRC. Many steps to improve quality of radiotherapy have already been taken and the potential for further improvements is clear. The mere fact that there is a heightened awareness regarding the potential as well as the pitfalls of radiotherapy for LRRC is a significant step forward. Aforementioned opportunities in relation to target volume delineation, dose-escalation, and the possible introduction of novel techniques such as intraoperative navigation and the MR-linac can all contribute to better radiotherapy for LRRC.

Improving patient selection

Careful patient selection is critical in the management of LRRC. Patients selected for treatment with curative intent undergo intensive treatment, consisting of nCRT, sometimes preceded by induction chemotherapy, and extensive multicompartmental resections.[1–3,16,65–67] Surgical procedures are associated with high postoperative morbidity and mortality, reflected in a high postoperative complication rate and a significant and prolonged impact on quality of life (QoL).[9–11,23,68] Therefore, selecting the right patients for curative treatment is essential to prevent unnecessary treatment.

On the other hand, patients selected for palliative treatment have a significantly lower OS than patients selected for a curative treatment and can also suffer a decreased QoL due

to issues such as tumour mass effect and pain.[9,69,70] Moreover, local palliative treatments such as radiotherapy often only relieve symptoms for a limited amount of time.[71,72] Withholding curative treatment in patients who may have benefited from a curative approach can therefore also be detrimental to OS and QoL.

In current practice, patients with non-metastatic and resectable local disease are often deemed eligible for curative treatment, while patients with metastatic or unresectable disease receive palliative care. However, this approach fails to consider individual patient or tumour-specific factors. Therefore, more sophisticated methods are needed to select and monitor patients throughout their treatment.

Neoadjuvant therapy provides a window of opportunity for patient selection. On the one hand, it provides time for clinicians to observe the biological behaviour of the local recurrence. If the local recurrence is progressive despite neoadjuvant treatment and becomes irresectable, or if distant metastases develop, this is a reason to not perform surgery. There is no oncological benefit of surgery if a macroscopically irradical resection is expected when compared to non-operative management.[73] OS of LRRC patients presenting with synchronous metastases is known to be worse compared to patients without (a history of) metastases, even in highly selected cohorts from tertiary referral centres.[74] It is therefore likely that the differences in outcome are even larger, as patients with extensive local or distant disease are usually not presented at tertiary expert MDTs.

Monitoring tumour response could also help to select excellent responders for a watch-and-wait (W&W) strategy, as in primary rectal cancer. In chapter 8, it is concluded that achieving a pathological complete response after neoadjuvant therapy is predictive of superior oncological outcomes, even compared to patients in whom an R0 resection is achieved.[45,75,76] In these patients, surgery could be avoided if it does not have an additional effect on oncological outcome. In near-complete responders, dose-escalation to maximize local control may be justified if surgery and thus its potential complications can be omitted, even if this would entail an increase in radiotherapy toxicity. However, selection for a W&W approach relies heavily on accurate identification of a (near-)complete tumour response in LRRC, which is difficult due to altered anatomy, postoperative fibrosis hampering MRI-based follow-up and the inability for endoscopic follow-up in a majority of patients.

Two studies have investigated response assessment in LRRC. Voogt et al. compared the use of the MRI tumour regression grade (mrTRG) to the pathological tumour regression grade (pTRG).[75] A high positive predictive value (PPV) for a major pathological response (pTRG 1-2) is achievable when evaluation is done by an expert radiologist. However, overestimation of response was seen in 17% of cases, which is a clear risk when selecting patients for a watch-and wait strategy. Van Zoggel et al. demonstrated that a PPV of 63% can be achieved for a major pathological response with an F18-FDG PET/CT but reported overestimation in 23% of cases.[76] Improving response assessment, potentially by combining T2-weighted MRI with DWI and an F18-FDG PET/CT, with new liquid biopsy biomarkers such as ctDNA should be a research priority given its potential implications for a W&W appraoch.[77]

The importance of patient selection is also reflected in Chapter 9. In up to 60% of patients undergoing surgical treatment for LRRC, a re-recurrence will occur.[16,23,73] In these patients, treatment options are often even more limited than in LRRC, as options may be exhausted. Even so, long-term survival following curative treatment is achievable and factors beyond metastases and resectability seem to play a role in patient selection. For example, the interval between LRRC surgery and re-LRRC presentation influenced treatment intent in re-LRRC patients. In patients treated with curative intent, the median interval was 16.1 months, whereas in patients treated with palliative intent, the interval was only 11.3 months. An interval between LRRC and rLRRC of less than 12 months was associated with a poor 3y OS of only 30%. It is likely that this short interval reflects poor tumour biology.
Apparently, clinicians already consider different clinical characteristics when choosing the most optimal patient approach. However, data that can confirm the prognostic value of these characteristics is lacking. Future research should therefore focus on prospectively confirming clinical characteristics as prognostic factors, as well as identifying new prognostic factors. Prospective data generated from the PelvEx II trial will facilitate this.

