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Knowledge-based intensity-modulated radiotherapy plans for cervical cancer with overlap volume of target and organs at risk

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Abstract

Objective: To compare the differences in the dose-volume histograms between knowledge-based intensity-modulated radiotherapy (K-IMRT) plans and conventional IMRT (C-IMRT) plans of 20 patients with cervical cancer.

Methods: A total of 70 cervical cancer patients were selected in the present study. Of these, 60 patients were selected randomly as a model group. The remaining 10 patients with overlap volume of target and organs at risk were categorized as group E1 for open-loop verification. A total of 10 patients from the model group were selected randomly as group E2 for closed-loop verification.

Results: The dose parameters of the target in the K-IMRT and C-IMRT plans showed no significant difference. The maximum dose and homogeneity index of group E2 showed no significant difference ($P > 0.05$) in their K-IMRT and C-IMRT plans. The dose parameters in the K-IMRT plans of organs at risk were superior to those in the C-IMRT plans. For group E1, V20 of the rectum, and V15, V20, and V25 of the left and right femoral heads in the K-IMRT plans decreased as compared with those in the C-IMRT plans ($P < 0.05$). For group E2, V25, V30, V35, and D50 of the bladder; V25 and V30 of the rectum; and V15, V20, and V25 of the left and right femoral heads in the K-IMRT plans decreased as compared with those in the C-IMRT plans ($P < 0.05$).

Conclusion: It is feasible to optimize the IMRT plans for cervical cancer patients with the overlap volume of the target and organs at risk using knowledge-based radiation treatment automatically.

KEYWORDS

cervical cancer, dose, intensity-modulated radiotherapy, knowledge-based model

1 | INTRODUCTION

Cervical cancer is the third most common type of cancer observed in women in developing countries.[1] Most cervical cancer patients undergo radiation therapy after surgery to improve their chances of survival and quality of life clinically. There are many organs at risk (OARs) surrounding the cervix uteri, such as the bladder, rectum, and left and right femoral heads, which makes it difficult to carry out conventional radiotherapy at the affected region. Intensity-modulated radiotherapy (IMRT) has been confirmed to deliver a higher dose to target volume while reducing the dose to OARs. IMRT is widely used in the treatment of cervical cancer.[2] The optimization of conventional IMRT (C-IMRT) plans is an iterative process using the trial-and-error approach to obtain a clinically acceptable plan.[3] It takes approximately 2–3 h to obtain an acceptable plan. Furthermore, it is difficult to judge whether the exposure dose to the OARs is optimal. An improvement in generating IMRT plans has an immediate and substantial clinical impact on cervical cancer treatment.

Knowledge-based radiation treatment (KBRT) was first proposed by researchers from Duke University. It is a technique to objectively incorporate prior experience into a radiotherapy treatment plan. All plans of therapeutic patients can be used to develop a knowledge-based model (KBM), and then this KBM can be further improved by more plans. This improved KBM is later used to generate treatment plans for new patients by searching patients with similar geometry features in the database. A KBM can analyze a new patient's geometry

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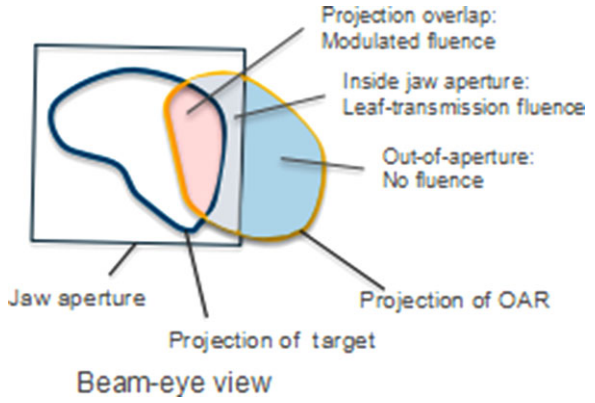

FIGURE 1 Segmentation of organs at risk (OARs) in experience-guided treatment planning systems

and dose distribution, especially for the separate and overlap between tumor target and surrounding OARs, and predict the dose-volume histograms (DVHs) for new patients.

The KBRT system used in our institution, Shandong Cancer Hospital and Institute (No. 440 Jiyan Road, Jinan, China), is developed by Varian Medical Systems Palo Alto, CA, USA. An OAR is divided into four parts in this system, as shown in Figure 1. The four parts are described as follows:

1. Out of field: without exposure dose.
2. Leaf transmission: with low exposure dose.
3. In field: with high exposure dose.
4. Projection overlap volume: with the same dose as the target.

