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Evaluating the accumulated dose distribution of organs at risk in combined radiotherapy for cervical carcinoma based on deformable image registration

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ABSTRACT

OBJECTIVE: To evaluate the feasibility and value of deformable image registration (DIR) in calculating the cumulative doses of organs at risk (OARs) in the combined radiotherapy of cervical cancer.

PATIENTS AND METHODS: Thirty cervical cancer patients treated with external beam radiotherapy (EBRT) combined with intracavitary brachytherapy (ICBT) were reviewed. The simulation CT images of EBRT and ICBT were imported into Varian Velocity 4.1 for the DIR-based dose accumulation. Cumulative dose-volume parameters of D2cc for rectum and bladder were compared between the direct addition (DA) and DIR methods. The quantitative parameters were measured to evaluate the accuracy of DIR.

RESULTS: The three-dimensional cumulative dose distribution of the tumor and OARs were graphically well illustrated by composite isodose lines. In combined EBRT and ICBT, the mean cumulative bladder D2cc calculated by DIR and DA was 86.13 Gy and 86.27 Gy, respectively. The mean cumulative rectal D2cc calculated by DIR and DA was 72.97 Gy and 73.90 Gy, respectively. No significant differences were noted between these two methods ($p > 0.05$). As to the parameters used to evaluate the DIR accuracy, the mean DSC, Jacobian, MDA (mm) and Hausdorff distance (mm) were 0.79, 1.0, 3.84, and 22.01 respectively for the bladder and 0.53, 1.2, 7.31, and 29.58 respectively for the rectum. In this study, the DSC seemed to be slightly lower compared with previous studies.

CONCLUSION: Dose accumulation based on DIR might be an alternative method to illustrate and evaluate the cumulative doses of the OARs in combined radiotherapy for cervical cancer. However, DIR should be used with caution before overcoming the relevant limitations.

Keywords: Cervical cancer; Radiotherapy; Brachytherapy; Deformable image registration; Organs at risk

Introduction

The combined external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the standard treatment for locally advanced cervical cancer (1), with a prescription dose of 45–50 Gy for EBRT and 30–40 Gy for ICBT. The goal of this care includes an equivalent dose at 2 Gy (EQD2) to the high-risk clinical target volume (HR-CTV) with a D90 of 80Gy_{EQD2} for small volume cervical cancer, and a total of ≥85Gy_{EQD2} for large-volume cervical cancer (2). The organs at risk (OARs) should be limited as per the guidelines with a D2cc≤75Gy_{EQD2} for the rectum, and with a D2cc≤90Gy_{EQD2} for the bladder (2,3).

According to the GEC-ESTRO recommendations, the conventional evaluation of the cumulative dose of the combined external and internal radiotherapy is to simply add the dose-volume histogram (DVH) parameters, including

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the D90 of HR-CTV and D2cc of the OARs based on the hypothesis that the locations of the regions of interest are identical in each therapy. If the regions of interest are not identical due to the movement and changes in shape, the high dose area will be inconsistent in each therapy. Therefore, the direct addition (DA) of DVH parameters may not accurately reflect the absolute dose-volume relationship. Moreover, the cumulative dose of the regions of interest, especially the OARs, may be overestimated. This would further restrict the increase of HR-CTV dose (4) .

What's more, the doses received by OARs are significantly associated with radiation-related toxicities. Mazeron *et al.* (5) reported that the 3-year risk of rectal fistula reached 12.5% after radiotherapy with the total D2cc of the rectum above 75 Gy. Zakariaee *et al.* (6) reported that bladder related side effects, such as urinary incontinence during the brachytherapy of cervical cancer, were related to the cumulative dose of bladder D2cc. Therefore, an accurate estimation of the cumulative irradiation dose for OARs is crucial. In recent years, deformable image registration (DIR) has been defined as the process of finding the corresponding relationship between images that are not connected by simple rigid movement and rotation, so as to minimize the difference between two or more groups of images. Currently, DIR is a key component in many radiotherapy applications (7). Although Christensen et al. reported that DIR-based dose accumulation with combined radiotherapy in cervical cancer is feasible to estimate the cumulative dose distribution for tumors and OARs for the first time in 2001 (8), the current data on the feasibility and value of DIR in combined radiotherapy of cervical cancer remain limited (9−10,21,22). Therefore, more evidence that better clarifies these findings is needed.

