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Original Research Article

An offline adaptive planning method based on delivered accumulated dose for brachytherapy in cervical cancer☆

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ABSTRACT

Background and purpose: In current clinical practice, independent treatment plan optimization for each fraction of brachytherapy might not be able to fully leverage the dosimetric advantage of the cervical cancer radiotherapy combining external beam radiotherapy (EBRT) and brachytherapy (BT). This study proposed an offline adaptive planning method based on accumulated dose for BT, aiming to improve the total dose distribution of the combined radiotherapy.

Methods and materials: This study retrospectively reviewed nine cervical cancer patients treated with EBRT followed by high-dose-rate BT. For each BT fraction, we used a multi-metric deformable image registration method to accumulate the dose distributions of previously delivered EBRT and BT. The accumulated dose distribution was then imported into a customized commercial BT treatment planning system as a background in the adaptive dose optimization. Main dosimetric parameters of the target and organs at risk (OARs) were compared between the adaptive BT (ABT) and conventional BT (CBT) planning methods.

Results: For approximately 70 % of the BT fractions, the ABT plans have lower D2cc to the bladder or rectum compared with the CBT plans. In terms of total dose evaluation, the ABT planning method resulted in a decrease in mean values of D2cc, V60 and V50 for the bladder (–1.9 ± 2.0 Gy_{EQD2}, –1.2 ± 1.2 %, and –0.9 ± 1.1 %) and rectum (–2.1 ± 1.8 Gy_{EQD2}, –1.2 ± 1.2 %, and –1.4 ± 1.3 %).

Conclusion: The offline adaptive planning method could help decrease the doses to OARs and improve the total dose distribution of combined radiotherapy, showing promising prospects for clinical use.

1. Introduction

Three-dimensional image-guided high-dose-rate (HDR) brachytherapy (BT) is commonly used to treat locally advanced cervical cancer in combination with external beam radiotherapy (EBRT) [1–3]. Typically, the HDR BT is delivered in 4–6 fractions. Both the applications and the patient's anatomy may vary significantly between different fractions. Therefore, the CT (or MRI) scan is performed in each fraction for treatment planning. The plans associated with different images are optimized and evaluated independently, without taking the previously delivered plans into account. However, this approach may result in an optimal fractional dose distribution but not an optimal total dose distribution. Therefore, it cannot fully leverage the dosimetric advantage of the combined radiotherapy. Furthermore, it is also inconvenient to evaluate the total doses to targets and organs at risk (OARs).

For cervical cancer, the nearest OARs to the targets are the bladder and rectum. A multicenter prospective cohort study shows that after chemoradiotherapy and MRI-based image-guided adaptive BT, actuarial cumulative 5-year incidence of grade 3–5 morbidity was 6.8 % for genitourinary events and 8.5 % for gastrointestinal events [4]. Many studies have indicated that morbidity is significantly correlated with the irradiated dose to OAR. For example, the incidence of rectal morbidity is less than 4 % with doses below 75 Gy and increases to 9 % with higher doses [5]. Similarly, the incidence of bladder morbidity is less than 3 % with doses below 80 Gy, 7 % with doses below 95 Gy and jumps to 22 % with higher doses [6]. To reduce morbidity and better protect OARs, it is

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necessary to improve the total dose distribution and decrease the doses to OARs. For the combined radiotherapy, the EBRT and each fraction of BT are interrelated. In order to achieve the optimal total dose distribution, we should optimize the dose distribution of each BT fraction based on its previously accumulated dose distribution using an offline adaptive planning technique. This has been widely used in EBRT. Its advantages have been fully confirmed in many studies [7–9].

To implement the offline adaptive planning for BT in cervical cancer, two steps are necessary: (1) individually mapping the dose distributions of delivered EBRT and BT (if applicable) to the current BT planning image by image registration and then accumulating them; (2) taking the accumulated dose distribution into account during dose optimization process of the current BT fraction. For the first step, several studies have investigated different algorithms for image registration [10–14]. Swamidas et al. and Kim et al. comprehensively reviewed the current status of image registration and dose accumulation for cervical cancer [15,16]. However, most of the studies focused on total dose evaluation rather than dose optimization. For step two, to our knowledge, there is no existing commercial BT treatment planning system (TPS) that supports dose optimization based on a background dose. We need to develop a new BT TPS to accomplish this.

