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## Locally recurrent rectal cancer: improving radiation treatment

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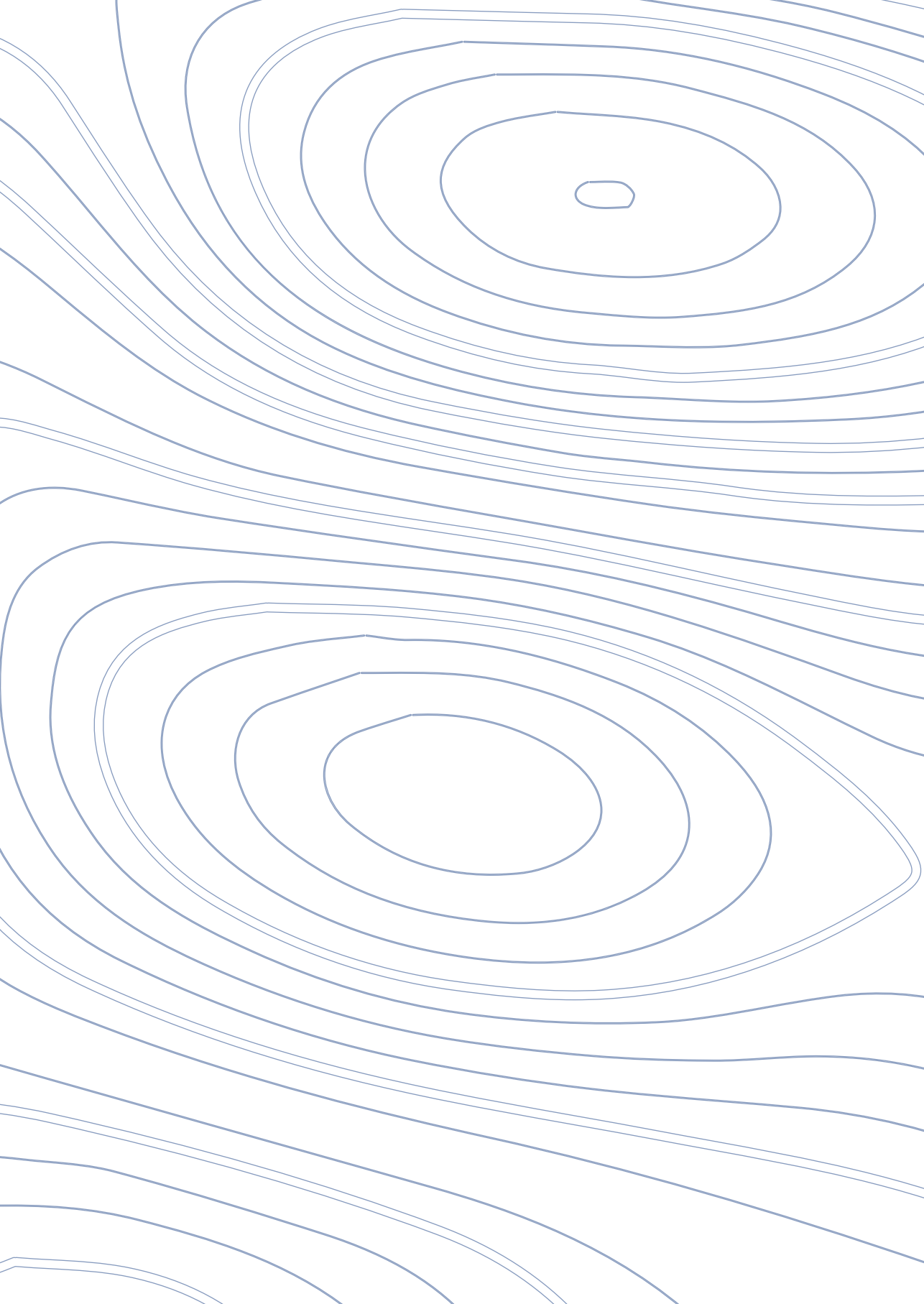
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# Part II

Improving radiotherapy for  
locally recurrent rectal cancer







# Chapter 4

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

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## ABSTRACT

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

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

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

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

## INTRODUCTION

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

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

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

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

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

## **MATERIALS AND METHODS**

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

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

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

Expert radiologists in colorectal imaging delineated macroscopic tumour on the planning CT in all 14 cases. A median delineation was constructed using an in-house script developed in RayStation 10B-SP1, incorporating each voxel that was deemed tumour by >50% of the radiologists. Additionally, a total delineation showing each voxel that was deemed tumour by at least one radiologist was provided.

ROs were asked to delineate the GTV on planning CT as in clinical practice. ROs delineated all 14 cases, seven without additional delineations and seven with the previously constructed

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

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

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

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

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

**Table 1.** Summary of baseline characteristics

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

## RESULTS

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

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

When disregarding this second lesion, IOV within the recurrence itself seemed little upon visual inspection.

DSC in all cases was lower amongst radiologists compared to radiation oncologists. As GTV volumes are consistently smaller amongst radiologists compared to ROs, as shown in Table S1, and DSC is heavily influenced by volume, direct comparison is not possible. Little variation is seen in seven cases based on SDSC and HD98% alone.

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

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



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

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

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

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

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

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

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

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

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

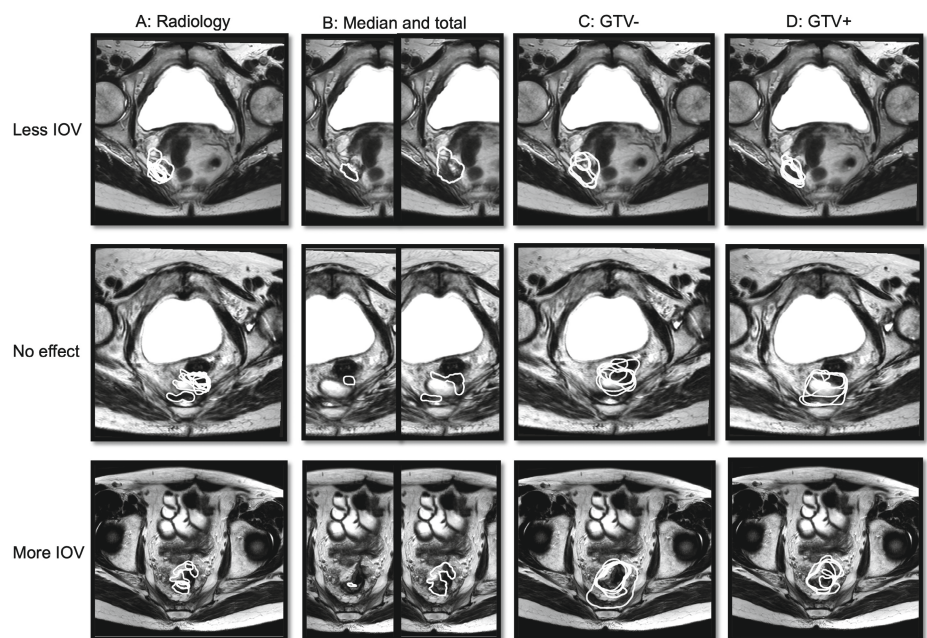
A: Cases included in the analysis of lateral recurrences: 1, 7, 8, 10

B: Cases included in the analysis of solitary lymph node recurrences: 7, 10

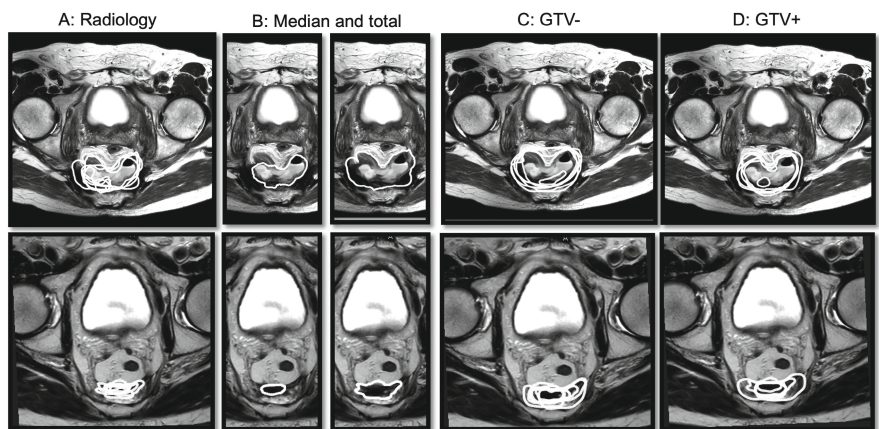
C: Cases included in the analysis of multifocal recurrences: 2, 4, 5, 6, 13

