Locally recurrent rectal cancer: improving radiation treatment

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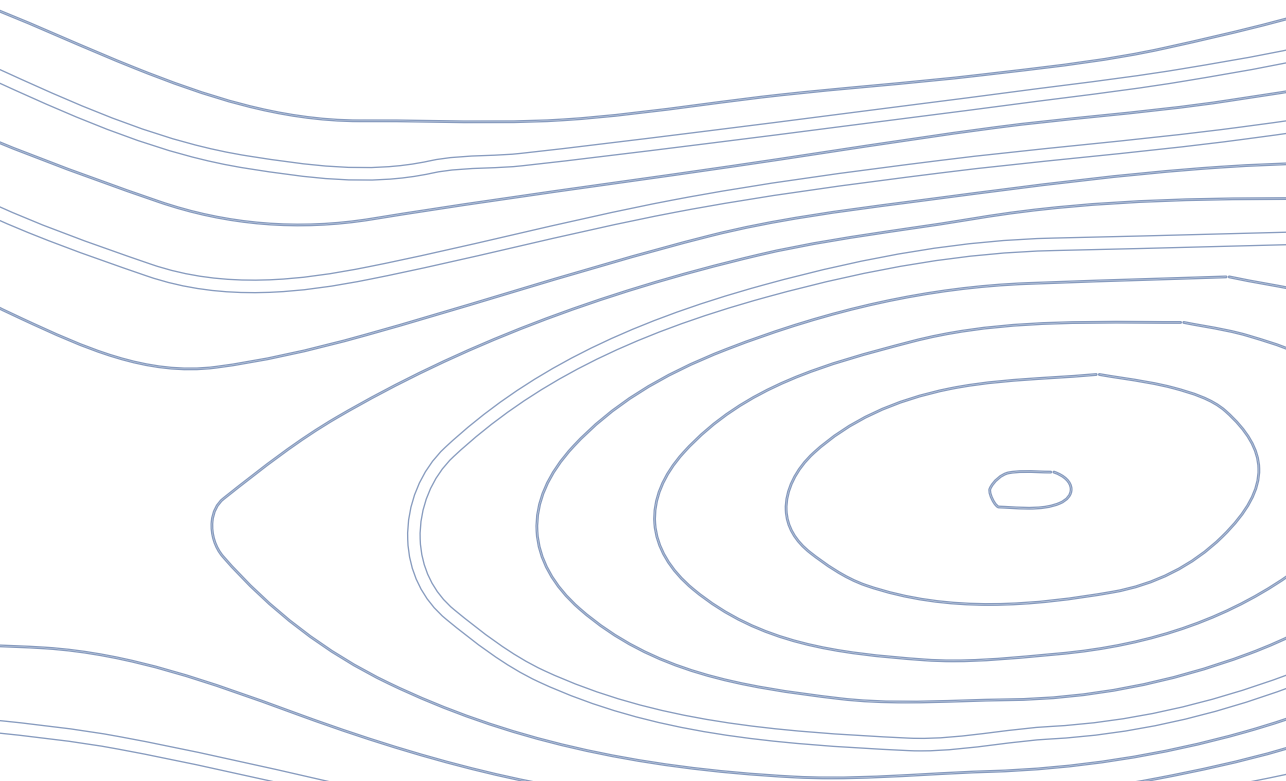
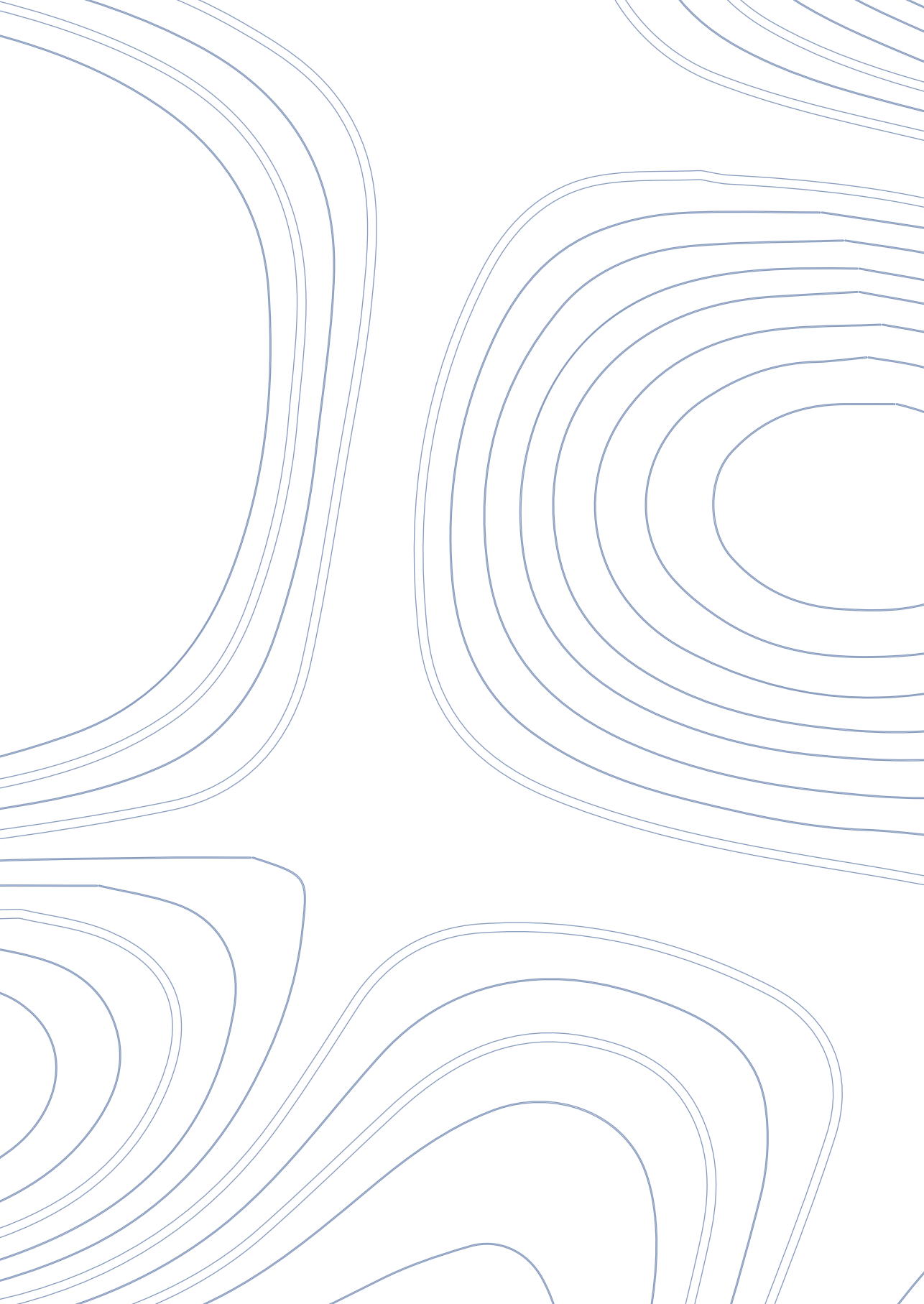
Part I