In this study, we used a multi-metric deformable image registration (DIR) method to realize dose transformation and accumulation across various images. Subsequently, we developed a research version of a commercial BT TPS to initiate dose optimization using the transformed dose distribution as a background, thereby developing the offline adaptive planning method for the combined cervical cancer radiotherapy.

2. Methods and materials

This study retrospectively selected nine patients with locally advanced cervical cancer (stages IB2-IIIC2r) from our previous DIR research [17]. The difficulty of registration is dependent on the changes in anatomy. To simplify the registration, the selected patients had relatively less anatomical changes throughout treatment, resulting in higher registration accuracy compared to other patients. Each patient received a combination of EBRT and HDR BT. CT scans were performed for both EBRT and BT planning, with a slice thickness of 5 mm for EBRT and 3 mm for BT, respectively. The EBRT was delivered to the pelvis with a dose of 45–50 Gy in 25 fractions using volumetric-modulated arc therapy with 6-MV X-rays. Four patients received an additional EBRT boost of 10–15 Gy to involved lymph nodes. The HDR BT was delivered in 6 fractions with a prescription dose of 5–7 Gy using tandem/ovoid (T/O) applicators and interstitial needles (if needed). A Flexitron afterloader unit with an ^{192}Ir source was used for the BT treatment. The activation step was 2 mm. All EBRT plans were designed and optimized using Pinnacle v9.1–16.2 (Philips Radiation Oncology Systems, Fitchburg, WI, USA) to ensure that at least 95 % of the target volume receives the prescription dose while minimizing the doses to OARs. All clinical BT plans were designed using Oncentra Brachy v4.6 (Elekta Brachytherapy, Veneedal, The Netherlands) and manually optimized on the basis of OAR dose constraints. The fractional dose was prescribed to cover 90 % of the high-risk clinical target volume (HR-CTV). For both EBRT and BT plans, the doses to OARs were within the dose constraints recommended by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines [18].

Utilizing the patient data mentioned above, we redesigned the BT plans using the offline adaptive planning method. As illustrated in Fig. 1, the complete offline adaptive planning method consists of three steps: CT scan and delineation, image registration and dose accumulation, and treatment planning.

2.1. CT scan and delineation

As this is a planning study, the CT scan and delineation have already been completed. However, there are some details that require further explanation. Due to limited time and resources, a CT scan was performed every two fractions, and each BT plan was delivered twice. Therefore, the total number of CT-guided BT fractions was 27. The number of catheters used in different fractions varied, ranging from 1 to 7. The most common was 3 catheters, which were used in 13 fractions. The target volume and OARs for BT were delineated on the planning CT according to GEC-ESTRO recommendations, including the HR-CTV, rectum, bladder, sigmoid, and bowel. MRI at diagnosis served as a reference. Additionally, we delineated the uterus and vagina (U + V) to include the entire applicator and vaginal packing. To address the issue of inconsistent intensity between the EBRT and BT images, the CT numbers within the bladder, rectum, and U + V contours were overridden to 0, 30, and 60 Hounsfield units, respectively.

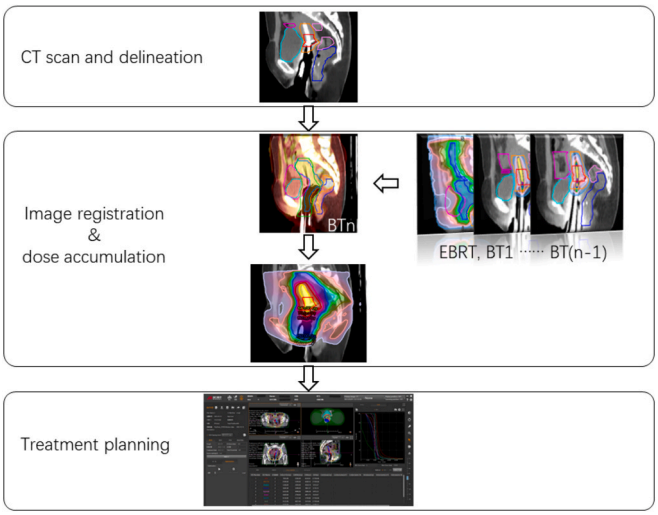

Fig. 1. Workflow of the offline adaptive planning method.