This study aims to verify the feasibility and value of this new method in routine clinical practice of cervical cancer radiotherapy with a larger sample size, as well as with a different commercial software named Varian Velocity 4.1.

Patients and methods

Patients

From January 2018 to September 2020, the patients diagnosed with cervical cancer received EBRT and six sessions of ICBT. Clinical characteristics and simulated CT images of EBRT and ICBT of all patients were collected.

Radiotherapy for cervical cancer

External beam radiotherapy

The rectum and bladder were requested to be emptied 1 h before the CT simulation. Next, the patients were told to drink 1000 ml of water immediately, and wait an hour to fill the bladder. Then, the patients were immobilized by heat shrink film. CT simulation was performed on all patients before external irradiation. After scanning, the images were imported into the treatment planning system for the delineation of the tumor and OARs. The CTV consisted of the cervical tumor, cervix, uterus, at least half of the vagina, parametrium, and the pelvic lymphatic drainage area with/without para-aortal lymphatic drainage area. The planning target volume (PTV) was created by expanding the CTV by 0.5–0.8 cm. The OARs mainly included bladder, rectum, colon, small intestine, bilateral femoral heads and bilateral iliac bones. EBRT was delivered to the PTV with a prescription dose of 45− 50.4 Gy in 25−28 fractions using the volumetric modulated arc therapy (VMAT) technique with 6-MV X-ray. Before each irradiation, patients were asked to perform the rectal and bladder preparations, as mentioned above.

Intracavitary brachytherapy

Defecated 1 h before brachytherapy. The patients were placed in lithotomy position on the gynecological bed in the operation room. Perineal disinfection was performed, and the following procedures were performed successively: (1) a Foley catheter was inserted into the bladder to drain the urine; (2) the vaginal speculum was inserted into the vagina for the examination; (3) the source applicator was implanted and immobilized; (4) One hundred fifty milliliter of normal saline was injected into the bladder before CT simulation. Then CT scan was performed with a slice thickness of 3 mm. The images were then imported into the treatment planning system. The HR-CTV, rectum, and bladder were contoured according to GEC-ESTRO recommendations (3). Three-dimensional (3D) iridium (Ir)−192 intracavitary brachytherapy was delivered as the internal irradiation with a prescription dose of 30 Gy in 5 fractions(30 Gy/5f) or 36 Gy in 6 fractions (36 Gy/6f). The schedule of 36 Gy/6f is frequently used for the patients who don't achieve complete response before the first session of brachytherapy, who present with large size tumor at diagnosis, who are diagnosed with more advanced tumor stage and who don't undergo the brachytherapy twice a week due to anemia, neutropenia, thrombocytopenia or individual reasons.

Dose accumulation of OARs based on DIR

We imported the simulated CT images of EBRT and ICBT into the DIR software of Varian Velocity 4.1, and then fused these seven sets of CT images. The cumulative doses of OARs were calculated with the method of DIR. Doses of EBRT and ICBT were converted into EQD2 using the linear quadratic model. For the tumor tissues, the α/β was 10 Gy. For the normal tissues, the α/β was 3 Gy.

Cumulative DVH parameters of OARs

According to the cumulative dose distribution, the cumulative DVH parameters, including D2cc of rectum and

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bladder, were calculated by DIR and DA methods, respectively.

Evaluation of the accuracy of DIR

According to previous studies, the accuracy of DIR is evaluated by quantitative indicators, including dice similarity coefficient (DSC), Jacobian, mean consistent distance (MDA) and Hausdorff distance (HD) (4,11,9). DSC is a similarity measure on sets, which is usually used to estimate the similarity between two sets. Its value ranges from 0 to one (0 means no overlap, and one means full overlap). If the Jacobian coefficient is greater than one, the image is enlarged; if it is less than one, the image is reduced; and if it is negative, the image deformation registration fails. MDA is defined as the average distance (mm) from each point on one contour to the nearest point of another contour. HD describes the maximum nearest distance (mm) of each vertex of two volumes. The closer the MDA and the HD value are to 0, the smaller the image displacements are.

