Title
Knowledge-based dose prediction models to inform gynecologic brachytherapy needle supplementation for locally advanced cervical cancer

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Purpose: The use of interstitial needles, combined with intracavitary applicators, enables customized dose distributions and is beneficial for complex cases, but increases procedure time. Overall, applicator selection is not standardized and depends on physician expertise and preference. The purpose of this study is to determine whether dose prediction models can guide needle supplementation decision-making for cervical cancer.

Materials and Methods: Intracavitary knowledge-based models for organ-at-risk (OAR) dose estimation were trained and validated for tandem-and-ring/ovoids (T&R/T&O) implants. Models were applied to hybrid cases with 1-3 implanted needles to predict OAR dose without needles. As a reference, 70/67 hybrid T&R/T&O cases were replanned without needles, following a standardized procedure guided by dose predictions. If a replanned dose exceeded the dose objective, the case was categorized as requiring needles. Receiver operating characteristic (ROC) curves of needle classification accuracy were generated. Optimal classification thresholds were determined from the Youden Index.

Results: Needle supplementation reduced dose to OARs. However, 67%/39% of replans for T&R/T&O met all dose constraints without needles. The ROC for T&R/T&O models had an area-under-curve of 0.89/0.86, proving high classification accuracy. The optimal threshold of 99%/101% of the dose limit for T&R/T&O resulted in classification sensitivity and specificity of 78%/86% and 85%/78%.

Conclusion: Needle supplementation reduced OAR dose for most cases but was not always required to meet standard dose objectives, particularly for T&R cases. Our knowledge-based dose prediction model accurately identified cases that could have met constraints without needle supplementation, suggesting that such models may be beneficial for applicator selection.

Keywords: knowledge-based; dose prediction; cervix cancer, brachytherapy; needle supplementation

Introduction

A brachytherapy boost after external beam radiation (EBRT) is considered to be the standard of care for cervical cancer patients (1, 2). Brachytherapy is often delivered using intracavitary applicators such as tandem-and-ring (T&R) or tandem-and-ovoids (T&O) (3). For more complex cases, for example those with large or asymmetric high-risk clinical target volumes (HRCTVs), interstitial needles are often added to better customize the dose distribution, reducing dose to organs-at-risk (OARs), and/or improving HRCTV coverage (4–6). However, using needles increases procedure time and complexity (7). Additionally, the decision to use needles is not standardized and depends on the expertise and preference of the physician. The increased procedural complexity and need for expertise may lead to barriers to brachytherapy implementation, which is problematic given that brachytherapy utilization is diminishing despite its proven benefit (2).

Knowledge-based models for plan quality analysis or automated treatment planning have been extensively studied in EBRT (8–10), with over a decade of development, many publications and existing commercial solutions. However, exploration of these methods are comparably rare in brachytherapy (11–13). Knowledge-based models use prior information from treatment plans to predict dose for new cases based on contours, distances from the target-to-OARs, and other geometric features (9).

Various EBRT studies have proven that the use of knowledge-based models improves plan quality, reduces planning variability and leads to more standardized plans with greater OAR sparing (14–17). Similar to EBRT, knowledge-based models could help to standardize future brachytherapy treatment planning and predicted doses could serve as quality assurance metrics. However, unlike EBRT, brachytherapy plan quality is largely dictated by the applicators and/or needles implanted. There are a variety of different applicators to choose from and strategies for implantation, which leads to large plan quality variations when coupled with variability in treatment planning. Knowledge-based models could play a unique role in brachytherapy, where dose predictions for different treatment types could help to inform the optimal treatment technique.

The purpose of this study is to determine whether knowledge-based models can predict cases where needle supplementation is required to meet dose objectives. To investigate this, existing intracavitary models were applied to hybrid cases treated with additional needles, and estimated OAR doses were used to predict cases that required needle supplementation. Accuracy of classification was verified by replanning all cases without needles, and

compared to the current classification in our clinic. Knowledge-based dose estimations could form the basis for more objective, standardized decision-making on necessity of needle usage.

Materials and Methods

Patient Cohort

Cervical cancer patients treated between 2017-2020 with image-guided high-dose-rate brachytherapy with T&O or T&R applicators and 0-3 implanted interstitial needles were included (UCSD IRB #200065C). Treatment planning, applicator reconstruction and contouring were performed based on computed tomography (CT) imaging. Cases implanted with both an intracavitary applicator and needles are referred to as "hybrid" cases. A "case" in this context is defined as a single fraction of a brachytherapy treatment, consisting of 3-5 fractions. Detailed information about the patient cohort is presented in Table 1. Organs and HRCTV (cervix, gross disease and any potential extension) were contoured on the CT. Clinical treatment planning was conducted according to most of the EQD2 dose objectives defined by EMBRACE II (18, 19), which include limits (HRCTV D90>85Gy, bladder D_{2cc}<90Gy, rectum D_{2cc}<75Gy and D_{2cc} sigmoid<75Gy) and soft planning aims (recommended but not required, bladder D_{2cc}<80Gy, rectum D_{2cc}<65Gy, and sigmoid D_{2cc}<70Gy). After normalization to point A, plans were optimized to meet objectives and minimize OAR dose. During this process, the overall EQD2 for HRCTV D90 and organ D_{2cc} values were projected using a spreadsheet and then compared to the dose objectives, to ensure that the treatment plan fulfilled all necessary dose criteria. All reported clinical parameters, e.g., D90, V100 and D_{2cc}, were exported directly out of the treatment planning system. All patients received prior EBRT, and the most common EBRT prescription was 45Gy in 25 fractions.

Knowledge-Based Dose-Prediction Models

Previously trained and validated dose-prediction models for intracavitary applicators were used. Full details about the algorithm can be found in Yusufaly *et al.* (13), which demonstrates the accuracy of dose-prediction models for cervical cancer patients treated with T&O. Briefly, DVH models are 1D radial models, which predict dose to OARs based on the radial distance from an OAR sub-volume to the HRCTV. OARs are divided into sub-volumes based on the boundary distance to the HRCTV contour by overlapping the OAR contour with 2mm shells expanding around the HRCTV. A differential DVH for each OAR shell is extracted from each treatment plan in the training set, and averaged to produce dose kernels as a function of radial distance. For model predictions, OAR

contours are discretized in the same manner, and the differential DVH of the considered OAR is calculated from the sum of differential DVH kernels, weighted by the volume of each OAR sub-volume (8, 13, 20). DVHs for new patients can be predicted using HRCTV and OAR contours alone. Additional details about models, are described in the Supplementary Materials. Two different models were trained for T&R or T&O applicators, since these applicators result in significantly different OAR dose (21, 22). The T&R (T&O) model was trained on 75 (80) intracavitary cases and validated on 38 (32) cases (see Table 1 for more details), achieving an approximately 70/30% split between training/validation.

Since OAR D_{2cc} is a common metric used to evaluate brachytherapy plan quality, these metrics were extracted from all DVHs. Unless otherwise stated, D_{2cc} values in results and figures are reported in absolute dose per brachytherapy fraction in Gy. Model performance was quantified using the difference between actual D_{2cc}s obtained from clinical plans and the predicted D_{2cc}s, i.e. ΔD_{2cc}, as well as the standard deviation over these $\sigma_{Model}(\Delta D_{2cc})$, representing model precision. The T&R (T&O) σ_{Model} was 0.66Gy (0.52Gy), 0.39Gy (0.70Gy) and 0.50Gy (0.46Gy) for bladder, rectum and sigmoid, respectively (see Supplementary Figure 4).