2.2. Image registration and dose accumulation

For the purpose of dose accumulation, the planning CTs of delivered EBRT and BT fractions should be registered to the planning CT of the current BT fraction. As reported in Ref. 17, we employed a multi-metric DIR method based on the SlicerElastix extension of 3D Slicer. The similarity metrics can be divided into two categories: mutual information (MI), which is an intensity-based metric, and kappa statistics (KS), which is a contour-based metric. In the registration process, we used the bladder, rectum, and U + V as three KS metrics. Additionally, a transform bending energy penalty was applied to regularize the nonrigid transformation. The image transformation employed a standard three-step strategy consisting of rigid, affine, and B-spline transformations. For the B-spline transformation, a six-level resolution registration strategy was implemented, with an advanced stochastic gradient descent method for optimization at each level.

The AAPM TG-132 report suggests that image registration evaluation involves both qualitative and quantitative methods [19]. Our clinician qualitatively evaluated the registration accuracy through the visualization of image fusion and confirmed that the transformation appeared reasonable, with no obvious errors or ill behaviors. For the quantitative validation, we calculated the Dice similarity coefficient (DSC) and Hausdorff distance (HD) between the deformed and reference contours for the bladder, rectum, and U + V. The mean DSC for the bladder, rectum, and U + V were 0.92 ± 0.05, 0.88 ± 0.03, and 0.94 ± 0.02, respectively. The mean HD for the bladder, rectum, and U + V were 12.06 ± 17.20, 7.37 ± 2.32, and 6.31 ± 2.88, respectively. However, due to the complex nature of the sigmoid and bowel as tubular structures that can easily twist, they were too complex to register accurately and

were therefore excluded from the analysis.

The transformed doses were directly accumulated only for the following dose optimization and were converted into equivalent doses in 2 Gy fraction (EQD2, using $\alpha/\beta = 10$ Gy for tumors and $\alpha/\beta = 3$ Gy for normal tissues) and then accumulated for total dose evaluation. Main dosimetric parameters including the HR-CTV D90 and D2cc of the bladder and rectum were recorded. The V60Gy and V50Gy values can reflect the dose contribution from the BT treatment part, which were also recorded as supplemental evaluation parameters.

2.3. Treatment planning

The adaptive BT (ABT) planning used a research version of Rongli Brachytherapy TPS (RL Electronics, Tianjin, China), which was specially modified to enable users to import the accumulated dose distribution as a background for dose optimization. In each iteration, the dose for each voxel is calculated using the equation: Dsum = Dcal + Dimp. Here, Dcal represents the dose calculated based on the standard 2D formalism given by the AAPM TG-43 report, while Dimp is the dose imported by the user. The summed dose map is then imported into the optimizer for the next iteration. The inverse optimizer used a quadratic penalty model, and the objective function is optimized using the L-BFGS method. We set the initial dose optimization objectives for targets and OARs according to the previously accumulated dose parameters and the dose constraints per fraction recommended by the NCCN guidelines, as detailed in Table 1. Our optimization aim is to maximize the dose to targets while minimizing the dose to OARs, and specially to avoid overlapping with previously delivered high-dose regions within the OARs as much as possible. We will adjust the objectives according to the results of each optimization process until we reach the best possible result.

For ease of plan evaluation, we also designed conventional BT (CBT) plans for each patient using the inverse planning algorithm of Rongli Brachytherapy TPS. The initial dose optimization objectives were similar to those used for the ABT plans except for not considering the background dose. All other optimization processes and plan evaluations were consistent with those used for the ABT plans. For the sake of comparison, the fractional prescription dose to 90 % of the HR-CTV for the CBT plans was normalized to be the same as for the ABT plans. The Wilcoxon signed-rank test at a 5 % significance level was used to make statistical comparisons between the ABT and CBT plans.

