# Development and clinical validation of Knowledge-based planning for Volumetric Modulated Arc Therapy of cervical cancer including pelvic and para aortic fields

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## A R T I C L E   I N F O

## A B S T R A C T

Background and Purpose: Knowledge-based planning (KBP) is based on a model to estimate dose-volume histograms, configured using a library of historical treatment plans to efficiently create high quality plans. The aim was to report configuration and validation of KBP for Volumetric Modulated Arc Therapy of cervical cancer.

Materials and methods: A KBP model was configured from the institutional database (n = 125), including lymph node positive (n = 60) and negative (n = 65) patients. KBP Predicted plans were compared with Clinical Plans (CP) and Re-plans (Predicted plan as a base-plan) to validate the model. Model quality was quantified using coefficient of determination $R^2$, mean square error (MSE), standard two-tailed paired t-test and Wilcoxon signed rank test.

Results: Estimation capability of the model was good for the bowel bag (MSE = 0.001, R2 = 0.84), modest for the bladder (MSE = 0.008) and poor for the rectum (MSE = 0.02 R2 = 0.78). KBP resulted in comparable target coverage, superior organ sparing as compared to CP. Re-plans outperformed CP for the bladder, V30 (66 ± 11% vs 74 ± 11%, p < .001), V40 (48 ± 14% vs 52 ± 14%, p < .001), however sparing was modest for the bowel bag V30 (413 ± 191cm³ vs 445 ± 208cm³, p = .037) V40 (199 ± 105cm³ vs 218 ± 127cm³, p = .031). All plans were comparable for rectum, while KBP resulted in significant sparing for spinal cord, kidneys and femoral heads.

Conclusion: KBP yielded comparable and for some organs superior performance compared to CP resulting in conformal and homogeneous target coverage. Improved organ sparing was observed when individual patient geometry was considered.

## 1. Introduction

Globally cervical cancer is the fourth leading cause of cancer death in women [1]. In India, it is the second most common cancer among women and contributes to 17% of the world burden [2–4]. The current evidence suggests that the use of advanced Image-Guided Intensity-Modulated Radiotherapy (IG-IMRT) in cervical cancer is associated with reduced early and late toxicity [5–10].

In recent years world over, an increase in the need for delivering IMRT for cervical cancer was observed especially in patients who are lymph-node positive or are receiving postoperative radiation [11]. Moreover in a clinical trial setting, where generating evidence is a

primary objective, consistent high-quality treatment plan is an essential component. Since there are no indicators for a "good plan", very often the plans are not adequately optimized enough to reduce the dose to OARs [12]. Moreover IMRT plan optimization is time-consuming, skill-dependent, sometimes achieving all complex dose constraints may take several hours. This can also be particularly challenging when performing nodal dose escalation using Simultaneous Integrated Boost (SIB) and extended targets as the patients are presented in a locally advanced stage [13]. Knowledge-based planning (KBP) which is a model built on a library of previously created treatment plans has been reported to produce high-quality consistent plans in an efficient manner [14].

KBP models for cervical cancer have been previously reported, albeit a handful, as compared to a large number of KBP models on other disease sites such as Head & Neck and prostate [14–20]. Moreover the existing models on cervical cancer have included patients without lymph nodal involvement or in post-operative settings with a single target dose level. In addition the existing models have a small number of patients in the training and validation dataset. It has been previously reported that KBP model performance can be limited by various factors, mainly by limited size of dataset and poor-quality data [13]. The current investigation on KBP in cervical cancer innovates earlier studies with the inclusion of both lymph node-positive (N+) and lymph node negative (N−) patients treating multi-target structures, with different levels of dose prescription in a single model, built with the largest sample size in the training set.

The purpose of this study was to investigate KBP predictive models, for dose-volume histogram (DVH) both for N+ and N− cervical cancer involving SIB technique. It was also investigated if plans can be improved by re-planning with KBP as a base-plan, taking into account the individual patient geometry.

## 2. Materials and methods

This current study was a part of the research protocol that was approved by our institutional review board for the purpose of investigating the use of KBP [21]. A KBP model was made for cervical cancer (Rapidplan, Varian Medical Systems v13.5.23) with a training data set of consecutive 125 patients, from the institutional database treated with an on-going international multi-centric trial protocol, (EMBRACE II, https://www.embracestudy.dk/) (Table 1), The protocol is described briefly as follows.

### 2.1. Contouring

Target delineation was performed after fusing contrast-enhanced planning CT images and the T2 weighted MRI. The gross tumor volume for the primary ($GTV_T$) was delineated as a high signal intensity region in the cervix and vagina on T2 weighted MRI. The gross pathological lymph nodes ($GTV_N$) were delineated from PET. The high risk clinical target volume ($CTV_{HR}$) included $GTV_T$ and any remaining cervix not infiltrated by the tumour. The low risk clinical target volume ($CTV_{LR}$) included parametria bilaterally, the whole uterus, bilateral ovaries, a margin of 20 mm below the lower extent of disease in the direction of vagina, sacrouterine ligaments and mesorectum if involved and invaded organs (bladder, rectum,bowel,sigmoid). The $CTV_N$ for the lymph nodes was generated from $GTV_N$ with a 5 mm margin. The elective nodal CTV ($CTV_E$) included the elective nodal regions according to the risk stratification and $CTV_N$. The internal target volume (ITV) was generated from $CTV_{LR}$ with a margin of 10 mm superiorly and anteriorly-posteriorly, 5 mm laterally and 0 mm inferiorly excluding muscles and bony structures. The planning target volumes ($PTV_{45}$) and $PTV_N$, were generated with an isotropic margin of 5 mm to $ITV_{45}$ and $CTV_N$ respectively. The OARs considered were the bowel bag, the bladder, the rectum, the sigmoid, the kidneys, the femoral heads and the spinal cord.

