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Clinical Trial

Multi-center dosimetric predictions to improve plan quality for brachytherapy for cervical cancer treatment

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ABSTRACT

Background and purpose: Image-guided adaptive brachytherapy (IGABT) is an important modality in the cervical cancer treatment, and plan quality is sensitive to time pressure in the workflow. Patient anatomy-based quality-assurance (QA) with overlap volume histograms (OVHs) has been demonstrated to detect suboptimal plans (outliers). This analysis quantifies the possible improvement of plans detected as outliers, and investigates its suitability as a clinical QA tool in a multi-center setting.

Materials and methods: In previous work OVH-based models were investigated for the use of QA. In this work a total of 160 plans of 68 patients treated in accordance with the current state-of-the-art IGABT protocol from Erasmus MC (EMC) were analyzed, with a model based on 120 plans (60 patients) from UMC Utrecht (UMCU). Machine-learning models were trained to define QA thresholds, and to predict dose D_{2cm3} to bladder, rectum, sigmoid and small bowel with the help of OVHs of the EMC cohort. Plans out of set thresholds (outliers) were investigated and retrospectively replanned based on predicted D_{2cm3} values.

Results: Analysis of replanned plans demonstrated a median improvement of 0.62 Gy for all Organs At Risk (OARs) combined and an improvement for 96 % of all replanned plans. Outlier status was resolved for 36 % of the replanned plans. The majority of the plans that could not be replanned were reported having implantation complications or insufficient coverage due to tumor geometry.

Conclusion: OVH-based QA models can detect suboptimal plans, including both unproblematic BT applications and suboptimal planning circumstances in general. OVH-based QA models demonstrate potential for clinical use in terms of performance and user-friendliness, and could be used for knowledge transfer between institutes. Further research is necessary to differentiate between (sub)optimal planning circumstances.

Brachytherapy (BT) is an important treatment component for locally-advanced cervical cancer (LACC) patients [1,2]. Image-guided adaptive brachytherapy (IGABT) is the current standard-of-care, and the use of interstitial needles in addition to intracavitary implants allows better shaping of the dose distribution, better tumor coverage, and better organ sparing [3]. However, such advanced implantations have increased the complexity of the treatment [4–6]. Moreover, the adaptive nature of the treatments and patient discomfort make IGABT workflows bound to time pressure, whilst these workflows require multiple steps of manual intervention. The combination of high complexity and time pressure may jeopardize the quality of the treatment plans [7].

Adequate target coverage is the primary goal in cervical IGABT planning. Additionally, the dose to the maximally exposed 2 cm^3 of individual Organ At Risk (OAR) volumes (D_{2cm3}) is constrained and defined invariant to tumor size or to patient anatomy [8]. The patient's anatomy, the use and position of interstitial needles as well as the planner's experience impact the planning procedure. To achieve treatment plans with sufficiently high quality, dummy-runs have been reported to improve compliance with the protocol and to homogenize results between institutes [9–12]. Analyzing cohorts within and between institutes can give insight in overall plan quality, but not in the quality of individual plans. To improve individual treatment plans, patient-specific quality-assurance (QA) is needed.

Knowledge-based QA can be used for this purpose. For this type of QA, a golden standard dataset is utilized as a reference dataset, with which unseen patient data can be predicted. A new patient's

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anatomy can be gauged to resembling anatomies in the gold-standard standard dataset, and from there a prediction can be made on achievable dose parameters [13]. Using this information, suboptimal plans can be identified that might benefit from further optimization. Within the same treatment protocol, these QA tools can also be utilized across centers. Overlap Volume Histograms (OVHs) have been demonstrated as a QA method to monitor the quality of BT treatment of cervical cancer patients in previous work from our group [14]. However, it is currently not know whether OVH-based QA can actually improve plan quality in brachytherapy treatment planning for cervical cancer.

The purpose of this study was to assess if treatment plan quality can be improved using OVH-based QA for cervical cancer patients across centers. Single-center data was used to construct QA models for rectum, bladder, sigmoid, and small bowel. These models were applied to the treatment plans of a patient cohort from a different institute. To test whether treatment plan quality can be improved, treatment plans that were identified as suboptimal were retrospectively replanned with information from the QA models and analyzed based on DVH parameters. If positive, this QA tool could be used to support the treatment planner in real time in determining whether treatment plan quality can still be improved.

