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Original Article

Patient-reported acute GI symptoms in locally advanced cervical cancer patients correlate with rectal dose

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ABSTRACT

Background and purpose: To investigate relationships between patient-reported acute gastro-intestinal symptoms in a locally advanced cervical cancer (LACC) prospective cohort and clinical and dosimetric parameters, while also taking spatial dose into account.

Material and methods: A total of 103 patients was included, receiving radiotherapy based on a plan-library-based plan-of-the-day protocol, combined either with concurrent chemotherapy or with neo-adjuvant chemotherapy and concomitant hyperthermia. Toxicity endpoints were extracted from questionnaires sent out weekly during treatment and regularly in the acute phase after treatment. Endpoints were defined for symptoms concerning obstipation, diarrhea, fecal leakage, bowel cramps and rectal bleeding. Dose surface maps were constructed for the rectum. Clinical parameters and dosimetric parameters of the bowel bag and rectum were collected for all patients.

Results: The use of concomitant chemotherapy and an increase in Planning Target Volume (PTV) resulted in a significant increase in reported diarrhea. The dose–volume parameters V_{5Gy}–V_{25Gy} of the rectum were found to be significant, unlike dose–volume parameters of the bowel bag. Additionally, a significantly higher dose to the inferior part of the rectum was found for patients reporting diarrhea. No significance was reached for fecal leakage and bowel cramps.

Conclusion: The significance of results for patients reporting diarrhea symptoms found for PTV volume indicates a potential benefit for a plan-of-the-day protocol. Additionally, the results suggest that a reduction of inferior rectum dose could decrease patient-reported diarrhea symptoms, while the administration of concomitant chemotherapy appears to lead to radiosensitizing effects that increase these symptoms.

In the treatment of locally advanced cervical cancer (LACC) patients, the current treatment of choice is the administration of external beam radiotherapy (EBRT) with concomitant chemotherapy and image-guided adaptive brachytherapy. Research has shown that this patient group suffers from a variety of side effects caused by the treatment. Patients report, among others, gastrointestinal (GI) toxicity, genitourinary (GU) toxicity and overall decrease in quality of life (QoL) in both the acute and late phase after treatment [1]. Dose–response relationships are most often physician-scored, based on scales defined by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) or in accordance with Common Terminology Criteria for Adverse Events (CTCAE) [2–4]. However, Patient-Reported Outcomes (PROs) are increasingly used for toxicity reporting, as physician-scored toxicity often underestimates patients' perception of the toxicity burden [4]. As PROs comprise the patient's perception of the toxicity burden, a dose–response model for PROs would capture this effect.

For GI toxicity within pelvic cancer cohorts, most research shows a relationship between dose–volume parameters and physician-assessed acute diarrhea symptoms on the RTOG/EORTC or CTCAE scales [2,3,5]. GI symptoms can affect patients' QoL and can stay persistent throughout follow-up [6,7]. As it is known for prostate cancer patients that acute GI toxicity symptoms are a significant predictor for late GI morbidity, special focus ought to be spent to decrease the occurrence of acute symptoms in LACC-cohorts [8]. Additionally, research has shown that the spatial configuration of the dose distribution, described by e.g. Dose Surface Maps (DSMs), can offer a more comprehensive view than solely

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dose–volume parameters [9–12]. DSMs can be used in a versatile way, which has been demonstrated for physician-graded late toxicity prediction in various studies [13–15]. Currently, no studies have been performed on correlations between dose and patient-reported GI toxicity in the acute treatment phase of a LACC-cohort. In prostate cancer cohorts, planned dose to inferior rectum has been found to be of influence for multiple acute patient-reported GI toxicity endpoints [9,16].

In this paper, we investigated relationships between clinical and planned dosimetric parameters and acute patient-reported GI toxicity. To include the possible influence of spatial effects, DSMs of rectum were constructed. To our knowledge, this is the first time these endpoints are investigated for a LACC-cohort treated with a library-of-plans based protocol.

