



Intensity-modulated radiotherapy combined with intracavitary brachytherapy for locally advanced cervical cancer with uterus didelphys

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ABSTRACT

The purpose of this study was to investigate the clinical application of intensity-modulated radiotherapy combined with intracavitary radiotherapy for locally advanced cervical cancer complicated with uterus didelphys. We retrospectively reviewed the medical records of six patients with locally advanced cervical cancer associated with uterine malformations treated at the National Cancer Center/Cancer Hospital (Beijing, China) between 2015 and 2018. Six cases, including cervical squamous cell carcinoma (n = 3), cervical adenocarcinoma (n = 2), and clear cell adenocarcinoma (n = 1) were identified by pathological diagnosis. Uterine malformation included uterus didelphys (n = 6), with vaginal subseptum (n = 2). Six cases were treated with pelvic intensity-modulated radiotherapy. Four patients received three-dimensional intracavitary brachytherapy based on computed tomography, and two patients received conventional two-dimensional intracavitary brachytherapy. The acute and delayed responses of gastrointestinal and genitourinary toxicities were \leq grade 2 in 5 patients. Five patients achieved clinical complete remission and four patients had no recurrence during the follow-up period. One patient with cervical adenocarcinoma expired due to progression of the disease. The clinical results suggest that advanced cervical cancer associated with uterus didelphys required individual radiotherapy. The use of intensity-modulated radiotherapy combined with three-dimensional intracavitary brachytherapy is recommended in concurrent chemoradiotherapy.

1. Introduction

Cervical cancer is one of the most common malignant gynecological tumors worldwide. The routine treatment of locally advanced cervical cancer is concurrent chemoradiotherapy, including external beam radiation therapy and intracavitary brachytherapy (ICBT) with concurrent chemotherapy.

Uterine malformation is caused by the failure of Müllerian duct fusion or absorption during development, with an incidence of 4–7% in the general population (Chan et al., 2011). Advanced cervical cancer associated with uterine malformation is extremely rare, which required individual treatment, especially for brachytherapy due to anatomical abnormalities.

In recent years, three-dimensional (3D) ICBT based on computed tomography (CT), magnetic resonance imaging, and other image reconstruction techniques has been applied to the treatment of advanced

cervical cancer. Compared with the traditional two-dimensional (2D) ICBT, 3D ICBT facilitates the individualization of treatment (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008; Haie-Meder et al., 2005).

This study retrospectively analyzed the clinical data of six patients with locally advanced cervical cancer associated with uterine malformations treated by intensity-modulated radiotherapy (IMRT) combined with ICBT (3D/2D) in our hospital. In addition, a comprehensive literature review of eight cases with these rare joint conditions was also performed.

2. Materials and methods

2.1. Patients

Between May 2015 and November 2018, six patients with stage

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IIB–IIIB cervical cancer according to the FIGO 2009 staging (cervical squamous cell carcinoma/adenocarcinoma/clear cell adenocarcinoma) were treated with IMRT and ICBT (3D/2D) plus concurrent chemotherapy at our institution. Detailed information is shown in Table 1.

Eight similar reports with these rare joint conditions since 1955 were retrieved from the PubMed database, China National Knowledge Infrastructure, and Wanfang Medical Network database (Gauwerky, 1955; Lee et al., 2000; Loo and Locks, 2010; Platta et al., 2014; Cordoba et al., 2017; Yavas et al., 2017; Ishibashi et al., 2018; Kaneyasu et al., 2019). Detailed information is shown in Table 2.

2.2. IMRT techniques

All patients underwent IMRT according to full-bladder CT-based planning with custom immobilization, intravenous contrast media, and a slice thickness of 5 mm. The clinical target volume (CTV) comprised the cervix, parametrium, uterus, upper third to a half of the vagina, and regional lymph nodes. The upper field border was at the level of the L4/L5 interspace. The caudal field border was at the lower margin of the obturator foramen. The gross tumor volume (GTV) comprised the cervical tumor, enlarged lymph nodes, and metastases in any region. We applied a margin (0–5 mm) around the CTV to create the planning target volume (PTV) (Fig. 1).

The IMRT plans consisted of 3–7 coplanar fields with 6 MV photon beams. The prescription doses to cover 95% of the PTV were 45–50.4 Gy. Each IMRT plan involved 25–28 fractions (over 5 weeks). The daily dose delivered to the PTV ranged 1.5–1.8 Gy.

