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Original Article

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Application value of personalized 3D printing vaginal model for the Image-guided adaptive brachytherapy of cervical cancer

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ABSTRACT

Objective: To explore the application value of using 3-dimensional (3D) printing (3DP) technology to create individualized vaginal molds for brachytherapy (BT) in high-dose-rate 3D cervical cancer through reverse engineering of needle placement.
Methods: Prospectively, 11 patients with cervical cancer were treated with 3DP-intracavitary/interstitial (IC/IS) BT using 3DP to create individualized vaginal molds. All patients were performed BT after completion of external beam radiotherapy (EBRT). Each patient was treated with BT 5 times, the prescription dose was 600 cGy/F, which was performed once or twice a week, 2 of them were freehand IC/IS BT, and 3 were 3DP-IC/IS BT. The relevant planning parameters (bladder, rectum, sigmoid colon, and small intestine) and target conformity index (CI) for high-risk clinical target volume (HR-CTV) and organs at risk (OARs) were compared between the groups.
Results: There were significant advantages in the 3DP-IC/IS BT group compared with the freehand IC/IS BT group: HR-CTV D_{90} (629.40±19.34 vs. 613.03±15.93 cGy, p=0.002), D_{95} (580.74±18.31 vs. 567.44±23.94 cGy, p=0.032), bladder D_{2cc} (431.11±23.27 vs. 458.07±23.27 cGy, p<0.001), bladder D_{1cc} and bladder $D_{0.1cc}$. There was no statistically significant difference (p>0.05) between the 2 groups in rectal D_{2cc} (352.30±42.42 vs. 361.29±42.42 cGy, p=0.470), sigmoid colon D_{2cc} (236.73±78.95 vs. 246.50±58.17 cGy, p=0.621), CI (0.79±0.04 vs. 0.79±0.039 p=0.773), HR-CTV V_{100}, V_{200}, D_{98}, D_{100} and other OARs parameters (p>0.05).
Conclusion: Compared with IC/IS BT, 3DP-IC/IS BT has apparent advantages with simple operation and high safety. In addition, individualized mold helps to improve the tumor target area's radiation dose while meeting the dose-limiting requirements for organs at risk and reduces the clinical proficiency requirements for operating physicians.

Keywords: 3D Printing; Cervical Cancer; Vagina; Intracavity Radiotherapy; Interstitial Radiotherapy

Synopsis

Three-dimensional printing (3DP) technology improved tumor high-risk clinical target volume D_{90} and target conformity index while reducing bladder D_{2cc} with a statistical difference compared with manual intracavitary/interstitial (IC/IS) brachytherapy (BT). In addition, 3DP-IC/IS BT has apparent advantages with simple operation and high safety.

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No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Cervical cancer is the fourth most common cancer in the world and the fourth leading cause of cancer death in women, In 2020, there was an estimated 604,000 new cases and 342,000 deaths worldwide. As early as 1999, the National Cancer Institute of the United States identified cisplatin-based concomitant chemoradiotherapy as the standard treatment for locally advanced cervical cancer (LACC) based on five randomized controlled studies [1-5]. The 2021 National Comprehensive Cancer Network guidelines in the United States recommend that the preferred standard treatment for LACC is cisplatin-based single-agent chemoradiotherapy, radical radiotherapy with external beam radiotherapy (EBRT) and brachytherapy (BT) combination. BT is an important component of radical radiotherapy for cervical cancer with the advantages of protecting normal tissues and providing high doses to primary tumors and is not suitable to be replaced by stereotactic body radiotherapy or intensity-modulated radiation therapy (IMRT) [6,7]. The efficacy of computed tomography (CT)/magnetic resonance (MR) image-guided intracavitary combined interstitial brachytherapy (IC/IS BT) in BT has been confirmed. Image-guided adaptive BT can improve the local control rate and survival rate of LACC patients compared with past X-ray-guided BT [8,9]. However, an analysis of the retro EMBRACE study showed that IC/IS BT alone also improves high-risk clinical target volume (HR-CTV) D_{90} and local control rate compared with IC BT. Improvements in local and pelvic control were associated with an overall 10% survival benefit compared with the historical cohort [10]. These findings suggest that the use of CT/MR image-guided IC/IS BT is the best means of BT at present. However, the specific application of IC/IS BT used by different institutions is heterogenous.