The dose distribution of a target is mainly affected by the projection overlap, as we deliver a higher dose to the target, while reducing the dose of OARs. The present study discusses the feasibility of using KBRT to generate IMRT plans for cervical cancer patients with the overlap volume of target and OARs, by comparing differences between the K-IMRT and C-IMRT plans of 20 patients.

2 | METHODS

2.1 | Patient selection

A total of 70 cervical cancer patients who received IMRT treatment, from May 2014 to July 2015, were chosen randomly for this study. The patients were aged 30–65 years, with a median age of 52 years. According to FIGO 2009 cervical cancer staging, 23 patients had stage IB disease and 47 had stage IIA disease. All the 70 IMRT plans were generated using the Eclipse system, with 6-MV X-rays, seven equal field angles, anisotropic analytical algorithm, and 2.5-mm computational grid. The planned dose was 36–45 Gy.

2.2 | Patient groups

A total of 10 patients with overlap volume of target and OARs were chosen as group E1, and the other 60 patients comprised the model group. A total of 10 patients with projection overlap were randomly chosen from the model group as group E2. The model group was used for the development and training of KBM. Group E1 was used for open-loop verification and group E2 was used for close-loop verification. The planned dose for patients in group E1 and E2 was 1.8 Gy multiplied by 20 fractions.

2.3 | Development of the model

Data of 60 cancer IMRT cases in a model group, including computed tomography images, tumor volume, dose distribution, and DVH, were input in the Eclipse treatment planning system (version 13.5; Varian Medical System) to obtain the DVH curve of surrounding OARs with regression analysis and develop the DVH-predicted KBM for cervical cancer. For a new patient, the DVH-predicted KBM compares the target and normal tissues with that in the database to find similar ones. Furthermore, the KBRT system will generate the exposure volume for OARs, such as the bladder, rectum, and femoral head; and give the optimal DVH curve for the plan, without any manual intervention. The DVH curve would be the dose limit for further optimization.[4,5]

2.4 | Training of the model and generating new treatment plans

The new KBM model was checked before use to avoid the errors caused by the data importing, target and OAR drawing, or planned doses. Five parameters were checked intensively:

1. Geometric distribution box plot, which showed the anatomical structure for the use of the training KBM model (Fig. 2).
2. Regression curve, which showed the relationship between geometrical characteristics and the DVH curve (Fig. 3).
3. Residual scatter diagram, which presented the difference between the true value and predicted value of DVH (Fig. 4).
4. DVH distribution in the aperture, which showed the relationship between the true value and predicted value of DVH in the aperture (Fig. 5).
5. In-field DVH plot, which showed the statistical characteristics for the fitting results (Fig. 6).

To check the outlier and influential points in the regression curve, the threshold values were set as follows: Cook's distance value >4, modified Z-score >3.5, student residual >3, and a real difference of estimate >3.

After the training of the model, the treatment plans for patients in groups E1 and E2 were generated and optimized by the DVH-predicted KBM for cervical cancer, with the same beam angle, planned dose, and calculation method.

2.5 | Evaluating the treatment plan quality

We evaluated the treatment plan quality considering the following four aspects:

