Original paper

Salvage interstitial brachytherapy based on computed tomography for recurrent cervical cancer after radical hysterectomy and adjuvant radiation therapy: case presentations and introduction of the technique

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Abstract

Purpose: Locally recurring cervical cancer after surgery and adjuvant radiotherapy remains a major therapeutic challenge. This paper presents a new therapeutic technique for such patients: interstitial brachytherapy (BT) guided by real-time three-dimensional (3D) computed tomography (CT).

Material and methods: Sixteen patients with recurrent cervical cancer after radical surgery and adjuvant external-beam radiotherapy (EBRT) were included in this study. These patients underwent high-dose-rate (HDR) interstitial BT with free-hand placement of metal needles guided by real-time 3D-CT. Six Gy in 6 fractions were prescribed for the high-risk clinical target volume (HR-CTV). D_{90} and D_{100} for HR-CTV of BT, and the cumulative D_{2cc} for the bladder, rectum, and sigmoid, including previous EBRT and present BT were analyzed. Treatment-related complications and 3-month tumor-response rates were investigated.

Results: The mean D_{90} value for HR-CTV was 52.5 ± 3.3 Gy. The cumulative D_{2cc} for the bladder, rectum, and sigmoid were 85.6 ± 5.8, 71.6 ± 6.4, and 69.6 ± 5.9 Gy, respectively. The mean number of needles was 6.1 ± 1.5, with an average depth of 3.5 ± 0.9 cm for each application. Interstitial BT was associated with minor complications and passable tumor-response rate.

Conclusions: Interstitial BT guided by real-time 3D-CT for recurrent cervical cancer results in good dose-volume histogram (DVH) parameters. The current technique may be clinically feasible. However, long-term clinical outcomes should be further investigated.

Purpose

Patients with recurrent cervical cancers represent a therapeutic challenge. Choosing an optimal treatment approach for recurrent patients who have undergone radical hysterectomy, adjuvant radiation therapy, and possibly, concurrent chemotherapy is a difficult task. Surgical resection with pelvic exenteration is considered the treatment of choice, but this is associated with a severe treatment-related morbidity [1,2,3]. Moreover, some patients with recurrence of cancer on their pelvic walls are considered inoperable. Re-irradiation by using external beam radiotherapy (EBRT) alone may be difficult for treatment of pelvic recurrences, due to the high risk of complications [4,5].

Another treatment option for patients with recurrent tumors is brachytherapy (BT). Traditional intracavitary BT, using vaginal cylinder and ovoid pairs, may be sufficient for small and superficial tumors [6,7]. However, recurrent cervical cancers with bulky tumors, anatomical distortion, or pelvic wall involvement are difficult to

cure by this technique, due to inadequate target coverage during intracavitary BT [8,9]. Interstitial BT, which has the ability to tailor the dose to the target, and allow for wider tumor coverage, is more advantageous than conventional intracavitary BT [10,11,12,13].

In this study, we introduce real-time interstitial BT guided by three-dimensional (3D) computed tomography (CT) as a treatment approach for recurrent cervical cancer after radical hysterectomy and adjuvant radiation therapy. This new technique may provide a simple and effective clinical treatment modality.

Material and methods

Patients and treatment

We analyzed consecutive patients who experienced isolated pelvic recurrences of cervical carcinoma, and had previously received initial radical surgery and adjuvant EBRT in our department, between December 2014 and May 2016. These patients underwent a systematic examination, including a pelvic MRI (magnetic resonance imaging) (1.5 T; 5 mm sections), a whole-body CT or positron emission tomography – computed tomography (PET-CT), and a gynecological examination. In all cases, either the recurrent tumors were inoperable or the patients refused surgical resection due to the possibility of serious complications. We performed re-irradiation on all these patients by using interstitial BT. A total of six high-dose-rate (HDR) interstitial BT procedures, using ^{192}Ir and implantation with metal needles, were carried out for 4-5 days per fraction. This study and the treatment procedure used for patients was approved by the ethics committee of our hospital. All patients signed informed written consents before undergoing BT.