The applicator is the channel where the radiation source resides in BT, and it plays a decisive role in the treatment planning of BT. The accuracy of implementing freehand IC/IS BT in clinical practice depends on the experience and proficiency of the operating physician. In order to make BT more accurate and stable, minimize errors in the insertion process, and reduce the complexity of the procedure, we decided to obtain CT images of the patients, delineate the ideal tumor target area and organs at risk, perform reverse needle placement, and pre-set the angles and depths of the needles to cover the target area as much as possible. Subsequently, we utilized 3-dimensional printing (3DP) technology to create personalized vaginal molds that guide the insertion of intracavitary/interstitial applicators. The aim was to explore the feasibility of routinely using these molds to assist with the insertion process and to conduct this single-center, prospective, single-arm, and non-randomized study.

MATERIALS AND METHODS

1. Case selection

From June 2021 to December 2021, 11 cervical cancer patients were enrolled in The Affiliated Cancer Hospital of Guangzhou Medical University for a prospective study. All patients received concurrent chemoradiotherapy for cervical cancer before BT. The EBRT method was IMRT. The prescribed dose is CTV:4,500 cGy/25F, GTVnd (metastatic lymph node):6,000–7,000 cGy/25–30F. Cervical cancer patients requiring radical radiotherapy were included in this study. The clinical characteristics of these patients are shown in **Table 1**.

Table 1. Patients and tumor characteristics

Patients	Average
Age (yr)	53.18±6.478
Median age	55
Pathological type	
Squamous cancer	9 (81.8)
Adenocarcinoma	1 (9.1)
Unspecific	1 (9.1)
Stages	
IIA1	1 (9.1)
IIA2	1 (9.1)
IIB	1 (9.1)
IIIB	1 (9.1)
IIIC1	5 (45.5)
IIIC2	2 (18.2)
Pathological grade	
Well differentiated	0 (0.0)
Moderately differentiated	5 (45.5)
Poorly differentiated	2 (18.2)
Unspecified	4 (36.4)

Values are presented as mean ± standard deviation or number (%).

2. Preparation before BT

For cervical cancer patients who underwent radical radiotherapy, 5 times of BT were started after the end of external irradiation. The prescribed dose was: HR-CTV: 3,000 cGy/5F and the total dose corresponds to the conventional 200 cGy fractional radiotherapy equivalent dose (EQD2) of 4,000 cGy.

BT related information was given to patients before surgery, and an informed consent form was signed. An anesthesiologist was consulted 3 days before BT, and BT under general anesthesia or local anesthesia was selected based on the evaluation.

The operating physician reviews and is familiar with the patient's pre-BT CT/MR images before surgery. The patients were sit on the gynecological examination bed, which can be used for transportation, getting lithotomy position, disinfection, laying sterile surgical drapes, and indwelling catheters. At this time, the anesthesiologist gave low-flow oxygen inhalation to the patients who were under general anesthesia and injected an appropriate amount of propofol intravenously. The operating physician conducted a gynecological examination on the patients. The examination was standardized and recorded in detail using the revised proportional clinical chart recommended by the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) [11]. By measuring the thickness, width, height, and parametrial infiltration of the lesion, it is convenient for doctors to refer when inserting the source applicator and delineating the target area. The vaginal dilator was inserted into the vagina, the cervix was exposed and the posterior fornix was disinfected. The uterine probe was used to probe the intrauterine tube. The appropriate curvature and length of the intrauterine tube was selected according to the probe results. The applicator was implanted into the cervical canal.

The patients were divided into 2 groups: the IC/IS BT group and 3DP-IC/IS BT group.

IC/IS BT group: After the intrauterine tube was implanted, the physician determined the required number, direction, and depth of implantation applicators through preoperative imaging. The sterile gel particles were fixed on the insertion applicator to mark the insertion

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depth. The applicator was inserted through the cervical interstitial according to the insertion direction around the cervix. Finally, a gauze was used to fix the applicator, and the transfer bed was used for transferring the patients to the CT room for positioning: 2.5 mm slice thickness scan images were reconstructed and transmitted to the Oncentra planning system.