The organs at risk (OAR) planning constraints were as follows: (1) rectum: maximal dose < 60 Gy, volume receiving > 50 Gy (V_{50}) < 20%; (2) bowel: maximal dose < 52 Gy, V_{40} < 60%; (3) bladder: V_{50} < 20%; and (4) intestines: maximal dose < 52 Gy, V_{40} < 50%.

Table 1

Case reports of patients with uterine malformation treated with brachytherapy in our hospital.

Age (yr)	FIGO stage	Path	Uterine malformation	EBRT	CS	ICBT (reference point; dose rate; applicator; dose)	Toxicity grade GU/GI	Concurrent chemo, regimen	Follow-up		
									Time (months)	Outcome	
1	50	IIIB	SCC	Uterus didelphys with vaginal subseptum	IMRT: 95% PTV 45 Gy/1.8 Gy/25 fr; 95% PTV 55 Gy/2.2 Gy/25 fr	N	HDR; 1 tandem + 1 flexible intrauterine catheter in each side of the uterine + 2 ovoids ± 1 interstitial needle; HR-CTV 20 Gy (5 Gy × 4)	2/1	w CDDP, 40 mg/m ² × 5	34	NED
2	46	II B	SCC	Uterus didelphys with vaginal subseptum	IMRT: 95% PTV 150 Gy/2.0 Gy/25 fr; 95% PTV 55 Gy/2.2 Gy/25 fr	N	HDR; 1 tandem + 1 flexible intrauterine catheter in each side of the uterine + 2 ovoids ± 1 interstitial needle; HR-CTV 26 Gy (7 Gy × 2 + 6 Gy × 2)	2/2	w CDDP, 40 mg/m ² × 5	20	NED
3	65	IIIB	SCC	Uterus didelphys	IMRT: 95% PTV 50.4 Gy/1.8 Gy/28 fr	N	HDR; 1 tandem + 1 flexible intrauterine catheter in each side of the uterine ± 1 interstitial needle; HR-CTV 24 Gy (6 Gy × 4), HR-CTV 26 Gy (7 Gy × 2 + 6 Gy × 2)	1/1	w CDDP, 40 mg/m ² × 5	59	NED
4	50	IIIB	AD	Uterus didelphys	IMRT: 95% PTV 50.4 Gy/1.8 Gy/28 fr	N	HDR; 1 tandem + 1 flexible intrauterine catheter in each side of the uterine ± 1 interstitial needle; HR-CTV 24 Gy (6 Gy × 4)	2/2	w CDDP, 40 mg/m ² × 6	8	DOD
5	65	IIB	CCC	Uterus didelphys	IMRT: 95% PTV 45 Gy/1.8 Gy/25 fr	N	Point A; 1 tandem in the uterine of tumor side + 2 ovoids; 7 Gy × 4	1/2	w CDDP, 40 mg/m ² × 5	36	NED
6	34	IIIA	AD	Uterus didelphys	IMRT: 95% PTV 150 Gy/2.0 Gy/25 fr; 95% PTV 245 Gy/1.8 Gy/25 fr	N	Point A; 1 tandem in the uterine of tumor side + 2 ovoids; 7 Gy × 5	2/3	w CDDP, 40 mg/m ² × 6	4	DOD

AD, adenocarcinoma; chemo, chemotherapy; BT, brachytherapy; CCC, cervical clear cell carcinoma; CS, WP dose up to the central shield; DOD, died of disease; EBRT, external beam radiation therapy; Ext., extended; FIGO, International Federation of Gynecology and Obstetrics; fr, fraction; GI, gastrointestinal; GTV, gross tumor volume; GU, genitourinary; HDR, high-dose-rate; HR-CTV, high-risk clinical target volume; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiotherapy; L, left; LDR, low-dose rate; LN, lymph node; N, none; NA, not available; NED, no evidence of disease; Path, pathology; RA, point A; PDR, pulsed-dose rate; PTV, planning target volume; R, right; SCC, squamous cell carcinoma; SP, small pelvis; w CDDP, weekly cisplatin; WP, whole pelvis; yr, years.

Table 2

Literature review of eight cases of patients with uterine malformation treated with brachytherapy.

