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Original Article

A model-based patient selection tool to identify who may be at risk of exceeding dose tolerances during pancreatic SBRT

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ABSTRACT

Purpose: Locally advanced pancreatic cancer (LAPC) patients are prone to experience daily anatomical variations, which can lead to additional doses in organs-at-risk (OAR) during SBRT. A patient selection tool was developed to identify who may be at risk of exceeding dose tolerances, by quantifying the dosimetric impact of daily variations using an OAR motion model.

Materials and methods: The study included 133 CT scans from 35 LAPC patients. By following a leave-one-out approach, an OAR motion model trained with the remaining 34 subjects variations was used to simulate organ deformations on the left-out patient planning CT anatomy. Dose–volume histograms obtained from planned doses sampled on simulated organs resulted in the probability of exceeding OAR dose-constraints due to anatomical variations. Simulated probabilities were clustered with a threshold per organ according to clinical observations. If the prediction of at least one OAR was above the established thresholds, the patient was classified as being at risk.

Results: Clinically, in 20/35 patients at least one OAR exceeded dose-constraints in the daily CTs. The model-based prediction had an accuracy of 89%, 71%, 91% in estimating the risk of exceeding dose tolerances for the duodenum, stomach and bowel, respectively. By combining the three predictions, our approach resulted in a correct patient classification for 29/35 patients (83%) when compared with clinical observations.

Conclusions: Our model-based patient selection tool is able to predict who might be at risk of exceeding dose-constraints during SBRT. It is a promising tool to tailor LAPC treatments, e.g. by employing online adaptive SBRT; and hence, to minimize toxicity of patients being at risk.

For some cancers, variations from standard clinical protocol can be applied in a patient-specific base to compensate for undesirable high doses to the surrounding organs-at-risk (OAR) during the radiotherapy treatment course. Anatomical regions prone to changes, such as the upper and lower abdomen, can potentially benefit from more personalized treatments. Several decisions can be taken to ensure a safer dose delivery to OAR according to patient-specific needs: tumor coverage can be compromised, treatment fractionation can be increased by reducing daily delivered doses, planning organs-at-risk volumes (PRV) can be defined to protect surrounding healthy tissues, or alternatively, daily plan adaptation in the form of library-of-plans or replanning, can be considered. Plan adaptation results into the culmination for overcoming day-to-day anatomical variations, since to a large extend, delivered doses can be adjusted to the patient anatomy of the treatment day. For instance, libraries-of-plans have been used to exploit predictable organ motion, such as bladder-induced or gas filling in the bowel [1–7]. For more complicated targets, such as locally advanced pancreatic cancer (LAPC), replanning has been implemented clinically [8–12] but hitherto has been limited to MR-Linac systems, which are not widely available.

In particular, LAPC patients have a poor prognosis, and in radiotherapy, it remains a contentious treatment site due to the proximity of the target volume to healthy tissues, whose sparing commonly compromises the delivered doses to the tumor. Chemotherapy followed by a stereotactic body radiotherapy (SBRT) has emerged as a promising option for unresectable LAPC [13–17]. At our institution, LAPC patients undergo a hypofractionated regime on the CyberKnife® system using Synchrony respiratory motion tracking (Accuray Inc, Sunnyvale, CA, USA) via fiducial markers [18,19]. SBRT delivers conformal doses with sharp gradients, resulting in improved local control [14,17] and reduced toxicities to healthy tissues. SBRT short treatment course can also reduce the delay of additional chemotherapy or surgery [20,21].

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Despite the precise delivery of these treatments, the risk of gastrointestinal toxicities due to daily anatomical variations still remains a major concern, and for this reason, the implementation of strategies as online replanning have been proved to be a solution for better OAR sparing and to increase target coverage when possible [8,10,20].

Personalized treatments, though, can be cost and resource intensive, besides requiring additional equipment and experts to control the overall implementation workflow and decision-making. In an attempt to optimize the clinical resources, the present study proposes a patient classification tool to identify prior to treatment those who might be at risk of violating dose-constraints during SBRT.