D: Cases included in the analysis of intraluminal recurrences: 3, 6, 9, 14

E: Cases included in the analysis of fibrotic recurrences: 2, 3, 11, 12



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



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

## DISCUSSION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## **CONCLUSION**

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



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## SUPPLEMENTARY DATA OF CHAPTER 4

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

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

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

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

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

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

### Case 1

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

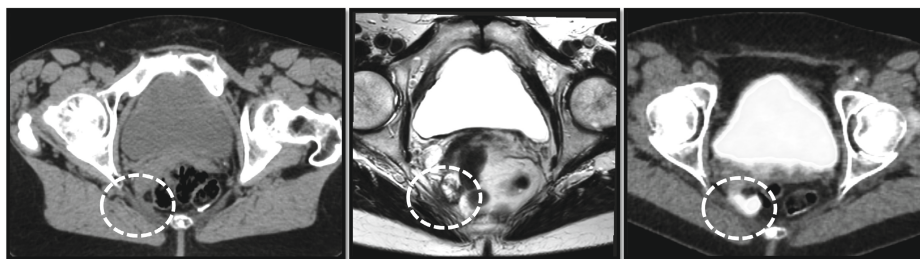
**Baseline MRI:** Suspicion of a local recurrence on the right pelvic side wall.

**Baseline PET-CT:** Suspicion of a local recurrence as described on MRI. No pathological lymph nodes or distant metastases observed.

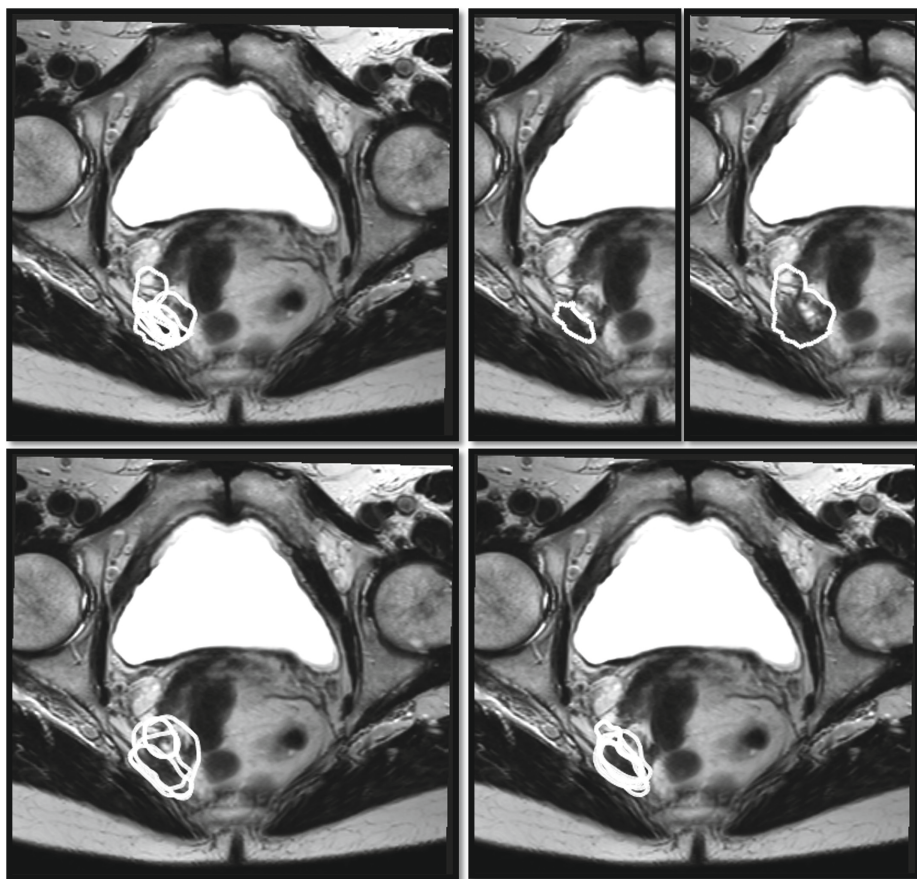
**PET-CT after induction chemotherapy:** Partial metabolic response with a decrease in SUV but a slight increase in size.

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

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



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



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

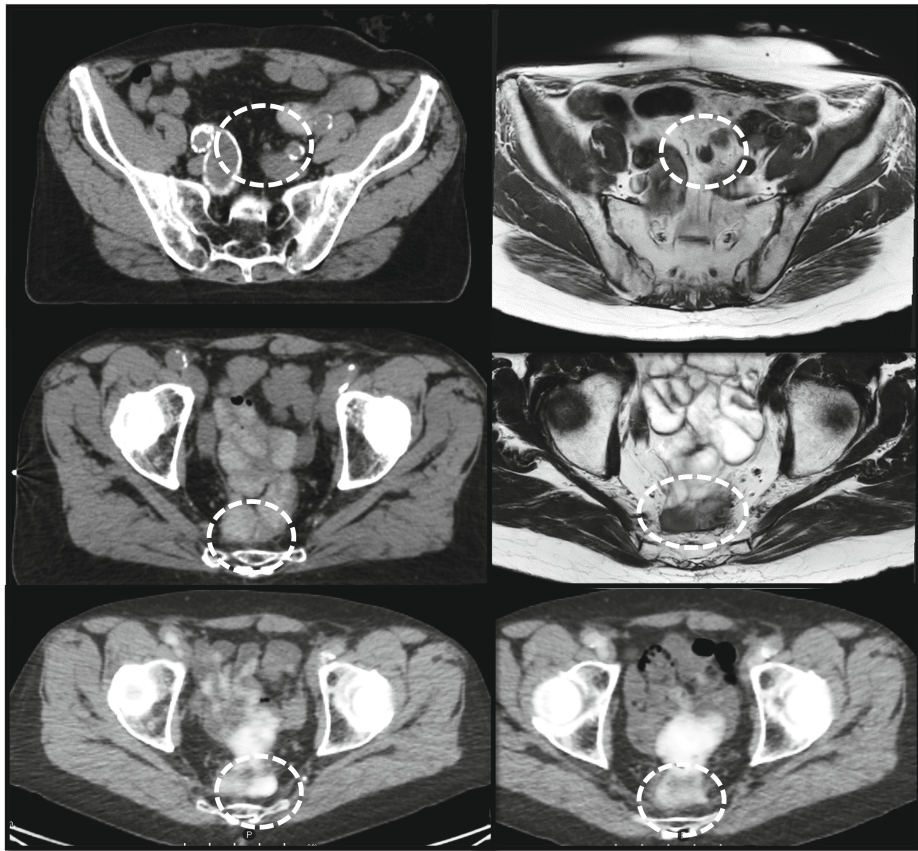
## Case 2

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

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

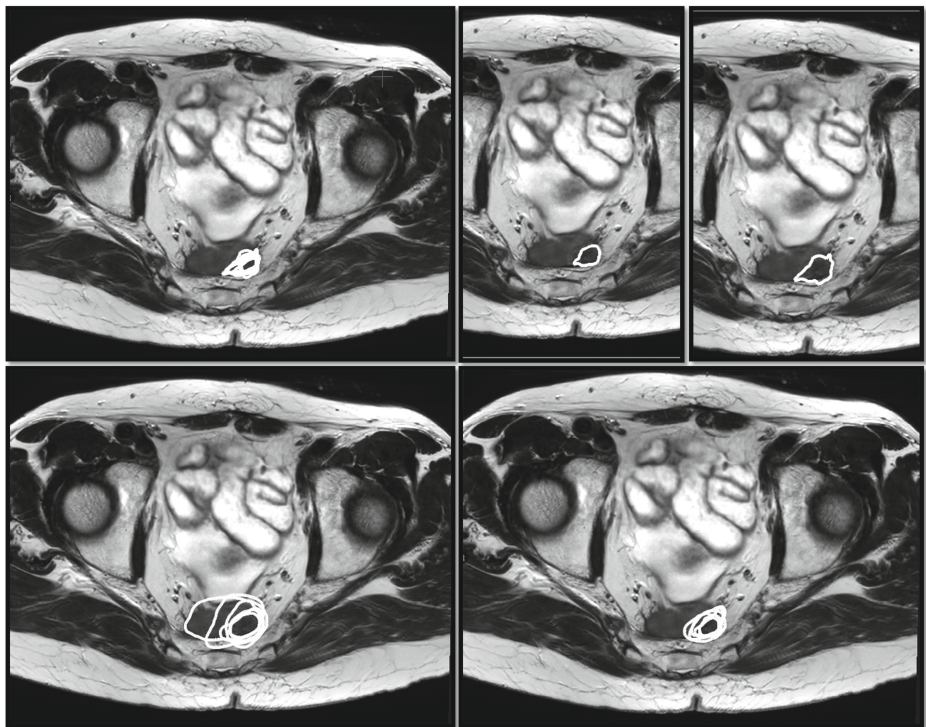
**Baseline PET-CT:** Suspicion of a lymph node metastasis in the trajectory of the inferior mesenteric vessels. Pre-coccygeal FDG-avid mass seen, possibly showing a presacral recurrence.