	Age (yr)	FIGO stage	Path	Uterine malformation	EBRT	CS	ICBT (reference point; dose rate; applicator; dose)	Toxicity grade GU/GI	Concurrent chemo, regime	Follow-up Time (months)	Outcome	Author, year
1	34	II	SCC	Uterus didelphys with vaginal subseptum	Point B; SP 3000–6000 r; deep X-ray	N	Point A; 7000 r, LDR; 1588 mgRa; 2 intrauterine tubes + 2 ovoids	–	N	12	NED	(Gauwerky, 1955)
2	45	IIA1	SCC	Uterus didelphys with double vagina	WP 45 Gy/25 fr	N	Modified point A; HDR; 2 tandems + 2 cylinders; 6 Gy × 1, 6.5 Gy × 1	0/1	Unknown	36	NED	(Lee et al., 2000)
3	58	IIA2	SCC	Bicornuate uterus	WP 50 Gy/25 fr	N	Defined point A; LDR; flexible intrauterine catheter (r × 1, 1 × 1) + cylinder; 9 Gy × 2	2/1	w CDDP, 40 mg/m ² × 5	24	NED	(Loo and Locks, 2010)
4	34	IIB	AD	Septate uterus	WP 45 Gy/25 fr, LN boost 9 Gy	N	Point A; HR-CTV HDR; Rotte + 2 ovoids; 5.5 Gy × 5	2/1	w CDDP, 40 mg/m ² × 6	20	NED	(Platta et al., 2014)
5	37	IIIA	AD	Uterus didelphys with vaginal simplex	Ext. field 50.4 Gy/28 fr, GTV 60 Gy/28 fr	N	HR-CTV; PDR; vaginal mold; 20 Gy; 0.5 Gy/h × 40 pulse	1/1	w CDDP, 40 mg/m ² × 5	30	NED	(Cordoba et al., 2017)
6	33	IIB	SCC	Septate uterus	WP 45 Gy/25 fr	N	HR-CTV Dgo; HDR; tandem in the RT side + 2 ovoids; 28 Gy/4 fr	–	w CDDP, 40 mg/m ²	–	–	(Yavas et al., 2017)
7	55	IIIB	SCC	Septate uterus	WP 50 Gy/25 fr	30 Gy	Point A; HR-CTV tandem in the RT side + 2 ovoids; 6 Gy × 4	2/2	w CDDP, 40 mg/m ² × 5	1.5	NED	(Ishibashi et al., 2018)
8	61	IIB	SCC	Uterus didelphys with double vagina	WP 50 Gy/25 fr	40 Gy	Point A; HDR; tandem (I × 3, r × 1) + 2 ovoids; 6 Gy × 4	1/1	w CDDP, 30 mg/body × 6	80	NED	(Kaneyasu et al., 2019)

AD, adenocarcinoma; chemo, chemotherapy; BT, brachytherapy; CCC, cervical clear cell carcinoma; CS, WP dose up to the central shield; DOD, died of disease; EBRT, external beam radiation therapy; Ext., extended; FIGO, International Federation of Gynecology and Obstetrics; fr, fraction; GI, gastrointestinal; GTV, gross tumor volume; GU, genitourinary; HDR, high-dose-rate; HR-CTV, high-risk clinical target volume; ICBT, intracavitary brachytherapy; IMRT, intensity-modulated radiotherapy; L, left; LDR, low-dose rate; LN, lymph node; N, none; NA, not available; NED, no evidence of disease; Path, pathology; RA, point A; PDR, pulsed-dose rate; PTV, planning target volume; R, right; SCC, squamous cell carcinoma; SP, small pelvis; w CDDP, weekly cisplatin; WP, whole pelvis; yr, years.

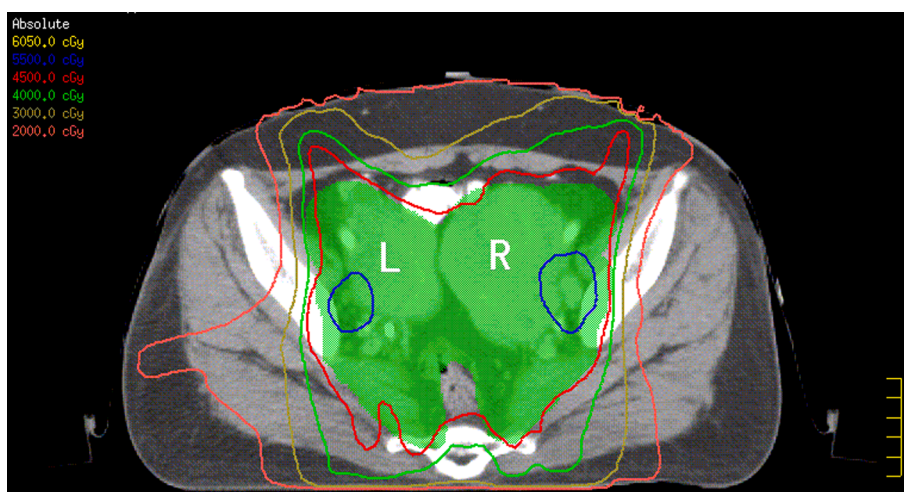


Fig. 1. The green area indicates the PTV. The red shows the 4,500 cGy isodose curve. PTV, planning target volume; L: left uterine; R: right uterine.

fractions) to 0.5 cm beneath the vaginal mucosa was delivered using a vaginal ovoid applicator before initiating ICBT involving a tandem applicator, brachytherapy using a tandem, and either ovoid pair or ring applicators.