3DP-IC/IS BT group: The vaginal dilator was removed after the intrauterine tube is implanted. The pre-designed and printed individualized vaginal mold was taken out under sterile conditions (the mold has pore channels for the intrauterine tube and 4–8 insertion applicators). The mold is implanted along the implanted intrauterine tube, and the correspondingly numbered applicators were implanted in sequence according to the pre-set length and track sequence. The mold was fixed with adhesive tape externally and the transfer bed was used to move the patients to the CT room for positioning. The images with a thickness of 2.5 mm were scanned for reconstruction and transmitted to the Oncentra planning system.

The production of a 3DP individualized mold and the actual operation of a patient is shown in **Fig. S1**.

3. Target volume delineation

The clinician delineated the target area in the Oncentra planning system. The HR-CTV and organs at risk (OARs) were delineated according to the standard of the GEC-ESTRO for delineating the BT target area under CT image. HR-CTV included the primary tumor, the upper vaginal segment, and part of the uterus (appropriately adjusted according to the results of gynecological examination and imaging examinations). In some cases, the HR-CTV delineation position was as low as the middle and lower vaginal segment. OARs included bladder, rectum, and sigmoid colon. The bladder included the entire outer wall of the bladder and the lower boundary located at the beginning of the urethra. The rectum included the outer wall of the rectum, and the upper boundary of the rectosigmoid junction. The sigmoid colon included the entire bowel and mesentery, and the lower boundary started from the rectosigmoid flexion level.

4. Plan design and grouping

After the target volume was delineated, the plan was designed on the Oncentra brachytherapy radiotherapy planning system. According to the CT image, the uterine canal and the insertion of applicators were reconstructed in the planning system, and the length of the uterine canal was set to 150 cm (step size 0.25 cm, offset value: 0.6 cm). The length of the applicator was set to 140.8 cm, (step size 0.25 cm, offset value: 1 cm). The IPSA inverse optimization was used, and a single radiotherapy dose required HR-CTV D_{90} to reach 600 cGy, that is, the 600 cGy dose volume surrounded at least 90% of the HR-CTV. Clinicians can manually optimize the plan according to the dose volume histogram to ensure that the total dose of EQD2 of external irradiation and BT is qualified (rectal D_{2cc} ≤6,500–7,500 cGy, bladder D_{2cc} ≤8,000 cGy) and try to make HR-CTV D_{90} up to standard. Priority was given to ensuring that the 600 cGy dose line wraps around the cervix, particularly the primary tumor.

The patients were treated with 5 BTs. The first and third BT was manual IC/IS BT; the second, fourth, and fifth were 3DP-IC/IS BT. That is, a total of two freehand IC/IS BT and three 3DP-IC/IS BT. The data were divided into 2 groups for analysis, the control group was the freehand IC/IS BT group, and the experimental group was the 3DP-IC/IS BT group.

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The planning design data of patients were collected, including HR-CTV D_{90}, D_{2cc} of each OARs (GEC-ESTRO recommends D_{2cc} as the main reference index for bladder and rectal OAR evaluation [12]), and the target conformity index (CI) was calculated.

$$CI=(VDT_{CTV}/V_{CTV})\times(VDT_{CTV}/VDT),$$

where VDT_{CTV} represents the volume of HR-CTV surrounded by the 100% prescription dose line, V_{CTV} represents the HR-CTV volume, and VDT represents the total volume wrapped by 100% prescription dose line, which is V_{600cGy} in this study.

5. Statistical analysis

The SPSS v26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and the normal distribution of the data in each group was verified. The t-test was used for the difference analyses if the data conformed to the normal distribution. It was considered statistically different when a p-value was less than 0.05.

RESULTS

By calculating the summation EQD2 of the HR-CTV D_{90} of single radiotherapy, the total dose of EQD2 for 5 BTs in each patient was above 4,000 cGy, with an average of 4,213±29 cGy, indicating that the HR-CTV D_{90} of each patient's BT met the clinical treatment requirements.