Statistical analysis

All cumulative DVH parameters calculated by DIR method and DA method were analyzed by Kolmogorov Smirnov (K-S) normal distribution test, and then compared by paired t test. SPSS software version 24.0 was used for all statistical analyses. $p < 0.05$ showed significant difference.

Results

Patient characteristics

Between January 2018 and September 2020, we reviewed clinical data of 30 patients who received definitive combined radiotherapy (EBRT: 50.4 Gy/28f; ICBT: 36 Gy/6f) for cervical cancer at our center. According to FIGO stage, there were one case in IB stage, seven cases in IIA stage, 12 cases in IIB stage, one case in IIIA stage, five cases in IIIB stage, three cases in IIIC stage and one case in IVA stage. KPS scores of all patients were greater than 80. Patients ranged in age from 38 to 80 years old, with a median age of 61 years old. Excluding the five unqualified patients, we preformed MRI examinations on all the remaining 25 patients before the EBRT, as well as about 1 month after the end of combined radiotherapy. However, due to the unavailability, patient's financial problems, and other personal reasons, patients are unable to receive MRI before each session of brachytherapy. Therefore, the brachytherapy in our center is based on CT, although MRI is regarded as the gold standard of image-guided adaptive brachytherapy (IGABT) for cervical cancer. According to the IBS-GEC ESTRO-ABS recommendations on CT-based contouring in IGABT for cervical cancer, HR-CTV was contoured before each session of brachytherapy, but GTV was not contoured (12).

Table 1
The comparison of cumulative DVH parameters of the OARs

Parameter	method	$\bar{X} \pm S$(Gy)	T-value	p-value
Rectum D2cc	DIR	72.97 ± 7.60	−0.799	0.431
	PA	73.90 ± 4.36		
Bladder D2cc	DIR	86.13 ± 6.02	−0.131	0.897
	PA	86.27 ± 6.10		

D2cc, the minimum dose to the most exposed 2 cm^3 of tissues; EQD_2, the biological equivalent dose at 2 Gy per fraction.

Cumulative dose distribution

The cumulative dose distributions of EBRT and six sessions of ICBT performed by the method of DIR were shown in Fig. 1. A series of steep isodose lines were around the tumor. The rectum was covered with approximately 70–75 Gy_{EQD2} and the bladder was covered with approximately 85–90 Gy_{EQD2}.

Comparison of cumulative dvh parameters of the OARs

The mean cumulative D2cc of the rectum in combined radiotherapy calculated by DIR was 72.97Gy, while the mean value calculated by DA was 73.90 Gy as shown in Table 1. The mean cumulative D2cc of the bladder calculated by DIR was 86.13Gy, while the mean value calculated by DA was 86.27 Gy. There were no significant differences between these two methods ($p > 0.05$) as shown in Table 1.

DIR accuracy evaluation

The parameters evaluating the accuracy of the DIR were estimated. As for the rectum, the mean DSC, Jacobian, MDA (mm) and HD (mm) were 0.53, 1.20, 7.31, and 29.58, respectively. As for the bladder, the mean DSC, Jacobian, MDA (mm) and HD (mm) were 0.79, 1.0, 3.84, and 22.01, respectively (Table 2). Additionally, the mean DSC of HR-CTV in brachytherapy was 0.76.

Table 2
The parameters of the accuracy for DIR (deformable image registration).

Parameter	method	$\bar{X} \pm S$(Gy)
Bladder	DSC	0.79 ± 0.02
	MDA (mm)	3.84 ± 0.41
	Jacobian	1.0 ± 0.04
	HD (mm)	22.01 ± 7.58
Rectum	DSC	0.53 ± 0.03
	MDA (mm)	7.31 ± 0.92
	Jacobian	1.20 ± 0.07
	HD (mm)	29.58 ± 13.5

DSC, dice similarity coefficient; MDA, mean distance to agreement; HD, Hausdorff distance.