2.5. Concurrent chemotherapy

All patients were treated with concurrent weekly cisplatin monotherapy (35–40 mg/m²) for 4–6 weeks.

2.6. Toxicities and follow-up

Acute and late toxicities were evaluated according to the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer toxicity criteria (Du et al., 2012).

Follow-up evaluation included physical examination, levels of squamous cell carcinoma antigen, blood counts, B scan abdominopelvic CT, and/or positron emission tomography-CT scans, if necessary. The initial tumor response was evaluated by an experienced gynecologic oncologist at 3 months following treatment and every 3 months thereafter. Outcome events were measured from the time of treatment

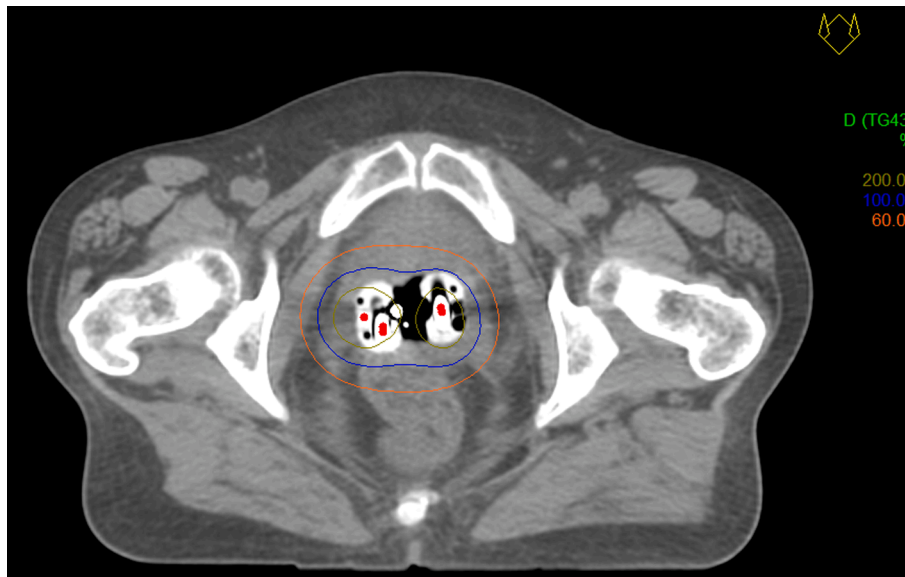


Fig. 2. Diagram of the computed tomography transverse plane after placement of the applicators. The color lines indicate the isodose curve.

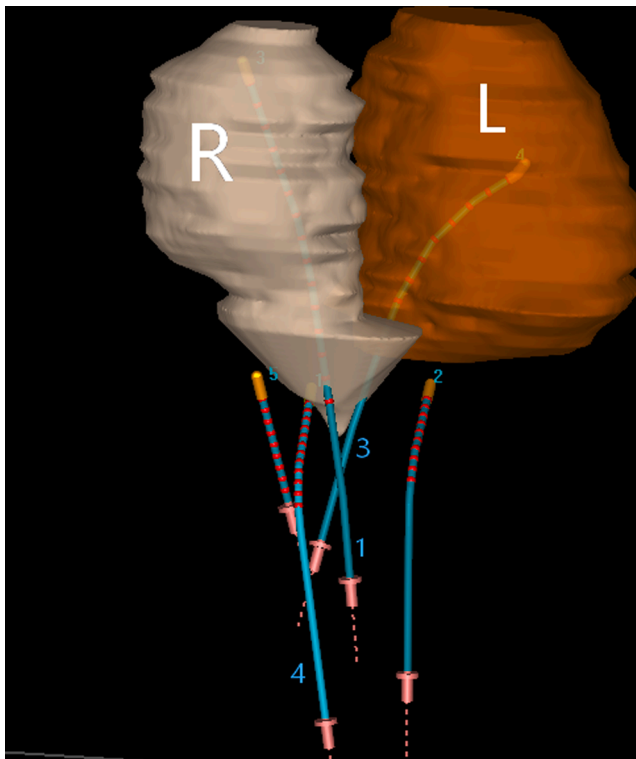


Fig. 3. Schematic diagram of a three-dimensional image reconstruction of the five-channel applicators. L, left uterine; R, right uterine; 1, tandem in the right side of the uterine; 2/4, two ovoids placed in vaginal fornices; 3, flexible intrauterine catheter in the left side of the uterine; 5, interstitial needle inserted in large tumors.

initiation.