**Table 1**
Summary of Knowledge Based Model in the current study – Training and validation data set details.

| Parameter | Model |
|---|---|
| Tumor site | Cancer of the uterine cervix with positive lymph nodes (N+) and without lymph nodes (N−). |
| Target structures (Dose prescription) | 45 Gy/25 fractions to $PTV_{45}$ (n = 124). 55 Gy/25 fractions to $CTV_N$ (n = 128) and 49.5 Gy to $PTV_N$ (n = 129). |
| Mean number of lymph nodes | 2.4 ± 1.4 (range 1–5) |
| OARs modeled | Bowel bag (n = 125), Bladder (n = 125), Femoral heads (n = 250), Rectum (n = 125), Sigmoid (n = 125), Kidneys (n = 250) and Spinal cord (n = 125). |
| Total number of patients in training set. | 125 (65 N− and 60 N+) |
| Number of pelvic and para aortic patients in training dataset. | 99 and 46 |
| Number of patients in validation dataset. | 10 N− 10 N+ |
| Number of pelvic and para aortic patients in validation dataset. | 14 and 6 |
| Validation 1: | Clinical plan versus Predicted plan. (Single optimization without any manual intervention) |
| Validation 2: | Clinical plans versus Re-plans over predicted plans. (Manual tweaking of objectives and priorities to meet DVH estimation from Predicted plans-single optimization). |

### 2.2. Model configuration and outlier analysis

The training dataset consisted of plans made using Volumetric Modulated Arc Therapy (VMAT, Photon Optimizer, Acuros-XB, Eclipse v13.5, Varian Medical Systems). Plan geometry consisted of two coplanar arcs of 360°, collimator angle of 5° or 355°, field size 16 × 35 cm², and met the dose-volume constraints of the protocol (Supplementary table 1). A brief overview of the basic principle of KBP model is provided in supplementary material Appendix 1 [22].

Three target structures ($CTV_N$, $PTV_N$, and $PTV_{45}$) and 8 OARs (bowel bag, bladder, rectum, sigmoid, femoral heads, kidney, spinal cord, help contour) were considered for modelling.

The KBP model creates regression models between geometric and dosimetric components, which can detect outliers that help in improving the predicting capability of the model. Geometric outliers were kept in the model as they do not negatively affect the model and may provide useful information for the model to estimate DVHs in plans with similar properties, such as pelvic PTV, PTV including paraaortic nodes, bowel bag, bladder of various volumes, the proximity between the PTV and OAR due to a structure being unusually large especially rectum, bladder and bowel bag. However, geometric outliers (n = 3) with large Cook's distances (approximately more than 40–50) were removed from the model, as they may negatively affect the model. Sub-optimal plans in the training set were manifested as dosimetric outliers that affect the model fitting parameters negatively. 5/125, such dosimetric outliers were deleted, re-planned, before, including them back in the model. A model analytics cloud based tool from MyVarian.com, also helps in analyzing the model quality, typically for identifying the outliers for each modelled structure.

Although RapidPlan can automatically generate priorities for OAR objectives, it was observed that, when generated priorities were used, PTV coverage was suboptimal. Hence suitable priorities were established using clinical experience (Supplementary table 2). Optimization rings to control the dose spillage outside the PTV were not used in the model. However, it was controlled by means of the normal tissue objective (NTO). The NTO parameter settings were based on clinical experience, priority was set to 190, distance from the target border was

0.4 cm, with a start dose of 100%, end dose of 60% and with a fall-off criteria of 0.4.

### 2.3. Model validation

The validation set consists of 10 each, N+ and N− patients, not included in the training set. For all validation plans, the same beam configuration as the clinical plan (CP) was used. Two types of validation were carried out (i) Comparing Predicted plans versus CP using single optimization without any manual intervention and (ii) Comparing Re-planned cases from the predicted DVH, versus CP. The first validation was a basic level validation of the KBP model in predicting the DVH, while the second validation is an advanced type of validation where the individual patient geometry and utilization of the optimization algorithm was taken into account. CPs made manually by an expert physicist for each patient was used as a reference plan. In Re-plans, the optimization objectives/priorities were manually tweaked such that the DVH of the OAR to be at the lower border of the estimation band of DVH prediction without compromising the target coverage, with a single optimization. Predicted plans were used as a starting point for Re-plans. The planner was blinded to CP, during Re-plan to ensure a fair comparison.

### 2.4. Evaluation

Model quality was quantified by the coefficient of determination $R^2$ (with values between 0 and 1, 1 being ideal), goodness-of-fit statistics $\chi^2$ (values of 1 or higher, with values near 1 implying a good fit), and by mean square error (MSE- closer it is to 0, better the estimation capability) between the original and estimate [22]. Cook's distance, the scaled change in fitted values, which is useful for identifying outliers (observations for predictor variables) also was considered [22]. Mean $\pm$ SD volumes of target, OAR, and overlap structures for training and

validation dataset were evaluated (Supplementary table 3). Quantitative comparison of the KBP (Predicated plan, Re-plan) and CP were established using the standard two-tailed paired $t$-test (for normally distributed data), and Wilcoxon signed rank test (for non-normal data). All differences were reported with 95% confidence interval (Table 2). The qualitative comparison was made by visual inspection of PTV/CTV coverage and OAR, in each slice on the CT image.