To our knowledge, only Bohoudi et al. [10] has previously suggested a criteria to identify LAPC patients likely to be at dosimetric risk, to consequently distinguish who might benefit from plan adaptation. Their suggested approach assesses the geometrical configuration of OAR with respect to the tumor location on the planning CT (pCT) anatomy, by concluding that the minimum distance from OAR to the tumor is a good indicator to classify LAPC patients. Nonetheless, around half of the cases not being at risk were misclassified, and hence, they overpredicted patients requiring an adaptive strategy. We consider that the planned dose distribution might also play a decisive role in how sensitive a plan may be to OAR daily variations. To test this hypothesis, we suggest to use a population-based OAR motion model trained with previously observed organ variations in LAPC patients [22], to further quantify the dosimetric impact of potential daily anatomical changes on the original treatment plan, as basis of our classification criteria. Alternative geometric and dosimetric measures will be also evaluated to test the added value of our approach.

Materials and methods

Patient data

A total of 133 scans from 35 LAPC patients were included in the study, after providing written informed consent. The study was in accordance with the recommendations of Declaration of Helsinki and approved by the Institutional Review Board with number NL49643.078.14. Patients had been previously treated with a hypofractionated SBRT regime of 40 Gy in 5 fractions, prescribed to the 80% isodose line. Each patient received a pCT scan and maximally 3 pre-fraction in-room CT scans (FxCT) performed under instructed end-expiration prior to treatment delivery, through an in-room CT-on-rails system integrated in the treatment room [23]. Dose–volume constraints were set at V35Gy < 1 cc to the three critical organs, including the stomach, duodenum and bowel. One to four fiducial gold markers were implanted in or around the tumor. Delineations of the Gross Tumor Volume (GTV) as well as the three OAR were performed in all scans, the latter by following the RTOG guidelines [24]. The Planning Target Volume (PTV) was obtained from the isotropic expansion of the GTV by 7 mm. The bowel was contoured until L4 as a single structure, including the individual loops of the small bowel and the colon. Delineations details can be found in Magallon-Baro et al. [22].

Clinical observations dataset

For each patient, rigid transformations were used to align daily to pCT scans, representing the couch positioning correction performed at the beginning of each fraction by the CyberKnife. The transformation consisted of a spine match (comprised by rotation and by a translation transformation) followed by a fiducial match correction (only translation), and was used to transfer the planned dose distribution from the pCT to the FxCT of each patient.

V35Gy values were collected in both the planning and daily scans to assess the recurrence of dose-constraints violations during treatment, and to establish the baseline to evaluate the model performance and other measures. To accurately compare V35Gy, sample points used in the pCT dose-volume histograms (DVHs) were non-rigidly transformed to daily CT organs, as done for dose accumulation purposes [25]. Transformations were estimated per organ between 3D surface meshes using the Thin-Plate Spline Robust-Point Matching (TPS-RPM) algorithm, available in-house [26,27], which parameters were previously optimized to obtain a submillimeter transformation accuracy on each organ.

To assess the effect of organ motion on the dose in the OAR, patients were categorized based on the OAR dose violations reported in the FxCT. If at least one OAR exceeded dose-constraints in any of the daily CT scans, the patient was categorized as a candidate being at risk. Otherwise, not (Fig. 1).

Individualized population-based DVHs using a statistical OAR variation model

For each patient, a population-based statistical OAR deformation-motion model was created by learning from organ variations observed in the remaining 34 patients of the database, by following a leave-one-out cross-validation approach (LOOCV). As described in our previous work [22], the training variations of the model correspond to non-rigid registrations performed from the pCT and FxCT to an average organ created on each patient, using the TPS-RPM method. All deformation vector fields (DVF) of each training patient were propagated to a common-frame-of-reference of a representative subject, and subsequently processed by a principal component analysis (PCA). PCA transforms the average and covariance matrix of the set of DVF into principal components or modes of variation, ordered by their ability to capture the variance in the data. First modes, hence, describe the most common geometric variation patterns that have been observed. As described in (1), new anatomical shapes (OAR_{new}) of the OAR can be created by linearly combining the average OAR shape (OAR_{mean}) and the weighted (b_l) sum of the first L modes of variations characterized by v_l.

$$OAR_{new} = OAR_{mean} + \sum_{l=1}^{L} b_l v_l \quad (1)$$

The model can be used on the left-out patient after non-rigidly registering its organ structure set on the reference patient (Fig. 1). This non-rigid registration is the bridge to propagate results retrieved by the model on the test patient.