Model training, validation and extraction of predicted DVHs were performed using automated scripts in MIM (v7.0.1, MIM Software Inc., Cleveland, OH). D_{2cc} calculation and data analysis was performed using MATLAB (R2019b, MathWorks, Inc., Natick, MA).

Replanning Procedure

Seventy (67) hybrid T&R (T&O) cases were replanned without loading the inserted needles to demonstrate the achievable dose using an intracavitary applicator alone (see Supplementary Figure 1, which describes the standardized replanning procedure). This process mimics manual, clinical treatment plan optimization with the addition of dose predictions to guide planning. Patient-specific dose objectives were calculated based on the total number of prescribed fractions and dose as well as the dose received in prior EBRT, to ensure EQD2 objectives were met. First, the clinical treatment plan was reset with standard loading of the intracavitary applicator. After normalizing to point A, the dose distribution was shaped to cover the HRCTV. If the first mandatory aim, HRCTV D90 ≥ 85Gy EQD2, was fulfilled then the plan was further tuned to reduce OAR dose, attempting to meet D_{2cc} constraints. The predicted doses were used to guide optimization; however, the aim was to minimize OAR dose, i.e., when possible, the plan was further improved until D_{2cc} values were lower than the predicted D_{2cc} values ± σ_{Model}. In

order to quantitatively replicate the visual evaluation that occurs while planning at our center (i.e., covering the HRCTV target with the prescription isodose) we also attempted to meet a third criteria, V100 ≥ 95% (where 100% corresponds to the prescribed dose per brachytherapy fraction as shown in Table 1), although this was prioritized last. All replans were created by a trained postdoctoral fellow and verified and/or further modified by experienced brachytherapy physicists (DB, DS, KK, XR). All treatment planning was performed in the same brachytherapy planning system (BrachyVision, v15.6, Varian Medical Systems, Inc., Palo Alto, CA). Replanned doses were compared to predicted and actual hybrid dose values using a two-sample Student's t-test (significance level of 0.05).

Receiver-Operating-Characteristic Analysis

In order to quantify the ability of the models to accurately identify cases that require needles, receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) determined. The "true condition" was defined by the replan: any intracavitary plan with an OAR dose exceeding the objective was identified as a case requiring needles. For the model, a threshold was used for needle classification. This threshold was taken as a percentage of the dose objective for an OAR, and was varied from 50% to 200% to reconstruct the ROC plot. Since all dose objectives are based on EQD2 including EBRT, we computed a patient-specific objective for a single brachytherapy fraction by assuming that all brachytherapy fractions received the same dose. Analysis was performed for two different sets of objectives – the dose limits and soft planning aims - since some clinics may use the more conservative aims to determine when to implant needles. True positives were defined as needle cases (any replanned OAR>dose objective) that were correctly identified as such by the model (any predicted OAR dose>threshold). Sensitivity and specificity of the model classification were then calculated for each OAR separately and combined, using the following equations, and positive/negative predictive value (PPV/NPV) were computed.

$$Sensitivity = \frac{¿\, cases\ with\ D\,2\,cc\,,\ replan\ \geq\ dose\ objective \wedge D\,2\,cc\,,\ predict\ \geq\ threshold}{¿\, cases\ with\ D\,2\,cc\,,\ replan\ \geq\ dose\ objective}$$

$$Specificity = \frac{¿\, cases\ with\ D\,2\,cc\,,\ replan < dose\ objective \wedge D\,2\,cc\,,\ predict < threshold}{¿\, cases\ with\ D\,2\,cc\,,\ replan < dose\ objective}$$

Because the hybrid dataset is biased towards cases requiring needles, an equivalent number of randomly selected intracavitary cases (70 T&R and 67 T&O) were added to the classification analysis. Any plans that did not fulfill HRCTV D90 85-90Gy were rescaled to ensure equivalent coverage to replans. Our current clinical status for

needle classification was also determined retrospectively for comparison, which is based on physician experience using knowledge from prior fractions (if any), clinical examination, D90 planning goals based on the number of planned fractions, or imaging. A patient that was actually treated with needles was classified by the physician as needing needles, and vice versa for an intracavitary applicator alone. The optimal threshold for model classification was determined using the Youden index, which maximizes sensitivity and specificity (23). The optimal threshold is defined as the point on the ROC curve that corresponds to the maximal Youden index.

Results

Comparison of Intracavitary Replans to Actual Clinical Hybrid Plans

Organ doses for intracavitary replans are compared to values from clinical hybrid plans in Figure 1. Overall, OAR dose sparing was improved with interstitial needles, especially bladder dose when using T&O. For a single brachytherapy fraction, clinical hybrid implant D_{2cc} for bladder, rectum and sigmoid were, on average, 5.23±1.01Gy (5.18±0.84Gy), 2.81±0.93Gy (4.07±0.96Gy), and 4.00±1.04Gy (3.89±1.05Gy), for T&R (T&O) applicators. The replanned OAR doses were higher, on average, with mean T&R (T&O) D_{2cc} of 6.02±2.33Gy (6.53±1.88Gy), 2.95±0.94Gy (4.69±1.86Gy), and 3.91±0.74Gy (4.32±1.61Gy) for bladder, rectum and sigmoid, respectively. Replanned and clinical doses were significantly different for bladder (mean deviation=1.11Gy and $p=0.01$ for T&R, 1.38Gy and $p<0.001$ for T&O) and rectum for T&O (mean deviation=0.83Gy, $p=0.02$).

Using our standardized procedure for replanning, a mean and standard deviation of the HRCTV D90 of 107±6% (105±7%) was obtained for all T&R (T&O) cases (see Supplementary Figure 3), where dose is relative to the prescription per brachytherapy fraction. The clinical plans featured greater variation in target coverage, with HRCTV D90 values of 114±13% (105±10%) for T&R (T&O) applicators. The replans indicated that 67% (39%) of the hybrid T&R (T&O) cases would have met the OAR dose limits and 43% (9%) would have met the softer planning aims without needles.

Comparison of Predicted and Replanned Intracavitary Dose

The predicted D_{2cc} were, on average for T&R (T&O), 6.02±2.03Gy (6.68±1.16Gy), 3.00±0.86Gy (4.70±0.75Gy), and 4.40±0.79Gy (4.33±0.87Gy) for bladder, rectum and sigmoid respectively. A comparison of predicted and replanned doses is shown in Figure 2 and Supplementary Figure 3. As can be seen in Figure 2 and

Table 2, most of the sigmoid and rectum replanned doses fell within precision of the model predictions (i.e. within the grey band), or below. The results for bladder were slightly more variable, particularly for cases exceeding the dose limits, but most cases fell within the diagonal quadrants (indicating that both replan and predicted doses were either greater or less than the dose limits). Besides the sigmoid for the T&R applicator ($p<0.001$), the replanned D_{2cc} did not significantly differ from predicted D_{2cc} values. The mean ± standard deviation of differences between replanned and predicted D_{2cc} (i.e. $D_{2cc,replanned}–D_{2cc,predicted}$) were 0.00±0.95Gy (-0.15±1.52Gy) for bladder, -0.06±0.43Gy (-0.01±1.56Gy) for rectum and -0.49±0.47Gy (-0.01±1.19Gy) for sigmoid for T&R (T&O). As shown in Table 2 and Figure 2, there were very few cases (≤ 10%) for which the replanned dose exceeded the dose limit, while the predicted dose met the limit (top left quadrant of plots in Figure 2). Considering all OARs together, 77% (68%) of T&R (T&O) cases had replanned D_{2cc} values lower than or within the uncertainty of the predictions.