## 3. Results

### 3.1. Model quality

The estimation capability of the model was good for bowel bag (MSE = 0.001, $R^2$ = 0.84), followed by kidney (MSE = 0.002, $R^2$ = 0.88), and modest for femoral heads (MSE = 0.004, $R^2$ = 0.71), followed by bladder (MSE = 0.008) (Table 3). Estimation capability of rectum and sigmoid was poor with MSE of 0.02 ($R^2$ = 0.78) and 0.029 ($R^2$ = 0.83) respectively (Table 3). Qualitative evaluation of the regression plots and DVH estimation band also have confirmed the above findings, and wherein, the estimation bandwidth was narrow for bowel bag, kidney, femoral heads as compared to the bladder, spinal cord, and rectum. Representative figures of regression plot and estimation band have been presented for bowel bag and bladder (Fig. 1a-d).

### 3.2. Validation

Rectum had the largest overlap of 65% with the target, followed by the bladder of 40%, and bowel bag of 8%. Other OARs such as kidney, femoral heads and spinal cord did not have much overlap with the target structures (<1%). The overlap volumes were similar between the training and the validation dataset, however, the mean volumes were different for target structures (PTV$_{45}$, CTV$_N$, PTV$_N$), and OARs such as bladder and bowel bag and similar for rectum, kidney and femoral heads
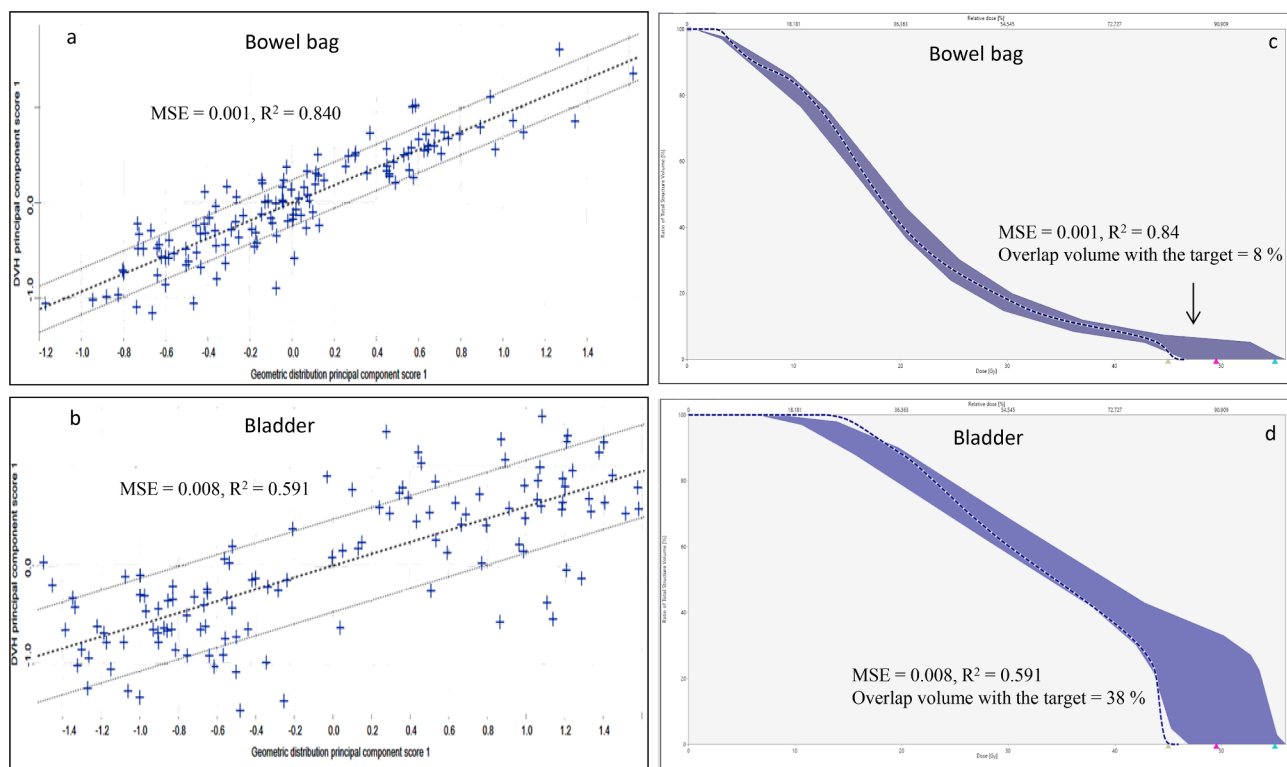


**Fig. 1.** Regression plot and estimation band of the model. a. Regression plot of bowel bag, b. Regression plot of bladder, c. Representative estimation band for bowel bag with dose-volume histogram obtained by predicted plan, d. Representative estimation band for bladder with dose-volume histogram obtained by predicted plan, the proportion of overlap volume is indicated as a broad band at the high dose region in c and d.

