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Dosimetric comparison between the use of insertion needles and Fletcher applicator in brachytherapy for cervical cancer

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► ***Original article***

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ABSTRACT

Background: To investigate the difference between CT-guided three-dimensional brachytherapy using insertion needles and Fletcher applicator brachytherapy. ***Methods and Materials:*** Ninety-three patients with cervical squamous cell carcinoma were included. Insertion needle or Fletcher applicators were used depending on tumor conditions. The target volume, target and organs at risk (OAR) dose, and treatment-related complications, in patients receiving the different brachytherapy techniques were compared. ***Results:*** The mean volume of the high-risk clinical target volume (HR-CTV) and intermediate-risk clinical target volume (IR-CTV) in the Fletcher applicator group were smaller compared with the insertion needle group ($P<0.05$). The mean values of D90 per fraction of the HR-CTV and IR-CTV in the Fletcher applicator group were 101 cGy and 60 cGy lower, respectively, compared with the insertion needle group ($P<0.05$). The mean bladder and rectum D0.1cm^3 per fraction, the mean sigmoid and small intestine D2cm^3 per fraction were statistically different between two groups (all $P<0.05$), the remaining dosimetric parameters were no significant differences ($P>0.05$). Following dose normalization, with the exception of the mean normalized sigmoid D0.1cm^3 per fraction for the received by the OAR in the Fletcher applicator group and the insertion needle group were significantly different ($P<0.05$). There was no serious complication in the brachytherapy of two types applicators. ***Conclusions:*** Brachytherapy using insertion needles enables the treatment of larger target volumes with higher target doses when compared with conventional Fletcher applicator brachytherapy. In addition, the doses received by the OAR are lower, indicating that it is a safe and effective technique that warrants wide adoption.

Keywords: *Insertion needles, Fletcher applicators, cervical cancer,brachytherapy, physical dosimetry.*

INTRODUCTION

Cervical cancer is the common cancer diagnosed in women worldwide, and cervical squamous cell carcinoma accounts for a larger proportion. Adequate radiotherapy dose is the primary factor for improving local control rates among patients with cervical squamous cell carcinoma [(1)]. Two types of radiotherapy are used for the treatment of cervical cancer: external beam radiation therapy and brachytherapy (also known as afterload). Brachytherapy is indispensable as a radical radiotherapy for cervical cancer. It possesses a physical dosimetric advantage, that is, the inverse square law, which enables tumors to receive relatively high doses of radiation while reducing the amount of radiation received by surrounding normal tissues. A dose of 80–100 Gy may be used for primary cervical lesions

without causing severe complications in surrounding normal tissues [2]. However, locally advanced tumors are relatively large and have invaded nearby cervical tissues. Therefore, conventional brachytherapy does not sufficiently cover the target volume, and often leads to uncontrolled tumors or recurrence. Interstitial brachytherapy using insertion needles can improve coverage of the target volume [3], thereby increasing the local control rate, which can translate into increased overall survival [4, 5].

To achieve better outcomes with brachytherapy, the use of the three-dimensional brachytherapy technique is necessary. Currently, the Group Européen de Curiétherapie–European Society for Radiotherapy and Oncology (GEC-ESTRO) recommends the use of magnetic resonance imaging (MRI) to define the dose constraints for target volumes and organs at risk (OAR). MRI provides high-resolution images of soft tissues [6] and allows the accurate delineation of target volumes. However, MRI is expensive, time-consuming, and requires a lot of human and material resources. In most centers, MRI only meets the demands for routine diagnostic tests. In addition, insertion needles are often made of metals, which are incompatible with MRI. This study utilizes computed tomography (CT)-guided brachytherapy, which is a more convenient approach. In addition, CT guidance facilitates the adjustment of insertion needle positions, allowing better dose distribution to the target volumes.