Needles implantation under real-time 3D-CT guidance

Each needle implantation procedure was performed with the patient under subarachnoid anesthesia in the lithotomy position. Interstitial metal needles (length =
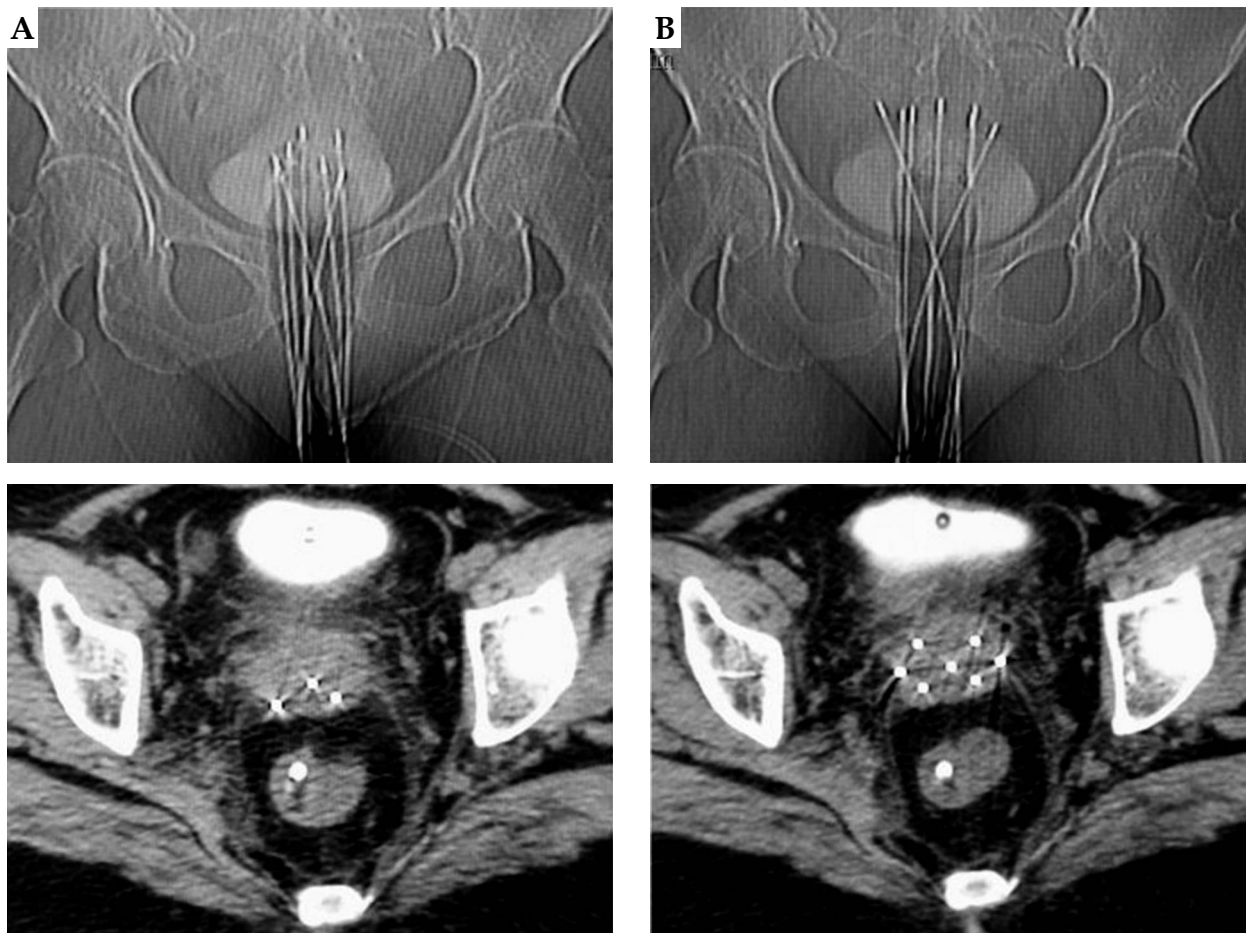

Fig. 1. Representative example of interstitial needle implantation guided by real-time three-dimensional (3D) computed tomography (CT), for recurrent cervical cancer. Five interstitial metal needles were inserted by free-hand placement into the central tumor parallel to the vagina, and two interstitial metal needles were inserted into the distal extension at certain angles to the vagina at a depth of approximately 10 mm, as a preliminary implantation. The direction and depth of the seven needles was adjusted until satisfactory positioning was observed by multiple CT scans. **A)** Preliminary distribution of the needle position on the poster anterior radiograph (upper) and the axial CT image (lower) before adjustment (**B**). Final distribution of the needle position on the poster anterior radiograph (upper) and axial CT image (lower) after adjustment

