Efficacy and safety of a 3D-printed applicator for vaginal brachytherapy in patients with central pelvic-recurrent cervical cancer after primary hysterectomy

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ABSTRACT

PURPOSE: Intracavitary and/or interstitial brachytherapy is an integral component of the management of patients with central pelvic-recurrent cervical cancer after primary hysterectomy, and is typically delivered using conventional applicators. We investigated the efficacy and safety of three-dimensional (3D)-printed, customizable applicators for those patients.

METHODS AND MATERIALS: Twenty-six patients were treated with combination external beam radiotherapy and brachytherapy. Patients with lesions ≤1 and >1 cm before brachytherapy were treated with intracavitary and interstitial brachytherapy, respectively. Dosimetric plans were compared between the vaginal cylinder and 3D-printed applicator for the first 9 patients. Outcomes and treatment-related complications were also investigated.

RESULTS: The median tumor size before brachytherapy was 0.81 cm. Intracavitary, interstitial, and combined interstitial-intracavitary brachytherapy were performed in 22 (85%), 3 (11%), and 1 (4%) of the patients, respectively. The clinical target volume (CTV) coverage goal was achieved with all 3D-printed plans but failed with three single-channel cylinder plans (33.3%). Owing to 3D-printed transvaginal applicator guidance, there was no need to adjust the needle position after implantation. The mean CTV dose for all patients was 71 ± 8.2 Gy; all met the dose constraints to the organs at risk, but 1 (4%) had a rectal D30 overdose. The 2-year local control, progression-free survival, and overall survival rates were 87.8%, 71.0%, and 91.6%, respectively. Four patients (21%) developed early grade 3–4 hematological toxicities and 1 (4%) developed a late grade 3 adverse event.

CONCLUSIONS: High-quality intracavitary and/or interstitial brachytherapy can be achieved using a 3D-printed applicator and yields favorable outcomes with acceptable toxicity.

Keywords: 3d-printed applicator; Vaginal brachytherapy; Cervical cancer; Hysterectomy, recurrence

Introduction

Cervical cancer represents an ongoing public health concern that affects women worldwide (1). It has been estimated that 30–45% of recurrences after radical surgery are central (2); the recommended treatment for these patients is definitive chemoradiotherapy combined with brachytherapy (3,4). Patients with a history of radiotherapy can also undergo re-irradiation if they meet stringent criteria (3,5,6).

It is recommended that superficial lesions ≤5 mm be treated with intracavitary brachytherapy (ICBT) using a vaginal cylinder (3,7). However, the most commonly used single-channel cylinders deliver inadequate dose coverages to the vaginal apex compared to multichannel cylinders owing to source anisotropy (8,9). Moreover, ICBT is associated with lower dose coverage to tumors with thick-
ness >5 mm when compared to interstitial brachytherapy (ISBT) (7).

At many centers, ISBT is often delivered using free-hand implantation (10), but this method requires a high skillset. Template-based technique seems to reduce the difficulty of the procedure (11–13). However, the commercial interstitial applicator is usually a transperineal template that is typically distant from the tumor’s location; this causes difficulty in implantation, inaccurate needle positioning, and damage to normal tissue. Additionally, both free-hand and template-based ISBT require repeated adjustment of the needle position until a satisfactory dose distribution is achieved through multiple computed tomography (CT) scans.

Three-dimensional (3D) printing techniques have enabled the physical creation of customized ICBT applicators that can provide satisfactory dose distribution (14), as well as 3D-printed transvaginal applicators that assist radiation oncologists in inserting needles accurately (15–17). However, the current literature around this topic mainly comprises case reports or else focuses on dosimetry. Since 2017, our center has used 3D-printed ICBT applicators to treat lesions ≤1 cm as well as 3D-printed transvaginal ISBT applicators to treat tumors >1 cm thick using vaginal brachytherapy. To that end, we investigated the clinical outcomes of patients with central pelvic-recurrent cervical cancer after primary hysterectomy who were treated with these devices; we also describe the characteristics of the 3D-printed applicators herein.