Standardizing locally recurrent rectal cancer care





Chapter 2

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

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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

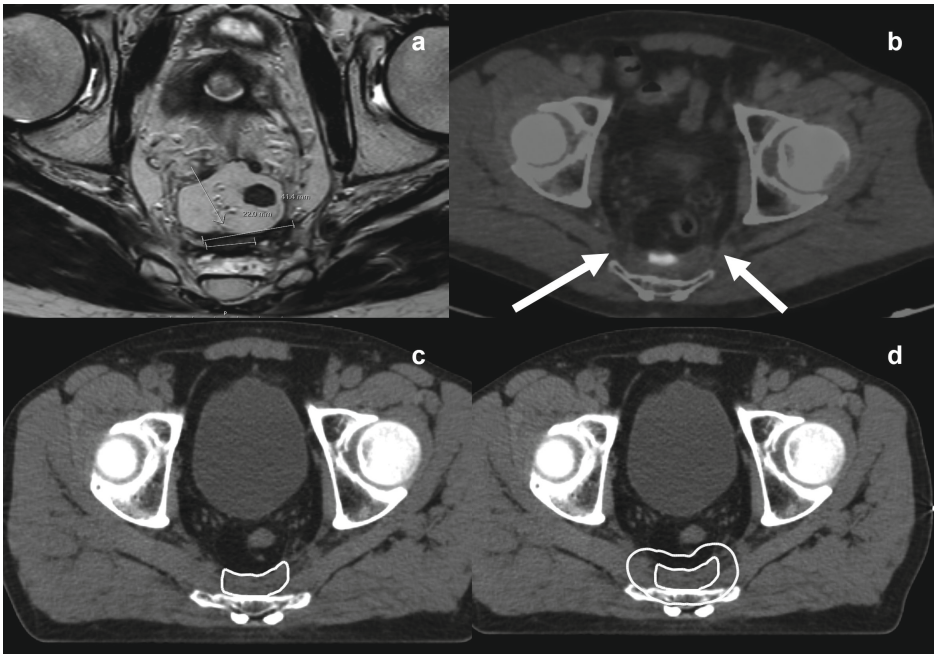

Figure 1. Consensus delineation for case 1.2 (and 2.1)