FIGURE 2 Geometric plot for the bladder. OAR, organ at risk

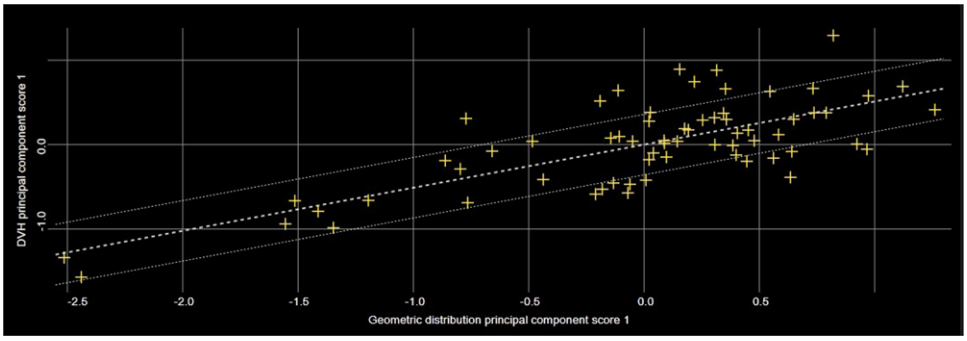

FIGURE 3 Regression plot for bladder. DVH, dose-volume histogram

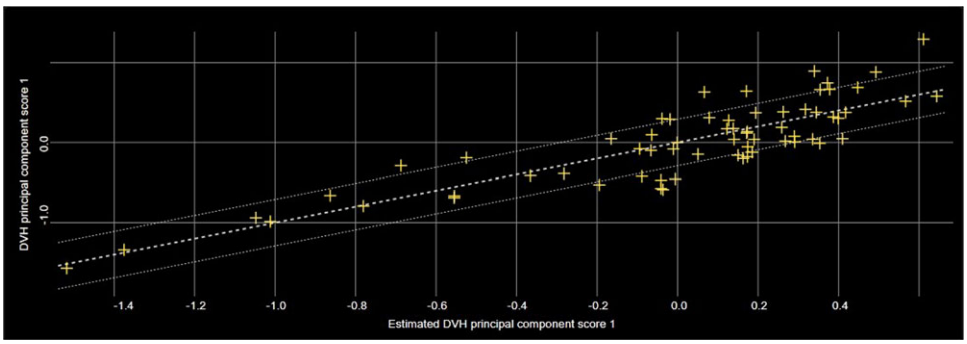

FIGURE 4 Residual plot for bladder. DVH, dose-volume histogram

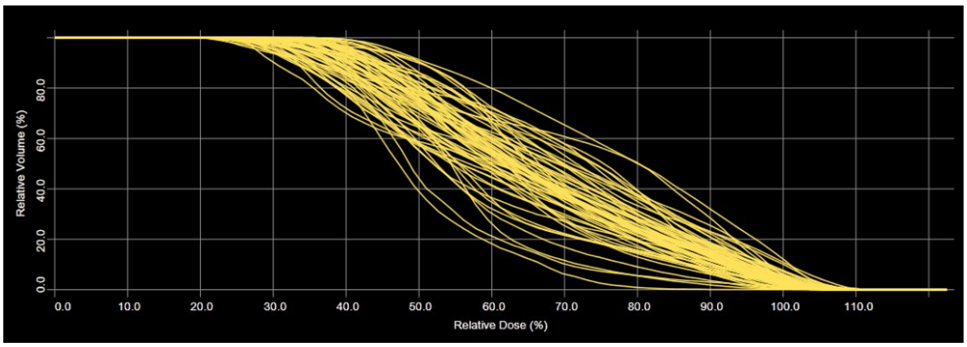

FIGURE 5 Dose-volume histogram plot for bladder

1. Planned target volume (PTV): We evaluated the maximum dose (D_{max}), minimum dose (D_{min}), homogeneity index (HI), and conformity index (CI) of the target volume with the DVH curve.

HI was calculated using the following formula:

$$HI = \frac{D_{max} - D_{min}}{D_{mean}} \quad (1)$$

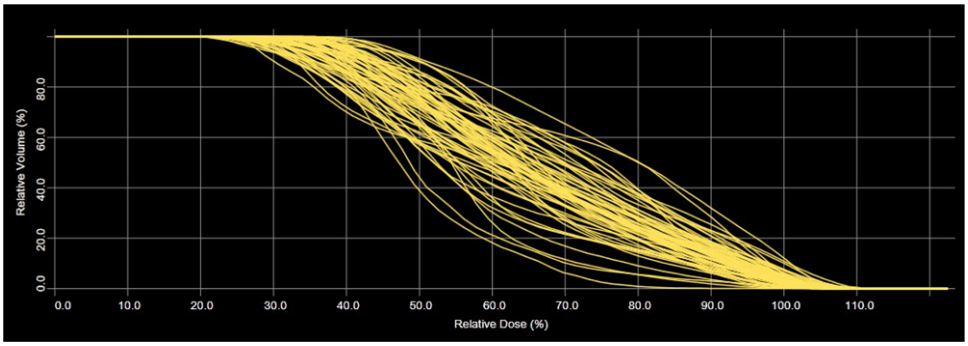

FIGURE 6 In-field dose-volume histogram plot for bladder

D_{max} is the exposure dose of 2% volume of target, D_{min} is the dose of 98% volume of target, and D_{mean} is the mean dose of the whole target. Lower HI means better homogeneity.[6] CI is calculated using following formula:

$$CI = \frac{VT_{ref}}{VT} \times \frac{VT_{ref}}{V_{ref}} \quad (2)$$

VT_{ref} is the target volume surrounded by the reference isodose curve. VT is the target volume. V_{ref} is the total volume surrounded by the reference isodose curve. CI ranges from 0 to 1. A higher CI means better conformity.[7]