Needle Classification Performance Using Dose Limits

ROC curves for model needle classification are displayed in Figure 3. The AUC using dose limits as decision criteria for needle supplementation were 0.89 (0.86) for T&R (T&O), indicating good model prediction accuracy. These plots use all organ doses to classify needle cases, while AUC metrics for a single organ are displayed in Table 2. The classification accuracy of our clinic based on the physician's choice of needle usage (red crosses on Figure 4) corresponds to a sensitivity of 72% (73%) and specificity of 56% (67%) for T&R (T&O), which was lower than what was theoretically achieved with the predictions as guidance (Figure 3A and B). The optimal threshold was determined to be 99% of the dose limit for T&R (providing a sensitivity of 78% and specificity of 85%), and 101% of the dose limit for T&O (providing a sensitivity of 86% and specificity of 78%) (black crosses on Figure 4). This corresponded to a PPV and NPV of 61% (74%) and 93% (88%) for T&R (T&O).

Needle Classification Performance Using Planning Aims

Classification results using planning aims as the decision boundary for needle supplementation were similar. AUC values were 0.88 (0.89) for T&R (T&O). The sensitivity and specificity of the clinical classification were determined to be 66% (60%) and 34% (81%) for T&R (T&O), respectively (Figure 3C and D). The optimal threshold for model classification was 104% of the planning aim for T&R (sensitivity=84% and specificity=81%)

and 110% for T&O (sensitivity=79% and specificity=91%). This corresponded to a PPV and NPV of 77% (96%) and 86% (58%) for T&R (T&O) cases.

Discussion

This study explores the benefits of knowledge-based models to guide brachytherapy needle supplementation decision-making. Although there are solutions for automating various aspects of brachytherapy treatment planning, such as applicator reconstruction (24–26) and inverse optimization (12, 27), there currently are no tools to guide gynecological applicator choice. Therefore, the addition of interstitial needles is not standardized and relies on the physician's preference and expertise, which is particularly challenging for inexperienced physicians. The proposed model predictions could help physicians make informed decisions based on quantitative metrics.

Relative Benefit of Needles vs. Standard Applicators

In this series, we found that needles were not always needed to meet the dose objectives. 67% (39%) of the T&R (T&O) hybrid cases could have met the OAR dose limits with an intracavitary applicator alone and 43% (9%) of the T&R (T&O) hybrid cases would have even met the planning aims. However, the use of needles can enable further OAR sparing and/or target dose escalation (28), and sometimes physicians will add needles to achieve either of these goals based on patient and tumor anatomy. The overall objective of treatment planning is to get the best coverage with the lowest OAR doses, and physicians in our clinic often add needles to meet softer planning aims rather than dose limits. Our data showed that supplemental needles resulted in significant dose reductions for bladder (0.78-1.35Gy on average) and rectum (0.43Gy, T&O only). The bladder seemed to benefit the most from needles; for 65% (34%) of T&R (T&O) cases, bladder was the only organ that exceeded the dose limit, indicating that the bladder was the limiting factor for needle requirement. Overall, the hybrid T&O cases had a larger HRCTV volume in comparison to the hybrid T&R cases (see Table 1), which might be linked to the greater percentage of T&O cases requiring needles. Hybrid plans featured a wider range of target coverage than our standardized intracavitary replans, though this may reflect different patient-specific clinical requirements, as opposed to non-standardization of planning or applicator differences. The slightly small HRCTV volumes in the hybrid patient

group (see Table 1) are likely due to the fact that purely interstitial cases and hybrid cases with more than 3 needles were excluded.

It is undeniable that needle supplementation can improve dosimetry, but it comes at the cost of increased procedure time and complexity, which is potentially a barrier to institutions that lack brachytherapy expertise or resources. The analysis and tools presented in this study could allow physicians to weigh the relative benefit of needles vs. standard applicators, and to make more informed decisions about needle supplementation that are appropriate for their center.

Model Dose-Prediction Accuracy

Dose-prediction models were fully implemented with scripting in MIM, meaning that once images were contoured, OAR dose predictions could be computed within seconds. The use of CT-based planning as opposed to magnetic resonance (MR)-based should not impact results, since the models rely only on the target and organ contours and were trained on cases with a wide range of HRCTV volumes. However, future work will examine model accuracy at institutions that use MR for contouring.

This manuscript mainly focuses on the application of knowledge-based models to needle discrimination, but the predicted doses could also be beneficial for patient-specific plan quality control during treatment planning. Model prediction precision ranged from 0.39-0.70Gy for intracavitary validation cases. Although the models were applied to more complex cases, the model performance was still reasonable. Replanned D_{2cc} values were within the precision of T&R (T&O) model-predictions or lower for 77% (68%) of cases considering all OARs. This result is surprising, given that the model was trained on intracavitary cases, where organ doses rarely exceeded the limits and the anatomy was less challenging. We suspect that prediction accuracy would improve if we added more complex cases to the training set, which would now be possible since we have intracavitary replans for all these patients. The fact that many replanned OAR doses were lower than predicted D_{2cc} - σ_{Model} (see Figure 2) is expected, because the models were produced using variable clinical plans, while replanning was performed using a standardized workflow guided by predictions. This effect has been observed in EBRT studies as well, where using knowledge-based planning significantly reduced OAR dose (29). The current model predictions are most appropriate for quality control of intracavitary treatment plans. Nonetheless, future work will develop separate models for hybrid and

interstitial cases in order to provide more accurate D_{2cc} predictions and valuable quality control for more complex cases.

Needle Classification Accuracy

The ROC analysis and AUCs, ranging between 0.88-0.89 (T&R) and 0.86-0.89 (T&O), demonstrated that knowledge-based models can effectively discriminate between cases that require needles and cases for which an intracavitary applicator is sufficient, with high sensitivity and specificity. The predicted classification was beneficial for needle supplementation guidance when reviewed retrospectively and not considering patient-specific needs. Using the planning aims to guide needle decision-making, which more closely reflects our clinical practice, the current sensitivity of needle selection is 66% (60%) and specificity is 62% (81%) for T&R (T&O), but includes other clinical factors not represented in the model. Dose predictions could improve sensitivity and specificity for T&R (T&O) to 84% (79%) and 81% (91%), respectively, using the optimal threshold of 104% (110%) of planning aims to indicate needle requirement. In practice, this means that one could run the model for a given T&R case and if predicted doses exceeded 104% of the planning aims, needles would be recommended. There would be an 84% chance that a case requiring needles would be accurately identified as such by the model, and an 81% chance that a case would be accurately identified as not requiring needles, if other clinical determinants did not favor needle use. We suspect that the current model predictions (both doses and classification) would be meaningful for any institution using standard T&R or T&O applicators and similar treatment planning criteria. Future work will test the accuracy and applicability of these models on datasets and workflows of independent institutions.