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)

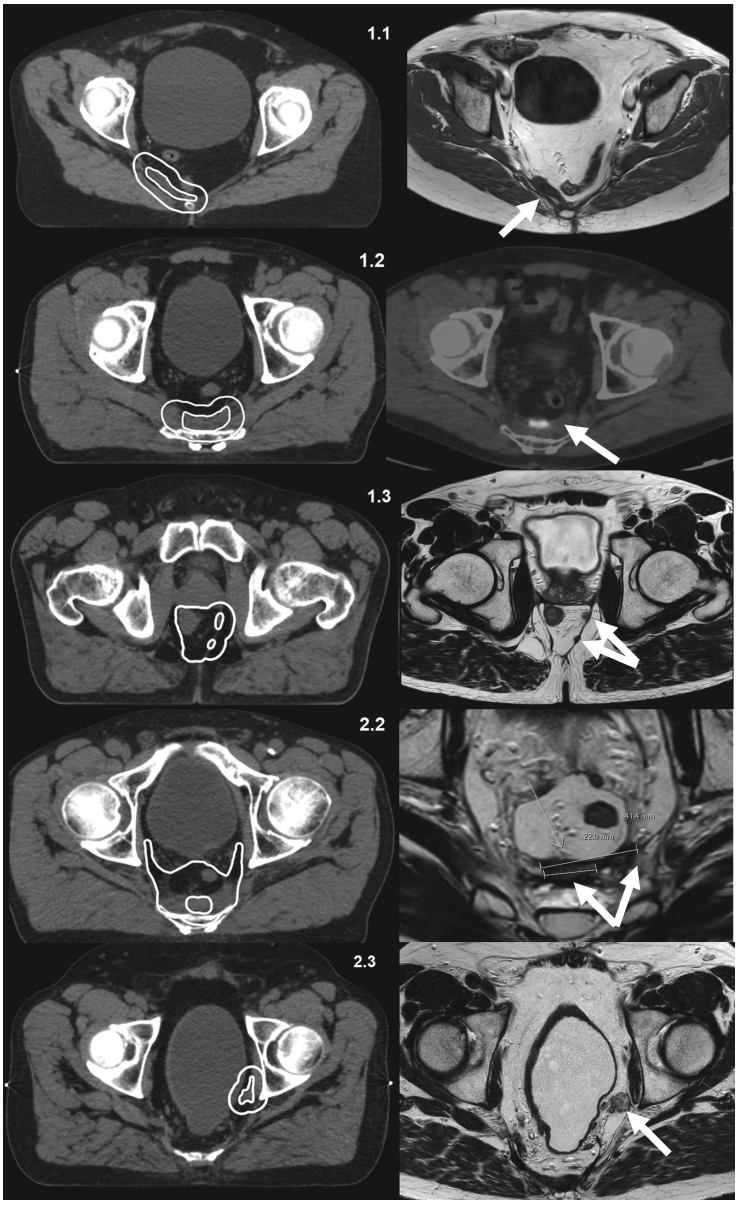

Figure 2. Consensus-based GTV and CTV for cases 1.1-2.3 (on the left), with diagnostic MRI (case 1.1, 1.3-2.3) or PET (case 1.2) imaging on the right.

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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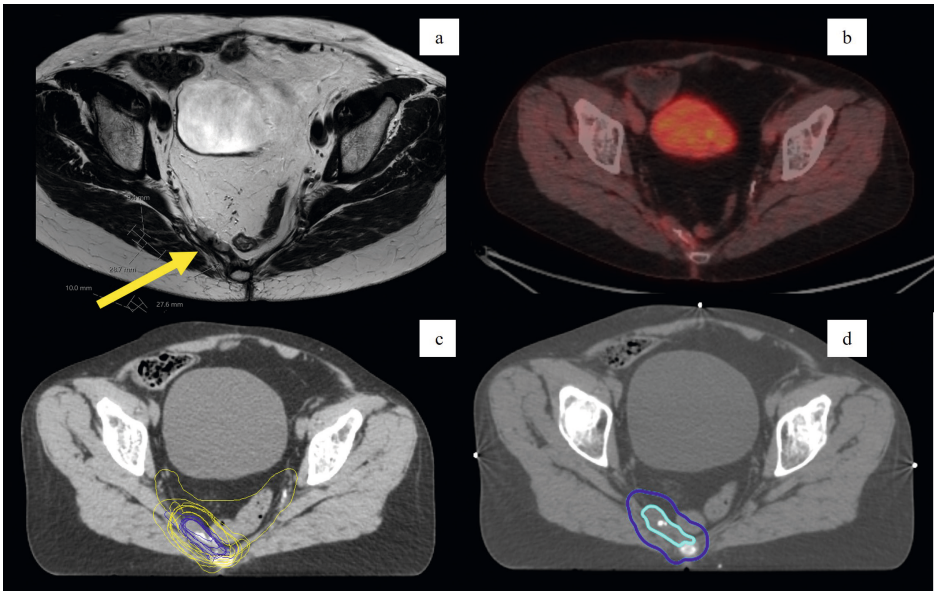
SUPPLEMENTARY DATA OF CHAPTER 2