16 cm, diameter = 1.3 mm, Elekta company, Elekta AB, Stockholm, Sweden) were inserted into the recurrent tumor at a depth of approximately 10 mm as a preliminary implantation, according to T2-weighted MRI and clinical gynecological examination before administration of BT. Specifically, metal needles were placed parallel to the vagina into the central tumor, and some tilted needles at different angles to the vagina were placed into the parametrial or lateral pelvic sidewall extensions, transvaginally. In case of a central tumor with anterior or posterior vaginal wall involvement, the needles were placed into the central tumor parallel to the vagina, but the inserted needles were close to the vaginal wall for optimal coverage of vaginal wall involvement. Vaginal packing was done by using gauze to push aside the rectum and the bladder, and to stabilize the metal needles.

After the initial implantation of needles, the bladder was filled with 50 ml of diluted urografin (dilution, 1 : 20) through a urinary catheter. Next, the process of final needles-implantation guided by real-time 3D-CT was performed. The direction and the depth of the metal needles were adjusted after every CT scan (Philips Healthcare, Eindhoven, The Netherlands, 4 mm slice intervals). Adjustment of needles was performed repeatedly through multiple CT scans until satisfactory distribution was achieved, including accurate needle-insertion in the recurrent tumor, and symmetrical needle-distribution in the tumor at a 1 cm distance from the central axis (Figure 1). Eligible dose-volume histogram (DVH) parameters for the target volume and the organs at risk (OAR) could be acquired with satisfactory distribution of needles in subsequent treatment planning.

Contouring and treatment planning

Using CT images, the high-risk clinical target volume (HR-CTV) that encompassed the volume occupied by the recurrent tumors, and OAR, including the bladder, rectum, and sigmoid, were contoured. Additionally, the T2-weighted MRI images and clinical gynecological examinations were also used as reference for tumor delineation.

The dose for the target volume during BT and the cumulative dose of OAR, obtained by combining previous EBRT and present BT, were all converted to the equivalent dose in 2 Gy (EQD_2) by applying the linear quadratic model using an α/β = 10 for target coverage, and α/β = 3 for normal tissue. The final dose objective was HR-CTV D_{90} (the minimum dose delivered to 90% of the target volume) ≥ 50 Gy EQD_2 for BT; the cumulative D_{2cc} (the minimal dose for the most irradiated 2 cm^3) for the bladder ≤ 90 Gy EQD_2; the cumulative D_{2cc} for the rectum and sigmoid ≤ 75 Gy EQD_2. For BT planning, needle applicators were initially reconstructed and registered to CT images (Oncentra Brachytherapy Treatment Planning System, Elekta). Subsequently, an inverse-planning simulated annealing (IPSA) was used with a 6 Gy prescription dose for the HR-CTV. Dwell positions and dwell weights of the radioactive source were manually adjusted until the dose distribution was optimally matched to our dose requirement when the first treatment plan based on IPSA did not meet the dose requirement (Figure 2).