Standardizing and centralizing LRRC care

It is clear that multidisciplinary collaboration and expertise are pivotal in improving LRRC care. Two LRRC guidelines have been developed and endorsed by a multidisciplinary team of experts. Close collaboration between radiologists and radiation oncologists has demonstrated the ability to enhance LRRC delineations. Multidisciplinary discussions have facilitated the formation of new hypotheses regarding LRRC target volumes. The

benefit of expert peer-review in LRRC delineation has been proven. These steps emphasize the value of multidisciplinary input and close collaboration amongst disciplines involved in LRRC treatment.

Currently, treatment is often centred around surgical expertise and there are no volume or expertise requirements for radiotherapy. This may hamper consistent, high-quality radiotherapy. Given the low incidence of LRRC, individual radiation oncologists have limited exposure to LRRC cases. During PelvEx II QA, nearly half of LRRC delineations were edited prior to nCRT, even though a delineation guideline was provided. A recent systematic review of radiotherapy QA measures in clinical trials showed that learning curves can rapidly diminish, even after benchmarking or peer review, and even in less complex primary cancer settings.[78] This, in combination with the low incidence and complexity of LRRC, makes it unlikely that individual radiation oncology departments will be able to develop sufficient LRRC-specific expertise.

Consequently, further centralizing LRRC-expertise into multidisciplinary expert teams, similar to those in the PelvEx II trial, may prove essential. Expert centres would be in charge of staging, restaging, determining indication and type of treatment, reviewing or performing target volume delineation and performing surgery. A minimum of 10 patients per year to define an expert centre is currently used in the PelvEx II trial but given the absence of a learning curve in LRRC delineation after ten cases, this norm may have to be increased. Patients could be referred back to local centres for the majority of care, as long as patients are discussed regularly in expert MDT-meetings. By doing so, patients can be certain that their individual treatment is up to the highest standards of care, whilst receiving care nearby, thereby enhancing care and collaboration in a physician- and patient-friendly manner.

In the meantime, a standardized radiological reporting protocol should be developed, incorporating information essential to radiation oncologists, such as a description of each (possibly) involved structure and clear demarcations of the tumour. Surgeons could detail their expected surgical approach and define where they anticipate the closest resection margins prior to delineation, as this impacts both GTV and CTV. Lastly, radiation oncologists should discuss delineations with colleagues at high-volume expert centres. The PelvEx II trial has already demonstrated how easily peer-review can be implemented in a manner that does not cause treatment-delay and does not require data transfers. Although these

are all relatively simple interventions, the combined effect in improving quality of care could be substantial.

All in all, significant improvements have been made in LRRC care. Although LRRC remains a complex and multidisciplinary challenge, the evolving understanding of patient selection, the standardization and centralization of expertise, and the further development of radiation treatment all provide hope for improved outcomes in this patient population.

FUTURE PERSPECTIVES

Ultimately, the implementation of an expert-centre structure for all patients with LRRC will improve care substantially and should be a priority. The steps that have already been taken, such as mandatory peer-review for PelvEx II trial delineations, should be continued and expanded for other LRRC patients. New efforts to further standardize, centralize and improve the quality of treatment and patient selection are essential.

Currently, ESTRO is developing a radiotherapy guideline for LRRC, covering radiotherapy indications, treatment planning recommendations, dose constraints, dose summation strategies, as well as the indications of novel techniques. This comprehensive guideline will greatly aid in internationally benchmarking LRRC radiotherapy and identifying additional research areas that require further exploration.

One of the major issues in LRRC is the lack of robust data to draw conclusions from. The PelvEx II and the (no longer recruiting) GRECCAR-15 trial will aid in providing high-quality, prospective data.[66,79] Both trials however only include(d) selected patients. Therefore, gathering comprehensive data of all LRRC patients in LRRC research centres is important. A new data-collecting initiative that aims to collect data on all LRRC-patients treated in- and outside of the PelvEx II trial is currently under construction. The aim is to gather clinical data, imaging, radiotherapy plans, tissue and liquid biopsies and create a large international LRRC data- and biobank. This will hopefully provide the knowledge that can be used to generate new research hypotheses, confirm others and improve care for LRRC patients.