3. Results

Fig. 2 compares the dosimetric parameters between the CBT and ABT plans for each BT fraction. If a minimal threshold of 0.1 Gy is used to determine whether the doses differ between the two plans, we found that the ABT plans differed from the CBT plans in 19 out of 27 fractions, all of which showed a decrease in D2cc to either the bladder, the rectum, or both. The mean values of the HR-CTV D90, bladder D2cc and rectal D2cc for the CBT plans were 5.6 ± 0.6, 4.3 ± 0.6, and 3.6 ± 0.9, respectively. For the ABT plans, the mean values were 5.6 ± 0.6, 4.1 ± 0.7 and 3.4 ± 0.8, respectively. Both the D2cc values for the bladder and rectum showed statistical significance, with p-values of less than 0.001 for each.

Table 1
The initial dose optimization objectives used for the ABT planning method.

Contour	Dosimetric Parameter	Dose (cGy)	Weight
HR-CTV	D90	600 + Background dose of HR-CTV D90	100
Bladder	Max Dose	450 + Max background dose of Bladder	20
Rectum	Max Dose	400 + Max background dose of Rectum	20
Sigmoid	Max Dose	400 + Max background dose of Sigmoid	10
Bowel	Max Dose	400 + Max background dose of Bowel	10

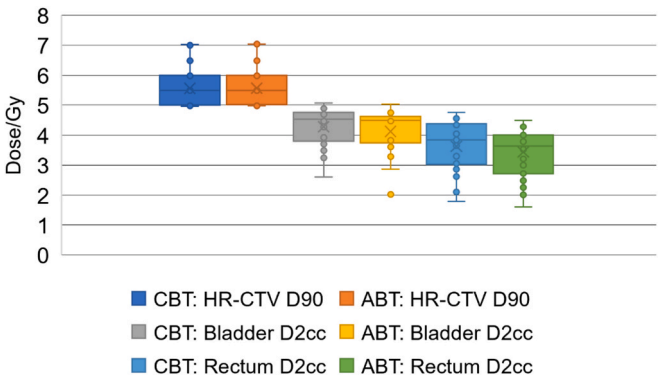

Fig. 2. Box plots of dosimetric parameters for the CBT and ABT plans.

The total dosimetric parameters of the 9 patients resulting from the two planning methods are listed in Table 2. Compared with the CBT planning method, the ABT planning method significantly reduced the doses to the bladder and rectum ($p \leq 0.02$). For the bladder, the D2cc, V60, and V50 were decreased by –1.9 ± 2.0 Gy_{EQD2}, –1.2 ± 1.2, and –0.9 ± 1.1, respectively. And for the rectum, they were decreased by –2.1 ± 1.8 Gy $_{EQD2}$, –1.2 ± 1.2, and –1.4 ± 1.3, respectively. However, there was no significant difference between the two planning methods for the two patients (Patient #3 and #8). Only one tandem application was used in the previous two BT fractions of Patient #3. Despite using three catheters for Patient #8, the application placements were too concentrated, leading to a limited number of catheters available.

4. Discussion

For the combined cervical cancer radiotherapy, it is ideal to optimize both EBRT and each BT fraction to achieve an optimal total dose distribution. Therefore, we propose an offline adaptive planning method that optimizes the current BT plan based on the accumulated dose distribution of delivered EBRT and BT. This method has been used commonly in EBRT but rarely in BT because dose accumulation is a complicated issue and such plan optimization is not yet supported by available commercial BT TPSs. In order to implement this method in the combined cervical cancer radiotherapy, we have made major improvements in these two aspects.

Accumulating dose in the pelvic region is particularly challenging due to large and complex deformations caused by tumor shrinkage, variations in organ filling, bowel gas, and the presence of a BT applicator and vaginal packing. As mentioned in Ref. 15 and 16, current DIR techniques are not yet mature enough for high-accuracy dose accumulation. To lower the difficulty of DIR, we specifically selected nine patients from our previous DIR research, as their anatomical changes throughout treatment were relatively less compared to others. This selection criterion also represents a limitation of this study. Furthermore, we adopted an advanced multi-metric DIR method to improve registration accuracy. This method could minimize both the intensity differences between the two images and the differences between corresponding contour surfaces. The registration results underwent both qualitative and quantitative validations. The AAPM TG-132 report recommends that the DSC value should be higher than 0.8–0.9, considering the uncertainties that exist in contour delineation. Our registration results showed that all DSC values met this accuracy requirement. Ideally, the accuracy of the DIR should be quantitatively validated on a voxel-by-voxel basis. However, this is not feasible due to the absence of ground truth data in patients, as stated in TG-132. In fact, such validation is also unnecessary for this study. Instead of focusing on the exact dose to each

Table 2
Comparison of total dosimetric parameters for the 9 patients between the CBT and ABT planning methods.