Methods and materials

Locally advanced cervical cancer patients in our institute have been enrolled in a library-of-plans based Plan-of-the-Day (PotD) protocol since 2012. A prospective cohort study was started after approval of the local ethics committee (MEC-2012-586). Patients were included after providing Informed Consent. Patients were treated between January 2012 and February 2018 in the Erasmus MC. QoL-questionnaires were sent out to patients at fixed points before, during, and after their radiation treatment.

Patient population and treatment

The patients included in this study received five cycles of concomitant (cisplatin) chemotherapy and radiotherapy (image-guided external beam radiotherapy and brachytherapy), abbreviated to CTRT, or six cycles of neo-adjuvant (paclitaxel/carboplatin) chemotherapy with radiotherapy (image-guided external beam radiotherapy and brachytherapy) and concomitant hyperthermia, abbreviated to NeoCT + HTRT. As part of the PotD protocol in our institute [17], patients were classified as movers or non-movers for their EBRT schedule, depending on the difference in uterus position between full and empty bladder. Patients were classified as a mover, when the tip of the uterus was displaced more than 2.5 cm between full and empty bladder CT scan. Since May 2014 rectum laxation with suppositories was added to the CT protocol [6]. An Internal Target Volume (ITV) was constructed based on these CT scans, after which a 1-cm margin was applied to construct the Planning Target Volume (PTV). Non-movers received one library plan encompassing the ITV from full to empty bladder, and a backup plan in case the library plan would not suffice. Movers received two library plans on top of the backup plan, one encompassing the uterus position from empty to half-full bladder, and one library plan based on half-full to full bladder. Library plans were delivered with IMRT before 2014, and after 2014 with VMAT. Patients received 45–48.6 Gy (1.8–2.0 Gy per fraction) with EBRT. At the end of external beam treatment patients were scheduled to receive 17–21 Gy (7.0–8.5 Gy per fraction) with brachytherapy. For further details we refer to Sharfo et al. and Heijkoop et al. [17,18].

Toxicity reporting

Patients were asked to fill in the EORTC QLQ-C30 and QLQ-CX24 questionnaires [19,20], which were sent out in before, during, and after treatment. For this study the GI-related questions were considered (referring to Q16, Q17, Q31, Q32, and Q33 of the combined questionnaire). This comprised the following questions:

1. Have you had constipation? (constipation)
2. Have you had diarrhea? (diarrhea)
3. Have you had cramps in your abdomen? (bowel cramps)
4. Have you had difficulty in controlling your bowels? (fecal leakage)
5. Have you had blood in your stools? (rectal bleeding)

Baseline data was defined as data reported at baseline or, when unavailable, at week 1 of external beam radiotherapy treatment. As this study focused on acute effects, maximum QoL deterioration was defined as the highest increase of score from baseline reported in either week 2, week 3, week 4, week 5 of radiotherapy, 1 week after completion of radiotherapy, 1 month after completion or 3 months after completion. Dichotomization was performed per question to create a binary classification for analysis. The questions allowed answers on a four-point scale, allowing a maximum possible deterioration of three points from baseline. Deterioration of two or three points was classified as a toxicity due to irradiation. Improvement, stabilization or deterioration of one point was considered not to be clinically significant.

The impact of the use of antidiarrheal drugs, which can affect diarrhea symptoms, is considered to be mitigated by investigating the maximum deterioration from baseline. By only taking into consideration a deterioration of two or more points, we aimed to only include clinically relevant worsening of symptoms.

Evaluation of dose distribution

Only external beam radiation dose was taken into account for analysis. Heijkoop et al. showed that most patients reached peak toxicity in week 3 and week 4 of treatment for GI symptoms, at which point no brachytherapy or sequential external beam boost had been delivered yet [6]. Dosimetric information was taken from the half-full to full bladder library plan in case the patient was classified a mover, and from the single library plan if the patient was classified to be a non-mover. The physical dose distribution was converted to a 2 Gy-equivalent dose using the linear-quadratic model (α/β = 10 for acute effects) to account for different fractionation schemes [21].