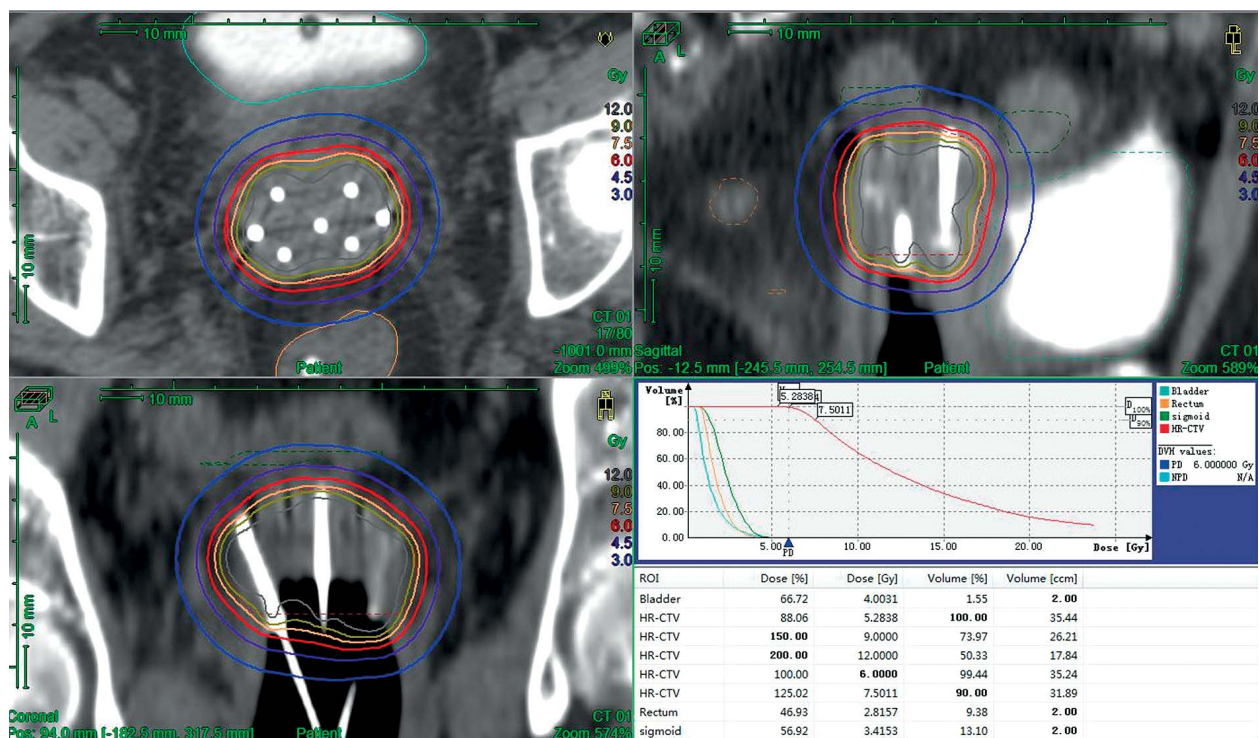| ROI	Dose [%]	Dose [Gy]	Volume [%]	Volume [ccm]
Bladder	66.72	4.0031	1.55	2.00
HR-CTV	88.06	5.2838	100.00	35.44
HR-CTV	150.00	9.0000	73.97	26.21
HR-CTV	200.00	12.0000	50.33	17.84
HR-CTV	100.00	6.0000	99.44	35.24
HR-CTV	125.02	7.5011	90.00	31.89
Rectum	46.93	2.8157	9.38	2.00
sigmoid	56.92	3.4153	13.10	2.00

Fig. 2. Representative treatment planning of interstitial brachytherapy, guided by computed tomography, for recurrent cervical cancer. A dose of 6 Gy was prescribed for high-risk clinical target volume (HR-CTV) by using seven interstitial metal needles inserted to the recurrent tumor

Results

Initial and recurrence tumor characteristics

Sixteen patients with recurrent cervical cancer were enrolled into this study. All patients had undergone radical hysterectomy with pelvic lymph node dissection, and post-hysterectomy adjuvant EBRT with a total dose of 45 Gy administered as 1.8 Gy in 25 fractions, using either the four-field or intensity-modulated radiation-therapy-based 3D-CT. Twelve patients received 5 cycles of weekly cisplatin chemotherapy (dose, 40 mg/m^2) and none of the patients were treated with initial vaginal BT. A summary of tumor characteristics at initial treatment and at the time of recurrence is presented in Table 1.

Dose-volume histogram parameters

Individual recurrent tumor characteristics and DVH parameters are shown in Table 2. Dose-volume histogram parameters related to HR-CTV D_{90} showed that our inter-

Table 1. Initial and recurrent tumor characteristics

Characteristic	Value
Median (y) (range)	52.4 (33-76)
Initial FIGO stage (%)	
IB1	2 (13)
IB2	5 (31)
IIA1	5 (31)
IIA2	4 (25)
Histology (%)	
Squamous cell carcinoma	14 (88)
Adenocarcinoma	1 (6)
Adenosquamous carcinoma	1 (6)
Pathological nodes	
No	6
Yes	10
Recurrence interval (months)	
< 12	9
> 12	7
Sites of recurrence	
Central only	8
Central and pelvic wall	8
OAR involvement	
Bladder	2
Rectum	1

FIGO – International Federation of Gynecology and Obstetrics, OAR – organs at risk

stitial technique resulted in a D_{90} of ≥ 50 Gy in 93.4% patients. The target volume dose was unsatisfactory only for one patient who had central and pelvic wall extensions. High-risk clinical target volume D_{90} for this patient was 45.1 Gy, which could be mainly attributed to dose constraint for the sigmoid (D_{2cc} for sigmoid was 78.9 Gy for this patient). The results of DVH analysis for OAR showed that two patients had a D_{2cc} of > 90 Gy for the bladder, and one patient had a D_{2cc} of > 75 Gy for the rectum, due to involvement of bladder and rectum, respectively.