Standardized Planning

The standardized planning workflow, driven by knowledge-based dose estimations, was another useful outcome from this work, and could be beneficial to implement in clinical practice. Using the predictions and dose criteria as guidance, a postdoctoral fellow was easily trained to produce clinically acceptable plans in reasonable timeframes (about 10 minutes, not taking catheter digitization and quality assurance into account). Only about 10% of the cases required adjusting after review by experienced brachytherapy physicists. This suggests that guiding treatment planning with predictions could be beneficial for training residents and inexperienced clinicians, and could potentially speed up treatment planning for experienced clinicians. Using patient-specific dose predictions as

targets, the planner could push harder on organ dose than they otherwise might have under time constraints, which is usually one limiting factor of plan optimization. This same effect has been reported for EBRT: when only static population-based limits were used to guide planning, high degrees of plan quality variability and excess dose to normal tissues were observed, while when patient-specific achievable dose limits were provided, variability and normal tissue doses were substantially reduced (30, 31). Standardized planning, guided by dose predictions, could help physicians and physicists create optimal treatment plans for patients and standardize plan quality.

Proposed Clinical Workflow Using Needle Supplementation Guidance

Models are most accurate for same-day predictions, and thus would be very beneficial for centers with image-guided brachytherapy suites (see Figure 4A for proposed workflow in clinical implementation). In this case, an intracavitary applicator should be implanted for each fraction, and after imaging and contouring, the models should be used to predict if needles should be added. Adding needles and re-imaging after initial imaging may only be feasible at a minority of centers (32), so we also propose the following alternative workflow (see Figure 4B). For the first fraction, prior knowledge from examination and imaging should be used to decide if needle supplementation is necessary, prioritizing the use of purely intracavitary applicators. If the patient anatomy includes specific features, such as irregular tumor topography, tumor size>4cm, bulky parametria disease or posterior bulky disease, needles should be implanted. After contouring on imaging, model-based predicted organ doses should be obtained. If any predicted organ dose exceeds 99% (101%) of the dose limit for T&R (T&O), the next fraction should be supplemented with needles. Physicians that prefer to implant needles to meet the planning aims would instead implant needles if any predicted OAR dose exceeded 104% (T&R) or 110% (T&O) of the planning aim. Although actual organ doses are available after treatment plan optimization, we still recommend using model predictions to guide decision-making in case treatment planning was suboptimal. This procedure should be repeated for each of the following fractions, such that the applicator decision is guided by dose predictions of the previous fraction. Physicians who are more comfortable with needle usage and prefer to err on the side of caution could choose to implant needles more often for the first fraction; however, the following workflow determining needle requirement for the following fraction could still apply. Finally, for any fraction treated without needles, we would recommend aiming for the predicted organ doses (minus model precision) when treatment planning, and comparing the final organ doses to predicted values as a means of quality control.

Using the models provides the following benefits to clinicians over current clinical practice. For one, current treatment planning is performed under time pressure, and thus clinicians may not be able to easily determine the optimal dose for a patient in the allotted time. For purely intracavitary implants, a clinician may believe that needles are needed for the next fraction, while more optimal treatment planning could have met constraints. The models provide reasonable estimates of achievable OAR dose with intracavitary applicators, which could speed up the planning process, provide additional assurance that the treatment plan is optimal and confirmation as to whether needles will be needed in future fractions. A physician may choose to insert needles for one fraction, but without replanning the case without needles, they may not know for sure whether needles were actually necessary to meet dose constraints. Our own data shows that needles were over-used, and thus there is room for improvement even within an experienced, busy brachytherapy clinic. The models can provide additional guidance on what to do for the next fraction on these borderline cases.

Limitations and Future Work

The models were trained on clinical treatment plans, but brachytherapy plans are not homogenous and a decent amount of variation between plans, individualized for the needs of each patient, is to be expected. This means some variability is incorporated into the models; however, we expect that much of this variation averaged out over the large patient cohort. The models are simple and make assumptions about dose conformality to the HRCTV, which do not perfectly hold for the standard pear-shaped distributions of cervical brachytherapy dose. The models also are less accurate when the tandem is not centered on the HRCTV, which necessitated an additional correction for HRCTV asymmetry to improve bladder dose predictions (see Supplementary Materials). Despite these limitations, the models were accurate for needle discrimination in their current form. Future work will explore 3D dose prediction, which can account for greater complexities in anatomy and applicator geometry.

One limiting factor is that dose-prediction models assume standard situations and do not account for any dose received in previous fractions or other individual patient needs (such as additional dose to the vagina). We recognize physicians consider additional clinical data and the full patient history during treatment planning. For instance, physicians may opt to increase target coverage, and this is not reflected in either the replanning or predicted doses. These factors influence of the clinical classification and retrospective analysis of sensitivity and specificity. To provide a more fair comparison, a prospective evaluation of physician classification based solely on

whether OARs are anticipated to meet dose objectives (i.e. without HRCTV dose escalation) is needed. This will be explored in future work. However, the models indicate what kind of dose is achievable if target coverage of D90 85-90Gy is met, and whether needles are required to meet dose objectives. Physicians could use this information to guide decision-making for a given case alongside other characteristics they value. If the models are employed at the first fraction, inter-fraction variability may be reduced, and the need to compensate for non-ideal dose from prior fractions could be alleviated.

The addition of the HRCTV V100 criteria to replanning objectives meant that HRCTV D90 could take on a range from 85 to 90 Gy EQD2. As a result, patients with different prescriptions could have slightly different target coverage, which could impact both organ D_{2cc} and needle classification in replans. In order to assess whether prescription was influencing results, we compared the following parameters between patients treated with different fractionation schemes using a Kruskal-Wallis test with a Bonferroni correction: $D_{2cc,replanned}$ – dose limit and $D_{2cc,replanned} - D_{2cc,predicted}$. A chi-squared test of independence was used to determine whether fractionation scheme was related to the following binary outcomes: $D_{2cc,replanned}$ greater or less than the dose limit and model classification accurate or inaccurate. All tests were insignificant, demonstrating that the variable prescriptions within our patient cohort were not systematically impacting any of our key results.

One drawback of the proposed algorithm is that the necessity of needle supplementation is evaluated after implantation of the applicator and imaging. This means that the model cannot guide needle decision-making for the first fraction, and so the decision purely depends on the physician expertise, preference and fractionation schema. However, predictions could still be used to inform needle implantation of subsequent fractions. In addition, our current models do not provide guidance on the number and location of needles required to meet dose criteria. Another limitation is that sensitivity and specificity of model classification was not tested on an independent dataset and this may bias our results towards better model classification. Future work will examine the utility of this decision-support tool and the standardized planning workflow in clinical practice.

Conclusion

The benefit of knowledge-based intracavitary models to support the decision to use needles was demonstrated. Standardized replanning of hybrid cases without needles confirmed model prediction accuracy. ROC curves and AUCs demonstrated the discrimination accuracy of the tool, which featured much higher sensitivity and

specificity than our current clinical process for needle classification. The analysis showed that needles are sometimes avoidable with little detriment to the patient, but could reduce organ dose, especially for the bladder. In summary, standardized planning driven by knowledge-based dose predictions could influence needle usage, serve as guidelines for physicians and decrease variations between treatment plans.