**PET-CT after induction chemotherapy:** Good metabolic response of the mesenteric lymph nodes and presacral lesion. No new lesions seen.



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





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

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

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

**Case 3**

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



**Sigmoidoscopy at baseline:** No mucosal lesions

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

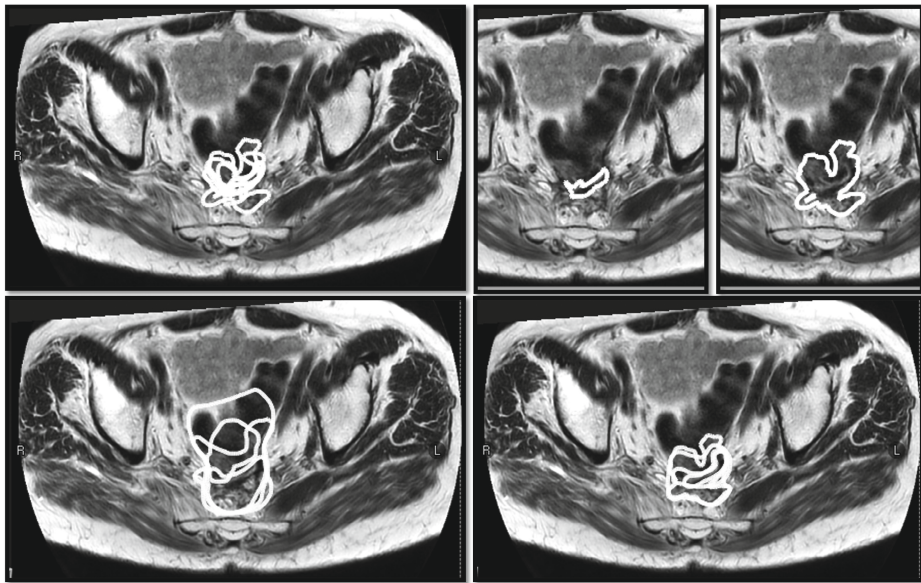
**Baseline PET/CT:** Suspicion of an anastomotic recurrence.

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

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



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



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

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

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

**Case 4**

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

**Baseline MRI:** Suspicion of a multifocal recurrence in the lesser pelvis. Multiple nodular depositions on the mesorectal fascia, left and right in the lesser pelvis. The largest deposition is +/- 2cm. 2 additional possibly malignant lymph nodes.

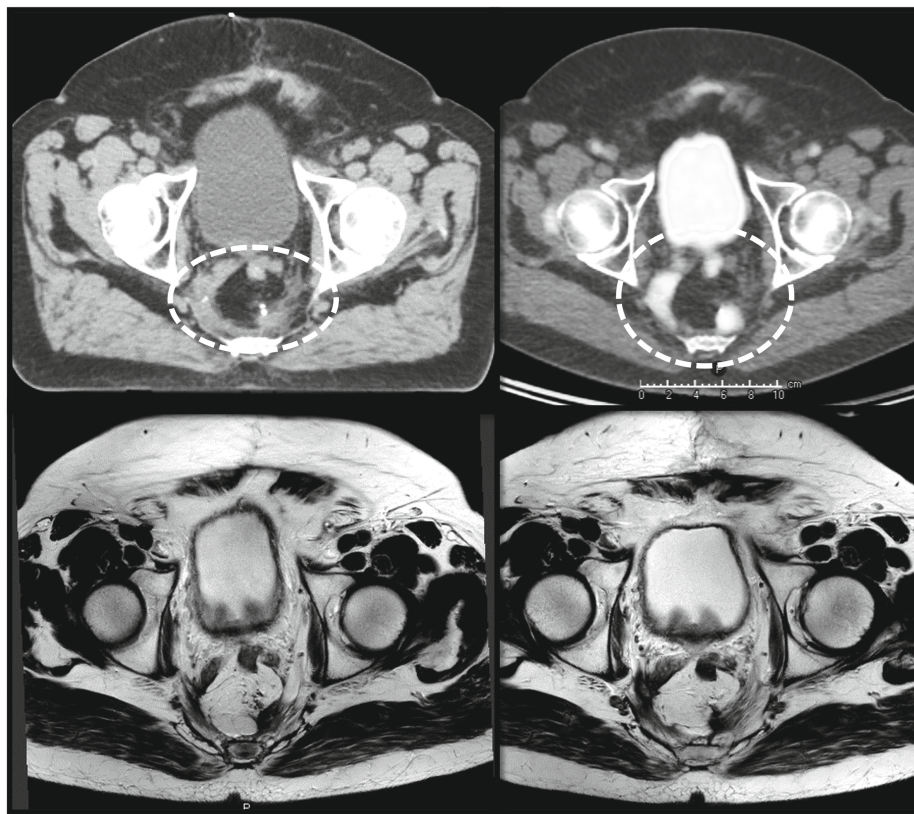
**Baseline PET/CT:** FDG-avid soft tissue in the pelvis, as on MRI, very suspicious for local recurrence. One FDG-avid presacral lymph node (on the right).

**MRI after chemotherapy:** No response to therapy, stable disease.

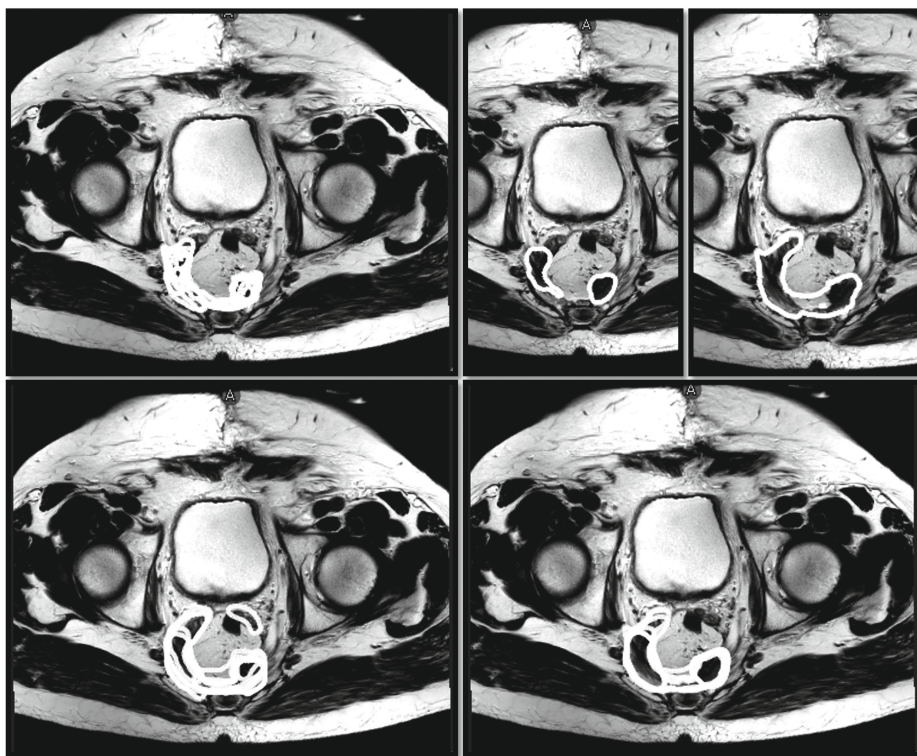
**PET-CT after chemotherapy:** No difference in PET-positive lymph nodes or local multifocal recurrence. No distant metastases.