(Supplementary table 3).

KB plans resulted in comparable and better plans as compared to CP, comparable for target coverage, and better for conformity (Figs. 2 and 3). Re-plans did not result in much improvement in target coverage as compared to CP. Most of the DVH parameters related to target structures were found to be statistically not significant comparing CP vs Predicted plan and CP vs Re-plan, however, KB plans resulted in homogeneous and conformal dose as compared to CP (Table 2).

Overall observation for OARs, was that CP and Predicted plans were comparable. However, Re-plans outperformed CP, especially for the bladder. Femoral heads also resulted in better sparing in Re-plans as compared to CP (Figs. 2 and 3). For bladder, CP and Predicted plans were comparable, however, significant sparing was observed in Re-plan, $V_{30}$ (73.9 ± 10.6% vs 65.7 ± 11.4%, $p < .001$), $V_{40}$ (52.2 ± 14.4% vs 47.8 ± 13.7%, $p < .001$), and $D_{max}$ (105.7 ± 4.4% vs 103.1 ± 0.98%, $p = .032$) (Table 2). For bowel bag, CP and Predicated plans were comparable; however, modest sparing was observed in Re-plan, $V_{30}$ (445 ± 191cm$^3$ vs 413 ± 191cm$^3$ $p = .037$) and $V_{40}$ (218 ± 127cm$^3$ vs 199 ± 105cm$^3$ $p = .031$). For rectum, all the three plans were comparable for $V_{30}$ (CP vs Predicted Plan vs RePlan; 93.1 ± 9.2% vs 93 ± 9.9% vs 90.9 ± 10.3%, $p = .683, 0.049$) and $V_{40}$ (77.4 ± 18.9% vs 76.6 ± 18.9% vs 73.8 ± 18.9%, $p = .690, 0.063$), however, $D_{max}$, was significantly less in KBP (104 ± 2.4% vs 101.9 ± 1.6%, $p = .001$) as compared to CP. Spinal cord and kidneys resulted in significant sparing in KBP as compared to CP (12.4 ± 12.7Gy vs 16.2 ± 16.9Gy, $p = .001$, 3.4 ± 4Gy vs 4.5 ± 5Gy, $p = .006$). However, femoral heads have resulted in significant sparing only in Re-plans ($p = .007$).

Both KBP resulted in highly significant conformal plans as compared to CP, (Conformity Index CI$_{43}$ and CI$_{36}$; 1.07 ± 0.05 vs 1.01 ± 0.02, 1.58 ± 0.11 vs 1.45 ± 0.06, $p < .001$) (Table 2). Number of monitor units required also was significantly less in KBP as compared to CP (541 ± 28 vs 643 ± 143; $p = .004$) (Table 2).

## 4. Discussion

In the current study, we have presented a KBP model for cervical cancer, configured from the database of our hospital, consisting of both N+ and N− patient data, treated as a part of an ongoing clinical trial. The KBP model performed well as compared to CPs both for target and for OARs efficiently. KBP as a baseplan followed by optimization to take into account the individual geometry results in superior plans as compared to CP.

KBP model performance can be limited by poor-quality data and limited size of dataset [13]. The training and validation dataset in the current study, is the largest series published so far in the literature for cervical cancer, consisting of well balanced sample size, between the two groups, N+(n = 60) and N−(n = 65), such that the prediction is good for all types of patients [14–20]. In addition, the data quality in the training set was maintained, as it was from a well monitored clinical trial [18]. The strength of this model was the training set data that describe all type of clinical situations, such as N+, N− patients with a multiple number of lymph nodes, PTV in pelvic region and extending upto the paraaortic region, bladder volumes of varying capacity, bowel volumes for pelvic PTVs and those extending upto the paraaortic region, so that, the prediction capability is good overall, considering the heterogeneous sample of patients in the training and the validation datasets (Table 3). Regarding the target, the current RapidPlan model was trained to handle both N− and N+, with distinct dose prescription levels, thus further increasing the model's scope. In the current study, 50% of the patients had a single dose level, and the rest had three dose levels. Hence, the dose scaling was different for these patients resulting in a large width of the estimation band for the overlapping part of the OARs (Fig. 1c-d). This doesn't mean that the DVH estimation was uncertain in that part of the OAR, but refers to the dose scaling effect.