Investigated OARs were the rectum and bowel bag, due to the focus on GI toxicity in this study. Delineations were made on the full bladder CT scan. The rectum structure was delineated from the ischial tuberosities up to the recto-sigmoid junction. The bowel bag was contoured to 3 cm above PTV according to EMBRACE II guidelines (outer contour bowel loops, including the mesentery) to encompass dose levels of 15 Gy and higher [22], and also included the sigmoid. Examples of delineations are displayed in Supplementary S.1. From the dose distribution dosimetric parameters were extracted for all patients for rectum, bowel bag and the Posterior–Inferior Border of Symphysis (PIBS) point as anatomical vaginal reference point. As the delineations of the rectum were based on anatomical landmarks, relative dose–volume parameters were considered. For bowel bag the absolute dose–volume parameters (in cc) were considered, as the interpatient bowel bag volume differed greatly due to the chosen superior delineation boundary.

Dose Surface Maps (DSMs) were made for the rectum, based on the strategy described by Hoogeman et al. [23]. The rectal structure as delineated on the planning CT was reduced to a central axis with a fixed number of equidistant (along the central axis) planes to describe the rectal curvature. On the cross-sections of the planes with the rectal structure, the planes were virtually unfolded along the dorsal side and resampled to an isotropic grid. Afterwards, the high dose regions of all patients were aligned and overlaid, in order to be robust to anatomical differences in uterus-to-rectum position. DSMs were constructed for all patients, after which average DSMs grouped by toxicity scoring were constructed. Significance testing was performed as described by Chen et al. [24]. A dose difference map corrected by the standard deviation was computed

after which permutation testing was performed (2500 permutations). For each permutation the 95th percentile of the corrected dose difference was computed, after which statistically significant regions were marked. Possible confounding in results was investigated with the help of a correlation matrix of DSM values on an isotropic evaluation grid. DSM analyses were done for the entire cohort, and for the two treatment groups separately.

Statistical analysis

All parameters were tested for significance with Fisher's exact test for binary variables or Wilcoxon test for continuous variables. Odds ratios were calculated with univariate logistic regression. Spearman's rank correlation coefficient was applied to investigate local dose dependence in DSMs. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed with MATLAB (Mathworks version 2017a).

Results

A total of 103 patients was included for this study based on the selection criteria. An overview of the patient characteristics can be found in the Table S.2 (Supplementary S.2). QoL data was collected for all patients and described time points, after which the maximum deterioration from baseline was computed. Patients filled in a median of 5 questionnaires. The overall incidence of a deterioration of two points or more was 10% for constipation, 59% for diarrhea, 36% for bowel cramps, 16% for fecal leakage and 2% for rectal bleeding. A graphical representation of the deterioration levels of all questions can be found in Fig. 1. Due to the relatively small cohort size and low incidence of constipation and rectal bleeding, statistical power for these symptoms was lacking. Consequently, neither of these symptoms was further analyzed.

PTV volume and the distance of the lower bound of the rectum structure to the PTV ($LB_{Rectum\text{-}PTV}$) were found to be significant for diarrhea symptoms, as well as treatment group (Table 1). When the treatment groups were considered individually, results persisted for PTV volume within the CTRT group, but not for $LB_{Rectum\text{-}PTV}$, while $D_{mean,\ Rectum}$ reached significance. For the NeoCT + HTRT group separately no parameters reached significance. For bowel cramps and fecal leakage no parameters were found to be significant for the treatment groups separately, and combined.