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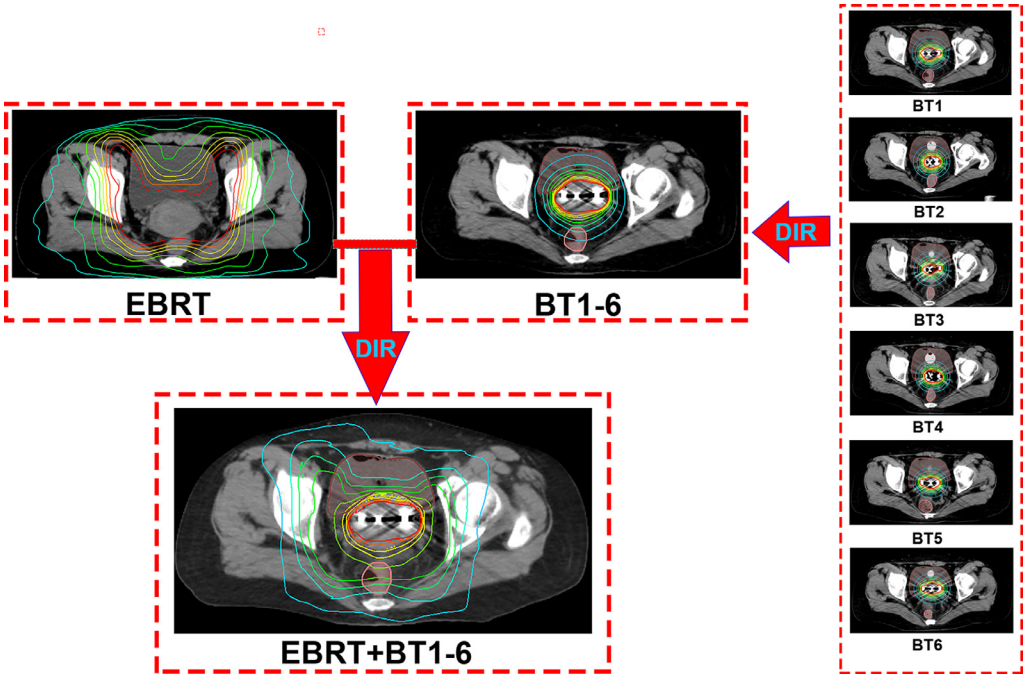

Fig. 1. Dose accumulation of the tumor and OARs based on DIR method. Six CT simulation images of brachytherapy (BT) were fused with CT simulation images of external beam radiotherapy (EBRT).

Discussion

Accurate evaluation of the cumulative dose of OARs in combined radiotherapy for cervical cancer is very important for increasing the tumor dose and reducing the dose of OARs, so as to improve the efficacy and reduce the radiation-related toxicity. Currently, direct addition of OARs dose is recommended by GEC-ESTRO as the conventional method to evaluate the cumulative doses based on the hypothesis that the sites of interest are consistent during the EBRT and ICBT. In recent years, this method is being challenged due to the development of new radiotherapy techniques, as well as the fact that high dose areas of the OARs are changing due to the movement of organs, the regression of tumor, and the changes of radiotherapies at different times and types. In this study, a new method of DIR was used to evaluate the cumulative dose of OARs, and this new method was compared with the traditional DA method. The results indicated that there were no differences between these two methods, however the new method can graphically and visually illustrate the cumulative dose distributions of the OARs compared with the conventional method.

In this study, after the accumulation of the dose distributions based on the DIR method, steep isodose lines around the tumor were clear, and were displayed in graphical manners (Fig. 1). This will help doctors evaluate the dose absorbed by the region of interest, and may help to optimize the dose distribution of the target volume. Previous studies also reported this advantage of the DIR (7,13−14). On the contrary, the conventional method cannot display the accumulated dose distribution by composite isodose lines, which makes DIR method superior to the conventional method.

