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The Preliminary Results of 3-Dimensional Printed Individual Template Assisted 192Ir High-Dose Rate Interstitial Brachytherapy for Central Recurrent Gynecologic Cancer

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Abstract

Objective: To evaluate the feasibility and safety of high dose rate interstitial brachytherapy (HDR-IB) assisted with 3-dimensional printing individual template (3D-PIT) for central pelvic recurrent gynecologic cancer (CR-GYN). **Methods:** Totally 32 patients diagnosed with CR-GYN received iridium-192(192Ir) HDR-IB assisted with 3D-PIT that was classified in 2 types(Type I: transvaginal template/ applicator, and Type II: transvaginal combined transperineal template). The prescribed dose to gross tumor volume (GTV) was 10-36 Gy in 2-6 fractions. We rely on a few dosimetric parameters for quality control. The short-term efficacy was evaluated by RECIST v1.1, and the adverse event was evaluated by CTCAE V4.0. **Results:** The median V100, D100 and D90 of per fraction among all the patients were 88.9% ± 9.8%, 3.45Gy ± 0.54 Gy, and 5.79Gy ± 0.32 Gy, respectively. Dosimetric comparison between preplan and treatment plan of 20/32 patients with Type II 3D-PIT showed no significant difference in GTV volume, V100, D100, D90, conformation index (CI) and homogeneity index (HI). No severe treatment complications occurred. Grade 3 or 4 late toxicities (fistula) were observed in 3 patients (9%). The local response rate (complete remission, CR + partial remission, PR) was 84.4% (27/32) 1 month after completion of treatment. The median time to progression (TTP) was 15.4 months (95% CI 11.3- 19.6 months), 1-year local control (LC) rate were 51.7%. **Conclusions:** HDR-IB assisted by 3D-PIT was a reliable modality for CR-GYN due to the clinical feasibility and accepted complications.

Keywords

gynecologic neoplasms, interstitial radiotherapy, brachytherapy, 3-D-printing, template

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Introduction

Recurrent GYN in a previously irradiated field is one of the most complicated challenges in clinical practice[1] Salvage surgery is a potentially curative treatment option for recurrent GYN or persistent cervical cancer after external beam radiotherapy (EBRT) which it results in 5-year survival rates >30%.[2,3] However, the complication rates of salvage surgery range from 30-60%; thus, it should only be used in a selected group of patients. Re-EBRT, which yields long-term survival rates that range from 20-50%, may be a curative treatment option for a highly selected group of patients.[4] As a high-precision brachytherapy modality, image-guided HDR-interstitial brachytherapy (HDR-IB) was prefered because of its dosimetric superiority[5] HDR-IB was recommended for post-hysterectomy gross residual disease, recurrence extending into the parametrium, and vaginal disease unfit for intracavitary (IC) treatment alone. In a comparison study show that patients salvaged with HDR-IB based reirradiation (IB group) survived significantly longer than those in the palliative group (palliative group): median postrecurrent survival, 31 months and 13 months, respectively; log-rank test, $P < 0.0001$).[4]

However, reirradiation with interstitial HDR brachytherapy was associated with significant morbidity. Improvement in BT

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techniques and increased availability of image guidance or template utility as well as interstitial techniques had renewed interest in BT. The American Brachytherapy Society (ABS) recommends the use of template-based HDR-IB in these patients.[6] The template-guidance technique can improve the accuracy of brachytherapy and simplify operative procedures. Traditionally, interstitial low dose rate (LDR) brachytherapy for prostate cancer was performed using a transperineal template under transrectal ultrasound guidance.[7] Commercially available template-based low-dose rate or HDR brachytherapy (BT) for r-GYN uses the same coplanar beam arrangement as that for prostate cancer.[8] However, the parallel needle directions were not always appropriate because of the extension of central r-GYN. To improve the accuracy of HDR brachytherapy, we designed individual templates using computer-aided design and 3-dimensional (3D) printing, and implanted IS needles using these templates under computed tomography (CT) guidance to evaluate the feasibility and accuracy of 3D-printed template-based ISBT.

Materials and Methods

A total of 32 patients who were diagnosed with central recurrent GYN in our center from Jun 2016 to Dec 2018 received 192Ir HDR-IB. The individual 3D-PIT were manufactured and utilized to guide interstitial puncture. The study protocol was approved by the ethics committee of our hospital. All patients signed informed consent to participate in this study.