DVH curves for the entire cohort are displayed in Fig. 2 for rectum or bowel bag, split by toxicity endpoint. A Wilcoxon test was performed per dose point of 1 Gy for the volumes of both the toxicity and no toxicity group, in order to identify possibly significant dose regions. The figures indicate a significant reporting in toxicity for dose values in the range of V_{5Gy}–V_{25Gy} for diarrhea symptoms and in the region of V_{15Gy}–V_{20Gy} for bowel cramps, both for the rectum structure. On the other hand, no significant relationships were found between bowel bag dose and toxicity endpoints. Spatial dose differences between endpoints for the entire cohort became visible with the help of DSMs in Fig. 3. For diarrhea complaints, a significant correlation between deposited dose and complaints can be found in the inferior part of the rectum, over the entire circumference. After evaluating the dataset by treatment group, similar characteristics are found for the groups separately, but only reach significance for the CTRT group (Supplementary S.4 and S.5). The DSMs for bowel cramps and fecal leakage do not show significant areas, before and after stratification.

To eliminate the possibility of confounding due to an increased dose deposition in the central (high) dose region of the rectum DSMs, a heat map of the correlation matrix of the DSM evaluation points is displayed in the Supplementary S.3. From this figure it can be deduced that no correlation higher than 0.5 can be found between points located in the inferior part of the rectum and the anterior part of the rectum, indicating a sole contribution of dose to the inferior part of the rectum to diarrhea complaints.

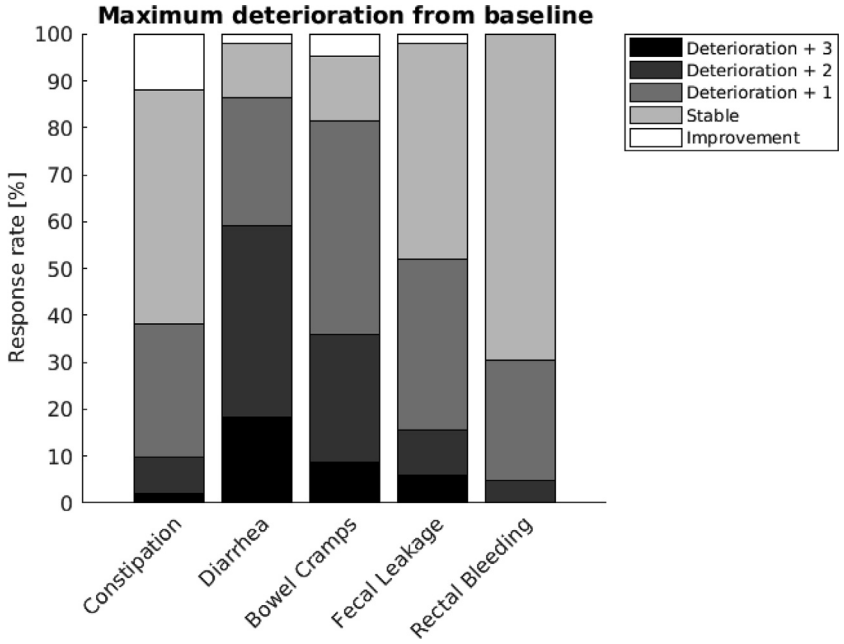

Fig. 1. Response rates for GI-related questions in QLQ-C30 and QLQ-CX24. Deterioration is defined to be the maximum deterioration from baseline at any point in the acute phase, and can be three at maximum due to the four-point scale of the questions.

Table 1
Results of the univariate analysis for diarrhea symptoms within the LACC-cohort. The toxicity incidence is given as the number of reported toxicities within the (sub)cohort over the total number of patients. Rows containing p-values smaller than or equal to 0.2 have displayed odds ratios.