Table 3 shows the mean DVH parameters derived for all patients and for the patients with different sites of recurrence, respectively. A double-sided t test for two independent samples was used to compare the mean values of DVH parameters between patients with central recurrence and patients with central and pelvic wall involvement. A significant decrease in the mean D_{90} value for HR-CTV was seen from the cases of central recurrence to those with central and pelvic wall involvement ($p = 0.04$). However, no statistically significant differences in the mean D_{100} value for HR-CTV, as well as the average D_{2cc} value for the OAR were noted between the two.

Characteristics of free metal needles

In all, 588 free needles were used for 96 independent interstitial BT procedures, and 95.9% of all implanted needles were useful for treatment. The mean number of free needles was 6.1 ± 1.5 for each application, the mean implantation depth of the needles was 3.5 ± 0.9 cm, and the mean implanted length of the needles beyond the tumor was 0.4 ± 0.3 cm.

Mean time from preliminary insertion of needles to completion of CT scans for each interstitial implantation was 30.9 ± 8.6 minutes, and the mean number of CT scans was 2.3 ± 1.2 for every placement of metal needles.

Complications and tumor response

During real-time 3D-CT guided interstitial needle implantation, one patient with bladder involvement had a bladder perforation, and two patients had slight perforation of the intestine. These patients did not require any additional treatment because no clinical effects were observed. However, the radioactive source could not be placed in the perforated area during subsequent treatment planning. Minimal post-procedure edema occurred in one patient. No case of obvious infection or severe bleeding with requirement for transfusion was founded during or immediately after implantation. At the 3 months' follow-up, one patient had bloody stools, which was resolved by treatment with clyster with styptic, hormones, and antibiotics. No serious complication was observed in the vaginal mucosa.

Initial response, defined as complete remission (CR) and partial remission (PR), was found in 13 (81.3%) patients, according to pelvic MRI findings and clinical gynecological examination at 3 months after interstitial BT. Of all the patients with initial responses, 6 (37.5%) exhibited CR, and 7 (43.8%) PR. The remaining three (18.7%) patients showed stable disease (SD) at 3 months after interstitial BT. No patient experienced progressive disease (PD).

Table 2. Recurrent tumor characteristics and dose-volume histogram parameters for all patients

Patient	Sites of recurrence	HR-CTV volume [cm^3]	OAR involvement	HR-CTV D_{90} [Gy]	HR-CTV D_{100}	Bladder D_{2cc}	Rectum D_{2cc}	Sigmoid D_{2cc}
1	Central only	37.1	None	59.4	33.2	80.2	67.8	73.1
2	Central only	99.3	None	55.1	30.1	89.3	71.6	72.0
3	Central only	85.8	None	52.8	31.8	76.9	72.3	55.8
4	Central only	47.9	None	54.6	26.8	86.0	60.6	73.3
5	Central only	34.6	None	57.2	28.8	83.9	74.5	61.0
6	Central only	43.9	None	50.4	25.1	88.0	70.3	70.1
7	Central only	50.8	None	51.7	26.3	89.1	71.0	74.7
8	Central only	118.7	Bladder	51.9	30.2	94.3	73.9	68.0
9	Central and pelvic wall	60.8	None	50.8	25.9	83.0	64.8	74.0
10	Central and pelvic wall	43.0	None	45.1	22.4	74.0	68.3	78.9
11	Central and pelvic wall	66.1	None	55.4	29.7	87.3	73.8	72.6
12	Central and pelvic wall	35.6	None	50.6	24.7	85.7	68.0	74.1
13	Central and pelvic wall	68.4	None	51.6	25.2	82.1	74.6	65.1
14	Central and pelvic wall	56.5	None	50.3	29.7	88.9	69.1	64.7
15	Central and pelvic wall	125.1	Bladder	52.3	29.6	96.6	73.8	65.6
16	Central and pelvic wall	98.2	Rectum	50.2	24.3	85.0	90.9	70.4