2. OARs: As reported, the probability of a toxic reaction to the rectum and bladder was related to the exposure volume. D50 was used as the dose parameter of OARs, which means the exposure dose of 50% volume of OARs. V15, V20, V25, V30, and V35 were used as the volume parameters of OARs, which means the volume percentage exposed to 15 Gy, 20 Gy, and so on.
3. Monitor unit (MU): MU is the sum for all fields' MU.
4. Optimization time.

2.6 | Statistical analysis

The data were analyzed with SPSS 17.0 (SPSS, Chicago, IL, USA), and the dose differences between C-IMRT and K-IMRT were analyzed with the Student's *t*-test, with $P < 0.05$ considered statistically significant.

3 | RESULTS

3.1 | Overlap volume

The overlap volume of the target and OARs for the model group, group E1, and group E2 was 1075.32 ± 104.10 cm^3, 875.71 ± 215.37 cm^3, and 962.64 ± 175.63 cm^3, respectively. The overlap volume of the target and bladder for groups E1 and E2 was 14.25 ± 10.37 cm^3 and 15.00 ± 17.38 cm^3, respectively. The overlap volume between the target and rectum for groups E1 and E2 was 12.56 ± 2.38 cm^3 and 13.77 ± 6.36 cm^3, respectively.

3.2 | Dose difference of target between C-IMRT and K-IMRT

As shown in Table 1 and Figure 7, D_{max} and CI of K-IMRT in group E2 was superior to that of C-IMRT ($P < 0.05$). All the dose parameters of the target in group E1 and D_{min} and HI in group E2 showed no difference between C-IMRT and K-IMRT ($P > 0.05$).

3.3 | Dose difference of OARs between C-IMRT and K-IMRT

As shown in Table 1 and Figure 7, V20 of the rectum, and V15, V20, and V25 of the femoral head in the K-IMRT plans were less than those in the C-IMRT plans ($P < 0.05$) in group E1. The V25, V30, V35, and D50 of the bladder; V25 and V30 of the rectum; and V15, V20, and V25 of the femoral head in K-IMRT were less than those in C-IMRT ($P < 0.05$). The other dose parameters of the bladder, rectum, and femoral head showed no difference ($P > 0.05$) between the C-IMRT and K-IMRT plans.

3.4 | Monitor unit

MU in K-IMRT plans was significantly less than that in C-IMRT ($P < 0.05$).

3.5 | Optimization time

The optimization time in K-IMRT was much less than that in C-IMRT. The optimization for one C-IMRT plan takes approximately 2–3 h, and it takes just 2–3 min for one K-IMRT plan. Furthermore, there was no manual intervention in generating K-IMRT plans.

4 | DISCUSSION

KBRT is verified to improve the quality of IMRT plans by many dosimetry studies.[8–13] KBRT includes two aspects: (i) the development of DVH predicts KBM; and (ii) the training of the model. The DVH-predicted KBM is developed by calculating the geometry-based expected dose for each organ of patients. At least 20 patients are required for the development of KBM. The geometry-based expected dose is used to evaluate the overlap volume, separation distance between the

TABLE 1 Open-loop verification and closed-loop verification groups of knowledge-based intensity-modulated radiotherapy and conventional intensity-modulated radiotherapy intensity modulated difference of statistical analysis