Toxicity incidence	Diarrhea					
	All patients		*CTRT*		*NeoCT + HTRT*	
	61/103		*47/71*		*14/32*	
	OR (CI)	*p*-value	OR (CI)	*p*-value	OR (CI)	*p*-value
Age*	1.02 (0.99–1.05)	0.30	1.03 (0.99–1.06)	0.18	1.00 (0.95–1.06)	0.94
Nullipara+	–	NS	–	NS	–	NS
Prior abdominal surgery+	–	NS	–	NS	–	NS
BMI*	–	NS	–	NS	–	NS
Smoker+	–	NS	–	NS	–	NS
OTT*	–	NS	–	NS	–	NS
NeoCT + HTRT+	0.39 (0.17–0.93)	**0.03**	N/A	N/A	N/A	N/A
VMAT +	–	NS	–	NS	–	NS
Prone+	0.57 (0.26–1.27)	0.17	0.52 (0.19–1.41)	0.19	1.15 (0.27–4.87)	0.85
Mover+	–	NS	–	NS	–	NS
PTV volume*	1.17 (1.01–1.37)	**0.03**	1.24 (1.01–1.53)	**0.03**	1.16 (0.91–1.47)	0.20
PTV/BMI*	1.02 (0.99–1.06)	0.12	1.03 (0.98–1.08)	0.25	1.03 (0.99–1.08)	0.13
$PIBS_{+2cm}$*	–	NS	–	NS	–	NS
PIBS*	0.98 (0.95–1.00)	0.07	1.00 (0.97–1.03)	0.87	0.99 (0.94–1.04)	0.63
$PIBS_{-2cm}$*	0.98 (0.96–1.01)	0.12	0.99 (0.97–1.02)	0.72	1.00 (0.96–1.04)	0.98
$LB_{Rectum-PTV}$*	0.95 (0.92–0.99)	**<0.01**	1.00 (0.98–1.02)	0.49	1.01 (0.96–1.07)	0.62
Iso_{V15Gy}*	–	NS	–	NS	–	NS
Iso_{V20Gy}*	1.01 (0.99–1.04)	0.32	1.03 (0.99–1.06)	0.15	1.01 (0.97–1.05)	0.70
Iso_{V25Gy}*	1.02 (0.99–1.06)	0.20	1.05 (0.99–1.11)	**0.05**	1.01 (0.96–1.07)	0.72
Iso_{V30Gy}*	1.04 (0.99–1.10)	0.12	1.08 (0.99–1.17)	0.07	1.03 (0.95–1.13)	0.42
Iso_{V35Gy}*	1.06 (0.99–1.14)	0.07	1.10 (1.00–1.21)	**0.05**	1.06 (0.94–1.18)	0.30
Iso_{V40Gy}*	1.08 (0.99–1.17)	0.07	1.12 (1.00–1.26)	**0.04**	1.06 (0.90–1.22)	0.36
Iso_{V45Gy}*	1.08 (0.97–1.21)	0.15	1.14 (0.97–1.33)	0.09	1.09 (0.91–1.29)	0.32
$D_{mean,\ Rectum}$*	1.13 (1.01–1.26)	**0.03**	1.18 (1.02–1.36)	**0.03**	1.00 (0.81–1.24)	1.00
$D_{mean,\ Bowelbag}$*	–	NS	–	NS	–	NS

BMI = Body Mass Index, CC – index = Charlson Comorbidity index, WHO score = World Health Organization, OTT = Overall Treatment Time, VMAT = Volumetric Modulated Arc Therapy (compared to Intensity-Modulated Radiation Therapy), PTV = Planning Target Volume in cc (OR defined per 100 cc), PTV/BMI = ratio of the Planning Target Volume over the Body Mass Index, PIBS = Posterior–Inferior Border of Symphysis, anatomical vaginal reference point, LB = Lower Bound, the cranial–caudal distance between rectum structure and PTV structure in mm, Iso_{VxGy} = Isodose Volume in cc of the body receiving × Gy or more (OR defined per 100 cc), $D_{mean,x}$ = the mean dose to structure x, NS = *p*-value higher than 0.2, OR = Odds Ratio, CI = 95% Confidence Interval. Symbols: * for continuous variables, + for binary variables.
Statistical significance was defined as $p < 0.05$.