1. 3DP-IC/IS BT group is non-inferior to IC/IS BT group

The comparison of various treatment planning parameters of the 2 groups is shown in **Fig. 1** and **Table 2**. There were significant advantages in the 3DP-IC/IS BT group compared with the freehand IC/IS BT group: HR-CTV D_{90} (629.40±19.34 vs. 613.03±15.93 cGy, p=0.002), D_{95} (580.74±18.31 vs. 567.44±23.94 cGy, p=0.032), bladder D_{2cc} (431.11±23.27 vs. 458.07±23.27 cGy, p<0.001), bladder D_{1cc} and bladder $D_{0.1cc}$. There was no statistically significant difference (p>0.05) between the 2 groups in rectal D_{2cc} (352.30±42.42 vs. 361.29±42.42 cGy, p=0.470), sigmoid colon D_{2cc} (236.73±78.95 vs. 246.50±58.17 cGy, p=0.621), CI (0.79±0.04 vs. 0.79±0.039 p=0.773), HR-CTV V_{100}, V_{200}, D_{98}, D_{100} and other OARs parameters (p>0.05).

2. 3DP-IC/IS BT has more advantages than IC/IS BT in the angle and number of applicators

Fig. 2 showed the treatment plan image of the upper cervical segment of 2 enrolled patients. It can be seen that the 600 cGy dose line of 3DP-IC/IS BT is more suitable for the target area. **Fig. 2A, B** and **Fig. 2C, D** are different application methods for 2 patient (#1, #2). Due to the existence of posterior uterine fibroids, the uterus is in an anterior position, which affected the angle of application. The applicator indicated by the green arrow was more posterior

Table 2. Planning parameters between the 3DP-IC/IS BT and the IC/IS BT groups

Group	HR-CTV D_{90} (cGy)	D_{2cc} (cGy)		
		Bladder	Rectum	Sigmoid
IC/IS BT (n=22)	613.03±15.93	458.07±25.08	361.29±48.42	246.50±58.17
3DP-IC/IS BT (n=33)	629.40±19.34	431.11±23.27	352.30±42.42	233.30±78.31
p-value	0.002	<0.001	0.470	0.502

Bladder D_{2cc} of CI, HR-CTV D_{90}, and OARs have statistical differences (p<0.05). Values are presented as mean ± standard deviation.
3DP, 3-dimensional printing; CI, conformity index; HR-CTV, high-risk clinical target volume; IC/IS BT, intracavitary combined interstitial brachytherapy; OARs, organs at risk.

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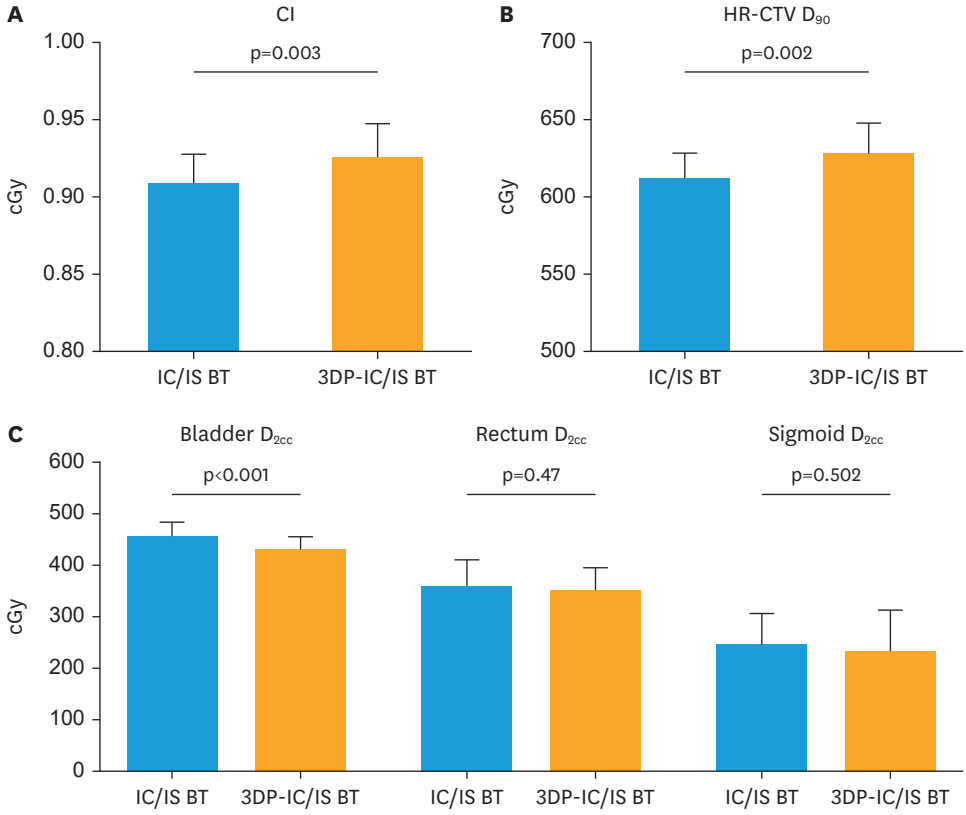