Individualized population-based DVHs were generated on each left-out patient, by simulating P (P ~ 5000) OAR variations of the pCT anatomy and using the planned dose distribution sampled on the simulated organs (Fig. 1). A Mersenne Twister Gaussian pseudorandom number generator was used to create values for the weights (b_l) in Eq. (1) on the first L modes. L was constrained to 43 modes, since they encapsulated 90% of the motion variance observed in the three critical organs [22]. The generated values followed a Gaussian distribution within ±3 standard deviations on each mode. Population-based DVHs were obtained by selecting the 95% confidence interval range at each bin of the P simulated DVHs. Bins were defined with a resolution of 0.0001 Gy.

Patient selection tool

The population-DVHs V35Gy bin was analyzed to retrieve the cumulative percentage of simulated organs exceeding dose-constraints (V35Gy > 1 cc). Next, this percentage was correlated to risk groups categories (low, mid-low, mid-high and high) based on the number of clinical observations that were exceeding dose-

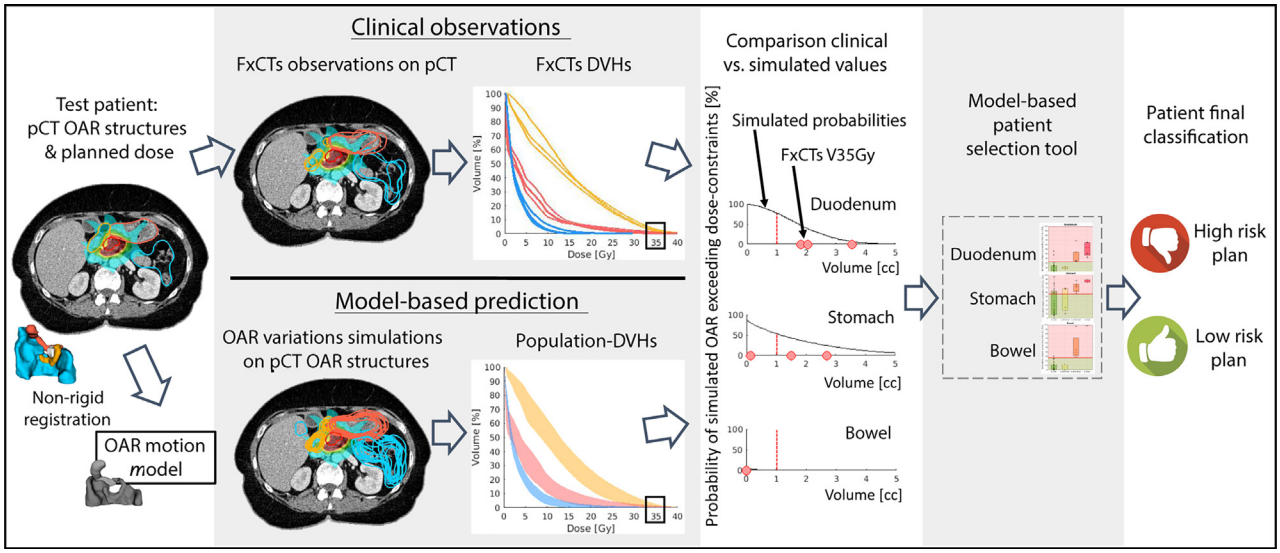

Fig. 1. Workflow followed for each tested (left-out) patient: OAR in pCT were non-rigidly registered to the model, which was used to simulate OAR variations. Tailored population-based DVHs using the planned dose distribution were generated. The simulated probabilities of violating the dose-constraint (V35Gy > 1 cc) were compared to clinically observed daily V35Gy, which were retrospectively collected for the same tested patient. A final classification was given after assessing the impact of OAR variations on the planned doses, by using our proposed model-based selection tool shown in Fig. 2.

constraints in the daily CT scans of the given patient, i.e. in zero, one, two or three fractions (Fig. 1). For each organ, a boxplot was created containing the distribution of patients in each risk category. Pearson correlation coefficients (R) were determined for each organ prediction, and a threshold on the simulated percentage exceeding the V35Gy constraints was established by dividing patients in risk categories based on simulations. This discrimination accuracy was assessed by accounting for misclassified patients according to the established thresholds.

The final patient risk classification relied on the combined OAR predictions. If the prediction of any of the three OAR was above the corresponding established threshold, then the patient was classified as being at risk, otherwise not. The patient classification was compared to the clinical observations dataset to determine the method accuracy. The sensitivity (ability of the model to correctly identify patients with a high risk plan) and specificity (ability to correctly identify patients with a low risk plan) were also abstracted.