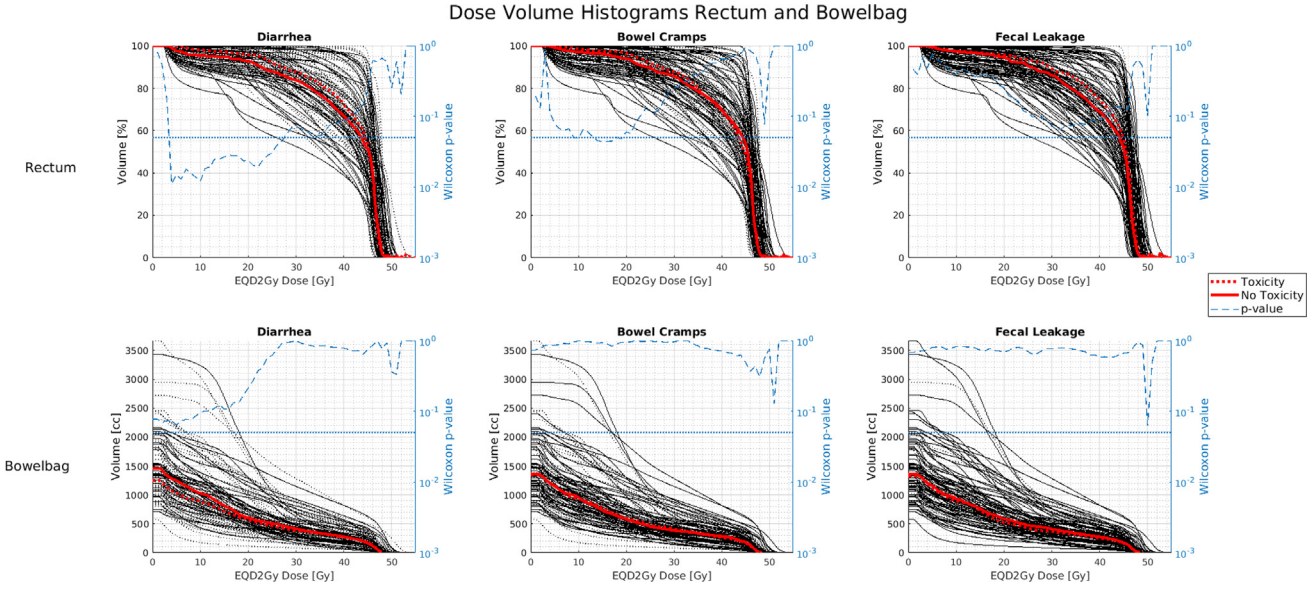

Fig. 2. Dose volume histograms for rectum (relative) and bowel bag (absolute). The upper row represents the histograms for rectum, the bottom for bowel bag. The histograms are depicted for the three toxicity endpoints as defined before and for all individual patients. In red the median curve for patients reporting toxicity and for patients who do not is shown. The Wilcoxon *p*-value is computed for each dose point of 1 Gy between the two groups. The right (logarithmic) *y*-axis corresponds to the Wilcoxon *p*-value, the blue dotted line represents $p = 0.05$.