LRRC knowledge is limited overall, but especially in the palliative setting. Importantly, palliative patients may be excellent candidates for dose-escalation trials in LRRC, with the goal of maximizing local control. In patients deemed ineligible for surgery, either due

to frailty, irresectable disease, or preference, definitive radiotherapy may be a valuable treatment alternative. Several cohorts have proven its feasibility in both RT naive and reirradiation LRRC patients, reporting progression free survival and overall survival rates similar to patients undergoing surgery.[26,80,81] When considering a reported 3-year OS of 20% in palliative patients overall, definitive radiotherapy could become a valid alternative and should therefore be explored in clinical trials.[70]

In the meantime, an additional data-collecting initiative for patients undergoing palliative radiotherapy is also being initiated, providing insight into which doses and schedules are used in palliative (re-)irradiation in the Netherlands. Once treatment variations have been established, efficacy of different schemes on oncological outcome can retrospectively be evaluated. In a "pick-the-winner" fashion, promising radiotherapy schedules could be researched prospectively. As an added benefit, the applicability of our delineation guideline could be evaluated in a palliative population.

Currently, we do not have enough data to support a W&W strategy in LRRC, in part due to the clinical doubts regarding the accuracy of determining a complete response through imaging. However, there are patients that will opt out of surgery, given the high morbidity and mortality associated with it, or patients in whom surgery is omitted for other reasons such as (new) comorbidities. Careful registration and follow-up, for example with three-monthly MRIs and CTs, of patients in whom surgery is omitted will hopefully help in determining the role of W&W in the future, provide valuable information on longevity of tumour response, and shape further research on this topic.

In conclusion, centralization and standardization of LRRC care as well as continuous clinical research is of the utmost importance for LRRC patients. Ongoing and future trials, as well as large-scale data-collecting initiatives will aid in further optimizing treatment for this challenging patient group. In the meantime, every effort should be made to provide patients with optimal treatment through rigorous and continuous multidisciplinary collaboration.

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Chapter 11

Summary

Nederlandse samenvatting

SUMMARY

Chapter 2 describes the development of the first delineation guideline for locally recurrent rectal cancer (LRRC). This was achieved through multidisciplinary case discussions with leading LRRC experts, as well as delineations by radiation oncologists participating in the PelvEx II trial. The study provided a first insight into delineation variation for LRRC and underscored the value of multidisciplinary collaboration in determining target volumes. The developed delineation guideline has been implemented across all PelvEx II trial centres, as well as nationally in the Netherlands, marking the first step towards further standardization of LRRC care.

In **Chapter 3,** a comprehensive narrative literature review was conducted to develop a formal Dutch national guideline for management of LRRC. To our knowledge, this is the first national guideline established for LRRC patients. The guideline provides an overview of patient management, from diagnosis through surgery. Furthermore, it advocates for a coordinating role of expert centres in LRRC patient management, ensuring consistent, high-quality care. This expertise should be present across all disciplines involved in LRRC management, underscoring the need for multidisciplinary collaboration.

In **Chapter 4,** a multidisciplinary delineation study was conducted to follow up on the significant interobserver variation (IOV) in target volume delineations reported in Chapter 2. Fourteen cases of LRRC were delineated by both radiation oncologists and radiologists, revealing substantial IOV within each group. While multidisciplinary collaboration in target volume delineation did reduce IOV amongst radiation oncologists, this effect was limited to selected cases. Furthermore, the results suggest that the lack of a standard terminology amongst radiologists and radiation oncologists may have hampered the results, underscoring the need for further interdisciplinary efforts to improve quality of care. Lastly, this study provided insights into which recurrence types may be more prone to IOV, which may aid with guideline refinement.

The second chapter of this thesis concludes that enhanced understanding of local re-recurrences is necessary to comprehend disease behaviour and optimize delineation guidelines accordingly. In **Chapter 5**, an initial exploratory analysis of re-recurrences after curative treatment of LRRC is performed. This analysis suggests that suboptimal treatment, primarily due to inadequate target volumes, may have contributed to treatment failure in over half of the discussed cases. Recommendations for target volume improvements are

made. Confirmatory studies with larger sample sizes and a control cohort without re-recurrences are however necessary to draw definitive conclusions.