Patient Characteristics

The median age was 52(range: 35-77) years old whose recurrent diseases localized in central pelvic. In terms of pathological types (Table 1): 17 of cervical cancer, 4 of endometrial cancer and 4 of vaginal cuff carcinoma were enrolled in this study. We define "central recurrence" as the lesion, that is localized to the vagina and cervix parametria and even extended to bladder base or rectal regardless of the distance deviated from the vaginal center. Regarding the primary treatment, 16 patients received surgery followed by postoperative pelvic EBRT, the cumulative equivalent dose in 2 Gy per fraction (EQD2) was 50 Gy. And 11 patients received definitive chemoradiotherapy (CRT), which the cumulative EQD2 was 83 Gy. The median interval from initial radiotherapy (RT) to re-irradiation was 12 months (range, 2-96 months). Median follow up time was 10 months (3-28months). No patients received chemotherapy combined with re-irradiation. Salvage HDR-IB was proposed for patients: i, previous pelvic RT; ii, no indication or desire for total pelvic exenteration; iii, reject palliative care.

Table 1. Patients' Characteristics (n = 32).

		n
Median age (range)	52(35-77) years	
Diagnosis	Cervical cancer	17
	Endometrial cancer	4
	Vaginal cancer	2
	Ovarian cancer	3
	Vaginal Cuff Carcinoma	4
	Vulval cancer	1
	Endometrial Stromal Sarcoma	1
Pathology	Squamous cell carcinoma	21
	Endometrioid carcinoma	4
	Ovarian serous carcinoma	3
	Adenocarcinoma	2
	Endometrial Stromal Sarcoma	1
	Small cell carcinoma	1
Initial FIGO stage	Ia	3
	Ib	9
	IIB	9
	III	8
	IV	3
History of hysterectomy		19
History of radical CCRT		11
Postoperative RT		16
Median previous dose EQD2	50 Gy	45-155Gy
Median interval between RT and relapse	12months	2-96 months
Median follow up time	10months	3-28 months

Abbreviations: CCRT, concurrent chemoradiotherapy; EQD2, equivalent dose in 2 Gy; FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy.

CT Simulation

Initially, each patient underwent a pelvic CT examination (Brilliance™ Big Bore CT; Philips Healthcare, Cleveland, OH, USA; at 120 kV and 150 mA, with a slice thickness of 5 mm) for CT simulation. To minimize patients' movements during the examination and needle insertion, they were immobilized in the lithotomy position for both procedures with the obturator in vagina using a combined external fixation/vacuum pad transfer bed (Figure 1), body surface marking was for body position verification. CT image data were imported into brachytherapy treatment planning system (B-TPS; Varian Medical Systems, Palo Alto, CA, USA), which was used for preplan.

Pre-Plan

The workflow of pre-plan as below: (1) Targets definition: The target volumes and organs (bladder, rectum, colon) at risk (OARs) were delineated on CT or MRI/CT fusion-based imaging in the B-TPS. MRI images were taken within 1 week of treatment (if used). We defined the imaging boundaries of each recurrent lesion as the gross tumor volume (GTV). (2) Prescription: the prescription dose to GTV was 10-36 Gy, 5-6Gy/fraction, 2-6 fractions. The history cumulative dose received and interval of the recurrence should be considered. The D2 cc of OAR was restrict to 60% of prescription dose. (3) Preplanning: dose optimization was performed using geometric optimization or dose point volume optimization followed by virtual catheter/

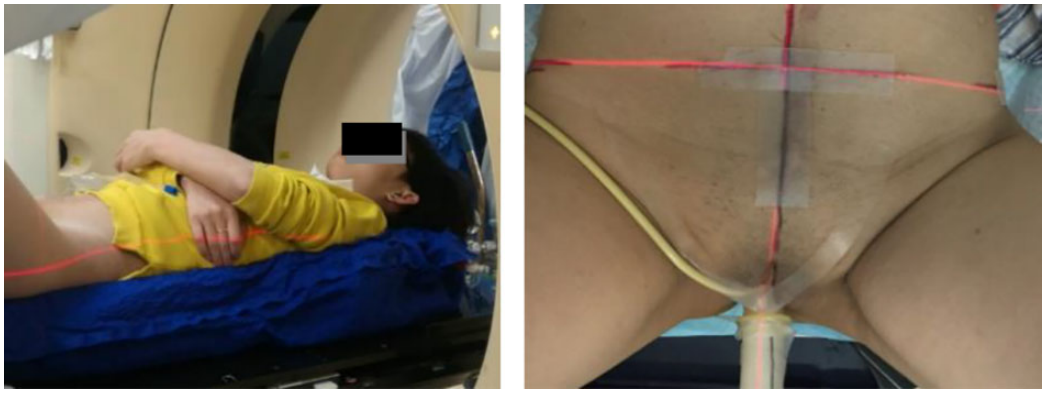

Figure 1. Patient immobilization in the lithotomy position with the obturator in vagina using a combined external fixation/vacuum pad transfer bed.