Fig. 1. The histograms comparing each treatment planning parameter between the 3DP-IC/IS BT group and the IC/IS BT group. (A) CI, (B) HR-CTV D_{90}, and (C) D_{2cc} for OARs.
3DP, 3-dimensional printing; CI, conformity index; HR-CTV, high-risk clinical target volume; IC/IS BT, intracavitary combined interstitial brachytherapy; OARs, organs at risk.

than the uterine canal and difficult to insert along both sides of the uterine canal (patient #1, **Fig. 2A and B**). Therefore, the 3DP-IC/IS BT applicator on both sides were more forward (**Fig. 2B**) than IC/IS BT (**Fig. 2A**). The CI for **Fig. 2A and B** were respectively 0.75 and 0.85. There are also improvements in HR-CTV D_{90} and OARs D_{2cc}. **Fig. 2C and D** are the comparison of different radiation applicators for another patient (patient #2). There were 7 interstitial applicators used for 3DP-IC/IS BT

3. 3DP-IC/IS BT has better stability

As shown in **Fig. 3** and **Table 3**, the position of the radiation applicators is relatively stable. The 3 times 3DP-IC/IS BT of each patients were compared, we found that 3DP-IC/IS BT has better stability in position and angle of the needle (**Fig. 3A-C** and **Fig. 3D-F**). The treatment planning parameters of 3 times 3DP-IC/IS BT of all patients were compared and shown in

Table 3. Three comparisons of 3DP-IC/IS BT treatment plan parameters (n=11)

3DP-IC/IS	CI	HR-CTV D_{90} (cGy)	D_{2cc} (cGy)		
			Bladder	Rectum	Sigmoid
One	0.9186±0.0182	622.24±17.40	436.31±15.67	366.78±28.64	208.64±75.28
Two	0.9324±0.0232	636.31±21.54	427.19±33.02	335.3±56.28	222.3±94.60
Three	0.9282±0.0205	629.66±17.92	429.84±18.67	354.83±34.84	268.95±52.99

One, Two, and Three were the first, second, and third 3DP-IC/IS BT in 11 patients, respectively. Values are presented as mean ± standard deviation.
3DP, 3-dimensional printing; CI, conformity index; HR-CTV, high-risk clinical target volume; IC/IS BT, intracavitary combined interstitial brachytherapy.