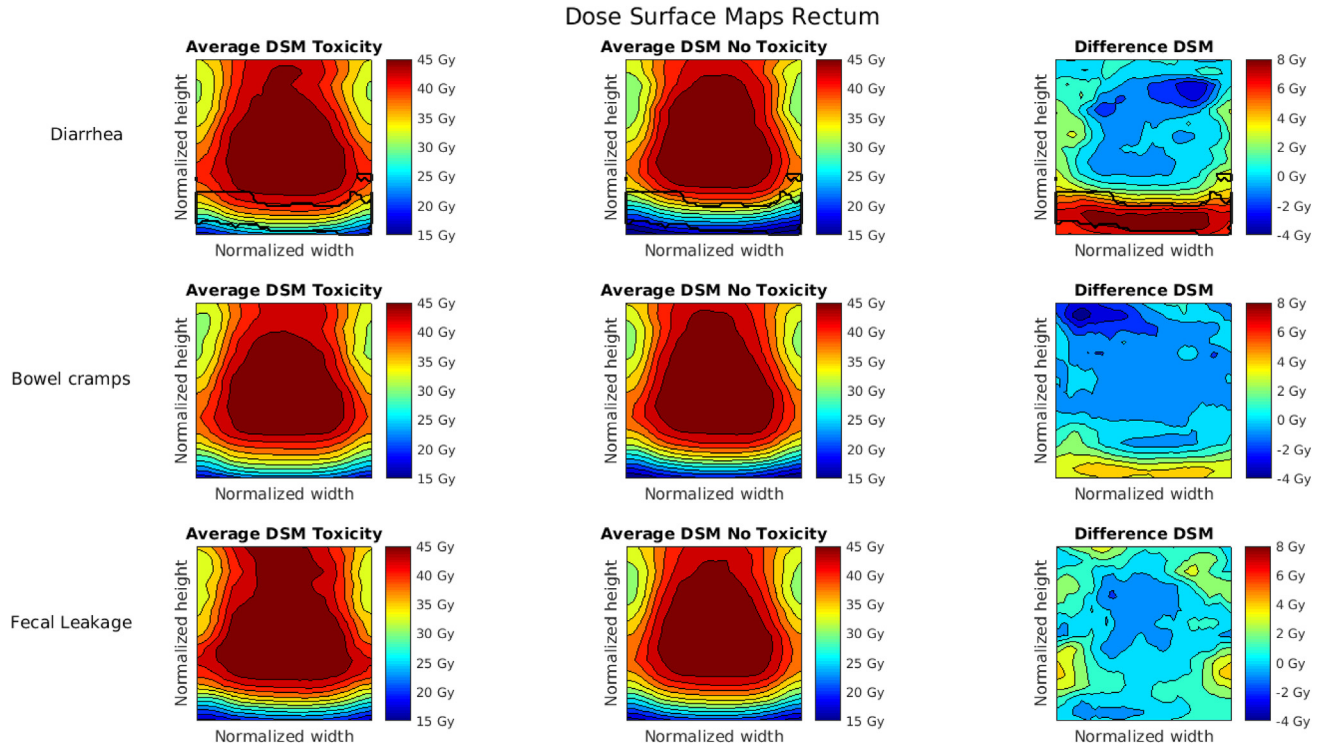

Fig. 3. Dose surface maps as constructed for rectum. Rows represent the results for the three different toxicity endpoints. Columns represent the average DSM for patients reporting toxicity, the average DSM for patients not reporting toxicity, the subtraction of the average toxicity DSM minus the average no toxicity DSM, for each endpoint respectively. The solid line represents the significant region of the 95%-percentile of the corrected dose-difference data. The line shows consistent (significant) deviations between groups for diarrhea symptoms.

Discussion

In this research we investigated the correlation between patient-reported acute GI toxicity and clinical and dosimetric factors, in a prospective LACC-cohort treated with a plan-library-based PotD approach. A relationship was found between PTV volume and diarrhea symptoms, indicating the benefit of our PotD approach which minimizes the PTV volume. The results also suggest that a higher dose to the inferior rectum causes a higher incidence of diarrhea complaints. No correlation between dose to the bowel bag and diarrhea was found in our results, which is in contrast with previous reports.

The relationship between small bowel dose and GI toxicity in the acute phase has been previously demonstrated by Chen et al. for rectal cancer, by Han et al. for anal and perianal cancer and Sini et al. for prostate cancer [25–27]. Chen et al. found a significant association between overall (patient-reported) gastrointestinal symptoms and V_{15Gy} of the small bowel. Han et al. found a significant correlation between small bowel dose and physician-graded diarrhea. However, a comparison of our findings with the results of these studies might not be entirely justified, as the work of Chen et al. and Han et al. investigated tumor sites that were part of the (ano)rectum structure. Interestingly, the significant correlation Han et al. found between small bowel dose and physician-graded diarrhea was not observed for patient-reported endpoints [26]. Jensen et al. confirmed this grading difference by describing a poor correlation between patient-reported EORTC-scored diarrhea and physician-reported CTCAE-scored diarrhea for cervical cancer patients [28]. Our study used patient-reported endpoints, which might therefore explain why previously reported bowel bag dose–volume parameters did not predict toxicity outcomes in our cervical cancer cohort. On the other hand, a significant relationship between small bowel dose and patient-reported GI toxicity as reported by Sini et al. was not found in our cohort. In this case, the mere difference between patient- versus physician-reported outcome does not explain these findings. One other hypothesis to explain these diverging results is the difference in contour delineation. Our results are based on the bowel bag structure, which differs from the small bowel structure that is reported amongst others by Sini et al. Different definitions of bowel delineation have been demonstrated to lead to significant dose–response relationships differences, also in gynecological cohorts specifically [2,3]. To summarize, several methodological choices regarding target group, patient- versus physician-reporting and bowel delineation method could explain why our results did not show previously reported correlations between bowel dose and diarrhea symptoms.