A prospective quality assurance (QA) program involving peer-review of target volume delineations is described in **Chapter 6**. This QA program aims to ensure homogeneous radiotherapy treatment within the PelvEx II trial and evaluate the applicability of and compliance to the established delineation guideline. The results reveal that target volumes are changed in nearly half of LRRC cases, underscoring the value of real-time peer-review. Based on these findings, adjustments have been made to the delineation guideline to improve protocol compliance and reduce the number of protocol deviations and ambiguities. By conducting this analysis while the PelvEx II trial is still ongoing, protocol modifications can be introduced and re-evaluated within the remaining trial duration.

In **Chapter 7,** the difference in postoperative complications before and after dose adaptation and escalation of intraoperative electron radiotherapy (IOERT) was evaluated. A previous comparison had suggested improved local re-recurrence-free survival (LrRFS) with intraoperative brachytherapy compared to IOERT, but at the expense of increased toxicity. It was hypothesized that this may be due to a higher surface dose with intraoperative brachytherapy. Therefore, the IOERT technique at the Catharina Hospital Eindhoven was modified to increase the radiation dose at the surface without increasing the dose at depth, with the aim of improving LrRFS without increasing toxicity. This initial analysis encouragingly showed no increase in postoperative complications despite the higher IOERT doses. As a result, the optimized IOERT technique remains in use. A comparison of LrRFS before and after IOERT dose adaptation will be performed once sufficient follow-up data is available.

Chapter 8 describes the difference in oncological outcomes between patients with and without a pathological complete response following LRRC treatment. In this retrospective cohort study, patients with a pathological complete response demonstrated statistically significantly higher overall survival, disease-free survival, and local recurrence-free survival compared to those without a pathological complete response. These findings suggest that pathological complete response may represent an important prognostic factor for patients with locally recurrent rectal cancer.

In **Chapter 9,** a retrospective review of the treatment of patients with re-recurrent rectal cancer is performed. Characteristics of patients undergoing treatment with curative and palliative intent are compared. Characteristics such as prior treatment, focality of disease, metastases at re-LRRC diagnosis and interval between local recurrence and re-recurrence seem to influence oncological outcome. These findings may give clinicians additional parameters to determine whether to go forward with curative or palliative intended treatment, beyond what is currently known and used.

NEDERLANDSE SAMENVATTING

In **Hoofdstuk 2** wordt de ontwikkeling van de eerste intekenrichtlijn voor het lokaal recidief rectumcarcinoom (LRRC) beschreven. Hiervoor werden multidisciplinaire besprekingen met LRRC-experts gepland, waarin intekeningen verricht door radiotherapeuten betrokken bij de PelvEx II studie werden besproken. In deze studie wordt inzicht gegeven in de mate van intekenvariatie tussen radiotherapeuten en wordt de waarde van multidisciplinaire samenwerking bij het bepalen van radiotherapeutische doelvolumes benadrukt. Deze intekenrichtlijn is zowel nationaal als in alle PelvEx II studiecentra geïmplementeerd. Deze intekenrichtlijn markeerde de eerst stap naar verdere standaardisatie van LRRC-zorg.

In **Hoofdstuk 3** werd een landelijke Nederlandse richtlijn voor de behandeling van het LRRC geschreven op basis van een uitgebreid literatuuronderzoek. Voor zover bekend is Nederland het eerste land dat een formele richtlijn voor de behandeling van het LRRC doorvoert. In de richtlijn worden handvatten gegeven voor de gehele behandeling van het LRRC, van diagnose tot chirurgie. Bovendien pleit de richtlijn voor een coördinerende rol van expertcentra, met LRRC-specifieke kennis bij alle betrokken disciplines, voor alle LRRC-patiënten, om kwaliteit van behandeling voor alle LRRC-patiënten te borgen. Deze richtlijn onderschrijft dan ook het belang van multidisciplinaire samenwerking.

Naar aanleiding van de intekenvariatie dat werd gerapporteerd in hoofdstuk twee, is een multidisciplinaire intekenstudie verricht in **Hoofdstuk 4**. Veertien LRRC-casussen werden ingetekend door zowel radiotherapeuten als radiologen. Een grote intekenvariatie werd gerapporteerd bij zowel radiotherapeuten als radiologen, maar samenwerking tussen radiologen en radiotherapeuten leidde in geselecteerde gevallen wel tot een vermindering van intekenvariatie. Het gebrek aan een gemeenschappelijke benadering lijkt echter de effectiviteit van de multidisciplinaire samenwerking te hebben belemmerd. Deze studie gaf inzicht bij welke recidieven intekenvariatie meer of minder voorkomt, wat kan bijdragen aan verdere ontwikkeling van de bestaande intekenrichtlijn.