Disclosure

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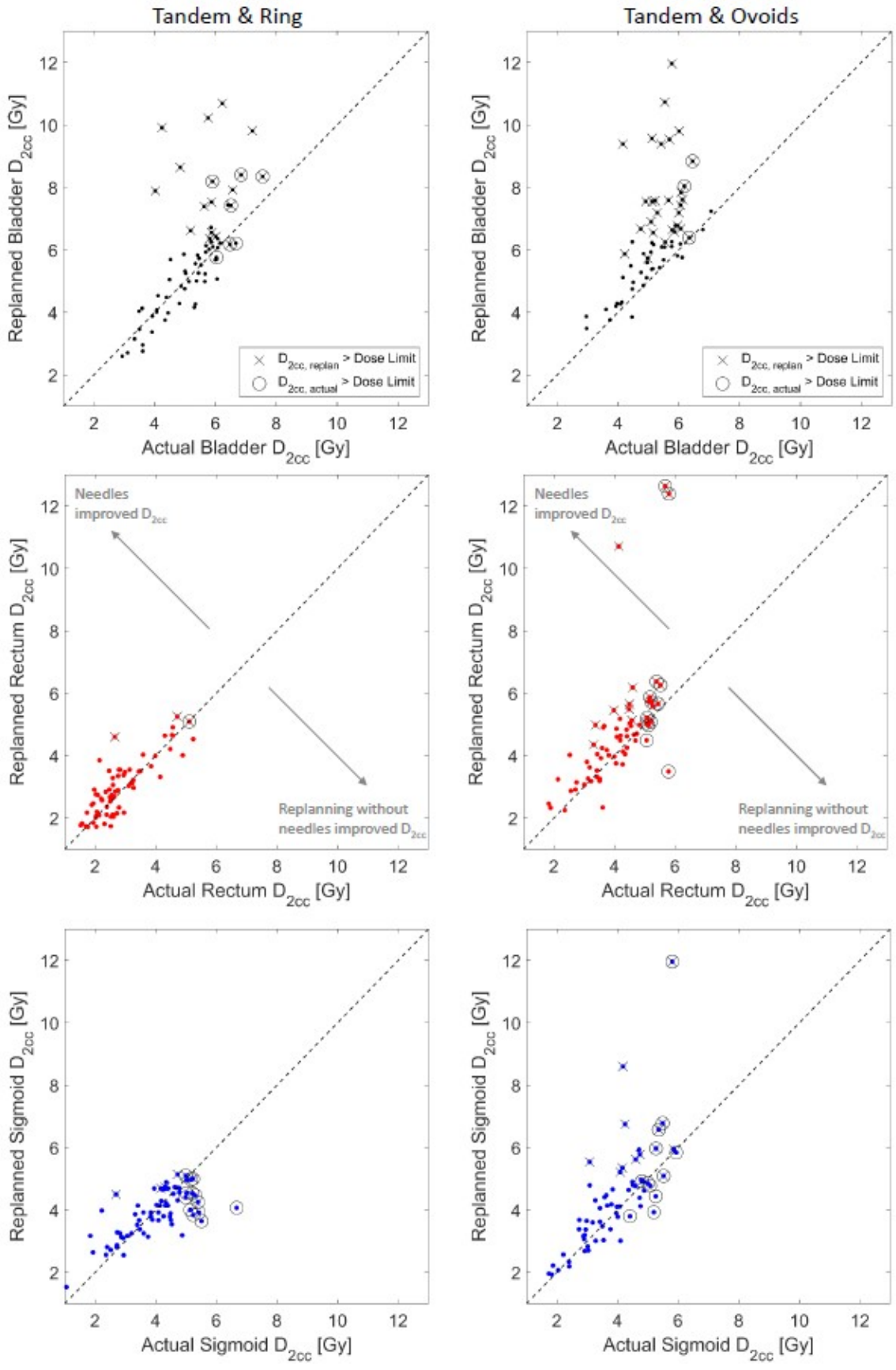
Tandem & Ring
Tandem & Ovoids
Replanned Bladder D2cc [Gy]
Actual Bladder D2cc [Gy]
D2cc, replan > Dose Limit
D2cc, actual > Dose Limit
Replanned Rectum D2cc [Gy]
Actual Rectum D2cc [Gy]
Needles improved D2cc
Replanning without needles improved D2cc
Replanned Sigmoid D2cc [Gy]
Actual Sigmoid D2cc [Gy]

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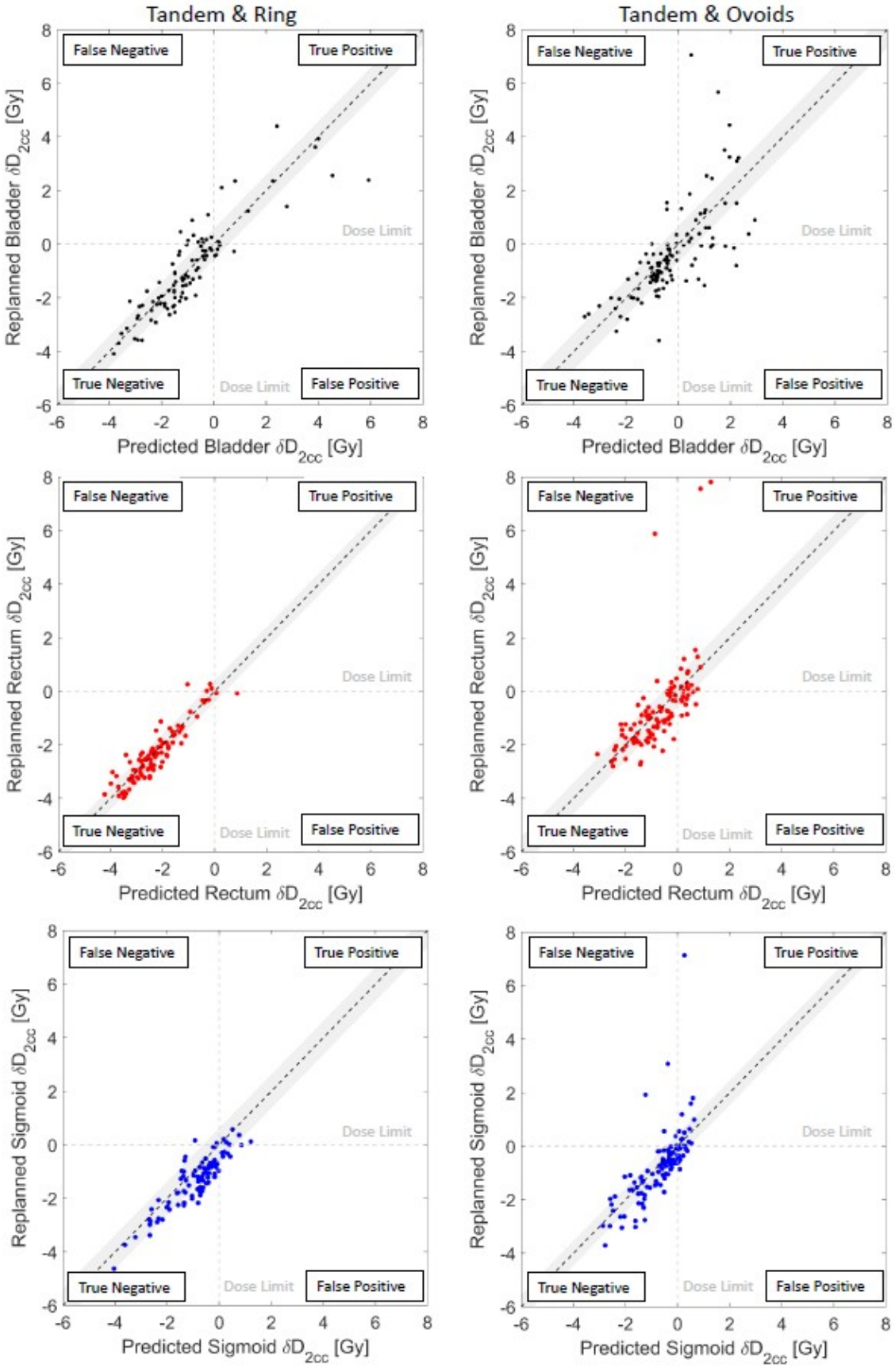
Figure 1. *D_{2cc} values established by replanning the hybrid cases to purely intracavitary treatment plans (i.e. organ dose without needles), compared to actual D_{2cc} values obtained from clinical hybrid plans (i.e. organ dose with needles). Replans required HRCTV D90 to fall between 85-90Gy EQD2. The dashed black line denotes the one-to-one line of replanned and actual dose. Values below the dashed line show cases where replanning without needles improved D_{2cc} values. Values above the dashed line show cases where the usage of needles improved the D_{2cc} values; x = $D_{2cc,\ replan}$ > dose limit; o = $D_{2cc,\ actual}$ > dose limit.*