Parameters		E1 group	*P*-value	E2 group	*P*-value
PTV	D_2/cGy	−38.66 ± 45.37	0.187	−34.87 ± 14.41	0.001
	D_{98}/cGy	−23.26 ± 45.16	0.079	15.08 ± 30.65	0.071
	HI	−0.01 ± 0.02	0.070	−0.01 ± 0.02	0.061
	CI	−0.02 ± 0.04	0.069	−0.02 ± −0.02	0.012
Bladder	V_{20}/%	−2.65 ± 8.25	0.052	3.33 ± 6.70	0.051
	V_{25}/%	−0.22 ± 6.35	0.090	2.85 ± 8.40	0.011
	V_{30}/%	−0.78 ± 4.31	0.076	2.73 ± 7.86	0.001
	V_{35}/%	−0.36 ± 2.39	0.053	0.79 ± 4.47	0.032
	D_{50}/cGy	−0.19 ± 2.24	0.083	2.63 ± 3.81	0.010
Rectum	V_{20}/%	2.85 ± 11.66	0.013	0.28 ± 7.11	0.072
	V_{25}/%	−3.79 ± 13.44	0.062	1.41 ± 9.02	0.033
	V_{30}/%	0.77 ± 11.34	0.086	2.01 ± 7.83	0.021
	V_{35}/%	0.59 ± 6.75	0.165	−0.12 ± 3.81	0.118
	D_{50}/cGy	0.15 ± 2.93	0.292	1.94 ± 2.23	0.350
Left femoral head	V_{20}/%	11.93 ± 13.72	0.024	4.20 ± 17.47	0.046
	V_{25}/%	6.14 ± 6.36	0.047	3.87 ± 9.67	0.037
	V_{30}/%	4.14 ± 1.64	0.005	2.06 ± 4.34	0.017
	V_{35}/%	0.35 ± 0.78	0.074	0.53 ± 1.01	0.132
	D_{50}/cGy	1.27 ± 1.45	0.122	36.88 ± 22.01	0.069
Right femoral head	V_{20}/%	7.08 ± 11.13	0.028	2.48 ± 17.63	0.036
	V_{25}/%	5.39 ± 4.92	0.040	3.99 ± 9.04	0.016
	V_{30}/%	4.26 ± 3.33	0.046	2.65 ± 3.94	0.043
	V_{35}/%	7.87 ± 15.74	0.326	0.64 ± 1.15	0.113
	D_{50}/cGy	0.71 ± 1.26	0.079	6.19 ± 19.57	0.063
MU		446.4 ± 113.17	0.001	295.40 ± 216.69	0.002

E1, open-loop verification; E2, closed-loop verification; MU, monitor unit; PTV, planned target volume.

target and OARs, and dose distribution in each field. The training of the model is to carry out the regression analysis for the geometry-based expected dose and DVH of the treatment plans with principal component analysis, to calculate the DVH and geometry correlation parameter. When the system generates new treatment plans, the DVH-predicted model would analyze the geometry of the target and surrounding OARs. It will then calculate the fluctuation range of DVH for all the possible treatment plans and choose the minimum dose depending on the optimization condition.

The influence of dose distribution on the overlap volume of target and OARs in KBRT was examined in the present study. The results showed that the dose distribution of the target in K-IMRT plans was similar to that in C-IMRT plans, both in group E1 and group E2. As shown in Figure 7, dose parameters of OARs for 85% K-IMRT plans were lower than or similar to those in C-IMRT plans in group E1. All parameters of OARs in K-IMRT plans were lower than or similar to those in C-IMRT plans in group E2. The result was in agreement with the result obtained by Good et al.[14] In addition, the present study showed that there was great improvement in MU and time of K-IMRT plans. MU in K-IMRT plans was reduced by 17.3% and 26.5% in group E1 and group E2, respectively, compared with that in C-IMRT plans. The optimization time in K-IMRT plans was reduced to several minutes compared with several hours in C-IMRT plans. The efficiency to generate treatment plans was improved greatly.

Yuan et al. applied knowledge-based plans to 24 prostatic cancer patients.[15] They found that the bladder dose in 34% knowledge-based plans decreased by 6%, and the rectum dose in 42% knowledge-based plans decreased by 10%, compared with that in original plans.

The present study focused on the algorithm analysis of DVH and could not determine the real dose distribution. In addition, this study focused on the application of knowledge-based plans and could not examine the quality of the plans themselves, as they could be affected by multiple factors, such as ray energy, number of fields, field angle, collimator angle, and bed angle. Studies have confirmed that the field angle has an influence on normal organs, and the ray angle has an influence on the radiotherapy quality.[16–18] Sung et al. found that the exposure dose to normal liver tissue of IMRT plans for five adjacent uneven fields was less than that of IMRT plans for five equational fields surrounding the target.[19] Therefore, K-IMRT should be used for the optimization of IMRT plans, and the field angle should be set manually