On these bases, we investigated the differences in the doses received by the tumor target volume and OAR between CT-guided three-dimensional brachytherapy using insertion needles and Fletcher applicator brachytherapy. Data presented herein could support the clinical application of this technique. In this study, when comparing the insertion needles and the Fletcher applicator dosimetry, the organ-at-risk dose was innovatively normalized to eliminate the influence of inconsistent prescription dose.

MATERIALS AND METHODS

Clinical characteristics

Between June 2017 and June 2018, 93 patients with cervical squamous cell carcinoma treated at the Department of Oncology of The Affiliated Hospital of Southwest Medical University were included. Patients were treated using either a Fletcher applicator or insertion needles. All patients had a diagnosis of squamous cell carcinoma confirmed viahistopathologic examination at our hospital. The patient characteristics are described in table 1.

Table 1. Clinical characteristics of patients with Fletcher applicator or insertion needles.

Characteristic	Fletcher applicator group (46 patients)	Insertion needle group (47 patients)
Age (y)		
Median (range)	52 (23–70)	50 (32–62)
Staging (%)		
Ib	6(13.0)	4(8.5)
IIA	17(37.0)	15(31.9)
IIB	17(37.0)	15(31.9)
IIIB	6(13.0)	13(27.7)
KPS (%)		
≥80	41 (89.1)	44 (93.6)
≥70, <80	3(6.5)	2 (4.3)
≥60, <70	2(4.4)	1(2.1)

KPS = Karnofsky performance status.

Treatment approach

All patients first underwent intensity-modulated external beam radiotherapy (IMRT) at a total dose of 45Gy/25F to the planning clinical target volume; IMRT performed on a 6EX (Varian) linear accelerator using 6 MV photon beam. For patients with positive lymph nodes revealed by imaging, the dose was increased to 60Gy/25F, with concurrent administration of single-agent cisplatin chemotherapy weekly at 40mg/m^2. Following external beam radiotherapy, Ir^{192} high-dose rate brachytherapy was initiated at a dose of 6Gy/ fraction, 1–2 fractions/week, for a total of 5 fractions. Brachytherapy was performed on

Ir192-source (mHDR, Elekta, Holland), with a microSelectron v3 afterloader (Elekta, Holland).

All patients underwent contrast-enhanced Magnetic Resonance Imaging (MRI, Achieva 3.0T, Philips, Amsterdam, Netherlands) of the pelvis and gynecological examination prior to external beam radiotherapy and brachytherapy to determine the tumor areas. Written informed consent was obtained from all patients before treatment initiation. Patients who were intolerable to pain received spinal subarachnoid anesthesia or sacral anesthesia prior to insertion needle–based brachytherapy, or general anesthesia prior to Fletcher applicator brachytherapy. All patients received diluted iohexol (10 ml added to 1000 ml of water) as a gastrointestinal contrast medium before brachytherapy. Patients also underwent enema and urethral catheterization before treatment. An experienced physician identified the uterine location and tumor features based on gynecological examination and MRI results to determine the accuracy of intrauterine tube placement and to arrange the positions for needle insertion.

Tube placement for insertion needle–based brachytherapy

This trial was registered in the Chinese Clinical Trial Registry (No. ChiCTR-TRC-12002321). All patients adopted a lithotomy position and routine sterilization and draping were performed. A speculum was used to dilate the vagina and expose the cervix and tumor. A metal probe was used to explore the uterus, and an appropriate intrauterine tube was inserted into the uterine cavity based on the depth and angle of the uterine cavity. Abdominal ultrasound was used for guidance if there was difficulty during tube placement. Next, based on the tumor location, metal insertion needles were inserted into the tumor. The positions of the intrauterine tube and insertion needles were fixed with gauzes, and the bladder and rectum were gently pushed to the side. Then, the patient was transported to the CT scanner for CT scanning (LightSpeed Plus 4, General Electric Company, USA), with slice thickness of 0.25cm. High-risk clinical target volume (HR-CTV), intermediate-risk clinical target volume (IR-CTV), and OAR (bladder, rectum, sigmoid, and small intestine) were identified by a radiation oncologist. The insertion depths and angles of the insertion needles were adjusted according to HR-CTV and IR-CTV. When necessary, the number of insertion needles was increased so that the needles were spaced at approximately 1–1.5cm apart on the tumor. This ensured the brachytherapy plan could achieve a satisfactory dose to the target volume while avoiding doses to the OAR. Urinary catheterization was performed according to different patient conditions. The bladder was instilled with 100–150ml of normal saline to appropriately fill the bladder. Enema was performed before treatment to reduce the gas and feces in the sigmoid colon and rectum.