OAR – organs at risk, CTV – clinical target volume, HR – high risk, IR – intermediate risk, HR-CTV – volume was generated based on CT, D_{90} and D_{100} – the minimum dose delivered to 90 and 100% of the target volume, respectively; D_{2cc} – the minimal dose for the most irradiated 2 cm^3
HR-CTV volume was generated based on CT
The dose for the OAR D_{2cc} are the cumulative total from previous external beam radiotherapy and present brachytherapy
Dose values are converted to the equivalent dose in 2 Gy (EQD$_2$; α/β = 10 Gy for tumor, α/β = 3 Gy for normal tissue)

Table 3. Dose-volume histogram parameters for entire patients and the patients with different sites of recurrence, respectively

Parameter	Entire population (n = 16)	Central recurrence (n = 8)	Central and pelvic wall involvement (n = 8)
HR-CTV D_{90}	52.5 ± 3.3 Gy	54.1 ± 3.0 Gy	50.8 ± 2.9 Gy (p = 0.04)*
HR-CTV D_{100}	27.7 ± 3.1 Gy	29.0 ± 2.8 Gy	26.4 ± 2.9 Gy
Bladder D_{2cc}	85.6 ± 5.8 Gy	86.0 ± 5.5 Gy	85.3 ± 6.4 Gy
Rectum D_{2cc}	71.6 ± 6.4 Gy	70.3 ± 4.4 Gy	72.9 ± 8.1 Gy
Sigmoid D_{2cc}	69.6 ± 5.9 Gy	68.5 ± 6.7 Gy	70.7 ± 5.2 Gy

CTV – clinical target volume, HR – high risk, IR – intermediate risk, D_{90} and D_{100} – the minimum dose delivered to 90 and 100% of the target volume, respectively, D_{2cc} – the minimal dose for the most irradiated 2 cm^3
Dose values are expressed as mean ± standard deviation (SD) equivalent doses for 2 Gy fractions (EQD$_2$; α/β = 10 Gy for tumor, α/β = 3 Gy for normal tissue)
*Statistically significant values compared with HR-CTV D_{90} for the patients with central recurrence (statistical significance was considered when p < 0.05)

Discussion

We studied the dosimetric results for treatment of 16 patients with recurrent cervical cancer who had received previous radical surgery and adjuvant EBRT with a novel form of interstitial BT that used free-hand placement of metal needles under guidance of real-time 3D-CT. Cervical cancer with parametrial extensions after surgery often reoccurs [14]. Salvage interstitial BT is an effective treatment strategy [15], especially for inoperable pelvic recurrence. However, the prescribed dose needs to

be strictly limited to avoid serious complications in OAR. A total dose of 40-50 Gy for BT alone might be effective and well tolerated [16]. Nag *et al.* reported the clinical outcomes of using interstitial BT for re-irradiation, with a median dose of 50 Gy for patients with recurrent gynecologic malignancies [17]. This study showed a 5-year local control of 54%. In the current study, a HR-CTV D_{90} of ≥ 50 Gy produced excellent results in > 93% of patients. High-risk clinical target volume D_{90} of the only one patient with central and pelvic wall extension was less than 50 Gy. This can be attributed mainly to dose constraint of the sigmoid. A compromise on the actual delivered HR-CTV dose in this patient had to be done in order to avoid potential radiation-related intestinal perforation. Dose constraints for OAR, with $D_{2cc} \leq 90$ Gy for the bladder, and $D_{2cc} \leq 75$ Gy for the rectum and sigmoid, were recommended by the American Brachytherapy Society (ABS) [18]. In this study, D_{2cc} for OAR in all patients reached 43.2 Gy EQD_2 because of prior pelvic irradiation. Resultantly, for the present protocol of interstitial BT, D_{2cc} for the bladder of ≤ 46.8 Gy EQD_2, and D_{2cc} for the rectum and sigmoid of ≤ 31.8 Gy EQD_2 were decided. It was important to consider the cumulative EQD_2 of OAR D_{2cc}, combining previous EBRT and present BT, because this was a setting for re-irradiation. Our results indicate that the cumulative EQD_2 of OAR D_{2cc} were generally eligible, except in two patients with bladder involvement, one patient with rectum involvement, and one patient with adherence of the sigmoid to the tumor. Although the mean HR-CTV D_{90} of patients with central and pelvic wall involvement was poorer than that of the patients with central recurrence, it can be mainly attributed to the difficulty in distributing needles effectively in the distal tumor; the mean HR-CTV D_{90} for these patients with central and pelvic wall involvement still reached 50 Gy. Our current clinical experience suggests that this technique has the potential to ensure relatively satisfactory dose-coverage to the HR-CTV, and reduce the irradiated dose of OAR in patients with recurrent cervical cancer.