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)

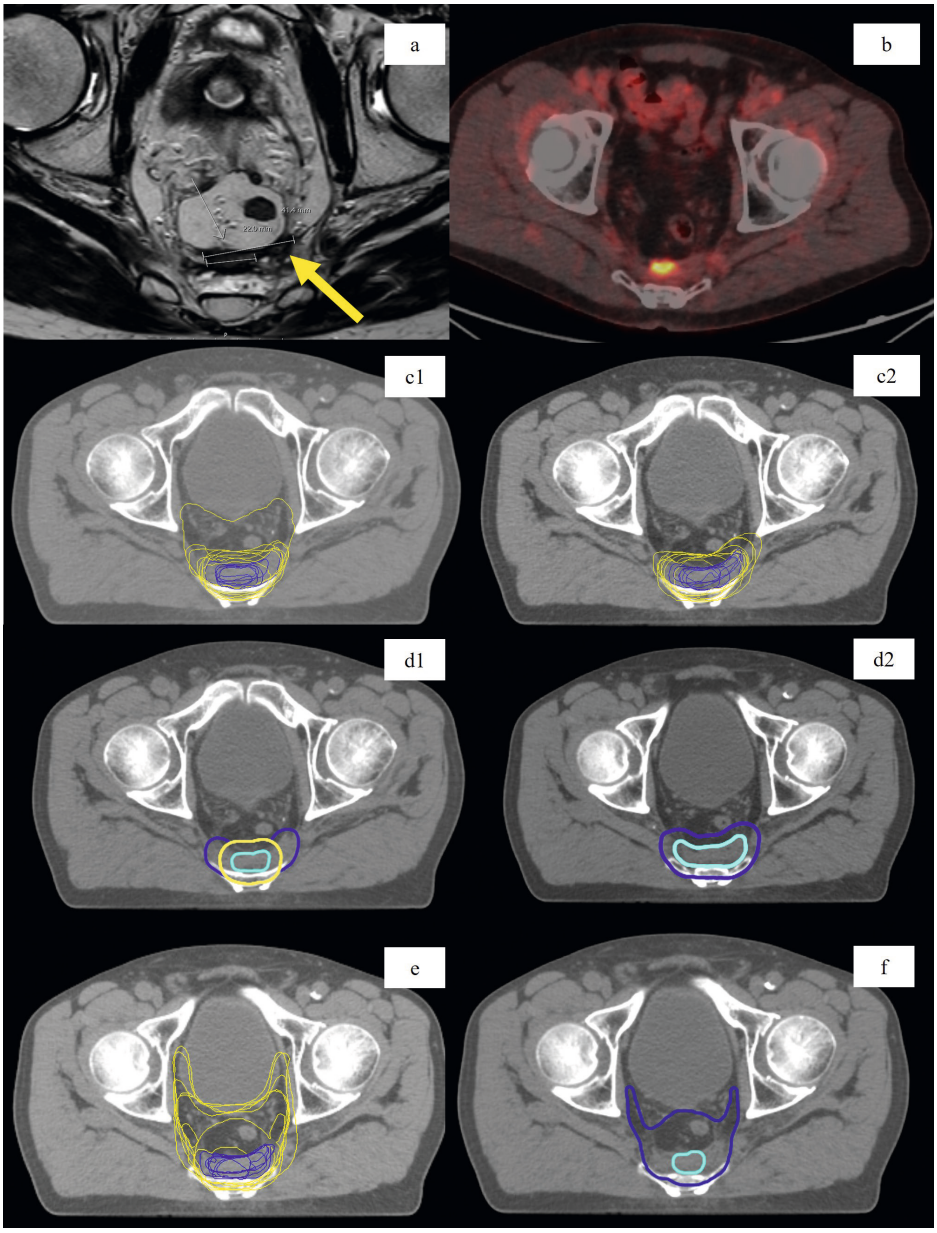
a + b. MRI + PET imaging of local recurrence