Tube placement for Fletcher applicator brachytherapy

All patients adopted a lithotomy position and routine sterilization and draping were performed. A speculum was used to dilate the vagina and expose the cervix and tumor. A metal probe was used to explore the uterus, and an appropriate intrauterine tube was inserted into the uterine cavity based on the depth and angle of the uterine cavity. Abdominal ultrasound was used for guidance if there was difficulty during tube placement. Next, 2 ovoids were placed in the vagina and fixed with gauzes. The bladder and rectum were gently pushed to the side. Then, the patient was transported to the CT scanner for CT scanning (LightSpeed Plus 4, General Electric Company, USA), with slice thickness of 0.5cm. Similar to the insertion needle–based brachytherapy, the bladder was filled and the gas and feces in the sigmoid and rectum were reduced.

Target volume delineation and treatment planning

CT images were transferred to the Oncentra 4.3 treatment planning software (Elekta Brachytherapy, Veenendaal, The Netherlands) to plan the brachytherapy. The target volumes were delineated on the CT images of both groups of patients, including the high-risk clinical HR-CTV, IR-CTV, and OAR (bladder, rectum,

sigmoid, and small intestine). HR-CTV included the entire cervix and residual tumor during brachytherapy. IR-CTV included all components of HR-CTV and areas with tumor invasion before external beam radiotherapy.

IMRT was used in this study, with a CTV D95 of 45Gy/25F/5w. The prescribed dose for brachytherapy was 6Gy/fraction for a total of 5 fractions. The linear quadratic equation was used to calculate the target and OAR doses based on the equivalent dose delivered in 2Gy fractions (EQD2) in a conventional fractionation schedule. The values of α/β of the tumor and OAR used were 10 and 3, respectively. Based on these parameters, the target doses were as follows: HR-CTV D90: EQD2≥85Gy, bladder $D2cm^3$: EQD2≤90Gy, rectum and sigmoid $D2cm^3$: EQD2≤75Gy, and small intestine $D2cm^3$: EQD2≤65Gy (based on values for endometrial carcinoma).

Repeated optimization of dose curves, using manually/graphically optimized approach of Oncentra 4.3 treatment planning software was implemented to ensure that the prescription dose of curve surrounded HR-CTV and OARs received a lower dose. The dosimetric parameters considered for the treatment plan included the following: V200/V150 – percentage volume of the tumor target receiving 200%/150% of the prescription dose, respectively; D95 (D90) –the dose administered to 95% (90%) of the tumor target volume, $D2cm^3$/$D1cm^3$/$D0.1cm^3$– $2cm^3$/$1cm^3$/$0.1cm^3$ of OAR received dose.

Statistical analysis

Data were analyzed using the independent samples *t*-test. The results are expressed as means ± standard deviations. All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). Analysis items with P<0.05 were considered as statistically significant.

