Universiteit
Leiden
The Netherlands

Locally recurrent rectal cancer: improving radiation treatment

Piqeur, F.

Citation
Piqeur, F. (2025, March 11). *Locally recurrent rectal cancer: improving radiation treatment*. Retrieved from https://hdl.handle.net/1887/4197385

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/4197385

Note: To cite this publication please use the final published version (if applicable).

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.

Submitted to Clinical and Translational Radiation Oncology.

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%).

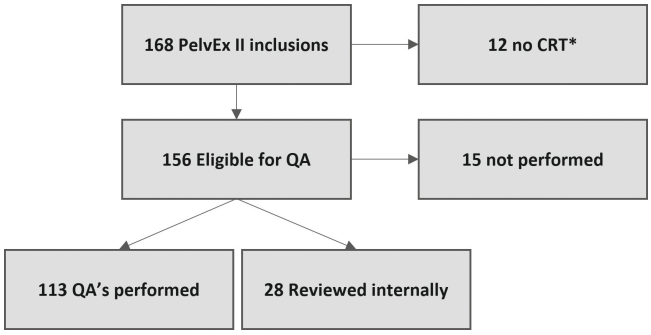

Figure 1. Flowchart of all PelvEx II patients randomized before 31-12-2023 that were eligible for Quality Assurance meetings. An overall QA compliance rate of 90% (141/156) of patients eligible for QA were reviewed. *CRT not performed due to withdrawal of informed consent, screening failures or progressive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

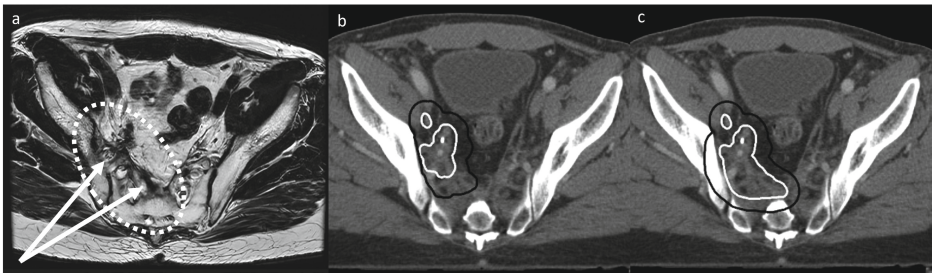

Figure 2. Example of an alteration made during a QA meeting. From left to right, the pre-treatment diagnostic MRI (a), planning CT with pre-QA target volumes (b) and planning CT with post-QA target volumes (c) are shown. The GTV is shown in white, the CTV in black. The original GTV was extended following 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.

REFERENCES

1. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: A systematic review. *Radiotherapy and Oncology*. 2014;113(2):151-157. doi:10.1016/j.radonc.2014.11.021
2. Gao Z, Gu J. Surgical treatment of locally recurrent rectal cancer: a narrative review. *Ann Transl Med*. 2021;9(12). doi:10.21037/atm-21-2298
3. Tanis PJ, Doeksen A, Van Lanschot JJB. Intentionally curative treatment of locally recurrent rectal cancer: A systematic review. *Canadian Journal of Surgery*. 2013;56(2):135-144. doi:10.1503/cjs.025911
4. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review. *Dis Colon Rectum*. 2016;59(2):148-156. doi:10.1097/DCR.0000000000000547
5. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. Locoregional Failure During and After Short-course Radiotherapy followed by Chemotherapy and Surgery Compared to Long-course Chemoradiotherapy and Surgery – A Five-year Follow-up of the RAPIDO Trial. *Ann Surg*. Published online January 20, 2023. doi:10.1097/SLA.0000000000005799
6. Detering R, Karthaus EG, Borstlap WAA, et al. Treatment and survival of locally recurrent rectal cancer: A cross-sectional population study 15 years after the Dutch TME trial. *European Journal of Surgical Oncology*. 2019;45(11). doi:10.1016/j.ejso.2019.06.016
7. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2007;14(2):447-454. doi:10.1245/s10434-006-9256-9
8. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. In: *The British Journal of Surgery*. Vol 100. ; 2013. doi:10.1002/bjs.9192
9. Collaborative P. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. *Cancers (Basel)*. 2022;14(5). doi:10.3390/cancers14051161
10. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28. doi:10.1093/annonc/mdx224
11. Federation of Medical Specialists. Dutch National Guidelines for Colorectal Cancer. Richtlijnendatabase.
12. 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
13. Harji D, Griffiths B, Evans M, Sebag-Montefiore D, Sagar P. Outcomes of complete pathological response after neoadjuvant chemoradiation for locally recurrent rectal cancer. *Colorectal Disease*. 2012;14:48. doi:10.1111/j.1463-1318.2012.03157.x
14. Nordkamp S, Piqeur F, van den Berg K, et al. Locally recurrent rectal cancer: Oncological outcomes for patients with a pathological complete response after neoadjuvant therapy. *British Journal of Surgery*. 2023;110(8):950-957. doi:10.1093/bjs/znad094
15. Voogt ELK, Nordkamp S, Nieuwenhuijzen GAP, et al. Curative treatment of locally recurrent rectal cancer: is induction chemotherapy warranted? *Br J Surg*. 2021;108(6). doi:10.1093/bjs/znab065
16. Voogt E, Van Zoggel DM, Kusters M, et al. High response rate and improved outcomes for responders after treatment with induction chemotherapy for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27:S19-S20. doi:10.1245/s10434-020-08278-z
17. Voogt E, Burger P. Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: the PelvEx II study. *European Journal of Surgical Oncology*. 2021;47(2). doi:10.1016/j.ejso.2020.11.204