The authors did attempt to re-plan the CPs for bladder sparing during the outlier analysis, however, was found that further optimization could not improve bladder sparing, without compromising the target coverage and losing the hard constraints, which may be attributed to the overlap volumes of the bladder with the target, which is about 40% (Supplementary table 3). When the overlap volume was less (<10% for bowel bag), CPs were optimal, while KBP did not result in much improvement. However, when the overlap volume was more, of the order of 40% in the case of bladder, CPs were suboptimal, while KBPs resulted in significant improvement, especially, in Re-plans, which took into account the
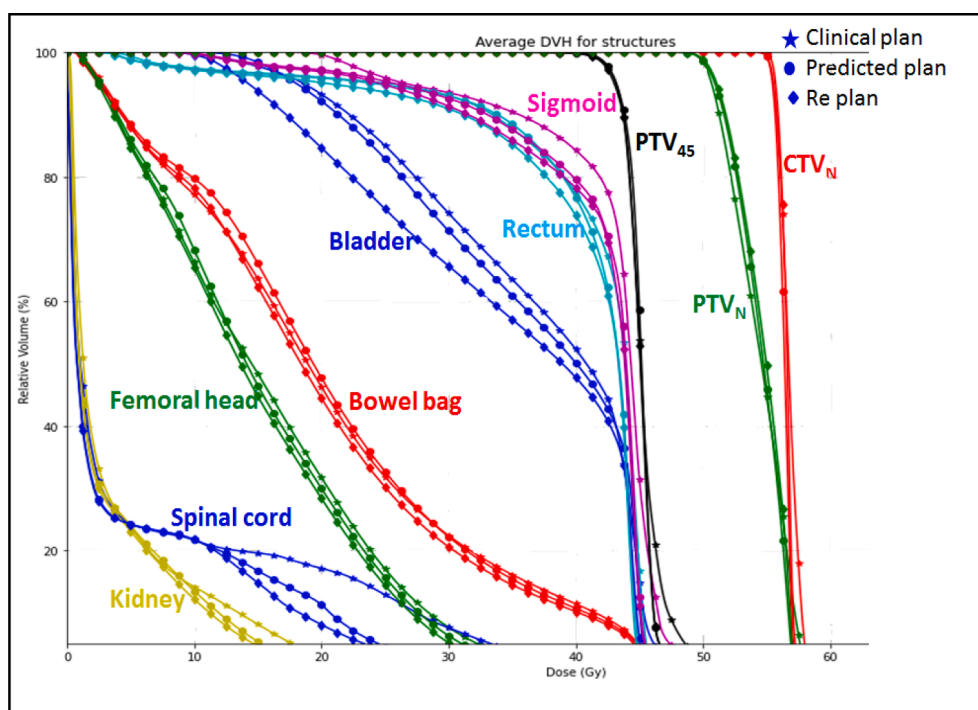


**Fig. 2.** Average dose volume histogram comparison of clinical plan, Predicted plan and Replan for various organs at risks.
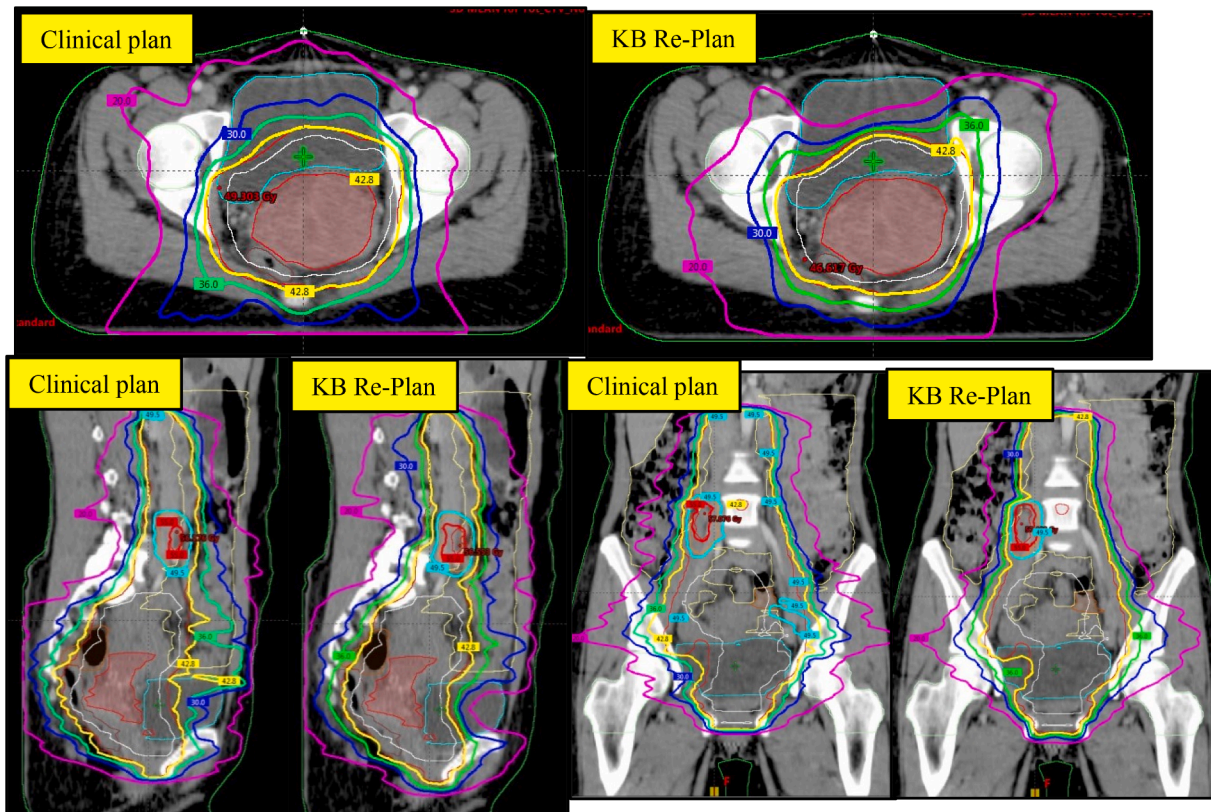
**Fig. 3.** A representative qualitative comparison of dose distribution of clinical plans and Knowledge based Re-plans.