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

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



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



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

### Case 5

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

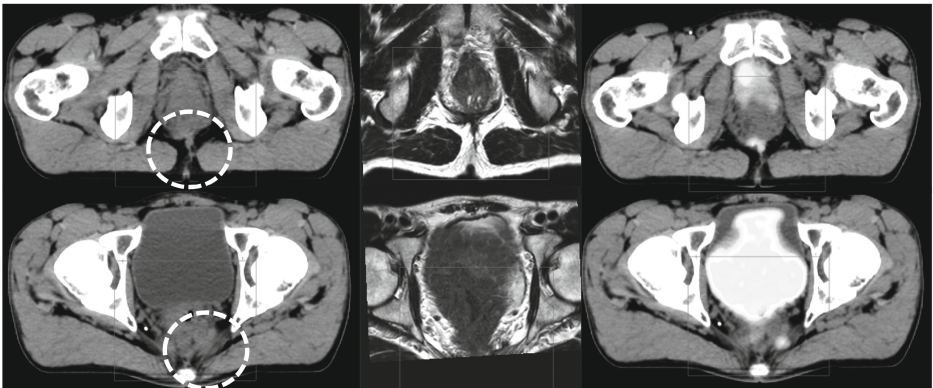
**Baseline MRI:** 2 presacral lesions of approximately 8mm, probably pathological lymph nodes.

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

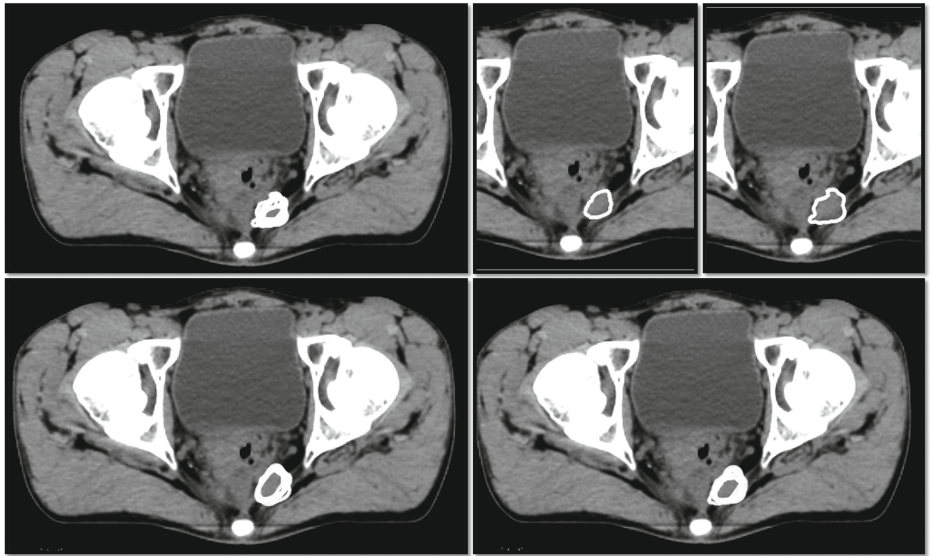


**Table case 5.** Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

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



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



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

**Case 6**

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

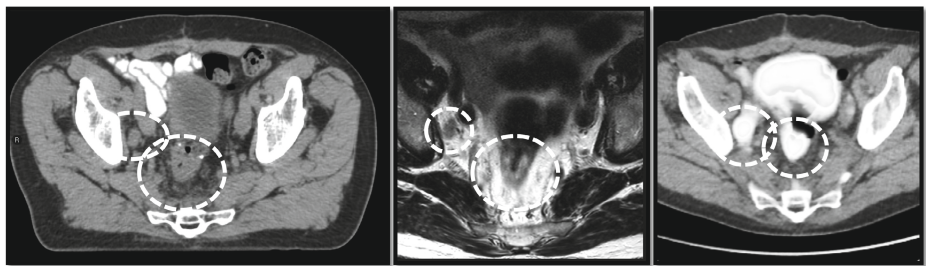
**Colonoscopy at baseline:** suspicious lesion on the anastomosis in the rectum. PA: adenocarcinoma.

**MRI at baseline:** Anastomotic recurrence presacral extending towards the sacrum, without evidence of involvement of the sacrum. Also suspicion of a nodal recurrence at the right. Central, right lateral and posterior compartment involved.

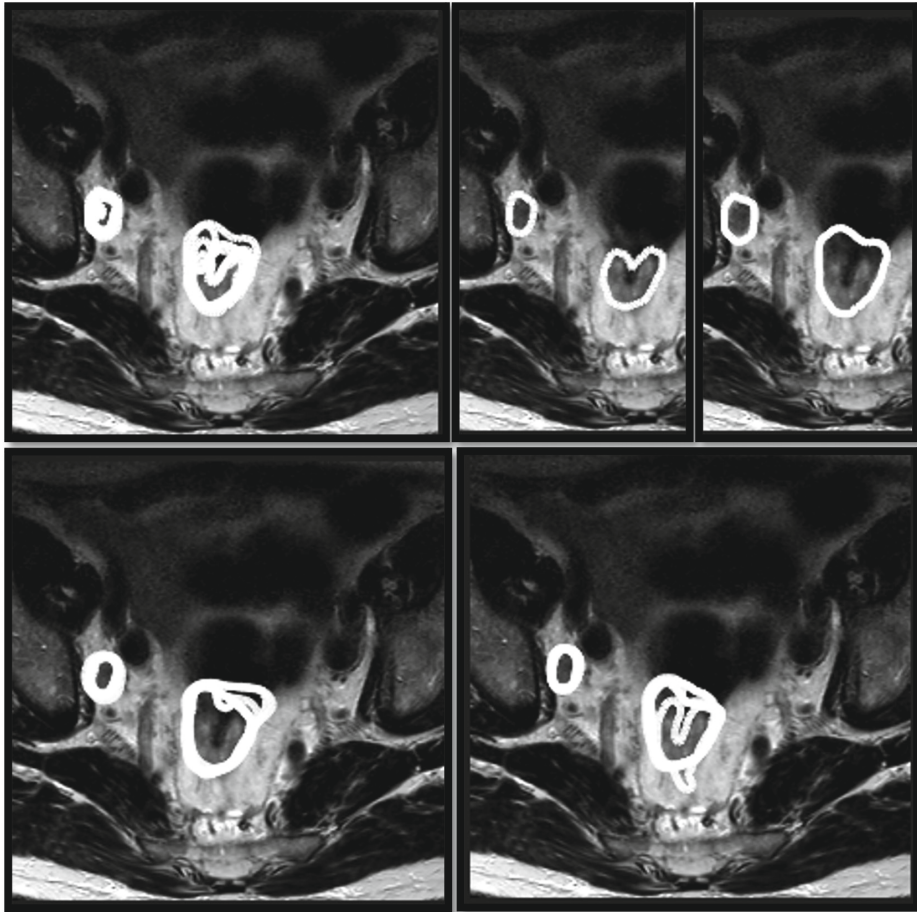
**PET-CT at baseline:** No distant metastases. Prominent local and nodal recurrence (near iliac vessels on the right).