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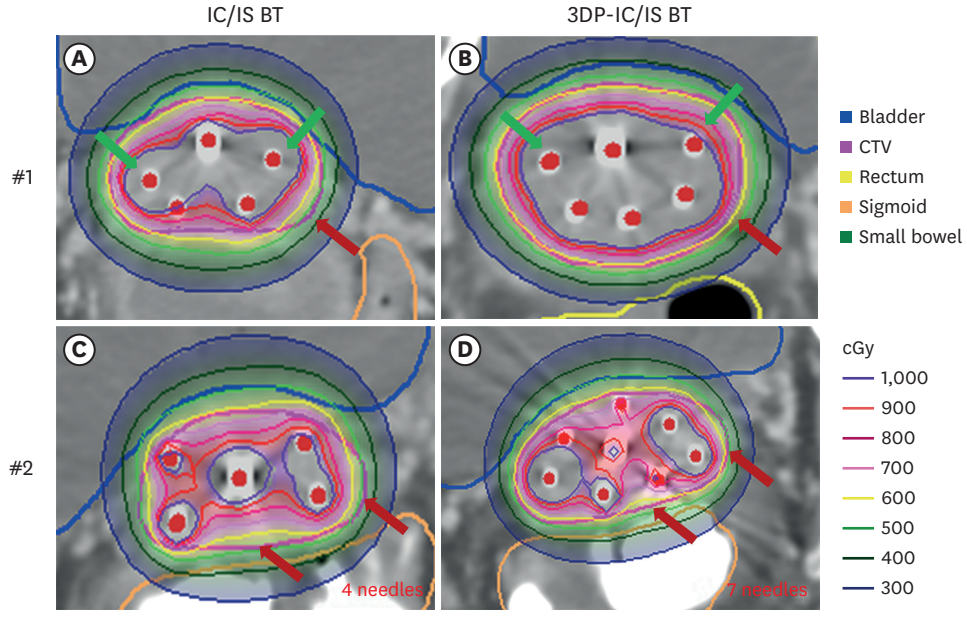

Fig. 2. 3DP-IC/IS BT has more advantages than IC/IS BT in the angle and number of applicators. (A, B) The radiation applicator of IC/IS and 3DP-IC/IS of patient #1. (C, D) The radiation applicator of IC/IS and 3DP-IC/IS of patient #2. The green arrows show the difference in the angle of the radiation applicators. The red arrow indicates the difference in coverage of the 600 cGy dose line.
3DP, 3-dimensional printing; CTV, clinical target volume; IC/IS BT, intracavitary combined interstitial brachytherapy.

Fig. 3G and **Table 3**. There was no statistical difference in CI, HR-CTV D_{90}, and OARs D_{2cc}, which indicated that 3DP-IC/IS BT had better stability.

DISCUSSION

The application of IC/IS BT depends on the proficiency of the operating physician, and it takes a long time for a radiation physician to become skillful on using it. In clinical practice, an uterine tumor might be eccentric, large size, irregular shape, involving parametrial tissues or causing virginal stenosis. Therefore, the operating physician might have a limited visualization under the speculum, making it difficult to achieve the ideal position and depth of needles for interpolation, causing deviation of radiation doses. In addition, the limitation of vaginal tamponade fixation technology might make BT unable to meet the clinical requirements. 3DP individualized models have attracted attention in recent years in adjuvant treatment for breast cancer, skin cancer, and cervical cancer due to their excellent performance in protecting target area and OARs [13-19]. Prospective studies in China have confirmed that using 3DP technology to make individualized vaginal models assisted inserting needle for radiation applicator improved tumor HR-CTV D_{90} and target CI while reducing bladder D_{2cc} with a statistical difference compared with manual IC/IS BT. The D_{2cc} of the rectum and sigmoid, although not statistically different, did not show a disadvantage, but indicated an advantage in protecting normal tissue from puncture [13-15]. Logar et al. [16] found that, after using 3DP mold-assisted MR imaging cervical cancer radiation applicator, the HR-CTV D_{90} increased while the mean D_{2cc} of OARs increased but was within the safety limit [16]. Although some studies have confirmed the advantages of 3DP individualization molds, specific shapes of molds and production processes are different for different institutions. We have explored