RESULTS

Baseline patient characteristics

The 93 patients were divided according to the 2009 International Federation of Gynecology and Obstetrics cervical cancer staging system into stages IB2–IIIB. There were 46 patients in the Fletcher applicator group and 47 patients in the insertion needle group. Among the patients in the Fletcher applicator group, 6 (13.1%) had stage IB2 disease, 14 (30.4%) had stage IIA disease, 18 (39.1%) had stage IIB disease, and 8 (17.4%) had stage IIIB disease. Among the patients in the insertion needle group, 4 (8.5%) had stage IB2 disease, 15 (31.9%) had stage IIA disease, 16 (34.1%) had stage IIB disease, and 12 (25.5%) had stage IIIB disease. Figure 1 shows the CT images and dose-volume histogram parameters for a patient belonging to the insertion needle group.

Comparisons of target volumes and target doses between the Fletcher applicator group and the insertion needle group

The mean values of D90 per fraction for the HR-CTV and IR-CTV in the Fletcher applicator group were 101 cGy and 60 cGy lower, respectively, compared with those of the insertion needle group (P<0.05). The V200 and V150 of the HR-CTV for the insertion needle group were 7.26% and 12.94% higher, respectively, than the Fletcher applicator group (P<0.05) (table 2).

Comparisons of OAR doses between the Fletcher applicator group and the insertion needle group

For the bladder, there were no statistically significant differences in the mean $D2cm^3$ and $D1cm^3$ per fraction between the two groups (P>0.05), the $D0.1cm^3$ per fraction in the Fletcher applicator group was 32 cGy lower than that in the insertion needle group (P<0.05). For the rectum, there were no significant differences in the mean $D2cm^3$ and $D1cm^3$ per fraction between the two groups (P>0.05), whereas the $D0.1cm^3$ per fraction in the Fletcher applicator group was 48 cGy higher than that in the insertion needle group (P<0.05). For the sigmoid, while the mean $D2cm^3$ per fraction in the Fletcher applicator group was 49 cGy higher than that in the insertion needle group (P<0.05), there were no significant differences in the mean

D1cm^3 and D0.1cm^3 per fraction between the two groups (P>0.05). For the small intestine, there were no significant differences in the mean D1cm^3 and D0.1cm^3 per fraction between the two groups (P>0.05), while the mean D2cm^3 per fraction in the Fletcher applicator group was 41 cGy higher than in the insertion needle group (P<0.05) (table 3).

Comparisons of normalized doses between the Fletcher applicator group and the insertion needle group

To rule out the effects of different target volume doses on the OAR, we divided each OAR dose by the D90 of HR-CTV to obtain the normalized dose ratios, which were used to assess the differences in OAR doses between the groups. Following dose normalization, with the exception the mean normalized sigmoid D0.1cm^3 per fraction, doses received by the OAR in the Fletcher applicator group and the insertion needle groups were significantly different (table 4).

Treatment-related complications during therapy

During the placement of applicators, patients experienced different degrees of pain. For patients who were intolerable to pain, anesthesia was administered to achieve better efficacy without causing notable adverse effects. A total of 6 patients underwent spinal anesthesia in this study. During the procedure, cervical perforation occurred in 2 patients (1 in the Fletcher applicator group and 1 in the insertion needle group). The applicators were later successfully inserted under B-scan ultrasound guidance. The patients did not receive special treatments, and no specific discomfort was reported. CT scans showed that the insertion needles were inserted into the intestines of 3 patients. For these patients, local reference points were marked to restrict radioactive source placement during treatment planning, and the doses were strictly controlled. No patients reported specific post treatment discomfort. There were no notable complications and no special treatment was needed. The insertion needles entered the bladder of 1 patient. The needle placements were adjusted, and the patient had no specific discomfort afterwards and no treatment was needed. Patients in the insertion needle group had different degrees of bleeding after needle withdrawal, and hemostasis was achieved by compression. A small number of patients required vaginal packing to stop bleeding. In 1 patient, extensive bleeding (approximately 200ml) occurred after the insertion needles were withdrawn. The patient received vaginal packing and compression, with concurrent intravenous administration of hemostatic agents and blood transfusion. The bleeding was alleviated after these treatments.