**Table 2**
Mean ± standard deviation of the dose-volume parameter of clinical plans as compared to validation plans – Predicted and Re-plan, p values are given for Clinical plan vs Predicted plan, Clinical plan vs Re-plan (p < 0.05 considered as significant). Clinically significant values have been marked in bold font.

| Organ | DVH parameter | Clinical plan | Validation | | P Values | |
|---|---|---|---|---|---|---|
| | | | Predicted plan | Re-plan | CP vs Predicted plan | CP vs Re-plan |
| CTV$_N$ | D$_{Max}$ [Gy] | 58.4 ± 0.6 | 57.5 ± 0.2 | 57.9 ± 0.4 | 0.000 | 0.015 |
| | D$_{98\%}$ [Gy] | 55.4 ± 0.2 | 55.3 ± 0.1 | 55.5 ± 0.2 | 0.646 | 0.174 |
| | D$_{50\%}$ [Gy] | 56.9 ± 0.4 | 56.4 ± 0.1 | 56.7 ± 0.2 | 0.009 | 0.240 |
| PTV$_N$ | D$_{98\%}$ [Gy] | 50.1 ± 0.3 | 50.2 ± 0.2 | 50.3 ± 0.3 | 0.434 | 0.252 |
| PTV$_{45}$ | D$_{Max}$[%] | 110.2 ± 4.9 | 108.7 ± 3.0 | 108.5 ± 2.5 | 0.078 | 0.232 |
| | V$_{42.8Gy}$[%] | 96.9 ± 1.1 | 97.0 ± 0.7 | 96.3 ± 0.6 | 0.780 | 0.007 |
| ITV$_{45}$ | D$_{Max}$[%] | 109.8 ± 6.4 | 108.0 ± 4.8 | 108.1 ± 4.5 | 0.093 | 0.101 |
| | V$_{42.8Gy}$[%] | 99.9 ± 0.2 | 100 ± 0.0 | 100 ± 0.0 | 0.161 | 0.575 |
| Help contour | D$_{Max}$[%] | 102.9 ± 1.6 | 102.3 ± 0.8 | 101.6 ± 0.8 | 0.208 | 0.008 |
| Bowel bag | D$_{Max}$[%] | 106.9 ± 4.6 | 104.7 ± 2.9 | 104.7 ± 2.7 | 0.061 | 0.135 |
| | V$_{40Gy}$[cc] | 218 ± 127 | 209 ± 112 | 199 ± 105 | 0.351 | 0.031 |
| | V$_{30Gy}$[cc] | 445 ± 208 | 446 ± 211 | 413 ± 191 | 0.940 | 0.037 |
| | V$_{15Gy}$[cc] | 1341 ± 442 | 1383 ± 462 | 1312 ± 448 | 0.088 | 0.296 |
| Sigmoid | D$_{Max}$[%] | 104.1 ± 3.7 | 102.1 ± 1.4 | 101.9 ± 1.3 | 0.021 | 0.002 |
| Bladder | D$_{Max}$[%] | 105.7 ± 4.4 | 103.6 ± 0.9 | 103.1 ± 1.0 | 0.108 | 0.032 |
| | V$_{40Gy}$[%] | 52.2 ± 14.4 | 50.1 ± 14.3 | 47.8 ± 13.7 | 0.041 | 0.000 |
| | V$_{30Gy}$[%] | 73.9 ± 10.6 | 71.3 ± 11.6 | 65.7 ± 11.4 | 0.118 | 0.000 |
| Rectum | D$_{Max}$[%] | 104.0 ± 2.4 | 101.9 ± 1.5 | 101.9 ± 1.6 | 0.001 | 0.001 |
| | V$_{40Gy}$[%] | 77.4 ± 18.9 | 76.6 ± 18.9 | 73.8 ± 18.9 | 0.690 | 0.063 |
| | V$_{30Gy}$[%] | 93.1 ± 9.2 | 93.0 ± 9.9 | 90.9 ± 10.3 | 0.683 | 0.049 |
| Spinal cord | D$_{Max}$[Gy] | 16.2 ± 16.9 | 13.2 ± 13.6 | 12.4 ± 12.7 | 0.001 | 0.001 |
| Femoral heads_L | D$_{Max}$[Gy] | 40.5 ± 4.5 | 40.5 ± 2.7 | 37.1 ± 3.7 | 0.709 | 0.007 |
| Femoral heads_R | D$_{Max}$[Gy] | 39.4 ± 5.2 | 39.1 ± 4.1 | 36.2 ± 4.9 | 0.752 | 0.014 |
| Kidney_L | D$_{Mean}$[Gy] | 4.2 ± 5.0 | 3.6 ± 4.3 | 3.4 ± 4 | 0.008 | 0.006 |
| Kidney_R | D$_{Mean}$[Gy] | 3.8 ± 4.3 | 3.5 ± 3.9 | 3.4 ± 3.7 | 0.126 | 0.073 |
| Conformity Index | CI$_{43}$ (V$_{43Gy}$ of Body/Volume of PTV) | 1.07 ± 0.05 | 1.03 ± 0.02 | 1.01 ± 0.02 | 0.001 | 0.000 |
| | CI$_{36}$ (V$_{36Gy}$ of Body/Volume of PT) | 1.58 ± 0.11 | 1.49 ± 0.07 | 1.45 ± 0.06 | 0.000 | 0.000 |
| MU | | 643 ± 143 | 541 ± 28 | 573 ± 36 | 0.004 | 0.041 |

individual variation in the organ geometry. On the other hand, in the rectum, the overlap volume was of the order of 65%, where, neither CP nor KB, including Re-plan, yielded any improvement (Supplementary table 3). Moreover, the volume of the bowel bag was more consistent, as compared to the bladder, due to variation in the filling capacity of the individual patient (Supplementary table 3). It is worth noting here that