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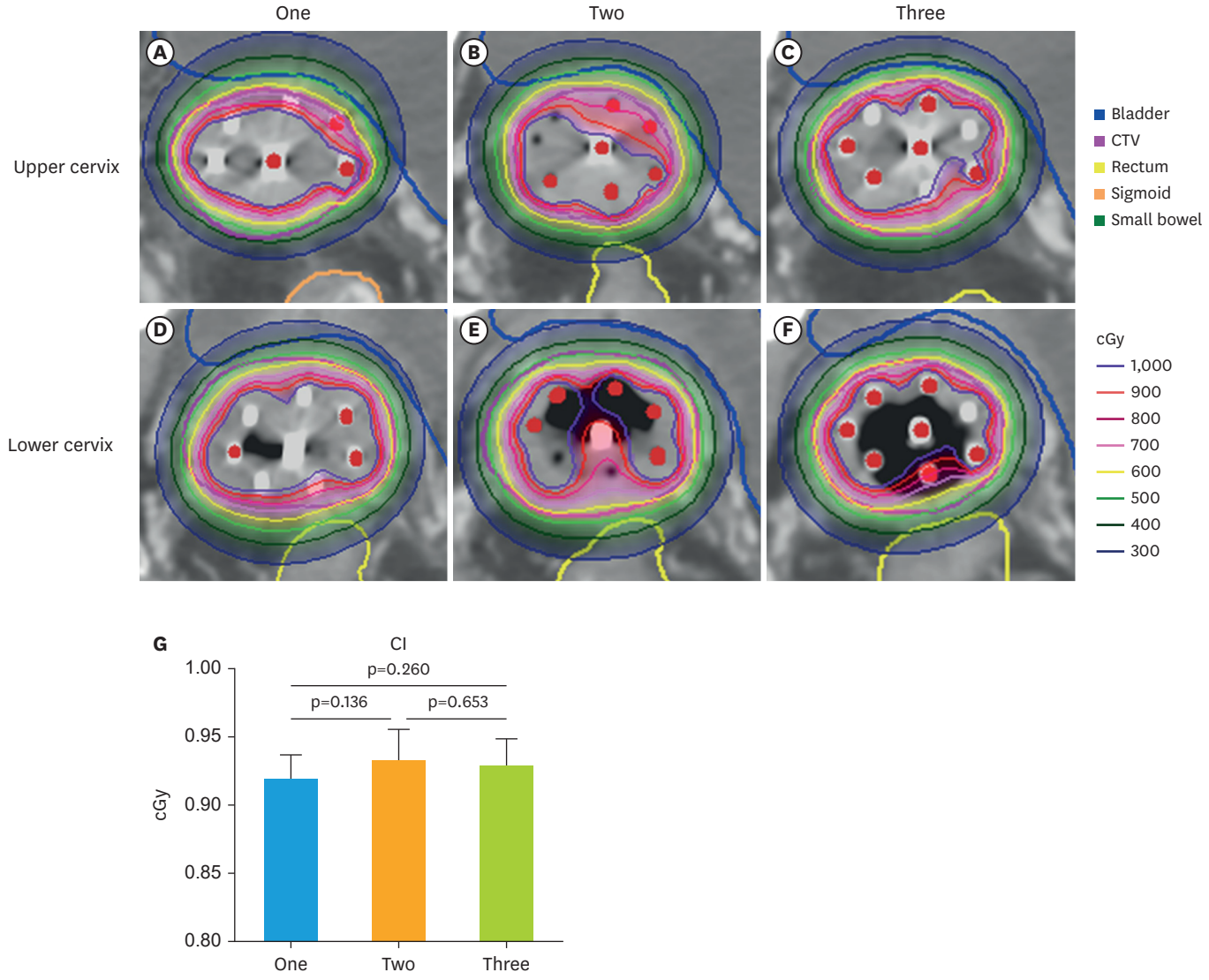

Fig. 3. 3DP-IC/IS BT has better stability in position and angle of the needle. (A-F) Three 3DP-IC/IS BT treatment plan images of the same patient, and 2 levels of the upper and lower cervical segments were taken. (G) CI of treatment planning parameters of 3 times 3DP-IC/IS BT of all patients.
3DP, 3-dimensional printing; CI, conformity index; CTV, clinical target volume; IC/IS BT, intracavitary combined interstitial brachytherapy.

mold production and improved the entire mold production process. Compared with freehand radiation application, the molds produced by our institution show non-inferiority. The use of virtual planning to make individualization molds and application paths in advance is the key to improve treatment planning in practice. This virtual plan is equivalent to putting the plan created by the clinician in the brain when performing IC/IS BT by hand into the computer. According to the patient's imaging anatomy, the ideal target area is drawn in advance, the applicator is placed virtually, and the application path is determined to improve the accuracy and stability of applicator between tissues.