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

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



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



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

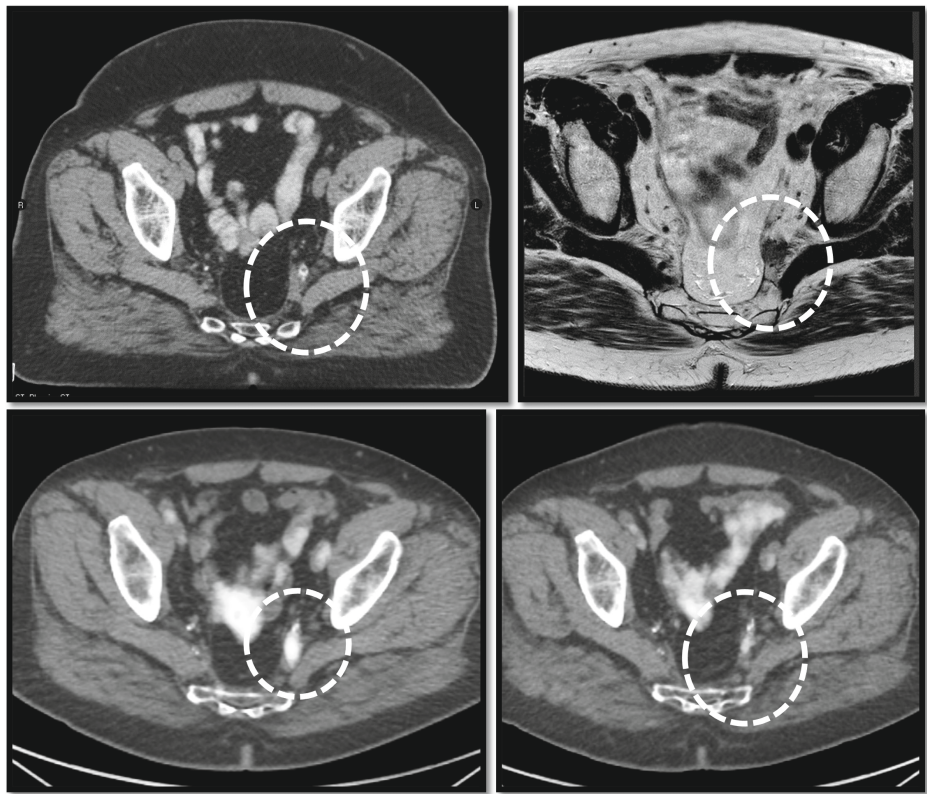
### Case 7

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

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

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

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

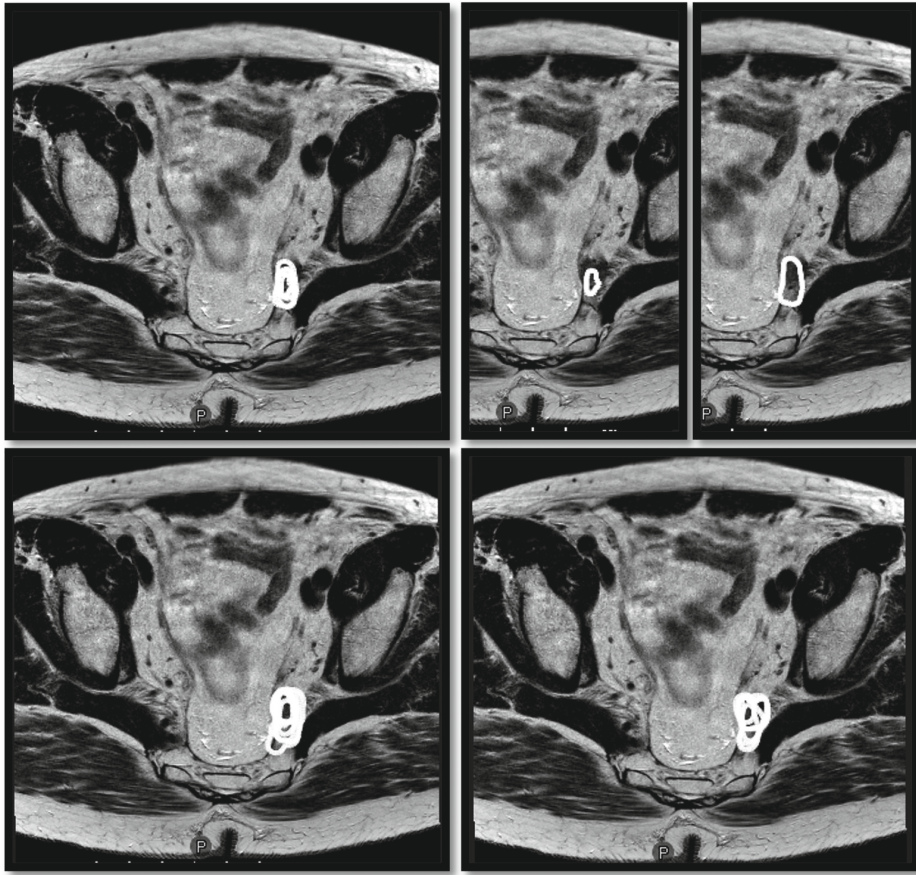


**Figure S7a.** Figure showing planning CT (top left), baseline MRI (top right), baseline PET-CT (bottom left) and PET-CT following induction chemotherapy (bottom right).

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

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





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

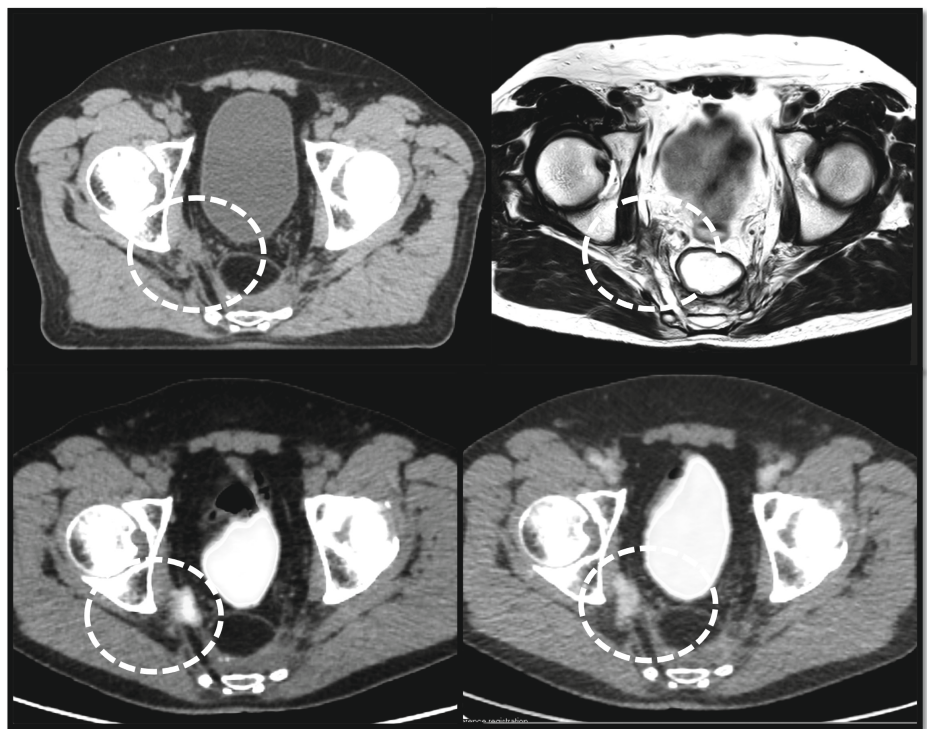
### Case 8

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

**Baseline MRI:** Suspicion of a unifocal local recurrence against the right pelvic side wall.

**Baseline PET-CT:** No suspicious lesions outside of the pelvis. Increased FDG uptake can be seen at the right pelvic side wall.

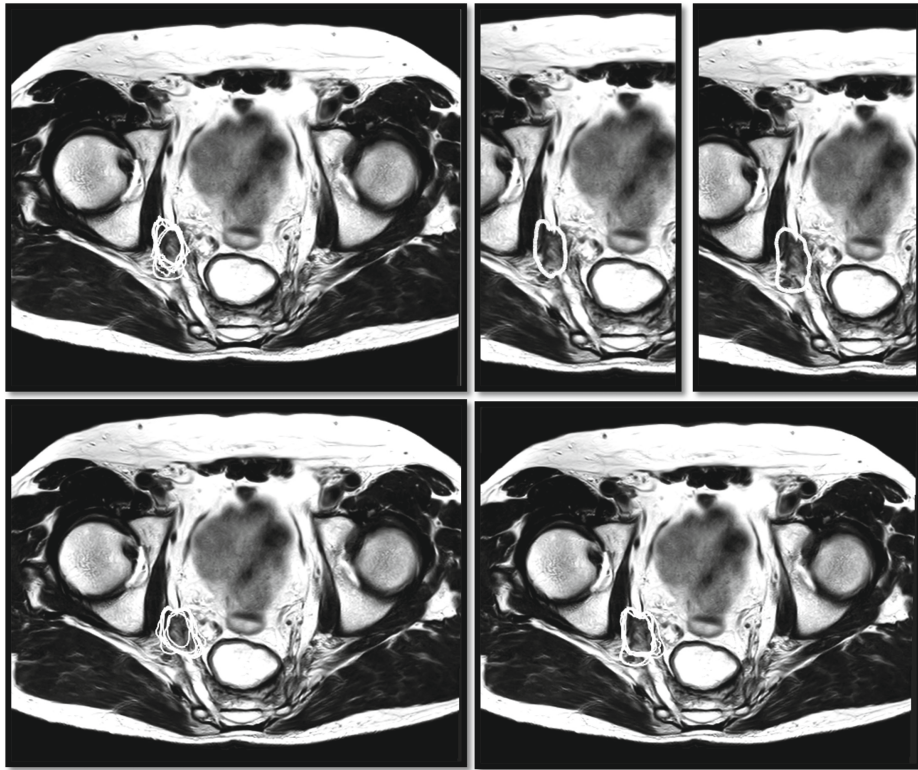
**PET-CT following induction chemotherapy:** Good metabolic response, possible complete response. No new lesions on PET-CT.