Our results suggest a correlation between diarrhea symptoms and the dose locally received by the inferior part of rectum. Comparable results were found by Wortel et al., who reported a correlation between higher doses to the inferior part of the rectum and patient-reported acute diarrhea symptoms [9]. Of note, Wortel et al. reported an incidence of diarrhea of 14%, versus 59% in our study. This could be explained by the bigger field sizes for radiotherapy and the administration of chemotherapy for the LACC-cohort. The similarity in spatial effect for both studies is nevertheless remarkable, since results are reported for a different gender, tumor site and age group.

Two treatment groups have been included in this study, consisting out of a CTRT group and a NeoCT + HTRT group. The groups were selected for analysis as they make up the first line of care for LACC-patients in our institute. Both groups received platinum-based chemotherapy, administered either before (NeoCT + HTRT group) or during (CTRT group) radiation treatment. Baseline values for the endpoints are not statistically different for both groups (Supplementary S.2). On the other hand, differences in the incidence of diarrhea symptoms between both groups indicate that the administration of chemotherapy during radiation

treatment might have a (radio)sensitizing effect on bowel or rectum mucosa. The PTV volume is significant within the CTRT group for diarrhea symptoms, possibly indicating a benefit for our PotD approach [29]. By further reducing the PTV volume, e.g. by expanding the plan library, a reduction in diarrhea complaints might be achieved [30]. Furthermore, no difference in toxicity was found for mover and non-mover patients, which also suggests that the PotD approach leads to the desired results. Indeed, non-mover patients receive smaller planning target volumes compared with population-based approaches due to the creation of the ITV – as applied by other institutes. Mover patients require bigger ITVs to encompass the bladder-related motion, but this is mitigated by the use of a plan library where the ITV is split in multiple (smaller) ITVs. This greatly reduces the overall irradiated volume compared to a fully encompassing ITV-based plan. As a consequence, both mover and non-mover patients benefit from our plan-library approach.

It is unclear why PTV volume does not reach significance in the NeoCT + HTRT group. The smaller cohort size could be a reason, and more research is needed for specific effects within this treatment group. The current recommendation of care for LACC-patients is radiotherapy with concomitant chemotherapy, but studies have shown (additional) benefit of the administration of deep hyperthermia [22,31]. As deep hyperthermia for LACC-patients is not widely applied, no literature is available for comparison with our results. Further research is necessary to support the findings for this treatment group.

In conclusion, we showed a correlation between PTV volume and patient-reported acute diarrhea symptoms, as well as a spatial dependency of rectal dose for these symptoms. To our knowledge, this is the first study demonstrating this analysis in the context of a LACC-cohort in the acute phase of the treatment for GI-related toxicity. The results justify current investments in adaptive strategies, as smaller PTV volumes appear to correlate to fewer diarrhea complaints. We aim to validate the findings prospectively in future studies. We hope the results presented in this paper can serve as a starting point to decrease in toxicity burden for LACC-patients in both the acute and late phase of their treatment.

Conflicts of interest

This work was in part funded by a research grant of Elekta AB (Stockholm, Sweden). Erasmus MC Cancer Institute also has a research collaboration with Accuray Inc, Sunnyvale, USA. The funders had no role in study design, data collection and analysis, and decisions on preparation of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.03.035.

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