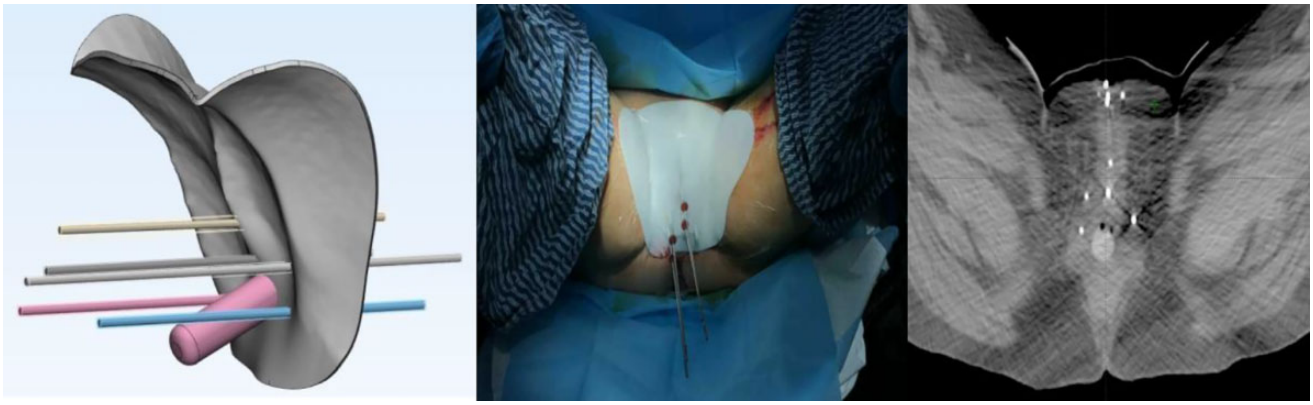

Figure 2. Reconstruction of the 3-dimensional appearance of the perineal region with needle passages.

needle pathway reconstruction, the catheter/needle entrance points, orientations, depths, and distribution were determined and the dose point in relation to the catheters and loading of the desired dwell positions were acquired at the same time. The dwell positions and lengths of the needles loaded were defined by manual graphic modifications to cover the GTV with the dose while minimizing the dose to the OARs. The actual dose distribution in the target volume was evaluated by means of a dose–volume histogram.

Design and Production of the 3D-PIT

Mimics 10.01 for Windows (Materialise NV, Leuven, Belgium) was used to read the CT and catheter/needle information generated by the B-TPS and reconstruct the 3D appearance of the perineal region and positions of the implantation needles (Figure 2). The 3D data were then exported into Geomagic 8.0 (Geomagic, Cary, NC, USA) in an STL file format. The 3D-PIT was designed using Geomagic 8.0 according to the 3D appearance of the skin and ideally covered marking point such as the pubis, enabling the vaginal obturator to facilitate placement of the template in the correct position. The thickness of the template and diameter of the IS catheter were then determined. According to the digital model, the individual template was printed using a rapid 3D forming machine (LITE450HD-B; Shanghai Liantai Technology Co. Ltd., Shanghai, China). 3D printing materials are in line with the European economic community (EEC) standard for medical curing resin IMAGINE 8 000. There are 2 types of individual 3D-printed template designed. Type I: transvaginal template/applicator with 6 needle passage, which is directly in contact with the vaginal stump, and the insertion needle is directly inserted into the tumor from the vaginal stump with little trauma. It is suitable for the patients with vaginal stump recurrence. Especially the maximum diameter of lesion localized central less than 2-3 cm. Type I template is an 3D-PIT reusable. Type II: transvaginal combined transperineal template (shown in Figure 3) with multilple individual needle passsages. It will be designed for others whose tumor volume is more larger or extensive. There are 3 points to consider when designing 3D-PIT in our center: i, The plate body should cover all needle passages and the reserved needle passages. Extra needle passages are reserved in case of the poor position verification of template. The distance between the edge of the plate body and the needle passage is