**Table 3**

Model quality statistical parameters: Goodness of fit – Coefficient of Determination $R^2$, Chi square, and Mean Square Error.

| OAR | Co-efficient of determination $R^2$ | Chi square | Mean square error between original and estimate |
|---|---|---|---|
| Ideal values (values) | 1 (0–1) | values near 1 (>1) | Close to 0 |
| Bowel bag | 0.84 | 1.05 | 0.001 |
| Kidneys | 0.88 | 1.05 | 0.002 |
| Femoral heads | 0.71 | 1.01 | 0.004 |
| Bladder | 0.59 | 1.05 | 0.008 |
| Spinal cord | 0.64 | 1.01 | 0.008 |
| Rectum | 0.78 | 1.06 | 0.020 |
| Sigmoid | 0.83 | 1.06 | 0.029 |

the geometric outliers were not excluded, especially for bladder, to increase the scope of the model for bladder volume variation. It was also previously reported that the exclusion of outliers did not change the prediction capability of the model [15,22]. In cervical cancer, most of the OARs are hollow in nature with varying volumes with respect to the content. Hence, to increase the scope of the model, geometric outliers were not excluded, especially for bladder, however, extreme outliers such as patients with large Cooks distance were excluded, and few dosimetric outliers were re-planned before including them back in the model [23,24].

KBP resulted in highly conformal plans as compared to CP, especially, for SIB of $CTV_N$ and $PTV_N$. According to the clinical protocol, SIB for lymph nodes was based on coverage probability principle, where the central part of the $CTV_N$ receives a higher dose, and the edges of $PTV_N$ are cooled down with a lower dose. During CP, these constraints were difficult to achieve, especially when the volumes were small, of the order of 10–15 cm³ for $CTV_N$, and with multiple nodes, requiring a number of optimization structures, to meet the dose constraints [15]. In the current model, for N−, patients, no new optimizations structures were used, thus saving a lot of time, however, for N+ patients, $PTV_{45}$, $ITV_{45}$ and OARs were cropped from $PTV_N$ when they were overlapping, as the dose levels were different. It is the principle of RapidPlan to partition automatically into sub-volumes (in-field, out-of-field, leaf transmission and target overlap) of the OARs.

In the majority of patients, Predicted plan produced comparable results with that of CP, however, Re-plans outperformed CP, especially, it resulted in significant sparing of the bladder, femoral head and spinal cord. This may be attributed to the tendency of planners, where, a lot of attention was given to the hard constraints for the target and salient OARs, such as bowel bag, bladder, rectum, while soft constraints were overlooked, however, in KBP, all the OARs were optimally spared irrespective of the nature of the constraints – soft or hard, where, a good trade-off was applied to all structures equally, such that one organ is not over spared at the cost of the other.

Any modifications to this model, such as new dose level, inclusion of new structure in the future, needs model configuration and validation again, which is a time consuming process [25]. Moreover, the current model was built on a certain clinical protocol, if in the future, we develop a new protocol based on the evolving evidence, for e.g., new dose constraints, dose levels, or new structures, it will not be possible to use this model. A new methodology for model training and validation may be needed to adapt to the changes, the automatic model configuration and validation method proposed by Li N et al, appears a promising tool, such that the modifications to the existing models can be made [18].

KBP was comparable, and for some OARs even outperformed as compared to clinical plans, while producing conformal, homogeneous target coverage. Improved OAR sparing was observed in Replans, when Predicted plans were used as a base plan, by tweaking dose volume objectives and priorities to take into account the individual patient

geometry.

## Advances in Knowledge

First single KBP model for cervical cancer, for lymph node-positive and negative patients including both pelvic and para aortic patients treated with different dose levels.

## 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.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.05.004.

## References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin 2018;68:394–424. https://doi.org/10.3322/caac.v68.610.3322/caac.21492.

[2] Bobdey S, Balasubramanium G, Kumar A, Jain A. Cancer screening: should cancer screening be essential component of primary health care in developing countries? Int J Prev Med 2015;6:56. https://doi.org/10.4103/2008-7802.160053.

[3] Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8:e191–203. https://doi.org/10.1016/S2214-109X(19)30482-6.

[4] Chopra S, Gupta M, Mathew A, Mahantshetty U, Engineer R, Lavanya G, et al. Locally advanced cervical cancer: A study of 5-year outcomes. Indian J Cancer 2018;55:45. https://doi.org/10.4103/ijc.IJC_428_17.

[5] Yeung AR, Pugh SL, Klopp AH, Gil KM, Wenzel L, Westin SN, et al. Improvement in patient-reported outcomes with intensity-modulated radiotherapy (RT) compared with standard RT: A report from the NRG oncology RTOG 1203 study. J Clin Oncol 2020;38:1685–92. https://doi.org/10.1200/JCO.19.02381.