Patient	HR-CTV		Bladder						Rectum					
	D90 (Gy_{EQD2})		D2cc (Gy_{EQD2})		V60Gy (%)		V50Gy (%)		D2cc (Gy_{EQD2})		V60Gy (%)		V50Gy (%)	
	CBT	ABT	CBT	ABT	CBT	ABT	CBT	ABT	CBT	ABT	CBT	ABT	CBT	ABT
1	86.86	88.48	71.16	69.50	10.69	9.27	43.59	42.23	72.27	70.47	9.75	9.26	25.25	24.62
2	84.53	89.70	87.03	83.79	14.84	14.77	36.74	37.25	55.72	53.00	3.12	1.97	9.26	7.57
3	84.27	84.19	85.26	86.78	13.41	12.93	37.05	36.73	79.66	75.13	16.64	14.08	33.20	30.82
4	87.97	87.44	95.54	95.12	19.01	18.90	36.45	36.42	54.86	54.37	2.23	2.07	7.35	7.00
5	96.91	96.02	84.97	82.59	23.06	20.70	51.71	49.07	87.17	85.83	17.80	14.91	33.57	30.79
6	101.60	99.25	89.85	84.57	11.63	9.21	37.12	34.97	54.18	53.52	0.83	0.63	11.23	10.29
7	89.34	89.26	73.63	71.89	6.79	6.49	27.60	27.18	77.60	73.22	14.30	12.59	30.48	28.93
8	113.30	116.39	89.83	89.24	50.30	49.78	70.16	70.01	76.37	76.88	23.23	23.69	49.92	50.95
9	103.40	102.40	85.37	82.12	42.54	39.15	66.50	65.18	77.74	74.47	16.69	14.88	32.49	29.39
Mean	94.24	94.79	84.74	82.84	21.36	20.13	45.21	44.34	70.62	68.54	11.62	10.45	25.86	24.48
SD	10.12	10.05	7.77	7.98	15.09	14.78	14.63	14.46	12.41	11.94	8.00	7.69	14.10	14.22
P-value	0.501		0.020		0.017		0.037		0.008		0.016		0.013	

voxel, the dose optimization mainly concerns the spatial distribution of high-dose regions and aims to avoid overlapping with these regions. Jamema et al. have confirmed that the spatial location of the D2cc region of the bladder and rectum remains consistent among BT fractions [20]. This may lead to repeated accumulation of dose hotspots and increase the risk of toxicity. This issue is precisely what our offline adaptive planning method aims to address.

Unlike EBRT, the research on adaptive planning methods for BT is very limited. Only Liu et al. examined and compared four adaptive planning strategies [21]. They concluded that offline adaptive planning techniques can shorten the time between the planning CT and treatment delivery, significantly reducing the chance of intrafraction motion. However, the dose optimization in their study is still confined to a single BT fraction, without taking the previously delivered EBRT and BT into account. To implement the ABT plan optimization, we need to not only modify the BT TPS but also adjust the optimization method. Typically, the optimization objectives for the CBT plan can be set according to the recommended dose constraints for a single BT fraction. However, the optimization objectives for the ABT plan should be set much larger due to the presence of background dose. As previously mentioned, the initial optimization objectives were the dose constraints for a single BT fraction plus the accumulated dose parameters. Then, they were adjusted several times to achieve an optimal result. Additionally, we recommend setting dose volume objectives for targets (e.g., D50, D20, D10), especially when there is significant variation in target position across different BT fractions.