Tandem & Ring
Tandem & Ovoids
False Negative
True Positive
True Negative
False Positive
Dose Limit
Replanned Bladder δD_{2cc} [Gy]
Predicted Bladder δD_{2cc} [Gy]
Replanned Rectum δD_{2cc} [Gy]
Predicted Rectum δD_{2cc} [Gy]
Replanned Sigmoid δD_{2cc} [Gy]
Predicted Sigmoid δD_{2cc} [Gy]

368

Figure 2. *Predicted deviations from dose limits compared to those of the replans, where* δD_{2cc} *=* D_{2cc} *–patient and organ-specific dose limit. Predictions were obtained from knowledge-based intracavitary models, while replan values were established by re-planning the hybrid cases without needles, requiring a HRCTV D90 of 85-90Gy EQD2. The dashed black line denotes the one-to-one line of replanned and predicted doses, and the model precision is displayed as the grey band. The four quadrants are labeled as if a threshold of 100% of the dose limits was used for model classification (although this threshold was varied in the ROC analysis). Cases located in the bottom left and top right quadrant were correctly predicted as not needing needles (true negatives) or needing needle supplementation (true positives). Cases in the top left quadrant were falsely classified that needles are unnecessary (false negatives), while cases in the bottom right quadrant were predicted to require needles but could have been met the dose limits with the standard applicator alone (false positives).*

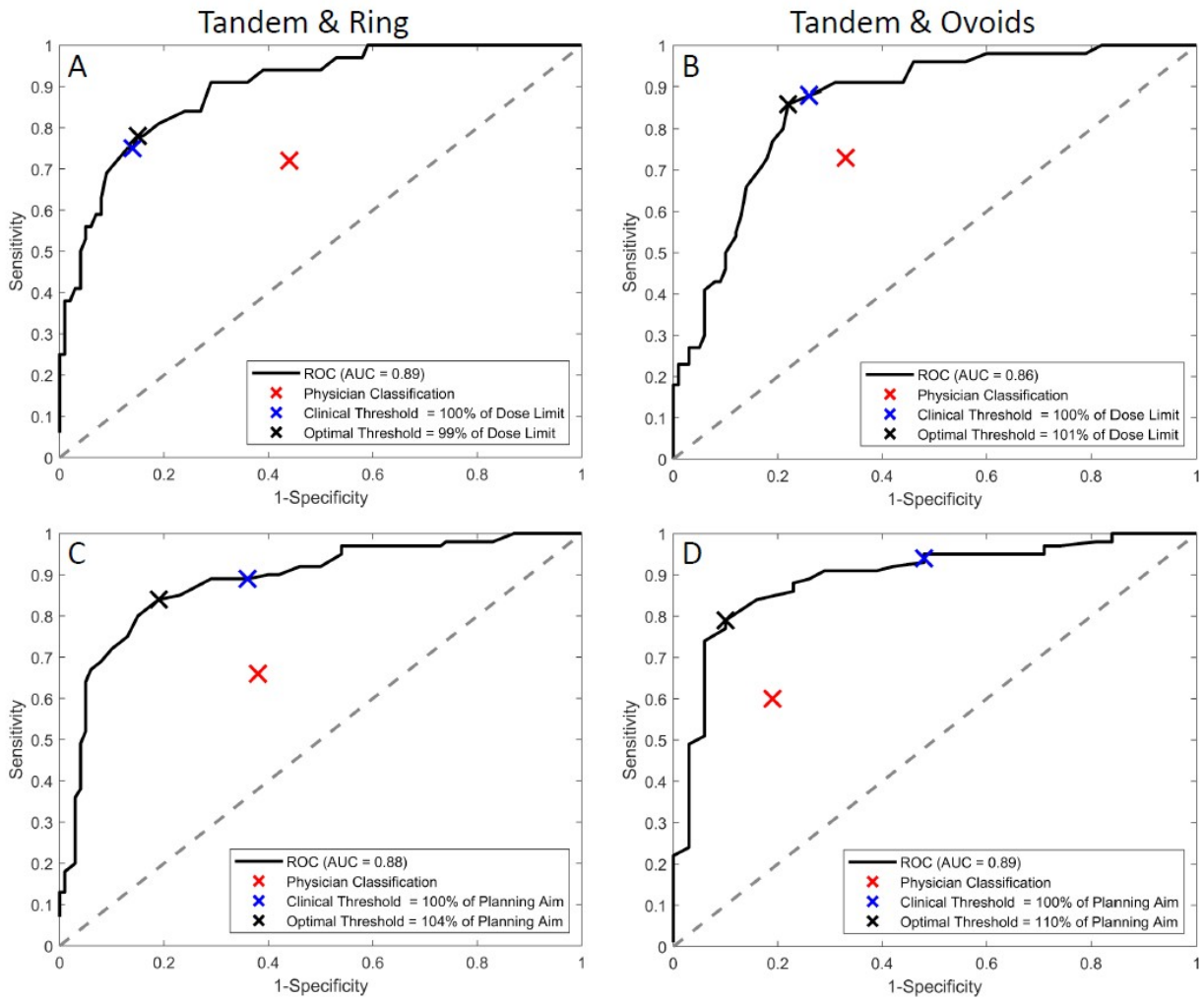


Figure 3. *ROC curve and corresponding area-under-curve (AUC) for both applicators, considering all organ doses. Replanned D_{2cc} values are used as true condition (where any case with an organ dose exceeding the dose limit (A and B) or the planning aim (C and D) is considered to be a true needle case) and compared to the predicted D_{2cc} values for varying thresholds. The red cross indicates our current clinically achieved values of specificity and sensitivity classified by the physician; --- boundary marking the goodness of the prediction being better than randomness.*