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

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

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



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

### Case 9

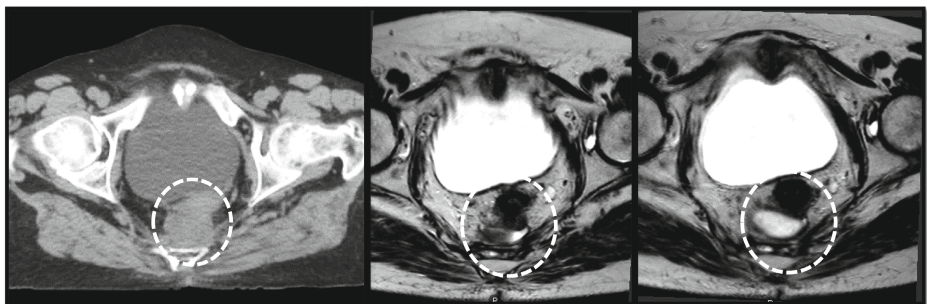
70-year-old female with a history of a LARC (cTNM stage unknown) for which she received CRT and a LAR (pT2N1). Patient was diagnosed with a distal LRRC. Patient has received 3 cycles of CAPOX induction chemotherapy and has now been referred for chemo reirradiation. Patient will undergo debulking surgery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

**Colonoscopy at baseline:** Suspicion of a local recurrence distally in the rectum. PA: Adenocarcinoma.

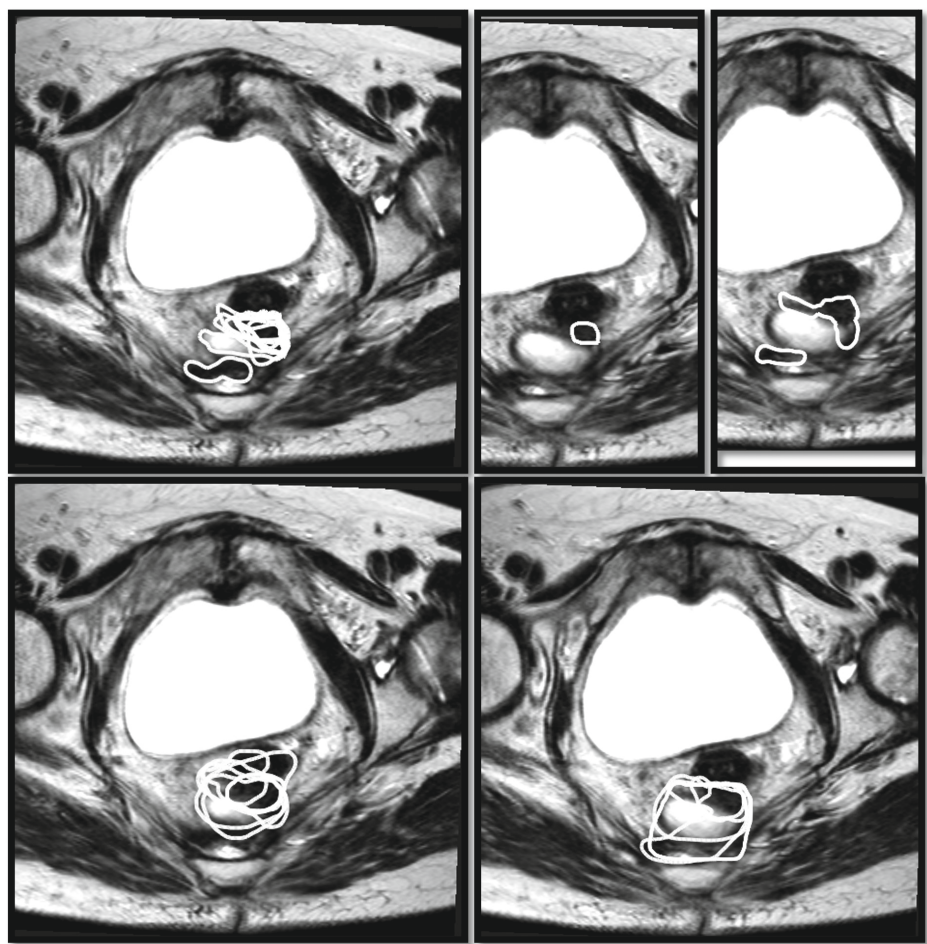
**MRI at baseline:** Anastomotic recurrence (+/- 2cm) with possible involvement of the cervix.

**MRI after induction chemotherapy:** The local recurrence in the rectal stump is no longer visible. Fibrosis visible. >75% decrease in volume.





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



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

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

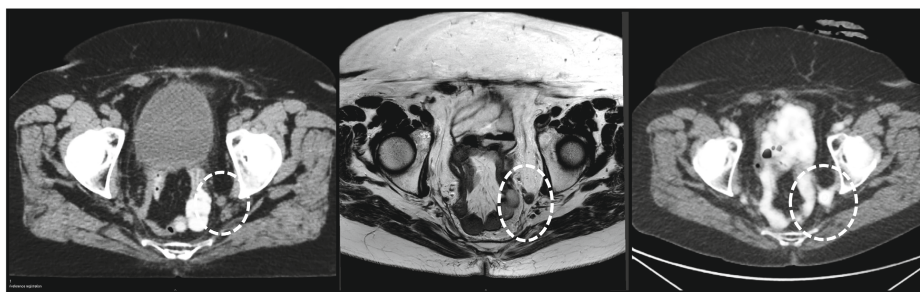
| Case 9      | RAD (n=8) |           | GTV- (n=6) |           | GTV+ (n=5) |           |
|-------------|-----------|-----------|------------|-----------|------------|-----------|
|             | Median    | Range     | Median     | Range     | Median     | Range     |
| Volume (cc) | 4.2       | 1.6-7.1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

**Case 10**

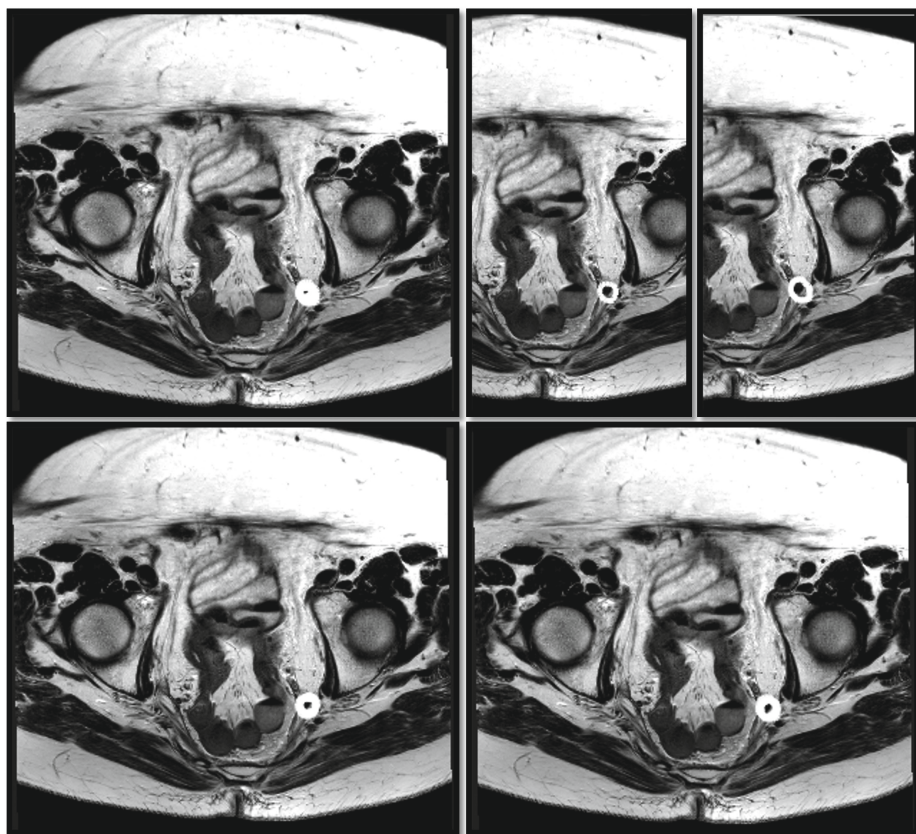
65-year-old female, with a history of a cT3N1 (MRF+) rectal cancer for which she was treated with 4 cycles of CAPOX induction chemotherapy, full course CRT and an APR (ypT2N0, R0). Patient presented with a solitary nodal recurrence and has been referred for chemo reirradiation. Patient is planned for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

**Baseline MRI:** Solid nodule in the lesser pelvis on the left, approximately 1.2cm, located in the obturator loge.

**Baseline PET/CT:** Lymph node dorsally in the obturator loge left, suspicious for a solitary lymph node metastasis.

**Figure S10a.** Figure showing planning CT (left), baseline MRI (middle), and baseline PET-CT (right).**Table case 10.** Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

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



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

### Case 11

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

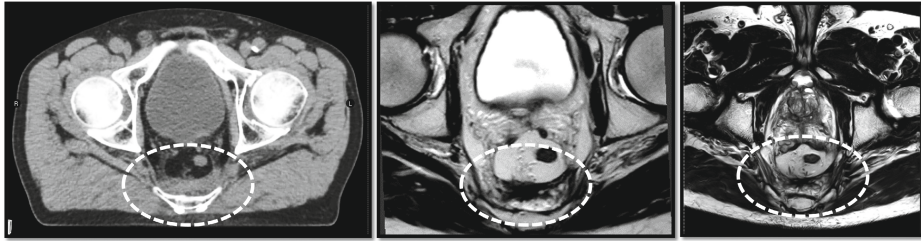
**Baseline MRI:** suspicion of a unifocal presacral (maximal diameter approximately 26mm).