Comparison of the prediction criteria to simpler metrics

To assess the added value of our model-based selection tool against other metrics, we compared the clinical observations risk categories with simpler geometric and dosimetric measures, such as: minimum distance from OAR to GTV and PTV, and tumor size as proposed by Bohoudi et al. [10], GTV and PTV coverage, and overlapping volume between OAR and PTV.

The decision-tree classification criteria presented by Bohoudi et al. was also tested in our data. Their criteria is summarized as follows: if the GTV volume is >41 cc, the patient should be classified as candidate for adaptation (i.e. dose tolerances exceeded on daily scans), if the minimum distance of the OAR to the GTV is greater than 3 mm, the patient can be excluded from the strategy. The remaining combination (GTV volume $\leq$41 cc with minimum distance GTV-OAR $\leq$3 mm) leads to an indefinite decision, therefore, the patient would be suggested to undergo adaptation.

Results

Clinical observations overview

V35Gy values were collected in the daily DVHs using transferred doses and daily OAR. In total, 34% of patients reported violations in daily duodenums, 31% in daily stomachs and 20% in daily bowels. Overall, dose-constraints were never exceeded in any of the organs of 15/35 patients (43%). According to these clinical observations, the remaining 20/35 patients would be at risk, as at least one OAR exceeded dose-constraints during treatment.

Dosimetric risk classification for each OAR

Simulated dose violation probabilities were clustered in four categories: low, mid-low, mid-high, and high risk corresponding to zero, one, two, and three observations of dose-constraint violations (V35Gy > 1 cc for each OAR) in the FxCT (Fig. 2). Pearson correlation coefficients of 0.8, 0.5, 0.8 were found between simulated risk and observed dosimetric changes, on the duodenum, stomach and bowel, respectively.

A maximum correlation with clinical results was found after establishing a threshold at 22%, 56% and 27% for simulated duodenums, stomachs and bowels, respectively (depicted with red horizontal lines in Fig. 2). These thresholds grouped mid-high and high risk patient groups into a single high risk category, which contained patients most likely to violate OAR dose-constraints due to moving tissues with respect to patients in lower risk categories. The discrimination accuracy of patients according to the established thresholds resulted in 89%, 71% and 91% for the duodenum, stomach and bowel predictions, respectively.

Validation of the patient risk classification

Patients were classified to be at risk if at least one simulated OAR prediction fell to the red zone of Fig. 2. In total, our model-based classification tool correctly predicted 29/35 subjects, i.e. coincided with the clinical observations. It resulted in a prediction accuracy of 83%, and a sensitivity and specificity prediction of 100% and 60%, respectively (20/35 patients were categorized as being at risk, 9/35 as not, 6/35 were misclassified as having a risk plan) (Fig. 3, Table 1).

Correlation of the prediction criteria with simpler metrics

Geometric and dosimetric measures were collected and evaluated to find correlations with the clinical observations risk groups