The ABT plan evaluation should not only consider whether the optimized total dose can meet clinical requirements but also ensure that the current fractional doses to OARs do not exceed dose constraints. When comparing the fractional dose between the ABT and CBT plans, we categorized the results into three cases. In the first case, the doses to the bladder, rectum, or both for the ABT plans were decreased by more than 0.1 Gy. This case represents approximately 70 % of all the BT fractions. The second case shows no significant dosimetric difference between the two plans. This is mainly because the undesired placement or small number of catheters limited the modulation capability of the plan optimization. Furthermore, the third case was found for several BT fractions. For instance, the dose to the bladder in the ABT plan was increased by 8 cGy for a single fraction but decreased by 9 cGy after physical dose accumulation when compared to the CBT plan. Although the difference is minor, we can infer that the locations of high-dose regions changed after the ABT optimization, thereby avoiding the overlap of certain high-dose regions. This special case is also what we had expected.

For total dose evaluation, it can be found from Table 2 that the ABT planning method resulted in a maximum decrease of 5.3 Gy_{EQD2} and an average decrease of 1.9 Gy_{EQD2} in the total dose to the bladder. Additionally, it resulted in a maximum decrease of 4.5 Gy_{EQD2} and an average decrease of 2.1 Gy_{EQD2} in the total dose to the rectum. Research on toxicities and dosimetry indicates that the mean rectal D2cc for patients with rectal toxicities (Grades 1–4) is 70.7 Gy_{EQD2}, compared to 68.5 Gy_{EQD2} for those without rectal toxicities (Grade 0). Similarly, the mean D2cc to the bladder for patients with bladder toxicities (Grades 1–4) is 99.4 Gy_{EQD2}, while it is 93.0 Gy_{EQD2} for those without bladder toxicities (Grade 0) [6]. Another research shows that the incidence of rectal toxicities was less than 4 % with doses of 75 Gy or lower and 9 % with higher doses. For the bladder, the incidence of toxicities was less than 3 % with doses below 80 Gy and 5 % with higher doses [5]. Therefore, it is reasonable to infer that the ABT planning method can help reduce the grade or incidence of toxicity.

In summary, this study showed that the ABT plan has dosimetric advantages compared to the CBT plan. Meanwhile, it enables radiation oncologists to immediately evaluate the total dose to targets and OARs. We hope that the offline adaptive planning method can be tested in clinical trials to further evaluate its clinical effects.

5. Conclusion

The offline adaptive BT planning method could help increase the dose coverage of target and decrease the doses to OARs. Compared with the conventional BT planning method, the total dose distribution was improved, indicating that this method holds promising application prospects.

CRediT authorship contribution statement

Qi Fu: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Yingjie Xu:** Investigation, Formal analysis, Data curation. **Xi Yang:** Visualization, Validation. **Jusheng An:** Resources, Validation. **Zhaohan Li:** Software. **Manni Huang:** Resources, Supervision. **Jianrong Dai:** Project administration, Supervision.

Declaration of competing interest

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

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Ethical approval

This retrospective study was approved by the review board of Cancer Hospital, Chinese Academy of Medical Sciences, and informed consent was waived.

Declaration of generative AI in scientific writing

There is no use of AI and AI-assisted technologies in the writing process.

Submission declaration and verification

This manuscript has not been published previously and it is not under consideration for publication elsewhere. Its publication is approved by all authors.

References

[1] Pötter R, Georg P, Dimopoulos JCA, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 2011;100(1):116–23. https://doi.org/10.1016/j.radonc.2011.07.012.

[2] Rijkmans EC, Nout RA, Rutten I, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gynecol Oncol 2014;135(2):231–8. https://doi.org/10.1016/j.ygyno.2014.08.027.

[3] 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(3):434–40. https://doi.org/10.1016/j.radonc.2016.03.020.

[4] Pötter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol 2021;22(4):538–47. https://doi.org/10.1016/S1470-2045(20)30753-1.

[5] Perez CA, Grigsby PW, Lockett MA, et al. Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. Int J Radiat Oncol Biol Phys 1999;44(4):855–66. https://doi.org/10.1016/s0360-3016(99)00111-x.

[6] Kim Y, Kim YJ, Kim JY, et al. Toxicities and dose-volume histogram parameters of MRI-based brachytherapy for cervical cancer. Brachytherapy 2017;16(1):116–25. https://doi.org/10.1016/j.brachy.2016.10.005.