**Baseline PET-CT:** High presacral uptake (S4), suspicion of a local recurrence. Two high uptake foci in the prostate, DD prostate carcinoma or focal prostatitis.

**Additional prostate MRI:** diffuse low T2 signal in the peripheral zone on the right, as fitting for prostatitis. No suspicion of a prostate cancer (PI-RADS 2).

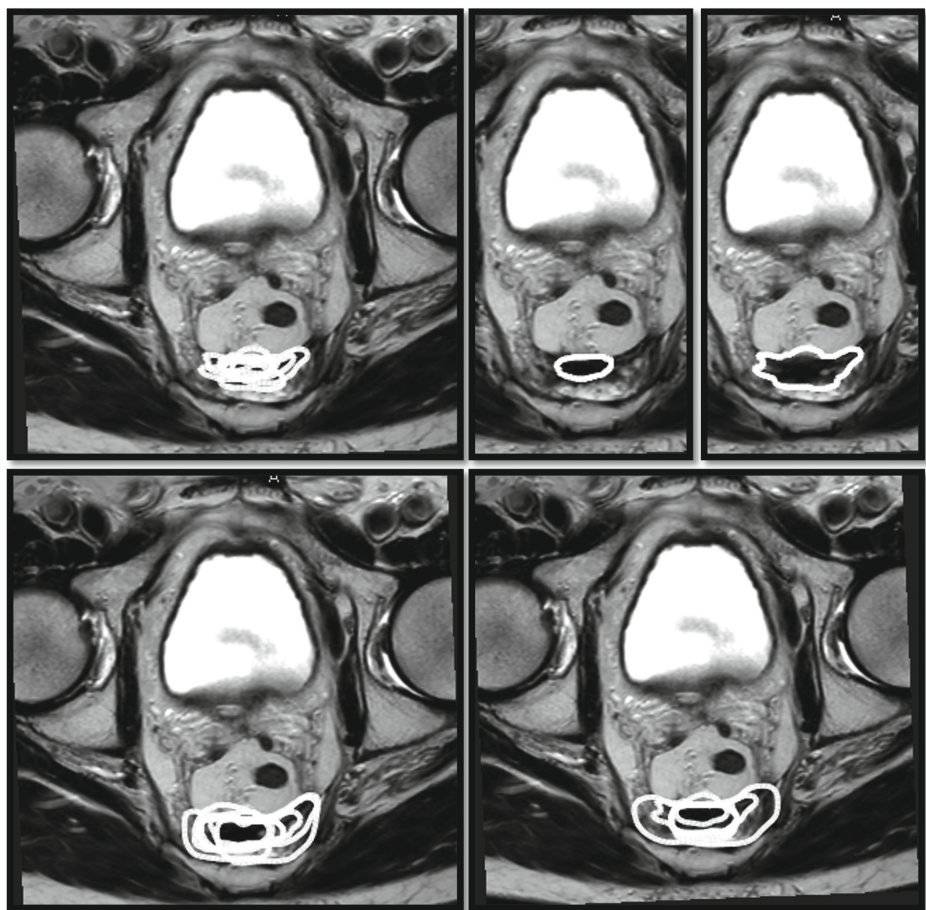
**MRI after chemotherapy:** Known presacral recurrence with only minimal response. There is still a suspicion of vital tumour.

**PET/CT after chemotherapy:** clear reduction of metabolic activity in the lesser pelvis at the known local recurrence. No distant metastases.



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





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

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

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

**Case 12**

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

**Baseline MRI:** Known presacral abscess. Inside the abscess is a large soft tissue mass of approximately 10cm up growing until the anus. Possible sacral involvement at S4.

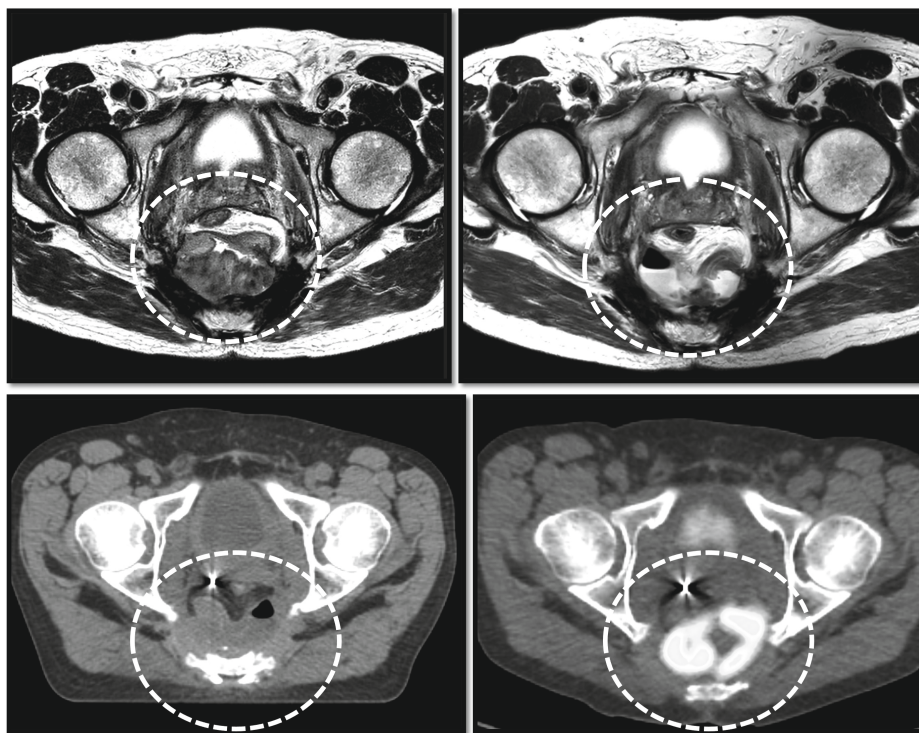
**Baseline PET-CT:** Intense FDG-uptake presacral. No evidence of distant disease or lymph node involvement.

**MRI after induction chemotherapy:** Evident response after chemotherapy, possibly residual soft tissue mass at S3-S4.

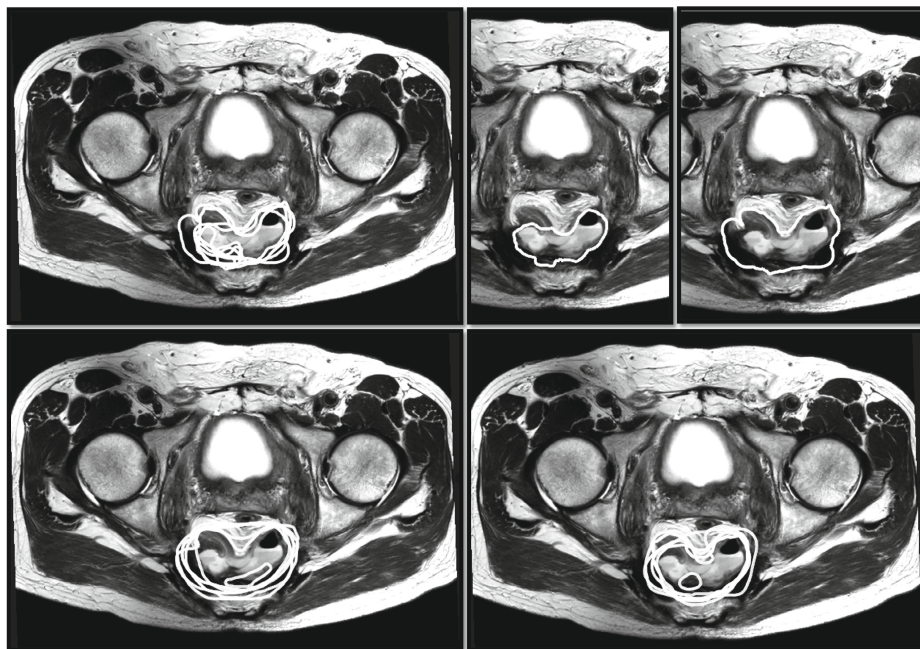
**PET-CT after induction chemotherapy:** Partial metabolic response of the local recurrence.