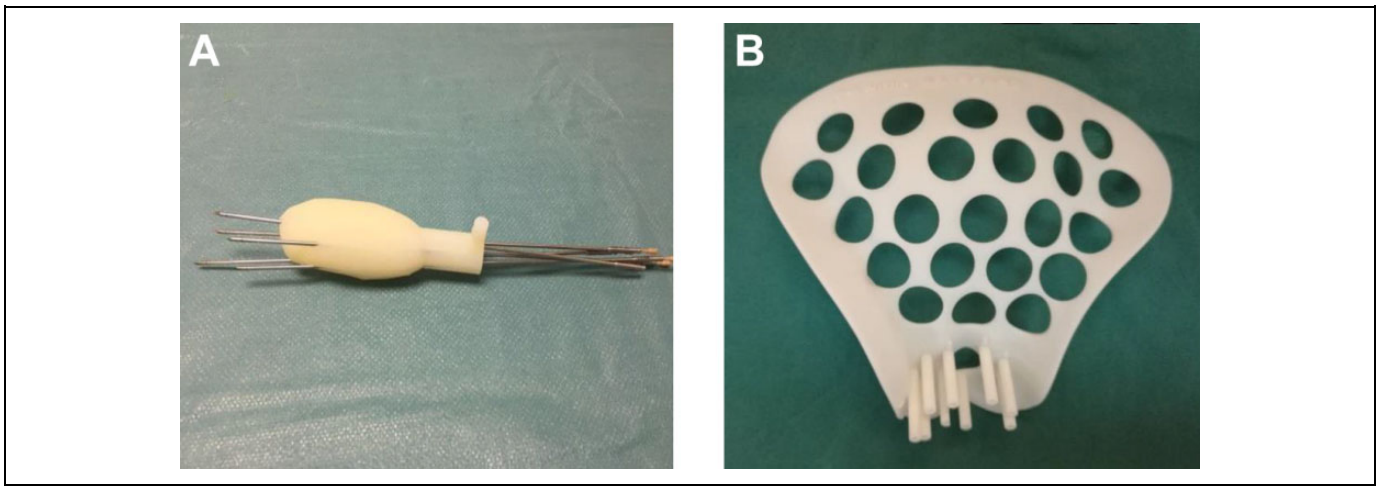

Figure 3. Individual 3-dimensional-printed transvaginal (A) and combined transvaginal/transperineal (B) insertion templates.

greater than 5 mm to ensure the rigidity of the template construction; ii, According to the anatomical characteristics of female perineum, the structures with certain fixed functions such as surface profile and vaginal column were designed; iii, The thickness of the template is 3 mm.

Interstitial Brachytherapy Procedure

All patients received an epidural or local anesthesia. The 3D-PIT assembly was fixed to the perineal skin with the vaginal dilator by corner stitches. The metal needles were inserted using the individual template under CT guidance to ensure that all needles were at the expected positions and depths according to the pre-plan. Finally, CT image with satisfied needle distribution will transferred to TPS. If the needle distribution can not lead to the good dose distribution, reserved needle passage will be considered.

Treatment Verification and Quality Assessment

The dosimetry parameters were recorded and analyzed: including the percentage of the target volume receiving at least 100% of the planned dose (V_{100}); the dose delivered to 100% of the target volume (D_{100}); the dose delivered to 90% of the target volume (D_{90}); and the maximal dose delivered to at least 2 cc of the organs at risk (OARs) (rectum, bladder, and intestine; $D_{2\ cc}$). The conformity of the dose distribution was evaluated using the conformation index, CI[9] via the following equation: $CI=(V_{T\ ref}/V_T)\times(V_{T\ ref}/V_{ref})$where V_T, is the target (GTV) volumes (cm^3); $V_{T\ ref}$, is the volumes of the GTV receiving the prescribed dose; and V_{ref}, is the total volumes in the prescribed dose. The best CI was 1, which means the GTV was just covered by the prescribed dose and the dose outside the GTV was lower than the prescribed dose. The volume exceeding the prescribed dose outside the GTV can be described by the external volume index, EI[10]: $EI=(V_{ref}-V_{T\ ref})/V_T\times100\%$. The best EI was 0. The dose received by tissue outside the GTV was smaller than the prescribed dose if the EI was 0. The greater the value of the EI, the greater was the prescribed dose received outside the GTV. The homogeneity of the dose distribution was evaluated by homogeneity index, HI[9]: $HI=(V_{T\ ref}-V_{T\ 1.5ref})/V_T\times100\%$. $V_{T\ 1.5ref}$ is the volumes of the GTV receiving the 150% prescribed dose. The best HI was 100%, The greater the value of the HI, the greater was inhomogeneity of the dose distribution of GTV. The placement of the needles was controlled accurately because a template was used. A pre-plan was performed to make sure the needles were not close to any critical organs, large blood vessels and nerves. Only dosimetry parameters of treatment plan were recorded. Dosimetry parameters of D90, D100, V100 of the GTV, D2 cc of normal tissue (rectum, bladder, and colon) as well as the EI, CI and HI of both preplan and treatment plan of 20 patients with Type II template based ISBT were recorded and analyzed using the pair-wised comparison with $P < .05$ being considered significant. SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

In total 32 patients, 205 needles were inserted for 153 treatments: a median of 6 (range, 3-14) needles per fraction, mean insertion depth of 8.3 ± 3.4 (range, 2-13.7) cm, and mean number of CT scans of 3 (range, 1-5). The mean V100, D100, V90 and D90 per fraction were 88.9% ± 9.8%,3.45Gy ± 0.54 Gy, 92.3 ± 6.3% and 5.79 Gy ± 0.32 Gy respectively; the mean D2 cc of rectum, bladder and colon per fraction were 3.14Gy ± 0.23 Gy, 3.76Gy ± 0.72 Gy and 2.47Gy ± 0.34 Gy respectively. The mean CI, EI and HI were 0.59 ± 0.12, 0.31 ± 0.16 and 0.47 ± 0.22.