18. 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
19. Nougaret S, Lambregts DMJ, Beets GL, et al. Imaging in pelvic exenteration for colorectal and gynaecological cancers - a multidisciplinary practice guide from the ESGAR-SAR-ESUR-PelvEx collaborative group. . *Eur Radiol*.
20. Ganeshan D, Nougaret S, Korngold E, Rauch GM, Moreno CC. Locally recurrent rectal cancer: what the radiologist should know. *Abdominal Radiology*. 2019;44(11):3709-3725. doi:10.1007/s00261-019-02003-5
21. Inoue A, Sheedy SP, Wells ML, et al. Rectal cancer pelvic recurrence: imaging patterns and key concepts to guide treatment planning. *Abdominal Radiology*. Published online 2023. doi:10.1007/s00261-022-03746-4
22. Dresen RC, Kusters M, Daniels-Gooszen AW, et al. Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: Prediction with preoperative MR imaging. *Radiology*. 2010;256(1). doi:10.1148/radiol.10090725
23. Nordkamp S, Voogt ELK, van Zoggel DMGI, et al. Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. *Br J Surg*. 2022;109(7). doi:10.1093/bjs/znac083
24. Joye I, Lambrecht M, Jegou D, Hortobágyi E, Scalliet P, Haustermans K. Does a central review platform improve the quality of radiotherapy for rectal cancer? Results of a national quality assurance project. *Radiotherapy and Oncology*. 2014;111(3). doi:10.1016/j.radonc.2014.03.003
25. Joye I, Macq G, Vaes E, et al. Do refined consensus guidelines improve the uniformity of clinical target volume delineation for rectal cancer? Results of a national review project. *Radiotherapy and Oncology*. 2016;120(2). doi:10.1016/j.radonc.2016.06.005
26. Brooks C, Miles E, Hoskin PJ. Radiotherapy trial quality assurance processes: a systematic review. *Lancet Oncol*. 2024;25(3):e104-e113. doi:10.1016/S1470-2045(23)00625-3
27. Brunskill K, Nguyen TK, Boldt RG, et al. Does Peer Review of Radiation Plans Affect Clinical Care? A Systematic Review of the Literature. *Int J Radiat Oncol Biol Phys*. 2017;97(1). doi:10.1016/j.ijrobp.2016.09.015
28. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Colorectal Disease*. 2011;13(7). doi:10.1111/j.1463-1318.2009.02167.x

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]