Materials and methods

LACC-patients treated with HDR BT were included from UMC Utrecht (UMCU) and Erasmus MC Rotterdam (EMC). The study was approved by the medical ethics committee under number MEC-2021-0337. A total of 60 patients (120 plans) from UMCU and 68 patients (160 plans) from EMC (EMC) were included, treated in accordance with EMBRACE II protocol. All UMCU patients were formally enrolled in the EMBRACE II study. Of 68 EMC patients, 15 patients were eligible to be enrolled in the study and formally enrolled. Details of the dosimetric aims for UMCU and EMC cohorts can be found in Table 1.

Planning BT MR images, structure sets and the three-dimensional dose distributions were collected for all plans of all patients. Treatment characteristics for all patients are reported in Table 2. OVHs between delineated OARs and HRCTV were used to quantify patient anatomy, analogous to the previously described method in literature [14,15]. Scaling of the full physical dose distributions was performed to account for differences in fractionation schemes. BT was prescribed in addition to a 25-fraction external beam radiotherapy course of 1.8 Gy fractions. BT was administered in four fractions (UMCU) or three to four fractions (EMC). Full dose distributions were scaled to $D_{90\%}$ of the HRCTV to 7.5 Gy, for inter-patient comparison and institute translatability. Physical dose scaling was chosen to achieve a total biological dose of the HRCTV of 88 Gy (α/β = 10) given in four BT fractions. Dose-volume histograms (DVHs) were constructed for all OARs based on the scaled (physical) dose distributions.

Table 1
Overview of the dosimetric criteria for the full treatment (external beam radiotherapy and brachytherapy) for the EMBRACE II protocol (applied for both UMCU and EMC cohorts). HRCTV = high-risk CTV, IRCTV = intermediate-risk CTV, EQD_{2Gy} = 2 Gy equivalent dose, α/β = 10 Gy is used for the HRCTV and IRCTV and α/β = 3 Gy for OARs.

Dosimetric criteria		UMCU and EMC	
Structure		*Constraint EQD_{2Gy}*	*Aim EQD_{2Gy}*
HRCTV	$D_{90\%}$	85 Gy	> 90 < 95 Gy
IRCTV	$D_{98\%}$	-	> 60 Gy
Bladder	D_{2cm3}	90 Gy	< 80 Gy
Rectum	D_{2cm3}	75 Gy	< 65 Gy
Sigmoid	D_{2cm3}	75 Gy	< 70 Gy
Small Bowel	D_{2cm3}	75 Gy	< 70 Gy

Table 2
Overview of the treatment characteristics of the clinical plans of the UMCU and EMC cohorts (UMCU and EMC, including applicator types (ovoid- versus ring-based) and application types (intracavitary only versus intracavitary with interstitial needles).

	UMCU (n = 120)	EMC (n = 160)
Ovoid-based applicator	56	157
Ring-based applicator	64	3
Intracavitary only	48	2
Intracavitary with interstitial needles	72	158

OVHs were constructed for all OARs separately with respect to HRCTV for all plans of UMCU and EMC. Points were sampled on the considered OAR, after which the closest distance to the target of interest was calculated for each sampled point. These distances were then combined into a histogram. Therefore, the construction of the overlap volume histogram does not necessarily require overlap between OAR and target, but merely describes the distance between OAR and target [14]. The full dataset comprised an OVH and a DVH for each included plan, and for each combination of OAR and HRCTV. To construct the QA models, the UMCU dataset was chosen as gold-standard, and consequently selected as reference dataset. This had two consequences –the UMCU dataset was used to train the QA tool model and the thresholds of the QA tool were defined by the confidence interval of the model outcome.

The first step was executed by training a random-forest model for each OAR, where random forest networks were selected for their relative robustness to overfitting [16]. The second step was to establish the thresholds of the QA models, where a leave-one-out approach of the training data was performed. For the first step, the training OVH data was reduced with Principal Component Analysis (PCA), after which a random-forest model was fitted to the remaining leave-one-out data. The model was then applied to the left-out OVH to predict the D_{2cm3} value and the planned (clinically delivered) D_{2cm3} and predicted D_{2cm3} values were registered. For the second step, the prediction interval was defined as the 95 % Confidence Interval (CI) of the difference between planned D_{2cm3} and predicted D_{2cm3} values. This interval reflects the natural distribution of the training dataset. The thresholds were defined by this interval. A trained QA model can predict a full DVH for an unseen OVH of one type of OAR and target structure, and flag the plan if a clinically-planned D_{2cm3} value is not within this interval. All code was implemented in Python 3.5.2 and DICOM handling was performed with in-house developed software Matterhorn. The Matterhorn platform is a software framework built from reusable components coded in C++ and Python, accessible through libraries in a development environment. Data preprocessing and machine-learning was performed with Scikit-learn version 0.19.2 [17].