Dosimetry parameters comparison between preplan and treatment plan of 20/32 patients with Type II 3D-PIT based HDR-IB show that there were no statistically significant ($P > 0.05$) difference in GTV volume (50.57 ± 25.75, 56.00 ± 25.37), V100(90.85 ± 6.28, 88.35 ± 4.87), D100(3.40 ± 0.82, 3.51 ± 0.56), D90(6.13 ± 0.88, 5.68 ± 0.46), CI(0.55

Table 2. Preplan and Treatment Plan Dosimetry Parameters in Target Volume of 20 Patients.

	GTV D_{100}(Gy)		GTV D_{90}(Gy)		GTV V_{100}(%)		GTV Volume(cm^3)		CI		EI		HI		Rectum D_{2cc}(Gy)		Bladder D_{2cc}(Gy)		Colon C_{2cc}(Gy)	
No.	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$	Pre	Treat $\bar{x}$
1	2.40	3.70	3.48	5.00	80	87	22.18	21.84	0.62	0.47	0.20	0.29	0.58	0.47	2.31	1.78	3.35	2.43	0.81	1.34
2	4.80	4.70	6.80	6.48	93	88	36.00	33.78	0.28	0.27	0.14	0.12	0.36	0.55	3.91	3.41	4.50	4.60	-	-
3	4.27	2.85	6.40	5.05	95	90	81.42	83.83	0.53	0.64	0.67	0.31	0.62	0.34	3.36	3.74	3.99	2.34	2.14	3.56
4	3.82	3.57	7.30	5.90	97	88	28.37	47.20	0.52	0.51	0.88	0.89	0.24	0.30	3.37	2.45	4.32	4.29	3.50	2.77
5	3.30	4.22	6.10	6.00	92	90	72.53	77.04	0.73	0.56	0.28	0	0.33	0.56	3.48	2.45	4.06	3.98	3.19	2.34
6	2.20	2.78	5.48	5.67	84	89	28.81	46.28	0.40	0.58	0.46	0.53	0.24	0.36	3.28	3.25	3.70	3.56	0.90	0.78
7	2.60	2.45	5.75	6.12	87	85	34.26	29.41	0.54	0.40	0.81	0.84	0.25	0.29	4.30	3.79	6.90	5.06	1.90	1.20
8	3.60	3.56	6.48	5.46	94	95	50.41	50.19	0.92	0.63	0.21	0.14	0.52	0.48	2.80	2.38	3.70	2.90	-	-
9	3.18	3.45	6.42	6.00	93	85	71.61	93.14	0.73	0.54	0.13	0.19	0.44	0.56	3.42	3.27	3.75	3.66	-	-
10	3.38	3.45	7.09	6.59	97	96	128.15	111.13	0.64	0.46	0.35	0.12	0.50	0.61	3.27	3.22	6.20	5.91	2.40	4.50
11	4.35	3.65	7.40	5.67	97	92	46.46	47.12	0.58	0.62	0.55	0.47	0.33	0.40	5.23	3.97	7.42	5.48	4.81	4.23
12	3.36	3.45	5.66	5.78	85	87	42.43	53.08	0.58	0.56	0.56	0.32	0.28	0.65	4.53	3.45	4.93	4.23	3.10	1.89
13	5.06	4.56	6.93	5.98	99	95	36.31	41.29	0.56	0.63	0.71	0.20	0.27	0.38	5.24	4.56	5.42	4.20	3.35	2.55
14	4.32	4.12	6.49	6.34	95	95	47.33	59.47	0.14	0.33	0.20	0.47	0.63	0.64	3.70	3.23	3.35	3.49	-	
15	3.00	3.42	5.89	5.97	89	91	49.91	76.06	0.46	0.65	1.02	0.11	0.27	0.67	4.00	3.41	3.86	4.10	1.30	3.43
16	3.12	3.22	6.08	6.34	91	88	64.24	63.71	0.62	0.62	0.32	0.09	0.70	0.65	3.40	3.29	3.67	3.54	-	-
17	2.34	3.27	5.10	4.98	93	87	59.86	57.73	0.44	0.61	0.37	0.26	0.63	0.42	2.12	1.98	2.45	3.40	2.20	3.60
18	3.00	3.67	6.22	6.02	95	93	16.01	14.00	0.32	0.40	0.72	0.26	0.18	0.58	3.22	2.98	3.56	3.88	1.30	2.05
19	2.56	3.12	6.09	5.67	78	77	29.25	29.70	0.77	0.74	0.23	0.34	0.35	0.32	3.55	3.89	3.29	4.02	2.30	3.56
20	3.24	3.11	5.56	6.09	81	79	65.97	84.06	0.69	0.52	0.27	0.14	0.54	0.50	2.35	3.78	3.44	4.23	2.19	4.23