Methods and materials

Patient selection and treatment strategy

This prospective study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. JS-2373) and written informed consent was obtained from each patient before treatment. The inclusion criteria were as follows: total hysterectomy as the primary treatment for cervical cancer, pathologic confirmation of recurrence, combination treatment of external beam radiotherapy (EBRT) using intensity-modulated irradiation, and brachytherapy using a 3D-printed applicator. Patients undergoing hysterectomy for other diseases, those who underwent surgical resection after recurrence, and those who refused the novel applicator were excluded from the study. Twenty-six patients who underwent primary radical hysterectomy, who experienced central pelvic recurrences at our department between January 2017 and November 2020, and who were treated with brachytherapy using 3D-printed applicators were investigated.

The EBRT field depended on the location of the lesions as well as radiotherapy history, and 45–60.4 Gy was administered to the clinical target volume (CTV) in 20–33 fractions. All patients without radiotherapy history received whole pelvic EBRT. Groins were included if the lower third of vagina were involved. As to patients with prior radiotherapy, re-irradiation fields covered the recurrence regions and drainage fields of the involved lymph. The brachytherapy dose schedule was 10–25 Gy in 2–6 fractions. The doses to the CTV and organs at risk (OARs) were converted to the equivalent dose in 2 Gy (EQD2), and the final goal was a cumulative dose to the CTV of ≥70 Gy as well as a cumulative dose to D2cc of ≤90 Gy to the bladder and ≤75 Gy to the rectum and/or sigmoid (18). Concurrent chemotherapy was administered if necessary.

For brachytherapy, the CTV was delineated on CT images registered with magnetic resonance imaging (MRI) and encompassed one-half, two-thirds, or the full length of the vagina according to tumor size, location of recurrence, and the presence of any residual lesions after EBRT. The ICBT technique was used for residual tumors with a maximum thickness of ≤1 cm beyond the applicator surface whereas ISBT or combined ICBT-ISBT was used for residual tumors with thicknesses >1 cm.

Applicator development and brachytherapy procedure

Different from the standard cylinder applicator, 3D-printed customized applicators have the individualized configuration, optimized arrangement catheters, and the catheters can be straight or curved according to the vaginal cavity and lesion position. The development of the 3D-printed applicator is shown in Fig. 1a, and the production details on CT imaging are demonstrated in Supplementary Fig. 1. Notably, the gauze strip is thin enough to fill the air gap at the vaginal apex, and it is vital that an experienced physicist designs the catheter and needle paths. 3D-printed applicator was made from a biocompatible OB-JET MED610 polymer (Stratasys Ltd., Rehovot, Israel) and produced by the Eden260VS 3D printer. After performing quality assurance on the 3D-printed applicators (including physical evaluation of material attenuation, path patency checks, and medical disinfection), they were available for clinical use. The examples of 3D-printed applicator used for ICBT, ISBT, and combined ICBT-ISBT technique were shown in Fig. 2.

The 3D-printed ICBT applicator was used in a manner similar to that of the vaginal cylinder while ISBT applicator should take into account certain considerations beforehand (Fig. 1b). A high-dose-rate 192Ir brachytherapy plan was generated using the Oncentra brachytherapy treatment planning system (Elekta, Stockholm, Sweden); the positioning device used during brachytherapy is shown in Supplementary Fig. 2.

Additionally, we compared the plan parameters of the vaginal single-channel cylinder (SCC) and 3D-printed applicators on the first 9 patients treated with ICBT.

Follow-up and statistical analyses

The cumulative EBRT dose combined with that of brachytherapy with respect to the CTV and OARs were de-
termined. Clinical outcomes including local control (LC), progression-free survival (PFS), and overall survival (OS) were assessed from the time of recurrence and were calculated using the Kaplan-Meier method. Factors that were potentially predictive of PFS and OS were determined using Cox proportional hazards regression analysis. Two-tailed p values <0.05 were deemed statistically significant. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0.

**Results**

**Patient characteristics**

The median interval between primary diagnosis and recurrence was 24.9 (range 5.8–50.0) months. A summary of the patient and tumor characteristics is presented in Table 1. Six patients (23%) received adjuvant radiotherapy during primary treatment. The median tumor thickness of all 26 patients before brachytherapy was 0.81 (range 0.50–2.40) cm. ICBT was administered to 22 patients (85%) with residual tumor thicknesses of ≤1 cm before brachytherapy. Among the remaining 4 patients with residual lesion thicknesses >1 cm, 3 (11%) underwent ISBT, and 1 (4%) was administered combined ICBT-ISBT. Eighteen patients (69%) were administered concurrent chemotherapy, while the remaining 8 (31%) received radiotherapy alone.