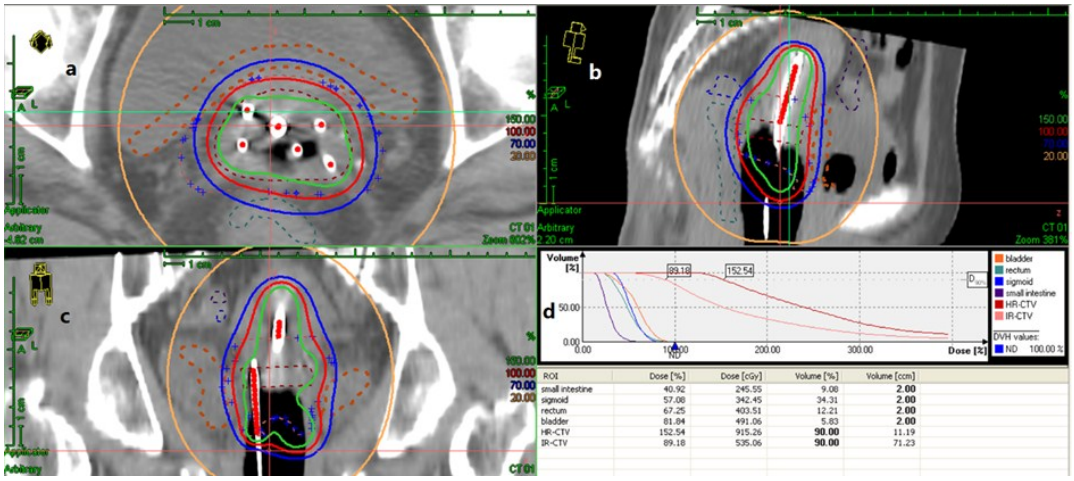

Figure 1. A CT-guided interstitial brachytherapy treatment plan for cervical cancer. **(a)** transverse position **(b)** sagittal position **(c)** coronal position **(d)** DVH diagram The patient's tumor was infiltrating the left side of the uterus. Interstitial brachytherapy used a cervical tube and 5 metal insertion needles. The prescription dose was 6Gy.

Table 2. Comparisons of mean target volumes and target doses between the Fletcher applicator group and the insertion needle group.

	Fletcher applicator group (46 patients)	Insertion needle group (47 patients)	P value
HR-CTV (cm^3)	14.25±7.28	28.61±21.33	<0.001
IR-CTV (cm^3)	61.33±17.37	85.79±39.26	<0.001
HR-CTV D90 (cGy)	594.28±87.63	695.55±82.21	<0.001
IR-CTV D90 (cGy)	374.96±55.03	434.01±69.61	<0.001
HR-CTV V_{200} (%)	27.69±10.84	34.94±12.37	<0.001
HR-CTV V_{150} (%)	51.97±12.93	64.94±12.95	<0.001

HR-CTV = high-risk clinical target volume; IR-CTV= intermediate-risk clinical target volume. V200/V150 = percentage volume of the tumor target receiving 200%/150% of the prescription dose, respectively; D90 = the dose administered to 90% of the tumor target volume.

Table 3. Comparisons of the mean OAR dose per fraction between the Fletcher applicator group and the insertion needle group.

The mean OAR dose per fraction	Fletcher applicator group (46 patients)	Insertion needle group (47 patients)	P value
Bladder D2cm^3 (cGy)	469.66±53.46	484.44±42.97	0.147
Bladder D1cm^3 (cGy)	504.08±90.04	521.32±38.33	0.231
Bladder D0.1 cm^3 (cGy)	584.40±80.36	616.37±63.78	0.022
Rectal D2 cm^3 (cGy)	401.31±80.17	376.66±62.49	0.101
Rectal D1 cm^3 (cGy)	455.35±91.69	431.69±55.78	0.135
Rectal D0.1 cm^3 (cGy)	568.84±125.54	521.15±74.09	0.043
Sigmoid D2 cm^3 (cGy)	228.89±99.99	179.97±115.79	0.032
Sigmoid D1 cm^3 (cGy)	275.80±95.80	241.12±115.63	0.119
Sigmoid D0.1 cm^3 (cGy)	348.32±111.98	341.27±144.09	0.796
Small intestine D2 cm^3 (cGy)	250.25±86.75	209.69±96.87	0.038
Small intestine D1 cm^3 (cGy)	287.104±83.68	252.67±106.35	0.089
Small intestine D0.1 cm^3 (cGy)	366.72±100.59	334.25±158.36	0.245