Abbreviation: Pre = preplan; Treat = Treatment plan; $\bar{x}$ = mean

Table 3. Comparison of Preplan and Treatment Plan Dosimetry Parameters (20 Patients).

	Pre		Treat			
Parameters	Region	Average ($\bar{x} \pm s$)	Region	Average ($\bar{x} \pm s$)	t	p
GTV Volume (cm3)	16.01-128.15	50.57 ± 25.75	14.00-111.13	56.00 ± 25.37	-2.264	0.036
GTV D_{100} (Gy)	2.20-5.06	3.40 ± 0.82	2.45-4.70	3.51 ± 0.56	-0.868	0.396
GTV D_{90} (Gy)	3.48-7.40	6.13 ± 0.88	4.98-6.59	5.68 ± 0.46	1.665	0.112
GTV V_{100} (%)	7899	90.85 ± 6.28	77-96	88.35 ± 4.87	1.170	0.135
CI	0.14-0.92	0.55 ± 0.18	0.27-0.74	0.54 ± 0.12	0.504	0.620
EI	0.13-1.02	0.45 ± 0.27	0.00-0.89	0.30 ± 0.24	2.492	0.022
HI	0.18-0.70	0.41 ± 0.16	0.29-0.67	0.49 ± 0.13	-1.788	0.090
Rectum D_{2cc}(Gy)	2.12-5.24	3.54 ± 0.84	1.78-4.56	3.21 ± 0.70	2.429	0.025
Bladder D_{2cc}(Gy)	2.45-7.42	4.29 ± 1.28	2.34-5.91	3.96 ± 0.89	1.736	0.099
Colon D_{2cc}(Gy)	0.81-4.81	2.72 ± 1.15	0.78-4.50	3.01 ± 1.12	-1.199	0.245

Abbreviation: pre = preplan; Treat = treatment plan; ($\bar{x} \pm s$) = mean ± standard deviation

± 0.18, 0.54 ± 0.12)and HI(0.41 ± 0.16, 0.49 ± 0.13). Treatment plan EI(0.30 ± 0.24) was lower than preplan (0.45 ± 0.27), and the difference was statistically significant (P = 0.022) (Table 2, 3). There were no statistically significant (P > 0.05) difference in D2 cc of bladder(4.29 ± 1.28, 3.96 ± 0.89) and colon(2.72 ± 1.15, 3.01 ± 1.12) between preplan and treatment plan. Treatment plan D2 cc of rectum (3.21 ± 0.70) was lower than preplan(3.54 ± 0.84), and the difference was statistically significant (P = 0.025) .

Median follow up time was 10 months (3–28 months). No severe puncture complications occurred. Grade 1 or 2 acute urinary side effect was 16%, Grade 3 or 4 late toxicities were observed in 5 patients (16%). Among them, fistula was observed in 3 patients (9%), hematuria in 1 patient, vaginal bleeding in 1 patient, and grade 3 proctitis in 1 patient. The local response rate (CR + PR) was 84.4% (27/32) 1 month later after completion of treatment. And the median TTP was 15.4 months (95% CI 11.3- 19.6months), 1 year local control were 51.7%

Discussion

Because of the complexity and diversity of recurrent lesions. 3D-PIT was proposed for patients: i, previous pelvic RT; ii, no indication or desire for total pelvic exenteration; iii, reject palliative care. We designed individual templates, which has many advantages: ① They contain information on the local pubic fascial features of each patient and can be fixed using a vaginal