In het tweede hoofdstuk van dit proefschrift wordt onder andere geconcludeerd dat een beter inzicht in lokale re-recidieven nodig is om de intekenrichtlijnen te optimaliseren. In **Hoofdstuk 5** wordt daarom een eerste retrospectieve analyse uitgevoerd van re-recidieven na een curatieve behandeling voor het LRRC. Er wordt geconcludeerd dat in meer dan de helft van de besproken gevallen een suboptimale behandeling mogelijk een rol zou kunnen

hebben gespeeld bij het locoregionaal falen, voornamelijk ten gevolge van suboptimale doelvolumes. Suggesties voor aangepaste doelvolumes worden gedaan. Bevestigende studies met grotere cohorten en tevens een controlegroep zonder re-recidieven zijn echter nodig om hier definitieve conclusies uit te trekken.

De implementatie van een prospectieve kwaliteitscontrole van intekeningen, in de vorm van een intercollegiaal consult, wordt beschreven in **Hoofdstuk 6.** Het doel hiervan is om de homogeniteit van de radiotherapiebehandeling binnen de PelvEx II-studie te waarborgen, maar ook om de toepasbaarheid en naleving van de richtlijn te evalueren. Er wordt aangetoond dat de radiotherapie doelvolumes in bijna de helft van de LRRC-gevallen worden aangepast. Op basis van deze resultaten zijn aanpassingen in de intekenrichtlijn doorgevoerd, met als doel om de naleving van de richtlijn te verbeteren, maar ook het aantal redenen om af te wijken van de richtlijn en het aantal vragen naar aanleiding van de richtlijn te verminderen. Door een eerste analyse uit te voeren terwijl de PelvEx II-studie nog patiënten includeert, kunnen richtlijnaanpassingen worden geïntroduceerd en worden beoordeeld terwijl de trial nog loopt.

In **Hoofdstuk 7** wordt het verschil in postoperatieve complicaties vóór en na een dosisaanpassing van intra-operatieve elektronische radiotherapie (IOERT) geëvalueerd. Een eerdere vergelijkende studie suggereerde een verbeterde lokale re-recidiefvrije overleving (LrRFS) na intra-operatieve brachytherapie (IOBT) vergeleken met IOERT, ten koste van meer toxiciteit. Dit zou mogelijkerwijs verklaard kunnen worden door een hogere oppervlaktedosis van IOBT. Daarom werd de IOERT-techniek in het Catharina Ziekenhuis Eindhoven aangepast om de stralingsdosis aan de oppervlakte te verhogen, zonder de dosis in de diepte te verhogen. De verwachting was dat hiermee een verbetering van LrRFS zou optreden, zonder de toxiciteit te verhogen. Deze eerste analyse toonde aan dat er geen toename was in postoperatieve complicaties, ondanks een hogere dosis. Daarom wordt de geoptimaliseerde IOERT-techniek momenteel nog steeds gebruikt, en zal een nieuwe vergelijking van LrRFS vóór en na IOERT-dosisaanpassing worden uitgevoerd zodra de data dat toelaat.

Hoofdstuk 8 beschrijft het verschil in oncologische uitkomsten bij patiënten met en zonder een pathologisch complete respons (pCR) na behandeling van een LRRC. In deze retrospectieve cohortstudie werd een significant hogere algehele overleving, ziektevrije overleving en LrRFS gerapporteerd bij patiënten met een pCR, in vergelijking met patiënten

zonder pCR. Deze data introduceren het bereiken van een pCR als een aanvullende prognostische factor voor patiënten met LRRC.

In **Hoofdstuk 9** wordt een retrospectieve analyse verricht van patiënten met een re-recidief (re-LRRC) na curatieve behandeling voor een LRRC. Hierin worden karakteristieken van patiënten die een curatieve behandeling ondergaan voor het re-LRRC vergeleken met patiënten die een palliatieve behandeling ondergaan. Karakteristieken zoals eerdere behandelingen, aantal laesies in het kleine bekken, metastasen bij re-recidief diagnose en interval tussen lokaal recidief een re-recidief lijken allemaal van invloed op de oncologische uitkomsten van patiënten. Deze parameters zouden dan ook mogelijkerwijs bij kunnen dragen bij de keus van behandelend artsen om wel of niet door te gaan met een curatief traject.