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)

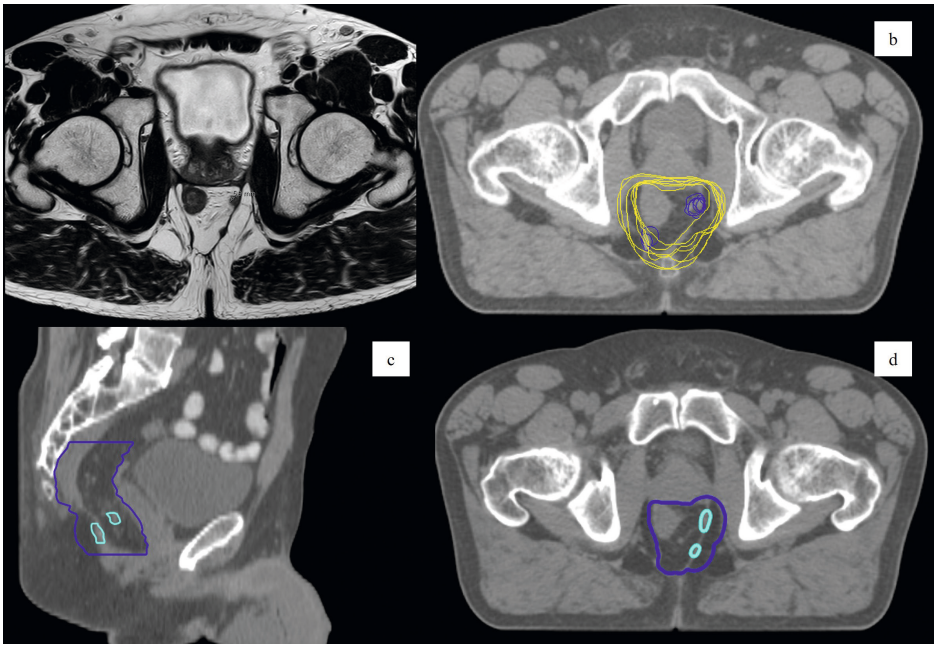
d. Example of a consensus delineation of GTV (light blue) and CTV (dark blue) if tumour can be distinguished from fibrosis (d1) or cannot be distinguished from fibrosis (d2).

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.

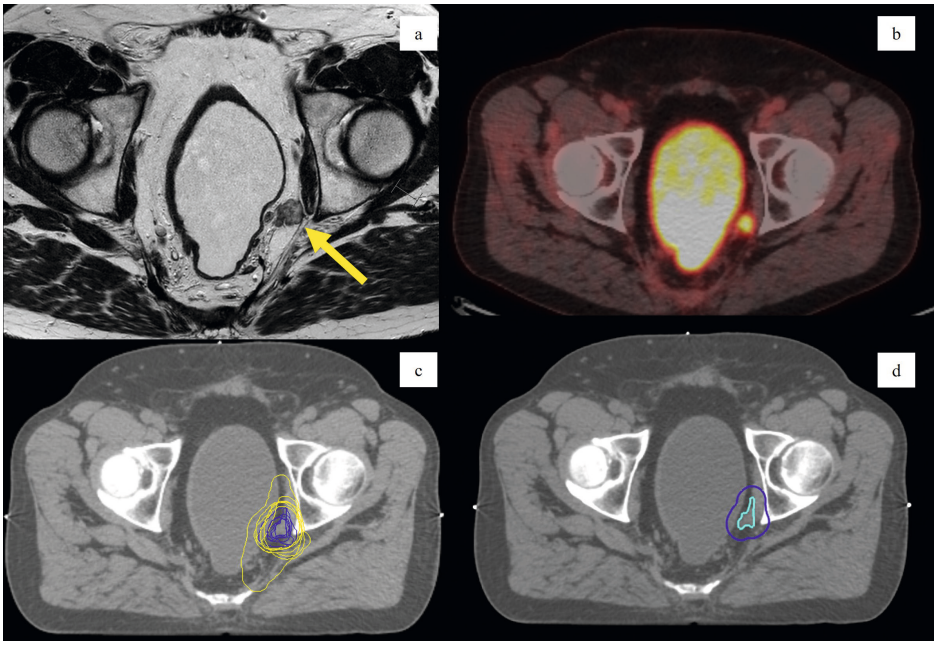


Supplementary figure 3. Multifocal recurrence (case 1.3)

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)