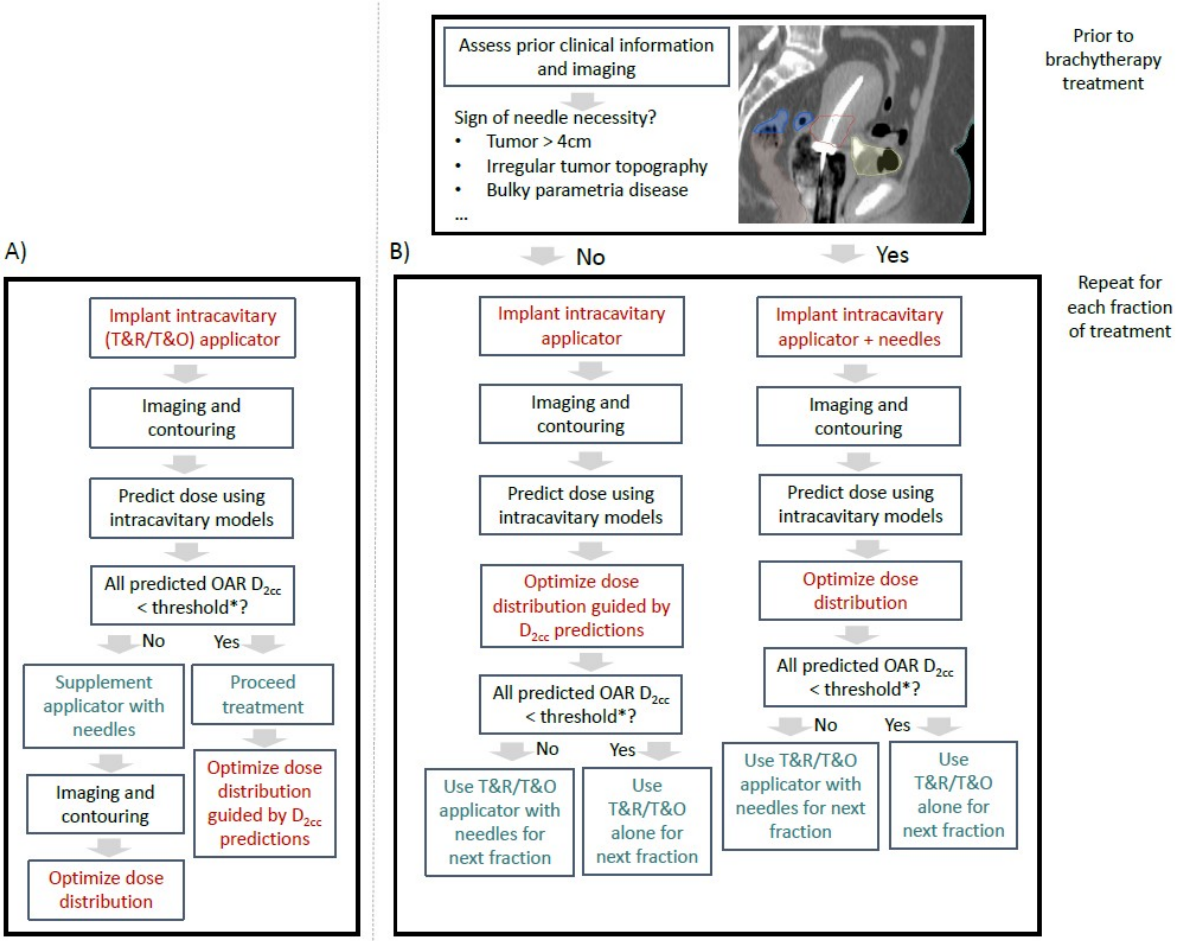


Figure 4. *Suggested clinical workflows using the dose predictions to guide needle supplementation and treatment planning. (A) proposed workflow for centers where adding needles after imaging and subsequent re-imaging are feasible, such as those with image-guided brachytherapy suites. If this is not feasible, (B) shows an alternative workflow where predictions are used to guide decision-making for the subsequent fraction. *Optimal threshold defined by the maximal Youden index, i.e. 99% (101%) of dose limit or 104% (110%) of planning aim for T&R (T&O), where use of dose limits or planning aims is based on physician preference.*

Table 1. *Summary of patient specifications of evaluated hybrid cases and intracavitary model data; IC = intracavitary; IS = interstitial; T&R = tandem and ring applicator; T&O = tandem and ovoids applicator; T&RN = hybrid tandem and ring applicator with needles; T&ON = hybrid tandem and ovoids applicator with needles; HRCTV = high-risk clinical target volume.*

Type	Parameter	Applicator	Specification	Value
Intracavitary	Number of included patients	T&R	Total	47
		T&O	Total	36
	Number of included fractions	T&R	Training cases	75
			Validation cases	38
		T&O	Training cases	80
			Validation cases	32
	HRCTV volume [cc]	T&R	Median (Range)	18.00 (4.9 – 40.2)
		T&O	Median (Range)	17.90.49 (7.7 - 65.7)
	Number of patients receiving each prescription (total number fractions x dose per fraction)	T&R	3 x 7.0Gy	2
			3 x 7.5Gy	2
			3 x 8.0Gy	12
			3 x 8.5Gy	1
			4 x 5.5Gy	1
			4 x 7.0Gy	29
			4 x 7.5Gy	1
			5 x 6.0Gy	3
		T&O	3 x 8.0Gy	3
			4 x 7.0Gy	15
			4 x 6.0Gy	1
			5 x 5.5Gy	4
			5 x 6.0Gy	12
			5 x 6.8Gy	1
	Number of patients with each tumor stage	T&R	I	22
			II	19
			III	5
			IV	1
		T&O	I	13
			II	20
			III	3
			IV	0
Hybrid (IC /IS)	Number of included patients	T&RN	Total	32
		T&ON	Total	28

	Number of replanned fractions	T&RN	Total	70
		T&ON	Total	67
	HRCTV volume [cc]	T&RN	Median (Range)	24.6 (9.7 – 73.4)
		T&ON	Median (Range)	30.60 (12.7 - 97.6)
	Number of patients receiving each prescription (total number fractions x dose per fraction)	T&RN	3 x 7.0Gy	1
			3 x 8.0Gy	9
			4 x 7.0Gy	21
			5 x 6.0Gy	1
		T&ON	3 x 7.0Gy	1
			3 x 8.0Gy	4
			4 x 7.0Gy	19
			4 x 7.5Gy	2*
			5 x 5.0Gy	2
	Number of patients with each tumor stage	T&RN	I	10
			II	15
			III	7
			IV	0
		T&ON	I	9
			II	10
			III	7
			IV	0

406 *for one patient, one of the fractions was treated with 5Gy

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Table 2. *Results of the comparison of the predicted D_{2cc} values to the replanned D_{2cc} values, where the replanned value represents the true result. Percentage of total amount of cases is shown where the argument stated as parameter is met. OAR = organs-at-risk; T&R = tandem and ring applicator; T&O = tandem and ovoids applicator; AUC = area under curve; σ_{Model} = model-prediction precision*

Parameter	OAR	Result	
		T&R	T&O
Replanned D_{2cc} < OAR limit	Bladder	71%	55%
	Rectum	96%	70%
	Sigmoid	91%	78%
	All OARs	67%	39%
Replanned D_{2cc} < actual clinical D_{2cc}	Bladder	40%	6%
	Rectum	36%	28%
	Sigmoid	49%	34%
	All OARs	21%	1%
Replanned D_{2cc} < predicted $D_{2cc}+\sigma_{Model}$	Bladder	83%	79%
	Rectum	87%	90%
	Sigmoid	97%	82%
	All OARs	77%	68%
D_{2cc} prediction met OAR limits, but replanned D_{2cc} > OAR limit	Bladder	10 %	6%
	Rectum	4%	7%
	Sigmoid	3%	6%
	All OARs	9%	-
D_{2cc} prediction > OAR limits, but replanned D_{2cc} < OAR limit	Bladder	4%	18%
	Rectum	3%	13%
	Sigmoid	9%	10%
	All OARs	11%	19%
AUC of hybrid + intracavitary cases considering dose limit	Bladder	0.82	0.88
	Rectum	0.97	0.90
	Sigmoid	0.92	0.86
	All OARs	0.89	0.86
AUC of hybrid + intracavitary cases considering planning aims	Bladder	0.83	0.86
	Rectum	0.92	0.93
	Sigmoid	0.92	0.86
	All OARs	0.88	0.90

References

[1] Gill BS, Lin JF, Krivak TC, et al. National Cancer Data Base Analysis of Radiation Therapy Consolidation Modality for Cervical Cancer: The Impact of New Technological Advancements. *Int J Radiat Oncol* 2014; 90: 1083–1090.