OAR = organs at risk; D2cm^3/D1cm3/D0.1cm^3– 2cm^3/1cm^3/0.1cm^3 of OAR received dose.

Table 4. Comparisons of the mean normalized OAR doses per fraction between the Fletcher applicator group and the insertion needle group.

The mean normalized doses per fraction for OAR	Fletcher applicator group (46 patients)	Insertion needle group (47 patients)	P value
Bladder D2cm^3/ D90	0.80±0.93	0.70±0.15	<0.001
Bladder D1cm^3/ D90	0.85±0.15	0.75±0.11	<0.001
Bladder D0.1cm^3/ D90	0.98±0.14	0.89±0.16	0.003
Rectal D2cm^3/ D90	0.69±0.15	0.54±0.11	<0.001
Rectal D1cm^3/ D90	0.78±0.17	0.62±0.11	<0.001
Rectal D0.1cm^3/ D90	0.97±0.23	0.75±0.13	<0.001
Sigmoid D2cm^3/ D90	0.39±0.17	0.25±0.16	<0.001
Sigmoid D1cm^3/ D90	0.46±0.16	0.34±0.17	0.001
Sigmoid D0.1cm^3/ D90	0.58±0.19	0.50±0.21	0.071
Small intestine D2cm^3/ D90	0.43±0.17	0.30±0.13	<0.001
Small intestine D1cm^3/ D90	0.50±0.17	0.36±0.15	<0.001
Small intestine D0.1cm^3/ D90	0.63±0.20	0.48±0.22	0.001

D90 = the dose administered to 90% of the tumor target volume; D2cm3/D1cm3/D0.1cm3– 2cm3/1cm3/0.1cm3 of OAR received dose.

DISCUSSION

This study compared the dosimetric outcomes of different brachytherapy techniques used in chemoradiotherapy for cervical squamous cell carcinoma. The results showed that under CT guidance, the dose in three-dimensional brachytherapy using

insertion needles was higher in comparison with conventional three-dimensional brachytherapy using Fletcher applicators. The results of this study demonstrated the superiority of the insertion needle technique with regards to differences in doses to the target volume and protection of normal organs.

Currently, many studies on insertion needle –based brachytherapy have shown that CT-guided brachytherapy using insertion needles is safe and effective [3, 7-9]. This technique delivers significantly increased doses to the target volumes and improved target coverage, with better local control rate and an acceptable toxicity profile. Liu *et al.* [10] Compared the difference between brachytherapy using insertion needles and conventional intracavitary brachytherapy in tumors larger than 5 cm. They found that the mean dose to the HR-CTV increased by 11.2Gy when using the insertion technique, which offered a significant dosimetric advantage. Our study also showed that the mean values of D90 for HR-CTV and IR-CTV increased by approximately 100 cGy when using the insertion technique compared with the Fletcher applicators, our study increased the dose more, but the dose of OARs was the same. Further, our study demonstrated that the sizes of the target volumes in the insertion needle group were larger compared with the Fletcher applicator group, while the doses to OARs were not increased. These findings suggested that compared with Fletcher applicator brachytherapy, the utilization of insertion needles for brachytherapy enabled the treatment of larger tumors and resulted in increased radiation doses to the tumors but not to the OARs. There are currently few reports comparing brachytherapy using the insertion technique and that using Fletcher applicators. A similar study conducted by Dang et al.[11] Also showed that incorporating brachytherapy using the insertion technique could result in higher doses to target volumes ad achieved higher local control rates compared with intracavitary brachytherapy. In addition, there were no differences in adverse effects on the bladder and rectum exerted by the two techniques. Our study showed that the insertion technique compared with the Fletcher applicators, improved dose coverage of target volume for large tumors and/or distal parametrial disease, maybe contributing to improved local control rates.