**Brachytherapy technique and cumulative dose**

Among the first 9 patients administered ICBT, the target dose was achieved with all 3D-printed plans but failed with 3 SCC plans (33.3%) (Table 2). Patients 3, 4, 5, 8, and 9 had poorer CTV coverage under the SCC plan than under the 3D-printed plan because they were restricted by the rectal D2cc. For patients who met the OAR requirements, both applicators achieved the same CTV D90, but the CTV D95 and OAR doses were more favorable under the 3D-printed plan than under the SCC plan. Interestingly, the sigmoid D2cc seemed to be higher in the 3D-printed group, although it remained within the dose constraints. Following the dosimetric comparisons, the 9 patients were treated with a 3D-printed applicator; the subsequent 13 patients were also treated with a 3D-printed applicator directly with no SCC plans made for them.
Table 2
Dosimetric comparison of clinical target volume and organs at risk between single-channel cylinder and 3-dimensional-printed plans in 9 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>CTV V100 (%)</th>
<th>CTV D90 (cGy)</th>
<th>CTV D98 (cGy)</th>
<th>Bladder D2cc (cGy)</th>
<th>Rectum D2cc (cGy)</th>
<th>Sigmoid D2cc (cGy)</th>
<th>Bowel D2cc (cGy)</th>
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<td>94</td>
<td>521</td>
<td>535</td>
<td>432</td>
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<td>488</td>
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</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>CTV V100 (%)</th>
<th>CTV D90 (cGy)</th>
<th>CTV D98 (cGy)</th>
<th>Bladder D2cc (cGy)</th>
<th>Rectum D2cc (cGy)</th>
<th>Sigmoid D2cc (cGy)</th>
<th>Bowel D2cc (cGy)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>88 ± 9</td>
<td>93 ± 3</td>
<td>490 ± 67</td>
<td>531 ± 25</td>
<td>370 ± 66</td>
<td>446 ± 27</td>
<td>422 ± 61</td>
</tr>
</tbody>
</table>

CTV = clinical target volume; V100 = percentage of target volume that received 100% of the prescribed dose; SCC = single-channel cylinder; 3D-p = 3-dimensional-printed; SD = standard deviation.
The dose prescribed to the CTV D90 was 5 Gy. Differences in CTV D90 coverage between the 2 plans are indicated in bold. Organs at risk of D2cc reached the cumulative dose limit of radiotherapy, and are indicated in bold italics.
Fig. 2. Representative examples of 3D-printed applicators for vaginal brachytherapy. (a) 3D-printed intracavitary applicator with curved catheters, (b) 3D-printed transvaginal interstitial applicator with non-coplanar metal needles, and (c) 3D-printed applicator used for combined intracavitary-interstitial brachytherapy.

The 4 patients who received ISBT had all their needles implanted per the planned direction and depth assisted by 3D-printed applicators on their first attempt, with no adjustment of the needle position necessary. The metal needle characteristics and dosimetric parameters for each implantation are summarized in Supplementary Tables 1 and 2. The insertion depth of the needles ranged from 1.8 to 3.0 cm while the number of needles for each patient ranged from 2 to 7. No significant bleeding or other acute complications related to the implantation procedure were observed.

Table 3 shows the cumulative EQD2 dose distributions to the CTVs and OARs of all the 26 patients. The mean dose to the CTV was 71 ± 8.2 Gy, and 16 patients (62%) received doses >70 Gy. All the patients met the OAR dose constraints except 1 whose D2cc to the rectum was 88 Gy. Her EBRT treatment was interrupted after 21 fractions because of thrombocytopenia, and she received 20 Gy/5 fractions of hyperfractionated supplemental radiotherapy.