We further compared the cumulative DVH parameters of OARs, including the D2cc of the rectum and the bladder. It was observed that compared with DIR method, DA method overestimated the cumulative DVH parameters. However, the differences were not significant (rectum D2cc:73.90 Gy vs. 72.97 Gy, $p=0.431$; bladder D2cc:86.27 Gy vs. 86.13 Gy, $p=0.897$). Abe *et al.* (10) also reported that the DA method induced an insignificant overestimation of cumulative DVH parameters of OARs (D2cc of rectum and bladder) compared with DIR method ($p>0.05$). Furthermore, Hayashi et al. (13) reported that the cumulative D2cc of rectum and bladder evaluated by DIR seemed to be lower than that of DA method in 14 cervical cancer patients. Teo *et al.* (14) also reported that the cumulative doses of OARs were overestimated by DA method in comparison to DIR method. Flower *et al.* (7) ever pointed out that organ movements, levels of bladder and rectum filling, urine volume, intestinal gas, or changes in the position of source applicator or fillers might result in overestimated total dose of OARs by direct calculation of DVH parameters. The results from our study, as well as the results of the previous studies aforementioned seemed to confirm the theoretical conjecture that DA may overestimate the cumulative DVH parameters. However, Kim *et al.* (15) reported different results that, there was an overestimation of cumulative DVH parameters in DIR method compared with DA method, which is inconsistent with our and previously published results. The possible primary rea-

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son might be that the uncertainties of the OARs lead to these results. Changes in the positions and shapes of the OARs during the whole radiotherapy reduced the consistency, and the high-dose regions in the bladder and rectum near the source applicator may partially deform on other images in the process of DIR. As a result, the D2cc estimated by DIR was higher than that by direct calculations, which is not uncommon in clinical practice. Second possible reason is that in Kim's study, the DIR was used for MRI, while DIR was used for CT images in our and other studies (15). Systematic errors of DIR can also occur in the recognition of "voxel". Further studies are required to further clarify how the fusion of images from different imaging modalities influences the DIR. Another possible reason is that DIR is an assumption based on the actual situation. Therefore, an overestimation might be caused by DIR. Kadoya *et al.* (16) pointed out that the residual error of DIR may lead to an overestimation of the cumulative dose compared with direct calculation. These inconsistent results may indicate the complexity of DIR, which requires more exploration. Our work echoes previous studies and reconfirms in a larger sample size that DIR seems to be an effective alternative to determine the cumulative dose volume relationship of combined radiotherapy for cervical cancer.

Although DIR is equivalent to DA in evaluating cumulative DVH parameters, the feasibility or accuracy of DIR needs to be evaluated through quantitative indicators. In fact, the accuracy of DIR is influenced by various factors, such as inaccuracy of delineation, inconsistency of the organs between different sessions of radiotherapy, and voxels differences (17,18,23−26). In the present study, the patients were requested to perform the preparations of the bladder and rectum as per the routine clinical protocols in our center to maintain the consistency of the position and shape of these organs throughout the entire radiotherapy. Furthermore, the target volumes and OARs were well delineated and checked in details by at least experienced associate consultant physicians. Moreover, the simulation CTs of EBRT and ICBT were scanned by the same CT machine to reduce the differences of voxels.