With the QA models for each OAR being trained and the thresholds defined, the models were applied to the OVH data of the EMC dataset to find the predicted D_{2cm3} values for this cohort. The difference between planned D_{2cm3} and predicted D_{2cm3} values was registered. Planned values outside of the prediction interval (outliers) were identified, as defined by the training set in the intra-validation phase. Plans having one or more OARs with outliers outside of the thresholds were classified as suboptimal and investigated. Notably, suboptimal is defined as having a higher dose to an OAR than is to be expected, based on the patient's anatomy. This also includes D_{2cm3} values that are below constraint values. An

example of a suboptimal plan might be a higher than expected dose to the bladder to improve coverage of the cranial part of the tumor coverage with an intracavitary applicator that is too short. Another example is the placement of interstitial needles more proximal to the small bowel loops than intended, resulting in less small bowel sparing in favor of target coverage. As the QA model assumes a good-quality brachytherapy application, these types of suboptimal plans ought to be flagged in the workflow.

Then, the plan statuses and remarks were retrieved from the patient record and verify system. In these statuses complications during planning are recorded, such as suboptimal location of the interstitial needles or suboptimal fit of the intracavitary part of the applicator. If plans were recorded to have had such problems, this plan was not used for further replanning and analysis. From a QA perspective, this plan was already considered to be suboptimal and the outlier status of the QA tool confirms it to be a true positive. If plans were not recorded to have problems, these plans were replanned to quantify if and how much improvement was achieved – and therefore if their outlier status was justified.

Replanning was performed by experienced brachytherapy radiotherapy technician M.H. Replanning instructions were given for all plans containing outliers. The instructions included the outlier status and the D_{2cm3} thresholds for each OAR of each plan (guided replanning). The radiotherapy technician then modified the flagged plans, aiming to maintain the achieved target coverage, whilst shaping the dose distribution such that all OAR thresholds were met. The starting point for the replanning was the clinically-used plan. If the technician was unsuccessful, the tumor geometry, applicator and needle positions were evaluated. Completed replans were evaluated by experienced radiation-oncologist J.W.M. who then evaluated the replans from a clinical perspective based on suitability for treatment. Evaluations were done based on needle and applicator loading, source positions, source dwell times, gross tumor volume coverage, HRCTV coverage, intermediate-risk CTV (IRCTV) coverage and dose from previously given BT fractions to the patient.

The impact of the QA tool's outlier detection was assessed based on (1) D_{2cm3} decrease after replanning, (2) outlier status after replanning, and (3) planning circumstances, as defined by the RTT, radiation-oncologist, and clinical remarks regarding the planning from the patient information system. Based on these results, a conclusion was drawn on the suitability of OVH-based models for plan improvement.

Results

A total of 36 plans of 29 patients was flagged as suboptimal by the proposed QA model, out of 160 plans of 68 patients. For the whole cohort evaluating 160 plans, only eight outliers were expected to be flagged under normal circumstances per OAR due to the 95 % CI, under the assumption that the distributions of planned D_{2cm3} values are similar between institutes. However, it was found that for this EMC cohort this number was higher (up to 16 for small bowel). The planned and predicted D_{2cm3} values of all OARs of the full cohort are shown in Fig. 1.

Out of 36 plans, 25 plans could be improved by an experienced RTT, of which the planned and predicted values before replanning are plotted in Fig. 2. A total overview of the results is shown in Table 3. For the remaining 11 plans that could not be improved, the quality of the application was suboptimal for the tumor geometry (eight plans). Examples include a suboptimal size or position of the intracavitary applicator (4), tumor coverage compensation to account for planning problems in prior fractions (2), or an insufficient number or unsuitable location of interstitial needles (2). These examples were not explicitly recorded in the record and verify system, as target coverage could still be met, but were found to be limiting factors in our retrospective analysis to improve plan quality. For three plans no reason could be found for lack of improvement. These plans sufficed at the time of clinical practice.