[2] Han K, Milosevic M, Fyles A, et al. Trends in the Utilization of Brachytherapy in Cervical Cancer in the United States. *Int J Radiat Oncol Biol Phys* 2013; 87: 111–119.

[3] Viswanathan AN, Thomadsen B, American Brachytherapy Society Cervical Cancer Recommendations Committee, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy* 2012; 11: 33–46.

[4] Lombe D, Crook J, Bachand F, et al. The addition of interstitial needles to intracavitary applicators in the treatment of locally advanced cervical cancer: Why is this important and how to implement in low- and middle-income countries? *Brachytherapy* 2020; 19: 316–322.

[5] Walter F, Maihöfer C, Schüttrumpf L, et al. Combined intracavitary and interstitial brachytherapy of cervical cancer using the novel hybrid applicator Venezia: Clinical feasibility and initial results. *Brachytherapy* 2018; 17: 775–781.

[6] Nomden CN, de Leeuw AAC, Moerland MA, et al. Clinical Use of the Utrecht Applicator for Combined Intracavitary/Interstitial Brachytherapy Treatment in Locally Advanced Cervical Cancer. *Int J Radiat Oncol* 2012; 82: 1424–1430.

[7] Dimopoulos JCA, Kirisits C, Petric P, et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: Clinical feasibility and preliminary results. *Int J Radiat Oncol* 2006; 66: 83–90.

[8] Appenzoller LM, Michalski JM, Thorstad WL, et al. Predicting dose-volume histograms for organs-at-risk in IMRT planning. *Med Phys* 2012; 39: 7446–7461.

[9] Ge Y, Wu QJ. Knowledge-based planning for intensity-modulated radiation therapy: A review of data-driven approaches. *Med Phys* 2019; 46: 2760–2775.

[10] Shiraishi S, Moore KL. Knowledge-based prediction of three-dimensional dose distributions for external beam radiotherapy. *Med Phys* 2016; 43: 378–387.

[11] Nicolae A, Morton G, Chung H, et al. Evaluation of a Machine-Learning Algorithm for Treatment Planning in Prostate Low-Dose-Rate Brachytherapy. *Int J Radiat Oncol* 2017; 97: 822–829.

[12] Shen C, Gonzalez Y, Klages P, et al. Intelligent inverse treatment planning via deep reinforcement learning, a proof-of-principle study in high dose-rate brachytherapy for cervical cancer. *Phys Med Biol* 2019; 64: 115013.

[13] Yusufaly TI, Kallis K, Simon A, et al. A knowledge-based organ dose prediction tool for brachytherapy treatment planning of patients with cervical cancer. *Brachytherapy* 2020; 19: 624–634.

[14] Cornell M, Kaderka R, Hild SJ, et al. Noninferiority Study of Automated Knowledge-Based Planning Versus Human-Driven Optimization Across Multiple Disease Sites. *Int J Radiat Oncol Biol Phys* 2020; 106: 430–439.

[15] Tol JP, Dahele M, Gregoire V, et al. Analysis of EORTC-1219-DAHANCA-29 trial plans demonstrates the potential of knowledge-based planning to provide patient-specific treatment plan quality assurance. *Radiother Oncol* 2019; 130: 75–81.

[16] Younge KC, Marsh RB, Owen D, et al. Improving Quality and Consistency in NRG Oncology Radiation Therapy Oncology Group 0631 for Spine Radiosurgery via Knowledge-Based Planning. *Int J Radiat Oncol Biol Phys* 2018; 100: 1067–1074.

[17] Giaddui T, Geng H, Chen Q, et al. Offline Quality Assurance for Intensity Modulated Radiation Therapy Treatment Plans for NRG-HN001 Head and Neck Clinical Trial Using Knowledge-Based Planning. *Adv Radiat Oncol* 2020; 5: 1342–1349.

[18] Pötter R, Haie-Meder C, Limbergen EV, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67–77.

[19] Chino J, Annunziata CM, Beriwal S, et al. Radiation Therapy for Cervical Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol* 2020; 10: 220–234.

[20] Covele BM, Puri KS, Kallis K, et al. ORBIT-RT: A Real-Time, Open Platform for Knowledge-Based Quality Control of Radiotherapy Treatment Planning. *JCO Clin Cancer Inform* 2021; 134–142.

[21] Biltekin F, Gultekin M, Yilmaz MT, et al. Dosimetric comparison of two different applicators and rectal retraction methods used in inverse optimization-based intracavitary brachytherapy for cervical cancer. *J Contemp Brachytherapy* 2020; 12: 35–43.

[22] Serban M, Kirisits C, de Leeuw A, et al. Ring Versus Ovoids and Intracavitary Versus Intracavitary-Interstitial Applicators in Cervical Cancer Brachytherapy: Results From the EMBRACE I Study. *Int J Radiat Oncol Biol Phys* 2020; 106: 1052–1062.

[23] Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biom J Biom Z* 2005; 47: 458–472.

[24] Damato AL, Viswanathan AN, Don SM, et al. A system to use electromagnetic tracking for the quality assurance of brachytherapy catheter digitization. *Med Phys* 2014; 41: 101702.

[25] Jung H, Shen C, Gonzalez Y, et al. Deep-learning assisted automatic digitization of interstitial needles in 3D CT image based high dose-rate brachytherapy of gynecological cancer. *Phys Med Biol* 2019; 64: 215003.

[26] Zhou Y, Klages P, Tan J, et al. Automated high-dose rate brachytherapy treatment planning for a single-channel vaginal cylinder applicator. *Phys Med Biol* 2017; 62: 4361–4374.

[27] Cv G, Kp A, R M, et al. Real-time inverse high-dose-rate brachytherapy planning with catheter optimization by compressed sensing-inspired optimization strategies. *Phys Med Biol* 2016; 61: 5956–5972.

[28] Fokdal L, Sturdza A, Mazeron R, et al. Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: Analysis from the retroEMBRACE study. *Radiother Oncol* 2016; 120: 434–440.

[29] Kaderka R, Mundt RC, Li N, et al. Automated Closed- and Open-Loop Validation of Knowledge-Based Planning Routines Across Multiple Disease Sites. *Pract Radiat Oncol* 2019; 9: 257–265.

[30] Moore KL, Schmidt R, Moiseenko V, et al. Quantifying Unnecessary Normal Tissue Complication Risks due to Suboptimal Planning: A Secondary Study of RTOG 0126. *Int J Radiat Oncol* 2015; 92: 228–235.

[31] Nelms BE, Chan MF, Jarry G, et al. Evaluating IMRT and VMAT dose accuracy: Practical examples of failure to detect systematic errors when applying a commonly used metric and action levels. *Med Phys* 2013; 40: 111722.

[32] Tambas M, Tavli B, Bilici N, et al. Computed Tomography-Guided Optimization of Needle Insertion for Combined Intracavitary/Interstitial Brachytherapy With Utrecht Applicator in Locally Advanced Cervical Cancer. *Pract Radiat Oncol*. Epub ahead of print 5 February 2021. DOI: 10.1016/j.prro.2021.01.008.