The excellent performance of molds on the fixation of the applicator, which resulted in increased needle entry angles and selectable needle counts, was also a factor in improving treatment plan. When IC/IS BT was performed by freehand, we generally use 4 needles insertion. This is because when delineating HR-CTV, a trapezoid-like or rectangular-like

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ellipse is often present on the cross-section of the cervix, and the center of which is the uterine canal. When the 4 needles insertion were evenly distributed in a rectangular shape around the cervical canal, the plan can often be optimized to an ideal state. However, when encountering tumors with eccentricity, large size, irregular shape, parametrial involvement, or vaginal stenosis, it is difficult to use applicators on the vaginal wall due to the limited angle under the speculum and the limitations of fixation techniques. It is challenging for clinicians to use the needles insertion accurately from vaginal wall. As shown in **Fig. 2A**, the individualized mold provides more angles for insertion because the applicator are fixed on the pre-set path by the mold, which is an obvious advantage of 3DP individualized molds in improving the treatment plan. Borot et al. [20] made a dosimetric comparison of treatment plans using 2, 4, 6, 8, 10, and 12 applicators in high-dose prostate cancer treatment. The results showed that with the increase in the number of applicators, there was an upward trend in the target area receiving doses, and the dose of organs at risk showed a downward trend on D_{1cc}, indicating that the increase in the number of applicators helped to improve the treatment plan to some extent [20]. The increase in the number of applicators increased the selection of the radioactive source stop point, and the shape of the formed dose line were more accurate and more suitable for the target area after optimization. As shown in **Fig. 2**, the routine 4 applicators of needles in C were increased to 7 needles in D, and the final CI increased from 0.75 in IC/IS BT (**Fig. 2C**) to 0.85 in 3DP-IC/IS BT (**Fig. 2D**), and the D_{2cc} of OARs in this patient also improved.

An increase in the number of applicators undoubtedly increases the risk of tissue puncture. In this study, a total of 252 cervical interstitial applicators were used, of which 3DP-IC/IS BT used 162 applicators for 33 treatments, with an average of 4.91 applicators per treatment and 22 treatments for IC/IS BT used 90 applicators. An average of 4.09 applicators were used per treatment, and no puncture of normal tissue was found. In the study of Wang et al. [15], the average number of applicators used by patients using the 3DP was 3.8, which was greater than 3.0 applicators in the control group. In the end, there was no puncture event in the experimental group. Compared with the 3 times puncture events in the control group, 3DP source applicators showed higher safety [15]. We believe that the safety of 3DP-IC/IS BT after the increased number of applicators depends on its pre-planning. Through pre-planning, the insertion angle and depth of applicators are pre-set to ensure safety, and we can boldly increase the number of applicators and make the risk even lower than freehand manipulation which has fewer stitches. This also illustrates the benefits of pre-planning.

The stability of 3DP-IC/IS BT is mainly due to the repeatability of mold implantation, Although the D_{2cc} of sigmoid colon was statistically different between the first time and the third time, the activity of sigmoid colon and the 2 times of after loading limited the dose of the endangered organ in the expected range, and we can still get the result of good stability of the 3DP personalized mold.

It should be noted that our research subjects were not screened for tumor volume and eccentricity, and 3DP individualized molds were not distinguished on difficult subjects. HR-CTV volume and total treatment time could affect the local control rate under the same irradiation dose [21]. Screening for tumors such as eccentricity, large size, irregular shape, parametrial involvement, or vaginal stenosis and treatment with molds will be a future research direction. Additionally, patients could be classified according to risk factors such as tumor size and extent of invasion, to improve the flexibility of individualized molds.

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In conclusion, compared with IC/IS BT, 3DP-IC/IS BT has apparent advantages with simple operation and high safety. In addition, individualized mold helps to improve the tumor target area's radiation dose while meeting the dose-limiting requirements for organs at risk and reduces the clinical proficiency requirements for operating physicians.

SUPPLEMENTARY MATERIAL

Fig. S1

(A) General flow chart of making a 3D printing individual mold and the operation diagram for applicators. (B) The operating physician determined the preset depth according to different tracks. (C, D) Real pictures of individualized vaginal molds of a patient. (C) The front view (close to the vulva) and (D) the back view (close to the cervix).

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