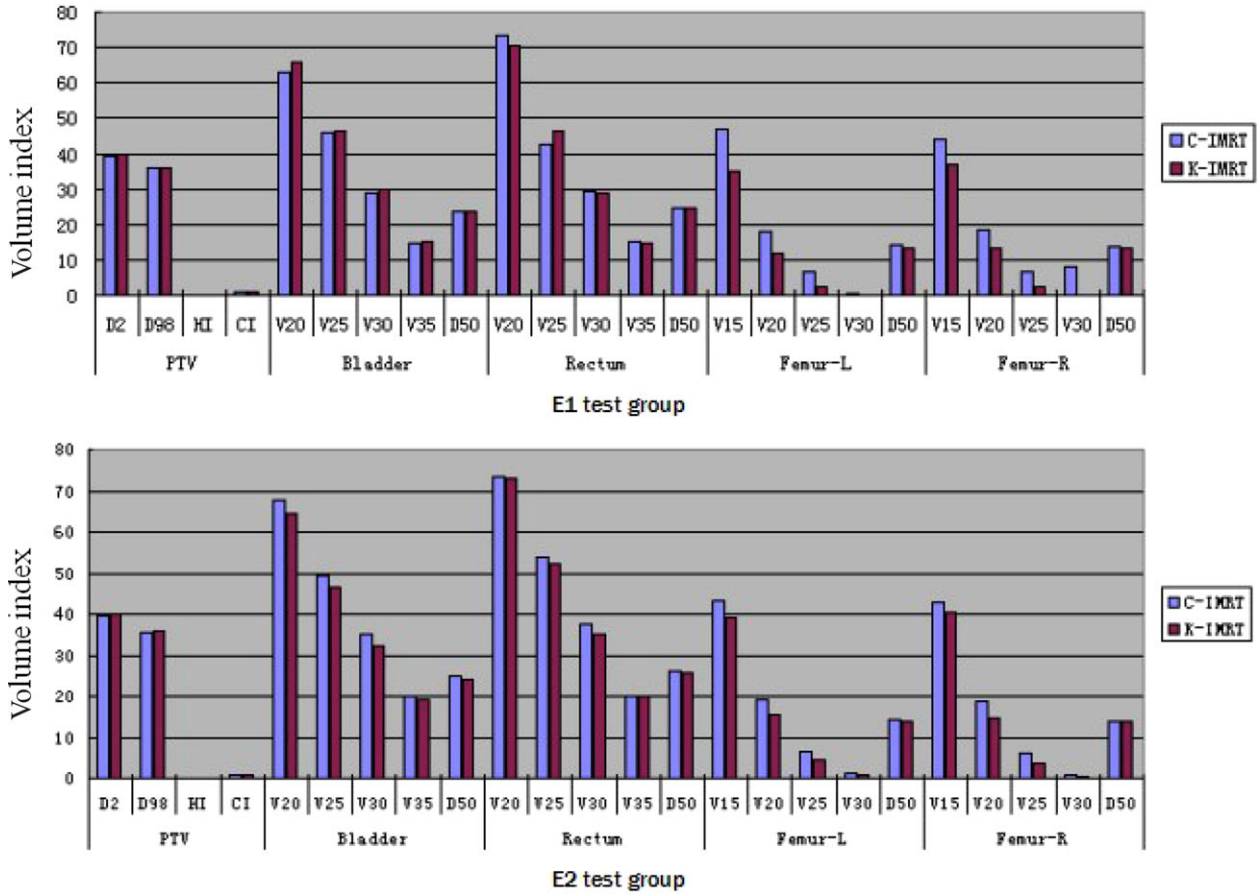

FIGURE 7 Target and OARs dose volume index in the conventional intensity-modulated radiotherapy (C-IMRT) and knowledge-based intensity-modulated radiotherapy (K-IMRT) plans. E1, open-loop verification; E2, closed-loop verification; PTV, planned target volume

by the radiotherapy physicist, according to the four basic principles of field angle and treatment experience.

In conclusion, K-IMRT is an application of big data. It can be trained using the radiotherapy plans of therapeutic patients and then used to optimize the radiotherapy plans of new patients. K-IMRT plans have similar quality compared with C-IMRT plans, with the advantages of time saving and high efficacy. However, the application of knowledge-based plans in volumetric modulated arc therapy and different beam angle should be studied further.

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