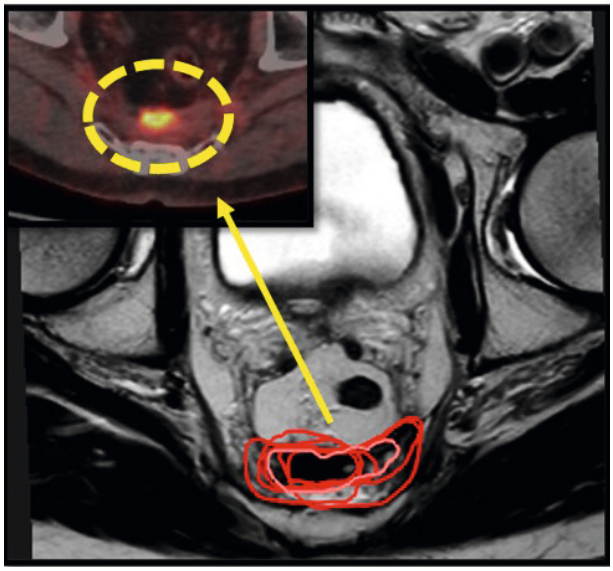

Figure 1. Delineation of a PET-positive tumour located in fibrosis. A (not yet published) delineation study showed differences in GTV interpretation in tumours located in fibrosis. 3/8 radiologists and 7/11 radiation oncologists delineated all fibrosis as tumour, whereas 5/8 radiologists and 4/11 radiation 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.

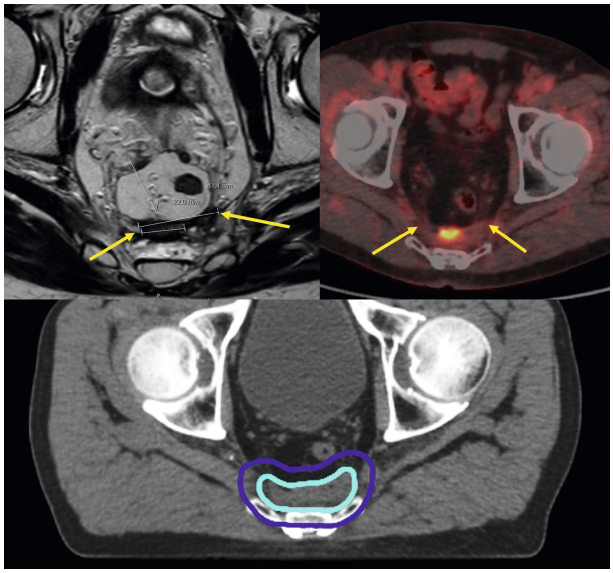

Figure 2. Example of how to delineate a presacral, fibrotic tumour. The GTV (light blue) should include all surrounding fibrosis. The CTV (dark blue) can then be extended towards the lateral sidewalls to guarantee that surgical resection margins are completely incorporated in the CTV. The CTV should 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.

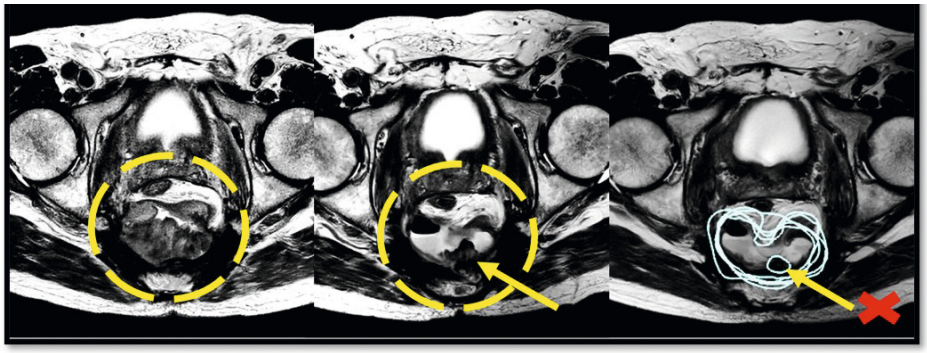

Figure 3. Example of a recurrence located in an abscess, before (left) and after (middle) induction chemotherapy. The whole remaining abscess should be delineated as GTV as shown on the right, instead of delineating only remnant solid tumour as GTV.