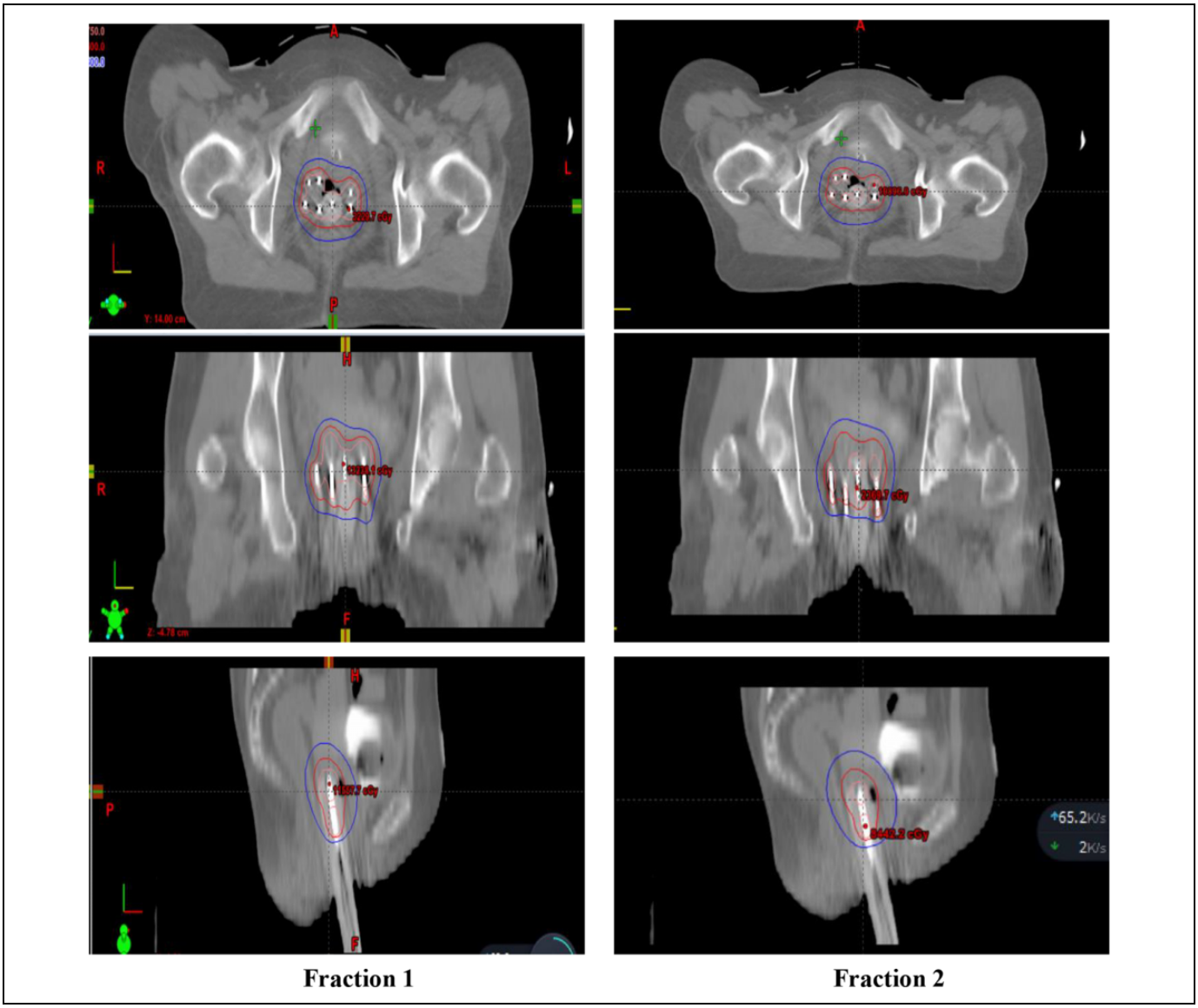

Figure 4. Dose distribution between the different fractions after template-assisted high-dose rate interstitial brachytherapy.

obturator, which decreases set up errors and stabilizes the template in the right position. ② They contain information on the direction and depth of the needles, which facilitates needle placement and minimizes the differences between brachytherapists. ③ In our result, Type II 3D-PIT based HDR-IB show that there were no statistically significant ($P > 0.05$) difference in GTV of V100, D100, D90 and the dose distribution index of CI and HI. We found that the treatment was well corresponding to the preplan. ④ Murakami et al[11] indicated that accurate target detection is critical: a geometric miss can directly influence LC. MRI-assisted HDR-IB is much more accurate for the definition of recurrent lesions. In this study, MRI was available during preplanning for GTV delineation, so preplanning not only facilitated needle insertion, but also delineated the treatment volume of the target clearly. Preplanning was applied to the procedure of ISBT which guarantee the treatment quality control. The consistency of dose distribution between the different fractions is shown in Figure 4. Noncoplanar 3D-printed templates overcome the limitations of classic coplanar transperineal templates, and the individual approach improve the efficiency and accuracy of treatment.