Clinical outcomes and toxicity

With a median follow-up of 24.9 (range 5.7–50.0) months post-recurrence, the estimated 2-year LC, PFS, and OS were 87.8%, 71.0%, and 91.6%, respectively (Fig. 3). Univariate analysis showed that initial International Federation of Gynecology and Obstetrics (FIGO) stage, radiotherapy history, and tumor size at recurrence were significantly associated with PFS, while initial FIGO stage and radiotherapy history were significantly related to OS (Supplementary Fig. 3). Multivariate analysis showed that both initial FIGO stage and tumor size at recurrence were sig-
Table 3
Cumulative dose to the clinical target volume and organs at risk in all patients (N = 26)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cumulative dose of EBRT combined with BT (Gy)</th>
<th>Mean dose (Mean ± SD, Gy)</th>
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<tr>
<td>CTV</td>
<td>≤55 (N)</td>
<td>55–60 (N)</td>
</tr>
<tr>
<td>OARs</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rectum</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Bowel</td>
<td>18</td>
<td>4</td>
</tr>
</tbody>
</table>

CTV = clinical target volume; OARs = organs at risk; EBRT = external beam radiotherapy; BT = brachytherapy; SD = standard deviation.

* Dose values are all converted to the equivalent dose in 2 Gy (EQD2; \(\alpha/\beta = 10 \text{ Gy for tumor, } \alpha/\beta = 3 \text{ Gy for OARs})).

![Fig. 3. Kaplan-Meier curves showing the (a) local control (LC), (b) progression-free survival (PFS), and (c) overall survival (OS) rates for 26 patients.](image_url)

Significantly associated with PFS, while radiotherapy history was a predictor of OS (Supplementary Table 3).

Six patients (23%) developed disease progression and had died by the time of data analysis. Three patients, 2 of whom had a history of radiotherapy, developed local recurrences. Moreover, 3 patients (12%) developed distant metastases; all had metastatic lesions in the lung while 1 also had a lesion in the vaginal orifice.

For early complications, 5 patients (19%) had grade 3, and 1 (4%) had a grade 4 hematological toxicities. No grades 3–5 acute gastrointestinal or genitourinary toxicities occurred. Furthermore, only 1 patient (4%) developed a grade 3 late adverse event; this patient had previously undergone radiotherapy twice and developed a rectovaginal fistula. The doses of rectal D2cc in three radiotherapy treatment sessions were approximately 47 GyEQD2, 36 GyEQD2 and 58 GyEQD2, respectively.

Discussion

This pilot study prospectively investigated the use of a novel 3D-printed applicator for vaginal brachytherapy in patients with cervical cancer who experienced central pelvic recurrence after primary hysterectomy. The excellent clinical outcomes after salvage treatment showed that patients with lesions ≤1 cm could be treated with ICBT through individual 3D-printed applicators. Moreover, ISBT can be guided by a 3D-printed transvaginal applicator rapidly, and with precision.

The reported outcomes of patients with recurrent cervical cancers who undergo salvage radiotherapy vary owing to many complex factors, including patient selection, doses and fractions, and radiotherapy technique (6). Kim et al. reported a 2-year LC rate of approximately 68% among 125 patients with recurrent cervical cancer after salvage radiotherapy performed with a median dose of 54 Gy (19). Murakami et al. found that the 2-year LC of patients who received salvage ISBT after pelvic recurrence was 60% with a median CTV D90 of 68.4 Gy; moreover, a CTV D90 of >65 Gy was associated with favorable local control (20). Yoshida et al. reported that a median CTV D90 of 85.7 Gy when treating patients with uterine cancers (80% of whom had cervical cancer) resulted in a 2-year LC rate of 85% for those who underwent primary radical hysterectomy and 75% for those who received adjuvant postoperative radiotherapy. A CTV D100 of ≥67.1 Gy tended to contribute to a higher LC rate (21). In our study, the 2-year LC was 87.8% after a mean dose of 71 Gy to the tumor volume; as such, our CTV dose was higher than that reported by Kim et al., and our LC rates were more favorable. Our cumulative dose was similar to that used by Murakami et al. while our LC rate was higher than theirs. The LC observed in our study was similar to that reported by Yoshida et al. although our CTV dose was lower than theirs; conversely. Although there are no clear guidelines for a recommended dose, it is generally believed that a higher CTV dose is associated with a higher LC (22). Dose escalation is a key consideration when deve-
oping radiotherapy-related technology, including intensity-modulated radiotherapy and image-guided brachytherapy, and has improved these modalities’ curative effects. The addition of 3D printing technology ought to further enhance the development of image-guided brachytherapy.