All plans were inspected in terms of target volume coverage by radiation oncologist J.W.M. Two of the 25 replanned plans reported

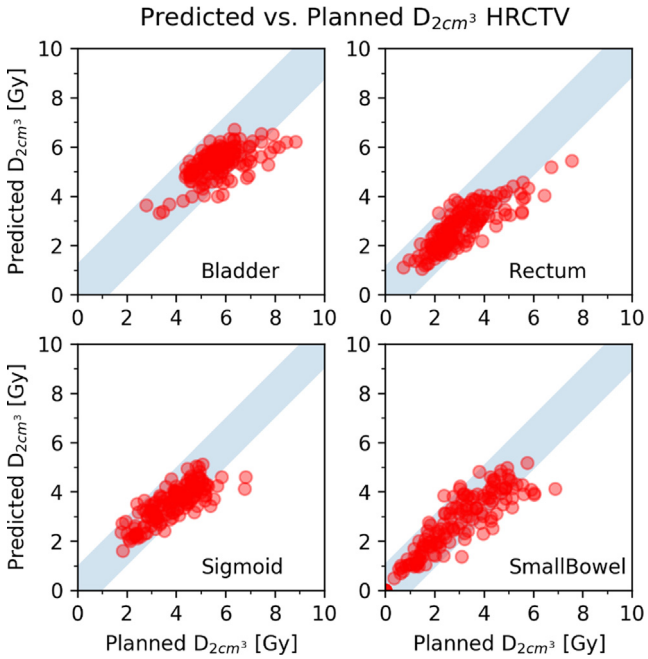

Fig. 1. Predicted and planned D_{2cm3} values for all 160 EMC plans. The light-blue shaded area represents the thresholds of the QA model based on the UMCU data. Outliers are defined as points outside of these thresholds. Outliers in the right-lower corners are suboptimal, as their predicted value is lower than the planned (delivered) value. Outliers in the left-upper corners are super-optimal, with predicted values being higher that the planned value.

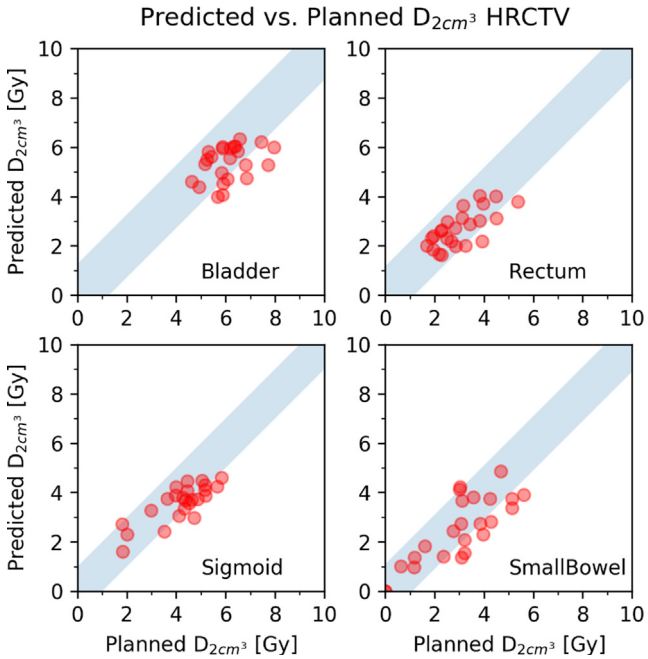

Fig. 2. Predicted and planned D_{2cm3} values for the EMC plans containing one or more OAR outliers that could be replanned. The light-blue shaded area represents the thresholds of the QA model based on the UMCU data. Outliers are defined as points outside of these thresholds.

Table 3
Number of outliers (outside of QA threshold) for the full EMC cohort per OAR and individual plan, as a part of the total per category. As an example, for the bladder 14 out of 160 plans were outside the UMCU-defined threshold (outliers), 5 of these 14 plans could not be replanned due to complicated implantations. The other 9 plans could be replanned, and after replanning 5 of these plans were still flagged as an outlier for the bladder. Replanning caused 10 out of 160 plans to still be flagged for an outlier for bladder, instead of 14 before.

No. outliers	Full cohort	Not replanned	Before repl.	After repl.	Full cohort after repl.
Bladder	14/160	5/14	9/14	5/9	10/160
Rectum	8/160	4/8	4/8	1/4	5/160
Sigmoid	16/160	5/16	11/16	7/11	12/160
Small Bowel	15/160	5/15	10/15	6/10	11/160
Total no.	53/160	19/53	34/53	19/34	38/160
No. plans	36/160	11/36	25/36	16/25	28/160

better OAR sparing with comparable HRCTV coverage, but lacked in IRCTV coverage and were therefore not clinically acceptable. After replanning, the adapted plans were assessed again with the OVH-QA method to determine the outlier status. Nine of the 25 plans were not identified any more as outlier after replanning, five plans improved but not within the CI.