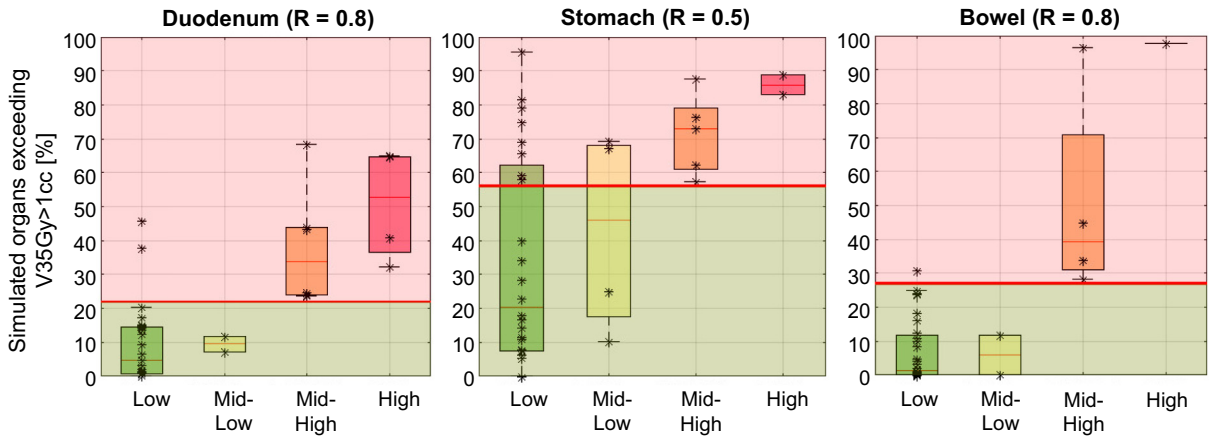

Fig. 2. Percentage of simulated OAR exceeding the clinical dose-constraints (duodenum-left, stomach-middle, bowel-right) clustered per risk group according to how many fractions resulted to exceed the dose-constraint in the clinic: 0/3 FxCT (low risk group), 1/3 FxCT (mid-low risk group), 2/3 FxCT (mid-high risk group), or 3/3 FxCT (high risk group). The thresholds established by the red horizontal line discriminate patients (depicted in *) who are in higher risk to exceed dose tolerances with the given planned doses, from the ones in a lower risk.

Fig. 3. Classification comparison retrieved from the model-based prediction, geometric measures assessment, and Bohoudi et al. decision-tree criteria [10], against the clinical observations performed over the daily CT scans.

Table 1
Performance measures calculated on the different classification criteria: model-based approach, OAR-PTV overlap derived criteria, and Bohoudi et al. decision-tree [10], according to our clinical observations. (TP – True Positives; TN – True Negatives; FP – False Positives; FN – False Negatives; Sn – Sensitivity; Sp – Specificity; Acc – Accuracy; PPV – Positive Predictive Value; NPV – Negative Predictive Value; N – Number of observed patients = 35).

Classification criteria	TP	TN	FP	FN	Sn (%) = TP/(TP + FN)	Sp (%) = TN/(TN + FP)	Acc (%) = (TP + TN)/N	PPV (%) = TP/(TP + FP)	NPV (%) = TN/(TN + FN)
Model-based	20	9	6	0	100	60	83	77	100
OAR-PTV overlap	18	6	9	2	90	40	69	67	75
Bohoudi et al.	20	5	10	0	100	33	71	67	100