Traditionally, interstitial BT for recurrent cervical cancer was performed using the classic transperineal interstitial applicators, including Syed-Neblett butterfly template [19,20] and Martinez Universal Perineal Interstitial Template (MUPIT) (Varian Medical Systems, Inc., Palo Alto, CA, USA) [9,21]. Limitations of both these techniques include the following: inaccuracy of needle positioning resulting from a long distance between the template and the tumor, leaving the applicators in place for a few days after implantation, and high risk of complications due to the need for multiple needles.

Free-hand placement of needles is conventionally used for recurrent tumors in many centers. However, accurate free-hand placement is difficult without guidance by real-time images. Guidance by real-time 3D-CT may overcome the shortcomings of traditional free needles. In the present study, real-time 3D-CT guided placement of the needles is performed, to ensure proper needle-positioning for effective target dose coverage. It is the most important procedure for adjusting the direction and depth of metal needles repeatedly, until satisfactory results are obtained through multiple CT scans. In our clinical experience, the

metal needles parallel to the vagina as well as at different angles to the vagina were used, according to various case scenarios of recurrence. Typically, the needles did not need to be inserted into the vaginal wall involvement but close to it; greater angulation of vagina and depth of needles were required in case of severe lateral involvement. Two experienced gynecologic radiation oncologists performed the entire process of needle implantation. Real-time 3D-CT guidance of the free needles provides some advantages, including flexibility and accuracy in needle positioning.

In the present study, more than 95% of all inserted needles were used for BT treatment. This indicates great efficiency of needles in performing dose-coverage of the target volume. The mean number of needles needed for each BT was significantly fewer than that required in a previous study, in which a median of 14 (range, 8-22) interstitial needles had been implanted using MUPIT applicator [22]. Undoubtedly, risks for complications, such as bleeding, increase proportionally with the number of needles. Therefore, this real-time CT guided method of needle implantation may present lower risks for patients than the classic transperineal interstitial method. Mean time of metal needle implantation in this study were relatively short, indicating the high efficiency and procedural simplicity of this technique. In addition, the metal needle is reusable and is available in most centers; this suggests that our technique is low-cost, easy to spread, and especially helpful for departments with limited resources.

The risk of complications such as perforation, bleeding, and infection for interstitial BT, during or immediately after implantation, may be inevitable [23,24,25]. In this study, a clinically insignificant bladder perforation was found in one patient with bladder involvement. Moreover, intestine perforation without any clinical effect occurred in other two patients. Our technique shows a low rate of perforation during implantation, which could be attributed to the use of real-time CT guidance. In our clinical practice, needle implantation is always performed cautiously with an adjustment of less than 1 cm depth after every CT scan to reduce occurrence of perforation-related complications. Incidence rate of post-procedure edema was low, probably because the number of free needles was low for each BT, and needles were inserted transvaginally, not transperineally. Slight bleeding often occurred due to the insertion of metal needles. However, as the needles were very thin, gauze padding was sufficient to resolve the bleeding.

At the 3 months' follow-up, we diagnosed treatment-related rectum morbidity, but during later follow-ups, the adverse effect had been resolved. The 3 month tumor-response rate was excellent; initial response was more than 80%. These results indicate that our technique was well tolerated by patients and exhibited an excellent initial curative effect.

Conclusions

Salvage interstitial BT with placement of free needles, under real-time 3D-CT guidance, is a particularly appealing treatment option for inoperable pelvic recurrence of

cervical carcinoma after radical hysterectomy and pelvic irradiation. However, the long-term curative effect and late toxicities of the current technique need to be evaluated further in future studies.

Disclosure

Authors report no conflict of interest.

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