The planned and predicted D_{2cm3} values of all OARs of the flagged cohort after replanning are displayed in Fig. 3. The changes in OAR D_{2cm3} dose before and after replanning are shown in Fig. 4. A median D_{2cm3} improvement of 0.62 Gy (interquartile range 0.31–1.28 Gy) was found for all OARs combined. Two out of 25 plans did not improve for all OARs combined, reporting outliers for rectum (-1.01 Gy) and sigmoid (-0.69 Gy). In the first case the bladder constraint was surpassed, and an improvement was reported of 0.80 Gy for bladder at the cost of the rectum, which increased but remained below the constraint. For the second plan the rectum D_{2cm3} value was reaching the constraint value, which was reduced by compromising on the sigmoid D_{2cm3} value. Both cases were examples of different clinical trade-offs between OARs, where plan quality improved despite reduced OAR sparing.

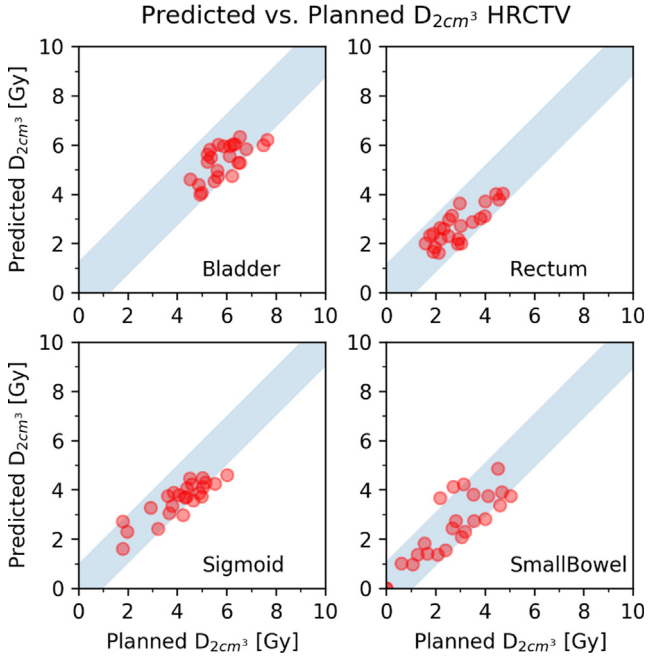

Fig. 3. Predicted and planned D_{2cm3} values for the EMC plans containing one or more OAR outliers that could be replanned, **after replanning**. The light-blue shaded area represents the thresholds of the QA model based on the UMCU data. Outliers are defined as points outside of these thresholds.

Discussion

In this paper a method is presented to detect suboptimal plans and improve plan quality in MR-based BT planning for cervical cancer patients in a multi-center setting. Single-institute clinical plans, tied to patient anatomy through OVHs, serve as a foundation for D_{2cm3} value predictions of another institute. This principle allows knowledge transfer on treatment planning quality between institutes without the exchange of privacy-sensitive data.

The use of patient anatomy for QA purposes for BT of cervical cancer patients has already been described by several studies [18–20]. These studies reported results for CT-based planning, where target delineation is shown to differ from a MR-based setting [21]. Additionally, the publications described single-center studies and do not include patients treated with the EMBRACE II protocol. Within a multi-center study setting, the method shows potential to identify protocol deviations in treatment planning between institutes. We believe this is the first study of its kind where patient geometry is incorporated to improve treatment planning for cervical cancer patients.

In this study three plans were found that could not be improved without evident reasons and two plans where IRCTV coverage was insufficient after replanning, potentially corresponding to a false positive detection. Out of 36 outlier plans, this would equal a 14 % false positive rate. Because suboptimal plans would otherwise not be flagged, the use of the tool seems to have added value, making this false positive rate acceptable. If this would not be the case, redefining the CI from 95 % to change the sensitivity of the outliers could modify the number of false positives according to the preference of individual institutes. This possibility has not been covered in this study.