[7] Foroudi F, Wong J, Haworth A, et al. Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. J Med Imaging Radiat Oncol 2009;53(2):226–33. https://doi.org/10.1111/j.1754-9485.2009.02066.x.

[8] Aristophanous M, Aliotta E, Lichtenwalner P, et al. Clinical Experience With an Offline Adaptive Radiation Therapy Head and Neck Program: Dosimetric Benefits and Opportunities for Patient Selection. Int J Radiat Oncol Biol Phys. Published online February 17, 2024. http://doi.org/10.1016/j.ijrobp.2024.02.016.

[9] Ferrara E, Beldì D, Yin J, Vigna L, Loi G, Krengli M. Adaptive Strategy for External Beam Radiation Therapy in Prostate Cancer: Management of the Geometrical Uncertainties With Robust Optimization. Pract Radiat Oncol 2020;10(6). https://doi.org/10.1016/j.prro.2020.05.006. e521 e528.

[10] Teo BK, Millar LPB, Ding X, et al. Assessment of cumulative external beam and intracavitary brachytherapy organ doses in gynecologic cancers using deformable dose summation. Radiother Oncol 2015;115(2):195–202. https://doi.org/10.1016/j.radonc.2015.04.002.

[11] Van Heerden LE, Houweling AC, Koedooder K, et al. Structure-based deformable image registration: Added value for dose accumulation of external beam radiotherapy and brachytherapy in cervical cancer. Radiother Oncol 2017;123(2):319–24. https://doi.org/10.1016/j.radonc.2017.03.015.

[12] Rigaud B, Klopp A, Vedam S, et al. Deformable image registration for dose mapping between external beam radiotherapy and brachytherapy images of cervical cancer. Phys Med Biol 2019;64(11):115023. https://doi.org/10.1088/1361-6560/ab1378.

[13] Flower E, Do V, Sykes J, et al. Deformable image registration for cervical cancer brachytherapy dose accumulation: Organ at risk dose–volume histogram parameter reproducibility and anatomic position stability. Brachytherapy 2017;16(2):387–92. https://doi.org/10.1016/j.brachy.2016.12.006.

[14] Zhen X, Chen H, Yan H, et al. A segmentation and point-matching enhanced efficient deformable image registration method for dose accumulation between HDR CT images. Phys Med Biol 2015;60(7):2981. https://doi.org/10.1088/0031-9155/60/7/2981.

[15] Swamidas J, Kirisits C, De Brabandere M, et al. Image registration, contour propagation and dose accumulation of external beam and brachytherapy in gynecological radiotherapy. Radiother Oncol 2020;143:1–11. https://doi.org/10.1016/j.radonc.2019.08.023.

[16] Kim H, Lee YC, Benedict SH, et al. Dose summation strategies for external beam radiation therapy and brachytherapy in gynecologic malignancy: a review from the NRG Oncology and NCTN medical physics subcommittees. International Journal of Radiation Oncology* Biology*. Physics 2021;111(4):999–1010. https://doi.org/10.1016/j.ijrobp.2021.06.019.

[17] Fu Q, Xie X, Xu Y, et al. Applying Multi-Metric Deformable Image Registration for Dose Accumulation in Combined Cervical Cancer Radiotherapy. J Pers Med 2023;13(2):323. https://doi.org/10.3390/jpm13020323.

[18] Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17(1):64–84. https://doi.org/10.6004/jnccn.2019.0001.

[19] Brock KK, Mutic S, McNutt TR, et al. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM Radiation Therapy Committee Task Group No. 132. Medical physics, 2017, 44(7): e43-e76. https://doi.org/10.1002/mp.12256.

[20] Jamema SV, Mahantshetty U, Tanderup K, et al. Inter-application variation of dose and spatial location of D(2cm(3)) volumes of OARs during MR image based cervix brachytherapy. Radiother Oncol 2013;107:58–62. https://doi.org/10.1016/j.radonc.2013.01.011.

[21] Liu H, Kinard J, Maurer J, et al. Evaluation of offline adaptive planning techniques in image-guided brachytherapy of cervical cancer. J Appl Clin Med Phys 2018;19(6):316–22. https://doi.org/10.1002/acm2.12462.