We followed the OAR dose constraints recommended by the American Brachytherapy Society. However, there is no clear guideline for patients undergoing reirradiation, and OAR dose constraints are usually determined on a case-by-case basis while maintaining target coverage (6). It has been reported that 4–33% of patients who receive salvage radiotherapy experience grade ≥3 late toxicities (19–21,23,24). However, it is difficult to compare the OAR-associated complications across studies, as many factors including patient selection, radiotherapy interval, and the cumulative dose of past and present irradiation can influence treatment-related toxicities. The single patient who experienced a late grade 3 adverse event in our study signifies a relatively low rate that oncologists will tend to favor.

A proper applicator is critical for successful ICBT. Although single-channel cylinders are the most widely used, multichannel applicators have become popular because of their more flexible dwell positions (25,26) and favorable CTV coverage ability (8,9). Singh et al. (27) used a multichannel cylinder applicator to treat 5 patients with lesions >5 mm; all tumors showed complete clinical and/or radiological responses, and no grade 3–4 toxicities had occurred by 2 years. In addition to the flexible dwell positions, air gaps also significantly affect the CTV coverage during ICBT; it has been reported that a displacement of 1 mm between the applicator and vaginal mucosa decreases the dose to the latter by 7–10% (28,29). Such air gaps can be caused by natural variations in vaginal shapes (30), different surgical techniques, radiotherapy history, and lesion response. Suitable cylinder applicators may not be available for vaginas with large "dog-ear" configurations (14), those carrying large tumors, and those with very narrow cavities (31); as such, patients with large air gaps may require customized applicators (18,32). In contrast to a standard cylinder with a regular shape and neatly arranged catheters, a 3D-printed ICBT applicator with an individualized configuration can fit snugly into the vaginal apex and minimize any air gaps. Furthermore, it can allow the use of curved catheters, and an optimized arrangement according to the CTV (Fig. 2a) (14). Recently, a novel intensity-modulated brachytherapy intracavitary applicator was developed using 3D printing techniques, and proved to be clinically feasible when treating vaginal tumors thicker than 10 mm (33).

In terms of technological advances in ISBT, some studies have found that 3D-printed individual transvaginal applicators can shorten the distance between the tumor and applicator (15,16,34). Our 3D-printed applicator had notable properties: First, unlike previously described counterparts that had regular cylindrical shapes, the profile of our applicator was confirmed to the vaginal shape; as such, it could be embedded in the vaginal cavity and maintain a stable and close connection between the source, tumor, and normal tissues. This applicator with individual configuration guaranteed the accuracy and reproducibility of each implant. Second, the distance between the applicator surface and tumor was as short as possible owing to the non–coplanar implant needle arrangement. A shortened implant depth may improve insertion accuracy and reduce harm to the patient. Third, the needle insertion depth could be precisely measured and determined before ISBT, which rendered the implantation process easier, and faster. Therefore, we did not need to adjust the needle’s position during ISBT, and the entire process was completed in approximately 10 min. While Laan et al. designed an MRI-compatible 3D-printed applicator with curved needle channels suitable for large tumors (35), we used reusable, readily available, CT-compatible, and more economical straight metal needles.

To our knowledge, ours is the first prospective cohort study to evaluate the efficacy and safety of 3D-printed applicators for intracavitary and/or interstitial brachytherapy. However, there were some limitations to this study, including the relatively small sample size, short follow-up time, and confinement to a single center. Furthermore, there are some drawbacks of 3D-printed applicator we should pay attention, including the requirement of experienced gynecologist oncologists and physicists, access to 3D printers, time and money costs, and challenge with training and quality assurance. As such, additional research is required to better define the role of 3D-printed applicators in brachytherapy.

Conclusions

In conclusion, incorporating the 3D-printed applicator into ICBT may be feasible for lesions thickness up to 1 cm by adapting to the vaginal morphology, and enabling individualized catheter arrangement. Moreover, the 3D-printed applicator may reduce complications caused by ISBT by consistently conforming to the vaginal cavity, and allowing for non–coplanar implant needle arrangement. All patients in our study received satisfactory dose distributions and achieved excellent LC with acceptable late toxicities.

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Prior presentation

The data described herein have not been previously presented elsewhere.

Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.brachy.2021.11.004.

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