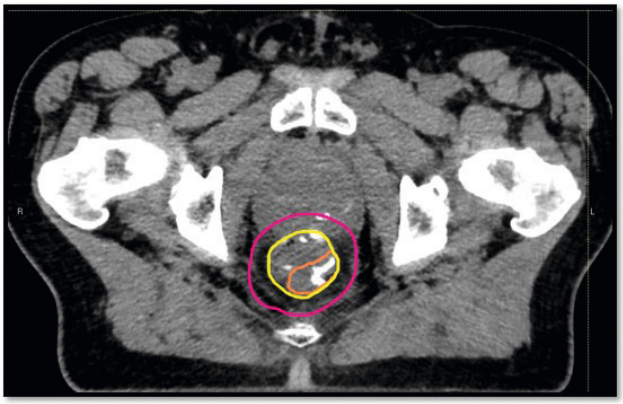

Figure 4. An example of an anastomotic recurrence previously reviewed during Quality Assurance. Consensus was reached to extend the original GTV (orange) to encompass the whole lumen (yellow).

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.

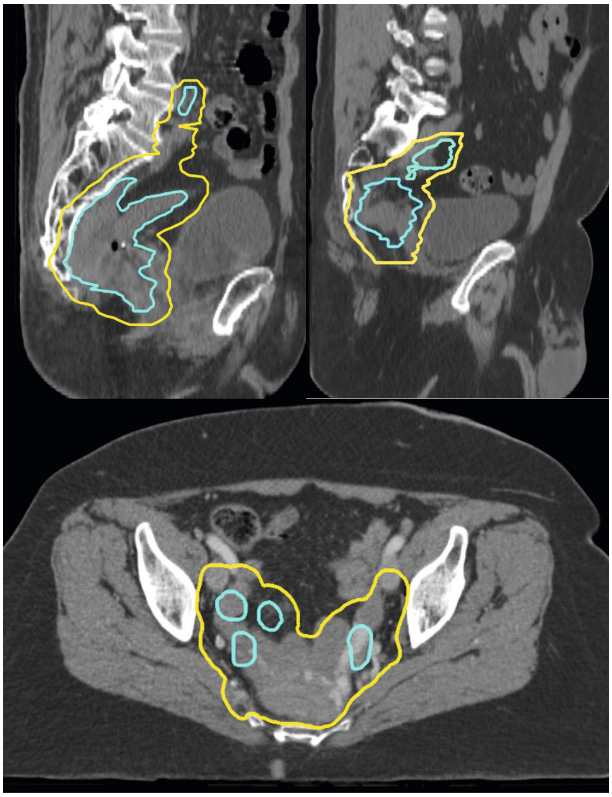

Figure 5. Three examples of multifocal recurrences. All GTV lesions (light blue) should be incorporated into one CTV with logical anatomical boundaries, irrespective of additional elective target volumes.

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.

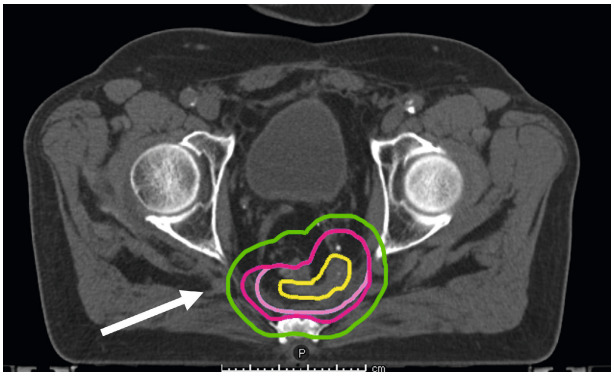

Figure 6. QA example in which the original CTV (light pink) was extended beyond the prescribed 1 cm margin, to ensure that surgical resection margins near the lateral side wall were adequately incorporated within the CTV (dark pink).

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.