In patients with a history of pelvic irradiation, re-irradiation is generally relative contraindications because the likelihood of severe sequelae. Therefore, recurrent GYN after pelvic EBRT remains a challenge. Our results showed the local response rate was 84.4% (27/32), and the median TTP was 15.4 months,2 year local control rate were 51.7%. Grade 3 or 4 late toxicities were observed in 5 patients, sigmoid vaginal fistula was recorded in 1 patient and vesico-vaginal fistula were in 2 patients shortly after completion of ISBT, the bladder or bowel wall were invaded showed in MRI image in these 3 patients. Vaginal bleeding in 1 patient 3 months later after ISBT, and

grade 3 proctitis in 1 patient, the symptoms were relieved after conservative treatment.

BT boost or salvage re-irradiation can be delivered by IC applicators, vaginal cylinders, or template-based HDR-IB[12] IS catheters are beneficial in patients with bulky lesions, yielding an increase in the 3-year local control rate of 10% relative to patients receiving intracavitary brachytherapy (ICBT) alone.[13] Another advantage of IS catheters is that they can reduce applicator shift between imaging and dose delivery[14] Various studies have demonstrated the effectiveness of HDR-IB for primary and recurrent gynecologic malignancies[13,15] With current developments in the application of templates and transrectal ultrasound-guidance techniques, BT is playing an increasingly important role in the treatment of prostate cancer, and the template-guidance technique has become standard treatment[16] The American Brachytherapy Society (ABS) recommends use of template-based HDR-IB in patients with post-hysterectomy gross residual disease, recurrence extending into the parametrium, and vaginal disease unsuited to IC treatment.[17] A recent study[18] showed promising clinical application of ICBT combined with free-needle ISBT for locally advanced cervical cancer. Reirradiation with interstitial implants has a distinct advantage over reirradiation with EBRT because ISBT can deliver radioactive sources directly into the tumor mass while sparing the surrounding normal tissues (eg, the bladder and rectum). However, like EBRT, reirradiation with interstitial implants is still associated with significant morbidity. In this study, V_{100} and D_{90} of GTV per fraction was 88.9% $\pm$ 9.8%, and 5.79 Gy $\pm$ 0.32 Gy. The mean $D_{2\ cc}$ of rectum, bladder and colon per fraction were 3.14Gy $\pm$ 0.23 Gy, 3.76Gy $\pm$ 0.72 Gy and 2.47Gy $\pm$ 0.34 Gy. These dose parameters were rather good for reirradiation and the response rate was 84.4%.

However, the plane-template-guidance technique, which can improve the accuracy of implantation and simplify operative procedures for HDR, has developed slowly for the treatment of malignant GYN. The 2 classic perineal template IS applicators are the Syed–Neblett Butterfly Template and Martinez Universal Perineal Template.[19,20] In 2009, use of the Utrecht Applicator[21] with IS catheters was described in 6 patients and achieved a dosimetric improvement to the D_{90} of -the high-risk CTV of 5.3 Gy; 2 anterior and 4 posterior catheters were attached to the tracts within the ovoids and inserted into the required lesion through the vagina. Clinical use of the Vienna Applicator or ring applicator[20,22] with IS catheters through the vagina has also been reported, and improves dose coverage.

Salvage HDR-IB is seldom available at cancer hospitals in China for many reasons. No surveys of HDR-IB utility have been conducted in China, but a survey performed in Canada[23] showed that while HDR-IB has been adopted by half of the responding centers, fewer than 10% of residents or fellows felt satisfied with HDR-IB teaching/training. The digitally modeled individual template used in this study is suitable for IS implantation in the central pelvic region and can improve implantation accuracy as well as simplify the procedure. Although the 3D printed template can simplify the intra-operative procedure, it also adds an extra step of design and manufacture of 3D-printing template. Further study and training in this technique is warranted.

There are limitations in this study. It was still a single center study and have limited patient recruitment andnd short follow up time. Statistics analysis is different when dose distribution index of EI was compared between preplan and treatment plan. Positioning uncertainties and, filling state of organs at risk such as bowl and bladder should be considered.

Conclusions

In conclusion, the prescription dose of 10-36 Gy, 5-6 Gy per fraction for re-irradiation is effective and the toxicities were acceptable. The use of 3D-PIT-based HDR-IB for central r-GYN is feasible and efficient, which permits the delivery of highly localized ISBT.

Authors' Note

Dr. Ping Jiang collected the data, drafted the manuscript and did the statistical analysis. Dr. Ang Qu was in charge of verifying patients' treatment plans and directing manuscript writing. Dr. Shuhua Wei collected the material, reviewed and corrected this manuscript. Haitao Sun, Xile Zhang and Xu Li were responsible for collection of clinical data. Dr. Junjie Wang was responsible for the supplementation/refinement of clinical data, and carried out statistical analyses.

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Declaration of Conflicting Interests

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