DSC is the most commonly used quantitative metric to evaluate the accuracy of DIR. In this study, the mean DSC was 0.53 and 0.79 for the rectum and bladder. However, there is no consensus of appropriate ranges for DSC yet. Historical data can be used as a reference. Abe *et al.* (10) reported that the values of DSC were 0.87 and 0.76 with a strict and good pre-image preparations of bladder and rectum. Teo *et al.* reported that the mean DSC for the rectum and bladder was 0.91 and 0.92, respectively, with adequate image pre-processing (14). These values appeared to be higher than those of our study. The probable primary cause was that the more adequate image preprocessing, and/or better preparations of the bladder and rectum were performed in Abe's and Teo's study. In Abe's study, the bladder volume was calculated by the simulation CT before EBRT, and then the bladder was filled with this volume of saline before every session of brachytherapy to maintain its shape and size. The rectum was requested strictly to be emptied before EBRT and ICBT. In Teo's study, images were pre-processed to correct for artifacts, air pockets, contrast material and variation in CT number within the bladder and rectum since they may not show a meaningful correspondence between different sets of images. In our study, no extra pre-imaging preparations were performed. All the patients complied with the routine preparations in our center and were told to drink 1000 ml of water and defecated one hour before CT simulation of EBRT. Then, before CT simulation of brachytherapy, the patients were told to empty the rectum, and the bladder was filled with 150 ml of saline. Therefore, the bladder volume before CT simulation of EBRT is not be the same as the volume before CT simulation of brachytherapy. In addition, some patients in our study did not empty their stools well, and / or residual large amounts of gas in the rectum, which obviously reduced DSC. What's more, the cumulative dose of HR-CTV in this study was higher compared with that in Abe's study. Higher dose of HR-CTV can more easily result in higher frequency and graded toxicities of bladder and rectum, such as frequent micturition, urgent urination, diarrhea and constipation, etc. These side effects will further adversely influence the preparation of rectum and bladder. The second possible cause might be the different types of DIR software. Abe and Teo used MIM Maestro in their studies, while we used Varian Velocity 4.1 software. Different types of software may use different DIR methods and / or different coefficients, resulting in different DSC values. Previously Kadoya et al. (16) applied different DIR techniques to estimate the cumulative dose of the rectum and bladder in 11 cervical cancer patients treated by combined internal and external irradiation and reported that DSCs were unidentical in different DIR techniques. The comparison analyses indicate that increasing the consistency of the OARs by high quality preparations can improve the accuracy of DIR, and thus, increase the reliability of DIR in combined radiotherapy of cervical cancer.

According to previously published data, HD, MDA, and Jacobian are also commonly used as quantitative metrics to evaluate DIR (4,11,9). In our study, the mean HD (mm) was 29.58 ± 13.5 for the rectum. Miyasaka *et al.* reported the mean HD (mm) of 18.2 (±12.7) for the rectum in cervical carcinoma. (19), which seemed slightly better than our findings. At present, as far as we know, the Jacobian and MDA data of combined radiotherapy for cervical cancer are still unavailable in previous studies. Therefore, the comparison between our study and the previous studies needs to be awaited. Although the optimal range of these parameters has not been determined yet, the error should be as small as possible.

It is noteworthy that the registration accuracy is usually higher for the bladder than for the rectum probably due to

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the following reasons: (1) The rectum is a hollow organ with an unstable shape; (2) Moreover, if the intestine is not well prepared, feces and intestinal gas may exist in the rectum. This will further lead to rectal contour registration errors.

There are several limitations in this study. The first one is that the DIR is based on the three-dimensional CT, not MRI. It is very well established that CT-based definitions of treatment volume and OARs are less accurate compared to MRI, which leads to uncertainties of the volume of interest. According to the "Consensus guidelines for delineation of clinical target volume for CT- and MR-based brachytherapy in locally advanced cervical cancer", the size of target volume or OARs is overestimated in CT compared with MRI, which reduces the reproducibility of the treatment, and leads to lower accuracy of DIR(20). Another one is the retrospective nature of this study which decreases the evidence level. Nevertheless, this study provides new evidence for DIR to clarify the cumulative dose distribution and evaluate the cumulative dose and DVH parameters in cervical cancer combined radiotherapy. Nevertheless, this study provided a new piece of evidence for DIR to illustrate the cumulative dose distributions and evaluate the DVH parameters in combined radiotherapy for cervical cancer in routine clinical practice.

Conclusions

For the combined radiotherapy of cervical cancer, DIR seems to be an alternative tool to graphically illustrate the 3D cumulative dose distributions, and evaluate the cumulative dose-volume parameters. However, it should be used with caution before overcoming the relevant limitations of DIR.

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