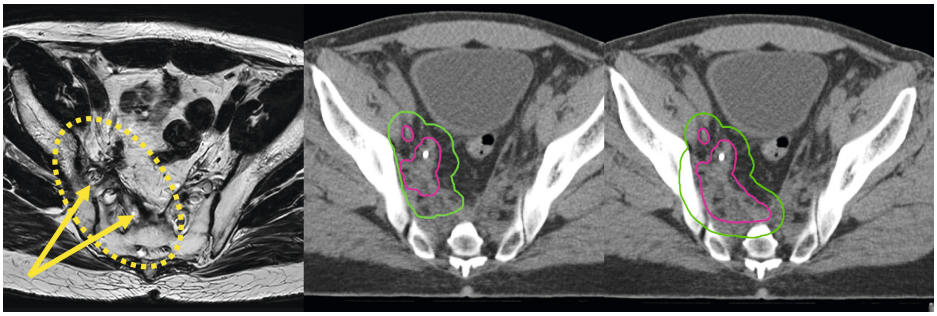

Figure 7. Example of a lateral recurrence in which GTV (pink) was extended from before to after QA (middle and right respectively) to encompass complete fibrosis. Subsequently, the CTV (green) was extended and performed editing towards the lateral sidewall was reversed, as there is a risk of undertreatment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

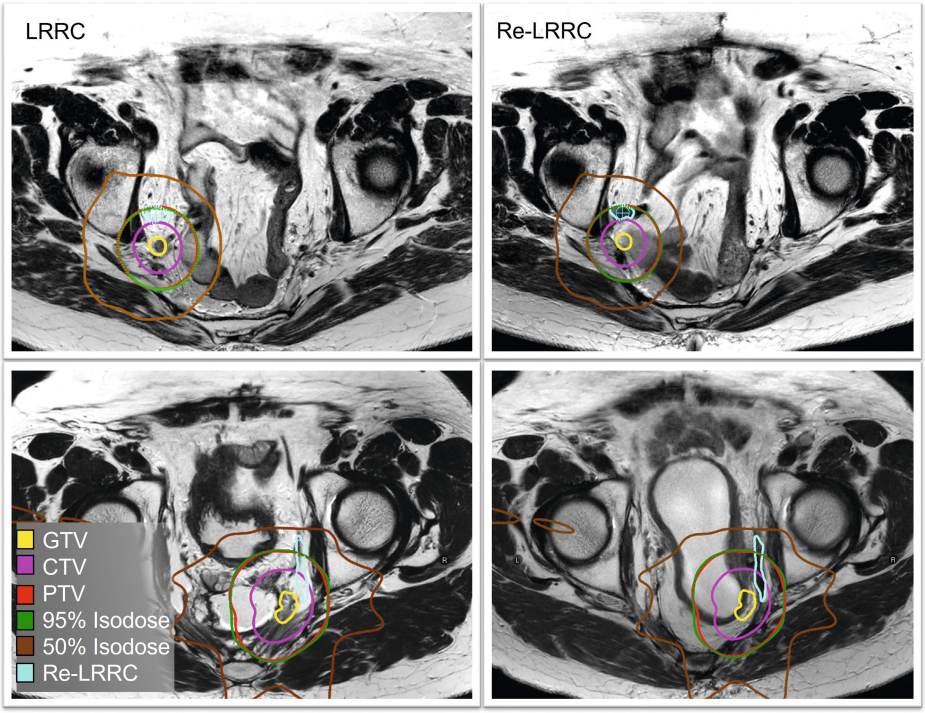

Figure 8. First (left) and second recurrence (right) shown on MRI of two individual cases (above and below). First and second recurrence MRIs have been matched to the LRRC planning CT, to be able to visualise the recurrence in the anatomy of the re-recurrence, and vice versa. The re-recurrence is shown 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

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, Hupkens B, Nordkamp S, et al. PD-0887 Quality assurance of delineation for locally recurrent rectal cancer: PelvEx II data (NCT04389086). *Radiotherapy and Oncology*. 2023;182. doi:10.1016/s0167-8140(23)09012-6
3. Inoue A, Sheedy SP, Wells ML, et al. Rectal cancer pelvic recurrence: imaging patterns and key concepts to guide treatment planning. *Abdominal Radiology*. Published online 2023. doi:10.1007/s00261-022-03746-4

4. Valentini V, Gambacorta MA, Barbaro B, et al. International consensus guidelines on Clinical Target Volume delineation in rectal cancer. *Radiotherapy and Oncology*. 2016;120(2):195-201. doi:10.1016/j.radonc.2016.07.017