Most studies evaluating OAR focused on $D2cm^3$ and found that the $D2cm^3$ of the bladder, rectum, and sigmoid colon, were not statistically different when using the insertion or Fletcher applicator techniques [10, 11]. These findings were consistent with the results of the present study. Our study also examined the $D1cm^3$ and $D0.1cm^3$ of these organs and included the small intestines. There were no differences in the mean $D2cm^3$ and $D1cm^3$ per fraction of the bladder and rectum when using either technique, but their $D0.1cm^3$ exhibited differences. This suggested that the insertion technique might increase the maximum dose delivered to the bladder and reduce the maximum point dose delivered to the rectum. The study was also the mean D2cc for the bladder in the insertion technique group was not lower than that in the Fletcher applicator BT group, to ensure the douse of HR-CTV [10]. Whether this is related to the filling status of the bladder or rectum is controversial and remains to be elucidated in future studies [12]. Regarding the sigmoid and small intestine, there were no differences in their mean $D1cm^3$ and $D0.1cm^3$ per fraction when using either technique. However, the mean $D2cm^3$ per fraction was approximately 40 cGy lower when using the insertion technique compared with Fletcher applicators, indicating the superiority of the insertion technique in protecting the sigmoid and small intestine.

In this study, the respective OAR dose was divided by the D90 of HR-CTV to obtain the normalized dose ratio for each OAR. This method enables the comparison of tolerance dose of the OAR and excludes the possibility of high OAR doses due to high doses given to the target volume. This eliminates the incomparable nature of doses and better evaluates the doses received by the OAR when using different techniques. Individual OAR doses without significant differences between the 2 groups were compared after dose normalization. The

results indicated significant differences after applying this method, only with the exception of the mean sigmoid D0.1cm^3 per fraction, which showed no significant difference between the Fletcher applicator and insertion needle groups. These results suggested that the insertion technique did not reduce the maximum point dose delivered to the sigmoid colon. Therefore, attention should be paid to control the dose delivered to the sigmoid among patients receiving brachytherapy using insertion needles.

Although the GEC-ESTRO recommends the use of MRI for the delineation of target volume and OAR, in developing countries with high incidence of cervical cancer, MRI examination is unavailable in some hospitals, especially in primary hospitals. In addition, it is difficult to meet the demands for MRI to treat patients. MRI is expensive and requires a lot of human and material resources, of which many hospitals and patients cannot afford. Our center performs a lot of MRI examinations for patients, and it is difficult to incorporate the use of MRI for patient treatment. Due to these factors, we utilized CT guidance. However, research indicates that under CT guidance, the HR-CTV of the tumor is approximately 10% larger compared with MRI guidance [13]. Compared with MRI, CT overestimates the width of the HR-CTV while underestimating its height and thickness, which lowers the dose delivered to the HR-CTV [14]. However, CT does not yield significantly different results from MRI for delineating normal organs. Therefore, even though there may be discrepancies from the actual situation when using CT-guided brachytherapy, this technique can nonetheless meet the treatment needs of patients in most centers, our study provides clinical support for the development of this technology.

CONCLUSIONS

Under CT guidance, interstitial brachytherapy using insertion needle applicators enables the treatment of larger target volumes with higher target doses when compared with conventional intracavitary brachytherapy using Fletcher applicators. In addition, the doses received by the OAR are lower, indicating that it is a safe and effective technique that warrants wide adoption.

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***Conflicts of interest*:** *Declared none.*

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