Appendices

LIST OF PUBLICATIONS

This thesis

1. **Piqeur F,** Hupkens BJP, Nordkamp S, et al. Development of a consensus-based delineation guideline for locally recurrent rectal cancer. *Radiotherapy and Oncology*. 2022;177:214-221. doi:10.1016/j.radonc.2022.11.008
2. **Piqeur F,** Creemers DMJ, Banken E, et al. Dutch national guidelines for locally recurrent rectal cancer. *Cancer Treat Rev*. Published online April 2024:102736. doi:10.1016/j.ctrv.2024.102736
3. **Piqeur F,**, van Gruijthuijsen DSC, Nederend J, et al. Multidisciplinary approach to target volume delineation in locally recurrent rectal cancer: an explorative study. Submitted to Practical Radiation Oncology.
4. **Piqeur F,** Coolen L, Nordkamp S, et al. Analysis of re-recurrent rectal cancer after curative treatment of locally recurrent rectal cancer. Submitted to Radiotherapy and Oncology.
5. **Piqeur F,** Hupkens BJP, Creemers DMJ, et al. Prospective radiotherapy quality assurance leads to delineation guideline refinements for recurrent rectal cancer: experience from the PelvEx II study. Submitted to Radiotherapy and Oncology.
6. **Piqeur F,** Peulen HMU, Cnossen JS, et al.Postoperative complications following dose adaptation of intraoperative electron beam radiation therapy (IOERT) for locally advanced or recurrent rectal cancer. Journal of Contemporary Brachytherapy. 2024 Apr; 16(2):85-94.
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8. Nordkamp S, **Piqeur F,** Banken E, et al. Locally recurrent rectal cancer: Treatment of a second local re-recurrence. Submitted to Annals of Surgery.

Other

9. Piqeur F, Nordkamp S, Coolen L et al. Inductiechemotherapie, 'to do or not to do' bij het lokaal recidief rectumcarcinoom: de PelvEx II studie. *Nederlands Tijdschrift voor Oncologie. 2023;20:120-5.*
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11. West CT, West MA, Drami I, et al. Beating the empty pelvis syndrome: the PelvEx Collaborative core outcome set study protocol. *BMJ Open*. 2024;14(2). doi:10.1136/bmjopen-2023-076538
12. West CT, West CT, West MA, et al. Empty pelvis syndrome: PelvEx Collaborative guideline proposal. *British Journal of Surgery*. 2023;110(12). doi:10.1093/bjs/znad301
13. West CT, West MA, Mirnezami AH, et al. The empty pelvis syndrome: a core data set from the PelvEx collaborative. *British Journal of Surgery*. 2024;111(3). doi:10.1093/bjs/znae042

CURRICULUM VITAE

Floor Piqeur werd geboren op 20 april 1996 te Rugby, Engeland. In 2014 behaalde zij haar Europees Baccalaureaat aan de Europese School III in Brussel. Hierna is zij begonnen aan de opleiding Geneeskunde aan de Universiteit Maastricht. Gedurende de studie was de interesse in de oncologie duidelijk. Floor volgde twee keuze coschappen bij de interne-oncologie en een keuzeblok bij de radiotherapie en rondde in december 2020 de opleiding af. Na de opleiding is zij gaan werken als ANIOS bij de interne geneeskunde in het Catharina Ziekenhuis te Eindhoven.

In juli 2021 is zij begonnen als PhD-kandidaat bij de onderzoeksgroep van Dr Pim Burger, onder begeleiding van Prof Dr Corrie Marijnen, Dr Pim Burger en Dr Heike Peulen, wat resulteerde in dit proefschrift. Haar onderzoek heeft tot een kwaliteitsslag geleid in de behandeling van het lokaal recidief rectumcarcinoom, onder andere in de vorm van zowel een internationale intekenrichtlijn als een nationale behandelrichtlijn. Haar werk is nationaal (LPRGE) en internationaal gepresenteerd (ESTRO, ESMO, PelvEx collaborative).

Na drie jaar fulltime onderzoek is Floor in september 2024 begonnen aan haar vervolgopleiding als AIOS Interne Geneeskunde in het Catharina Ziekenhuis te Eindhoven.

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