Overall, a higher number of plans was flagged as suboptimal in the EMC protocol than expected, based on the 95 % CI interval. This is potentially explained by the early phases of the introduction of the EMBRACE II protocol of the EMC patients, as all flagged plans were clinically administered in the first one and a half years after protocol implementation. It is likely that a learning curve was present in the earlier phases of the implementation of the protocol, indicating the merit for OVH-based QA in multi-center studies. It should be noted that the EMBRACE II protocol is implemented in both centers, and is considered to be a tightly descriptive protocol. As a result, the number of outliers from the QA tool and the dosimetric improvements after the QA phase were expected to be limited, which was shown in the study. Larger dose differences could be expected from such QA workflows for centers which follow a less tight dose prescription protocol, but a validation of the QA tool should be performed beforehand.

Furthermore, the QA models capture two types of outliers – clinically suboptimal plans with correct implantation that benefit from further optimization, and clinically suboptimal plans with problematic implantation that cannot be further optimized. An assumption is made for the models that the HRCTV and IRCTV

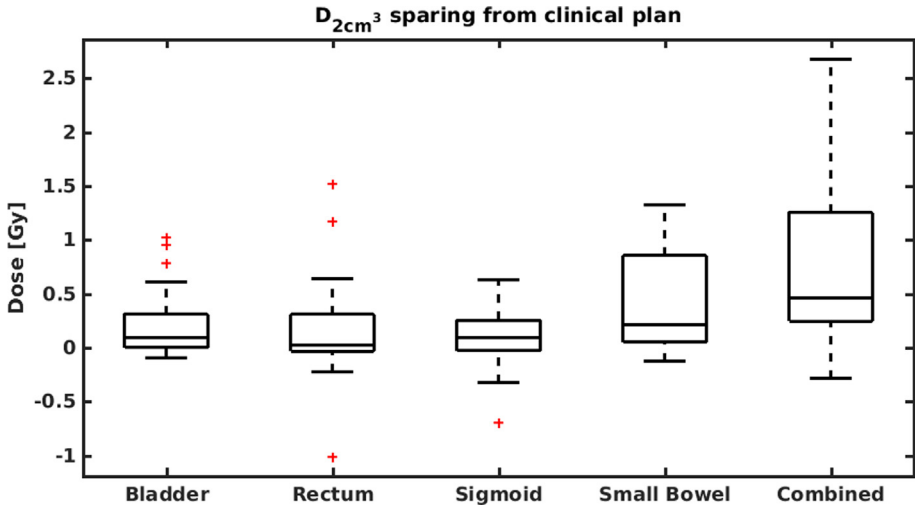

Fig. 4. Dose difference in Gy of D_{2cm3} values between the clinically-used and replanned plan for all OARs, and all OARs combined. A negative dose difference indicates that the clinically-used plan value was lower than the replanned plan. The combined dose difference can be negative due to trade-offs between OARs.

are adequately covered by the applicator and needle insertion to adhere to the clinical protocol. For problematic implantations this is clearly not the case, resulting in dosimetric predictions that cannot be abided. It is a shortcoming of our model that such differences cannot be discerned through the QA model. Further research is necessary to distinguish these two type of outliers.

To distinguish these cases, fully-automated planning could improve consistency of planning. It has been demonstrated for LACC patients that fully-automated planning can provide high-quality plans [22–26]. Fully-automated planning could generate consistent datasets to improve the prediction accuracy of OVH models. However, a necessity for QA will still remain to also validate the quality and optimality of fully-automated clinical plans [27]. This was beyond the scope of this research, but ought to be considered for future studies.

The QA model predictions that resulted in replanning facilitated a median 0.62 Gy improvement for all OARs per patient. These improvements can be considered modest, and are slightly lower than results of a study in fully-automated planning for a comparable cohort, where mean bladder and rectum D_{2cm3} reductions were reported to be 0.87 and 1.4 Gy, respectively [22]. The main strength of OVH-based QA is the prediction speed, where near real-time feedback could aid the planning procedure. The OVH-based models are fast to train – less than a minute – and D_{2cm3} predictions for all OARs can be made in mere seconds, which is significantly faster than fully-automated planning options. Additionally, the models are more easily transferable to other institutes and swiftly retrained and redistributed if necessary, which are both desirable characteristics in a multi-center setting.

Conclusion

In this study we have presented the impact of multi-center, OVH-based QA for BT of cervical cancer. Predicting feasible dosimetric values aids planners, as it provides guidance to focus on specific OARs to improve plan quality within the limited time that is available for BT treatment planning. OVH-based QA can provide knowledge transfer to train inexperienced institutes within a multi-center clinical protocol. Future studies ought to include the quality of the applicator implant and the effect of fully-automated planning in prediction quality.

Conflicts of interest

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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