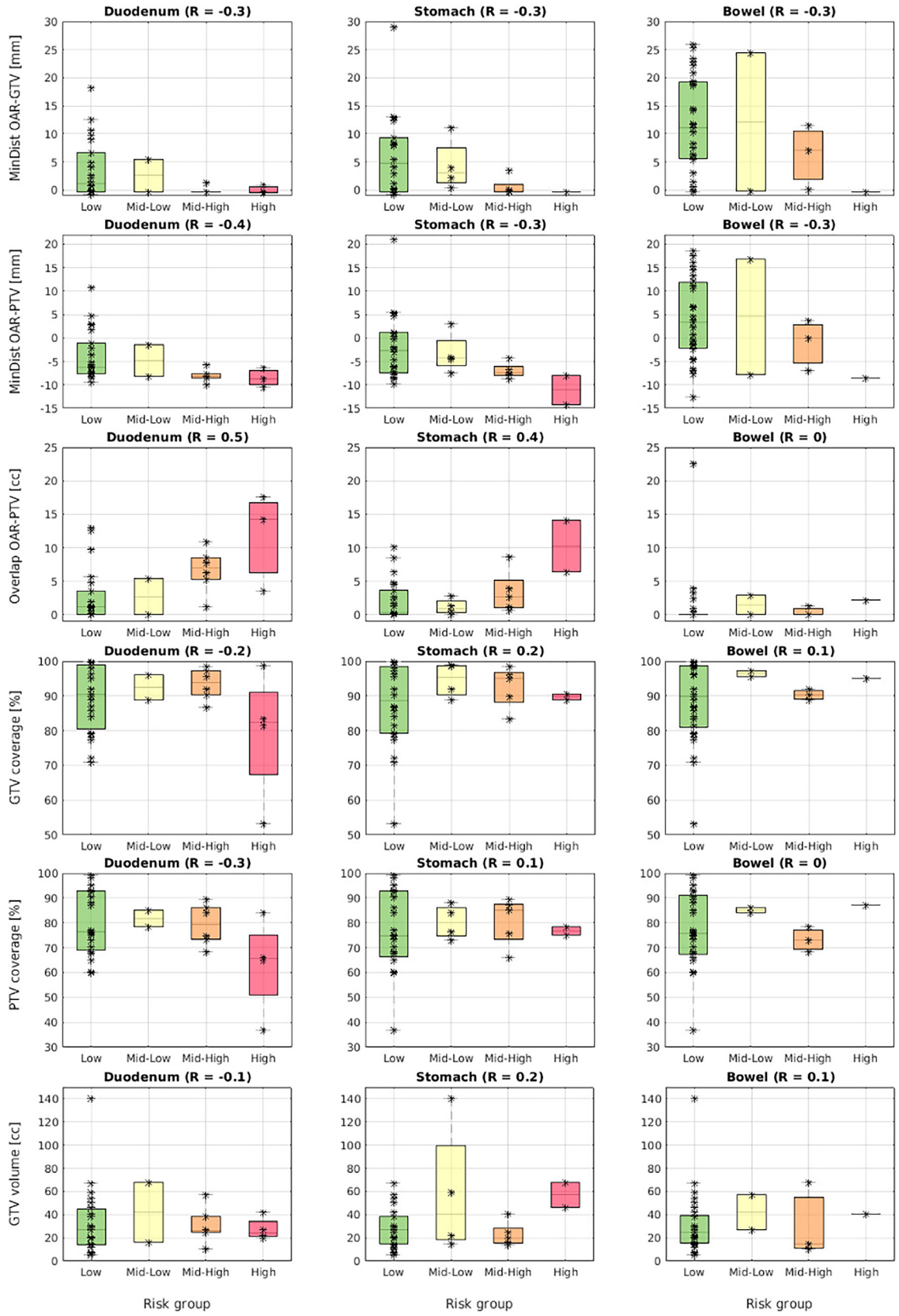

Fig. 4. Minimum distance from GTV to OAR (1st row), from PTV to OAR (2nd row), overlapping volume between PTV and OAR (3rd row), and GTV (4th row), PTV coverage (5th row) and GTV volume (6th row) distributions according to each dosimetric risk groups determined by the clinical observations (0-Low: 0/3 daily dose-constraints violations observed, 1-Mid-Low: 1/3 cases, 2-Mid-High: 2/3 cases, and 3-High risk: 3/3 cases). From left to right, depicted results on the duodenum, the stomach and the bowel.

(Fig. 4). Weak Pearson correlations (−0.3 < R < 0.3), either positive or negative, were found in all collected parameters (minimum distance from GTV-OAR and PTV-OAR, PTV overlapping with OAR, GTV and PTV coverages). Only the overlapping volume of PTV with the duodenum presented a moderate correlation with a $R = 0.5$ coefficient, and $R = 0.4$ with the stomach. If establishing thresholds at 5 cc and at 1 cc on the respective organs, a patient classification accuracy of 69% would be achieved (24/35 subjects would coincide with the clinical observations), with a sensitivity and specificity prediction of 90% and 40%, respectively (Fig. 3, Table 1).

Metrics used in the decision-tree classification criteria of Bohoudi et al. [10], which include tumor size and minimum distance from GTV to OAR, were used to classify our patients (Fig. 3, Table 1). It resulted in a patient classification accuracy of 71%. The sensitivity and specificity predictions of their approach were 100% and 33%, respectively (20/35 patients were categorized as needing daily adaptation, 5/35 as not, 10/35 were misclassified in favor of adaptation when not needed).

Discussion

The present study investigated if a model-based approach is a valuable tool to identify patients at risk in exceeding OAR tolerances due to daily anatomical deformations. Selected patients can then be eligible to receive an adaptive treatment or undergo alternative solutions, such as PTV coverage reduction, risk-adapted fractionation or PRV margins inclusion in the treatment plan. This is the first study to derive a patient selection tool only based on the planning CT anatomical information, that estimates a prediction by quantifying the sensitivity of planned doses to individual OAR deformations. Our clinical observations on daily V35Gy dose-constraint reported that 43% (15/35) of our patients did not present events of dose-constraint violations with the planned doses, although anatomical changes occurred. Our proposed method accurately predicted 83% of the patients (29/35).

The distinguishing feature within our study is the use of prior knowledge acquired from other LAPC patients to predict how an unknown patient will behave. We already tested the performance of the OAR model in our previous work [22]. By using 43 modes, population-DVHs could reproduce more than 90% of daily DVHs. The current study focuses on the V35Gy prediction retrieved from these population-DVHs. The V35Gy is a small absolute volume which may be susceptible to small perturbations in the analysis, so it may not be the most robust parameter to make constraint violation predictions. However, despite the small volumes at stake, the model still proved sufficient accuracy for risk prediction since presented strong correlations with clinical observations (Fig. 2).