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

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



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



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

### Case 13

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

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

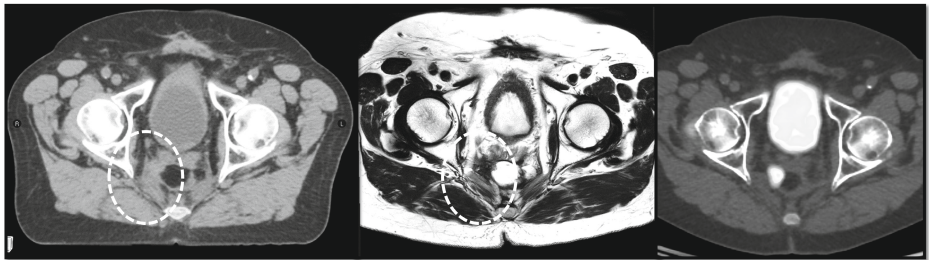
**Baseline PET-CT:** Strong suspicion of a local recurrence on the right pelvic floor. Second small focus very caudally at the anus, possibly inflammatory, but recurrence cannot be ruled out. No distant metastases.

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

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

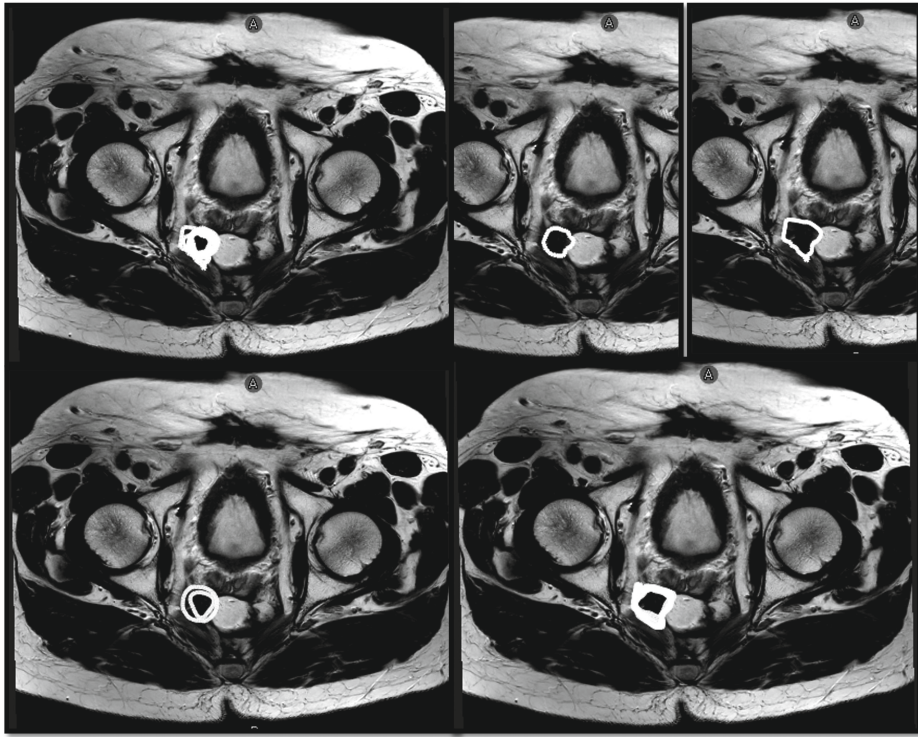
**Table case 13.** Median volume, SDSC, DSC and HD98% (with range) of RAD, GTV- and GTV+.

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



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





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

#### Case 14

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

**Colonoscopy at baseline:** At 5cm from the anorectal junction a cancerous lesion is seen (ulcerating). Biopsy: adenocarcinoma.

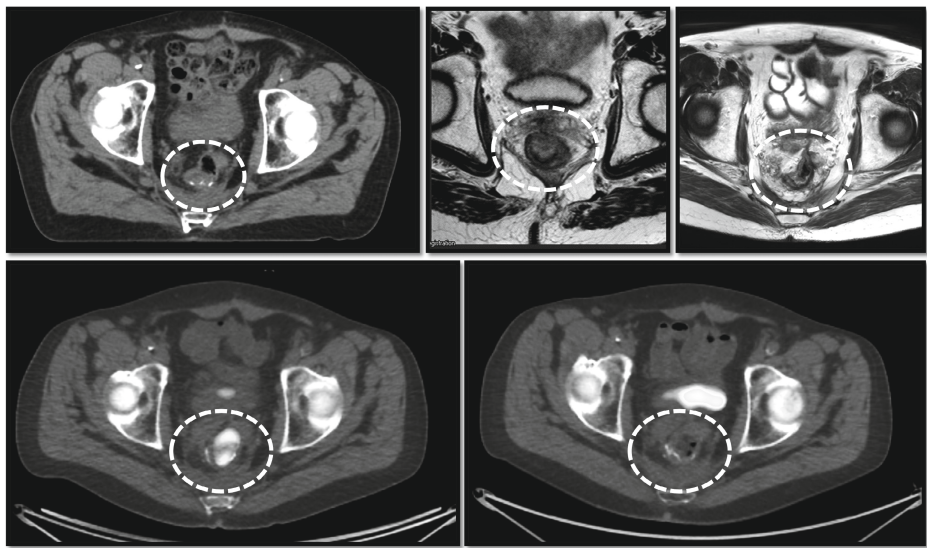
**MRI at baseline:** Tumorous soft tissue visible at the anastomosis of approximately 2.6x3.2cm. There is ventral involvement of the seminal vesicles. No involvement dorsally of the mesorectal fascia.



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

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

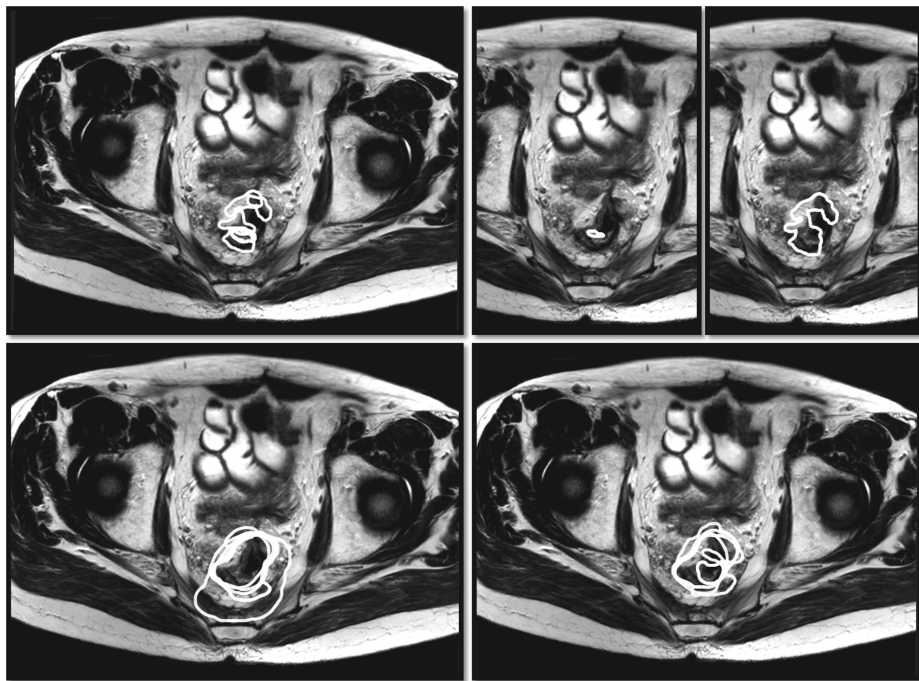
**PET-CT after induction chemotherapy:** Significant reduction of size and metabolic activity of anastomotic recurrence. Small focal metabolic activity fitting with tumorous tissue.



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

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

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



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