[6] Chopra S, Engineer R, Mahantshetty UM, Dora T, Kannan S, Phurailatpam R, et al. Phase III RCT of postoperative adjuvant conventional radiation (3DCRT) versus IGIMRT for reducing late bowel toxicity in cervical cancer (PARCER) (NCT01279135/CTRI2012/120349): results of interim analyses. Int J Radiat Oncol Biol Phys 2015;93:S4. https://doi.org/10.1016/j.ijrobp.2015.07.016.

[7] Lin Y, Chen K, Lu Z, Zhao L, Tao Y, Ouyang Yi, et al. Intensity-modulated radiation therapy for definitive treatment of cervical cancer: a meta-analysis. Radiat Oncol 2018;13. https://doi.org/10.1186/s13014-018-1126-7.

[8] Mittal P, Chopra S, Pant S, Mahantshetty U, Engineer R, Ghosh J, et al. Standard chemoradiation and conventional brachytherapy for locally advanced cervical cancer: is it still applicable in the era of magnetic resonance-based brachytherapy? J Glob Oncol 2018:1–9. https://doi.org/10.1200/JGO.18.00028.

[9] Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Radiother Oncol 2018;127:404–16. https://doi.org/10.1016/j.radonc.2018.03.003.

[10] Chopra SJ, Mathew A, Maheshwari A, Bhatla N, Singh S, Rai B, et al. National Cancer Grid of India Consensus Guidelines on the management of cervical cancer. J Glob Oncol 2018:1–15. https://doi.org/10.1200/JGO.17.00152.

[11] Chuang L. Can we apply National Cancer Grid of India Consensus Guidelines for the management of cervical cancer in low-resource settings? J Glob Oncol 2018;4:1–4. https://doi.org/10.1200/JGO.18.00074.

[12] Alnaalwa B, Nwankwo O, Abo-Madyan Y, Giordano FA, Wenz F, Glatting G. A knowledge based quantitative approach to characterize treatment plan quality.

Application to prostate VMAT planning. Med Phys 2021;48:94–104. https://doi.org/10.1002/mp.14564.

[13] Ge Y, Wu QJ. Knowledge-based planning for intensity-modulated radiation therapy: A review of data-driven approaches. Med Phys 2019;46:2760–75. https://doi.org/10.1002/mp.13526.

[14] Sharfo AWM, Breedveld S, Voet PWJ, Heijkoop ST, Mens J-W, Hoogeman MS, et al. Validation of fully automated VMAT plan generation for library-based plan-of-the-day cervical cancer radiotherapy. PLoS ONE 2016;11:e0169202. https://doi.org/10.1371/journal.pone.0169202.

[15] Hussein M, South CP, Barry MA, Adams EJ, Jordan TJ, Stewart AJ, et al. Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. Radiother Oncol 2016;120:473–9. https://doi.org/10.1016/j.radonc.2016.06.022.

[16] Ma Changdong, Luo J, Zhang Z, Ma Changsheng. Knowledge-based intensity-modulated radiotherapy plans for cervical cancer with overlap volume of target and organs at risk Prec. Radiat Oncol 2018:1–7. https://doi.org/10.1002/pro6.39.

[17] Ma C, Huang F. Assessment of a knowledge-based RapidPlan model for patients with post-operative cervical cancer. Prec Radiat Oncol 2017;1:102–7. https://doi.org/10.1002/pro6.v1.310.1002/pro6.23.

[18] Li N, Carmona R, Sirak I, Kasaova L, Followill D, Michalski J, et al. Highly efficient training, refinement, and validation of a knowledge-based planning quality-control system for radiation therapy clinical trials. Int J Radiat Oncol Biol Phys 2017;97:164–72. https://doi.org/10.1016/j.ijrobp.2016.10.005.

[19] Tinoco M, Waga E, Tran K, Vo H, Baker J, Hunter R, et al. RapidPlan development of VMAT plans for cervical cancer patients in low- and middle-income countries. Med Dosim 2020;45:172–8. https://doi.org/10.1016/j.meddos.2019.10.002.

[20] Yusufaly TI, Meyers SM, Mell LK, Moore KL. Knowledge-based planning for intact cervical cancer. Semin Radiat Oncol 2020;30:328–39. https://doi.org/10.1016/j.semradonc.2020.05.009.

[21] Pötter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, Nout R, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 2018;9:48–60. https://doi.org/10.1016/j.ctro.2018.01.001.

[22] Fogliata A, Cozzi L, Reggiori G, Stravato A, Lobefalo F, Franzese C, et al. RapidPlan knowledge based planning: iterative learning process and model ability to steer planning strategies. Radiat Oncol 2019;14. https://doi.org/10.1186/s13014-019-1403-0.

[23] Delaney AR, Tol JP, Dahele M, Cuijpers J, Slotman BJ, Verbakel WFAR. Effect of dosimetric outliers on the performance of a commercial knowledge-based planning solution. Int J Radiat Oncol Biol Phys 2016;94:469–77. https://doi.org/10.1016/j.ijrobp.2015.11.011.

[24] Alpuche Aviles JE, Cordero Marcos MI, Sasaki D, Sutherland K, Kane B, Kuusela E. Creation of knowledge-based planning models intended for large scale distribution: Minimizing the effect of outlier plans. J Appl Clin Med Phys 2018;19:215–26. https://doi.org/10.1002/acm2.12322.

[25] Kalet AM, Luk SMH, Phillips MH. Radiation therapy quality assurance tasks and tools: the many roles of machine learning. Med Phys 2020;47:e168–77. https://doi.org/10.1002/mp.13445.