Individual organ risk predictions had an accuracy around 90% for the duodenum and the bowel, but around 70% for the stomach, whose Pearson coefficient was also the lowest. The model learns from variations with respect to an average anatomy on each patient, with the aim to remove possible biases between the samples of each subject. In this study, OAR variations were applied directly to the pCT anatomy. Stomachs can change on average up to 1/3 of their volume with respect to the pCT anatomy [22]. Therefore, if the pCT organs of the tested patients are not close to their hypothetical average anatomy, our predictions will be overestimated. Organ overestimation can lead to higher risk probabilities, and hence, a worse patient prediction. Further investigations have to be done in an effort to overcome this limitation.

Institutions treating LAPC patients on the MR-Linac have evaluated the impact of plan adaptation based on daily re-optimized plans [8–10,20,28]. The main outcome reported by plan adaptation studies has been the successful prevention of delivering high fraction doses to OAR during treatment, although toxicity details have not been reported yet. Remarkably, Bohoudi et al. have noted that not all fractions or patients might require plan adaptation, similarly to our conclusions; and Tyran et al. highlighted that the evaluation of planned doses on daily recontoured anatomies is a good indicator for assessing if plan adaptation might be beneficial on a given fraction or not. Despite daily plan adaptation benefits have not been compared to our patient predictions in the current study, we feel confident, then, to rely on our clinical observations dataset, and consequently, that our estimations can be promising for a patient risk assessment.

To our knowledge, only Bohoudi et al. also tried to derive a patient selection tool for pancreatic SBRT [10] from their analysis on daily re-optimized plans. Our results on geometric measures analysis strengthen their conclusions in remarking that if the minimum distance of the GTV to the duodenum and stomach is >3 mm, then dose tolerances might not be exceeded during treatment. Based on our boxplots in Fig. 4, risk groups would also maximally discriminate low risk candidates by the same threshold at 3 mm on both organs (Fig. 4). Bowel comparisons cannot be assessed since no dose violations were observed in their daily bowels. Conversely, GTV volumes presented weak correlations with our clinical results. Therefore, by applying Bohoudi criteria on our patients, 30/35 patients would be identified as at risk, while only 5/35 as not. Eight risk candidates were classified as such for having a GTV volume >41 cc, thus, was the default selection for the remaining 22/35. Although up to 10 patients were misclassified, overall Bohoudi parameters achieved a good classification accuracy on our independent cohort. However, their criteria does not seem representative enough since the majority of patients fell into an "indefinite" classification. We believe this is the reason why it resulted into more false positive. Despite Bohoudi et al. derived their criteria by using the data of all fractions, our model learnt from multiple observed cases in the whole cohort. With our approach, we could not only achieve the same prediction than by following their criteria, but also provided clearer indications where Bohoudi method was limited to, i.e. in patients presenting a small tumor (>41 cc) close to OAR (>3 mm), by correctly identifying 4 more candidates being at low risk (Fig. 4).

Regarding the other evaluated metrics, only the OAR-PTV overlapping volume measure abstracted moderate correlations for the duodenum. A worse classification prediction than with Bohoudi et al. criteria was achieved (Table 1). The remaining geometric and dosimetric measurements did not report promising correlations with our clinical observations to be further used as predictors.

To summarize, a model-based prediction tool learning from previously observed OAR variations resulted in a robust approach to identify patients that might be at risk of exceeding dose tolerances during treatment, outperforming geometric metrics based on patient anatomy. New patients can be assigned to a risk group based on simulations for each individual gastrointestinal organ. The correct classification of patients based on the pCT anatomy can help to individualize treatments only when needed, e.g. by risk-adapted fractionation or employing online adaptation. Besides maximum patient comfort, this could be beneficial to optimize the clinical resources: avoiding the logistical challenges of altering clinical protocols for both patients and staff. An external validation of our tool and a further clinical implementation should be considered as future practical applications of our work.

Conflicts of interest

This work was in part funded by a research grant of Accuray Inc., Sunnyvale, USA. Erasmus MC Cancer Institute also has a research collaboration with Elekta AB, Stockholm, Sweden.

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