3. Results

3.1. Patients

The mean age of the 6 patients was 51.7 years. Among them, two patients were aged 30–50 years and four patients were aged ≥ 50 years.

Pathology revealed cervical squamous cell carcinoma ($n = 3$), cervical adenocarcinoma ($n = 2$), and clear cell carcinoma ($n = 1$). According to the International Federation of Gynecology and Obstetrics staging, one, two, one, and two cases had stages IIa, IIb, IIIa, and IIIb cancer, respectively. Uterine malformation included uterus didelphys ($n = 6$), with vaginal subseptum ($n = 2$).

3.2. Treatment modalities

Weekly treatment with cisplatin $35\text{--}40\text{ mg/m}^2$ was used for concurrent chemotherapy in 6 patients. IMRT was performed in six patients. Four and two cases underwent treatment combined with 3D-ICBT based on CT and traditional 2D ICBT, respectively. All cases were treated with HDR. Applicator placement methods in the uterine cavity included simultaneous catheterization of the bilateral uterine cavity ($n = 4$) and catheterization of the lesion side ($n = 2$).

3.3. Outcomes and toxicity

Of the 6 patients, one had grade 3 genitourinary and grade 2 gastrointestinal toxicity, while the remaining 4 patients had \leq grade 2. Five patients achieved complete clinical remission and one patient expired due to progression of the disease during treatment. Follow-up time ranged 4–34 months. Four patients had no recurrence during the follow-up period. One patient with cervical adenocarcinoma expired at follow-up (8 months).

4. Discussion

Local advanced cervical cancer with uterine malformation is extremely rare, and treatment with concurrent chemoradiotherapy is mostly reported in individual cases. Uterine malformation is mainly classified into uterus didelphys, septate uterus, bicornuate uterus, etc. Approximately 30% of patients with uterine malformation have urinary system malformation; especially, uterus didelphys with unilateral renal agenesis is more common.

Current external beam radiation therapy techniques for locally advanced cervical cancer include traditional pelvic 4FB, IMRT, volumetric modulated arc therapy, etc. Retrospective studies have shown that IMRT is superior to the traditional 4FB technique. Du et al. found a significant difference between the 5-year overall survival rate (71.2% vs. 60.3%, respectively) and 5-year progression-free survival rate (64.9%

vs. 44.3%, respectively) (Veldeman et al., 2008). Veldeman et al. compared the toxicity of IMRT and 4FB through a systematic review, and found that the toxicity of the former was markedly lower than that of the latter (Mundt et al., 2003). Mundt et al. reported that the late gastrointestinal toxicity rate of IMRT \geq grade 2 was significantly lower than that of 4FB (3% vs. 20%, respectively) (Brixey et al., 2002). Similarly, in patients receiving concurrent chemotherapy, Brixey et al. found that the incidence of acute hemotoxic IMRT \geq grade 2 was lower than that of 4FB (31% vs. 60%, respectively) (Chassagne and Tubiana, 1968).

Local advanced cervical cancer complicated with uterine malformation is special, requiring individualized radiotherapy. The appropriateness of IMRT or 4FB for external irradiation is inconclusive, because of the limited number of relevant studies. Theoretically, IMRT is more individualized and precise than 4FB in terms of target area design, local boost dose, and OAR protection. Hence, it is more suitable for radiotherapy of locally advanced cervical cancer with uterine malformation. However, compared with traditional 4FB for the treatment of cervical cancer, IMRT has been widely used clinically only for >10 years, and its planning design and implementation are more complex than those of 4FB, with more interfering factors. Further observations and analyses are warranted to determine whether IMRT is appropriate for the external irradiation of advanced cervical cancer with uterine anomalies.

In this study, seven of the 14 patients were treated with 4FB external irradiation, while the remaining seven underwent IMRT. Acute and delayed gastrointestinal and bladder reactions were \leq grade 2 in 13 patients; only one patient treated with IMRT developed a grade 3 acute bladder reaction. All seven patients exposed to 4FB achieved complete clinical remission and had no recurrence during the follow-up period. Among the seven patients treated with IMRT, six patients achieved complete clinical remission, whereas one patient with cervical adenocarcinoma progressed and expired.

In the 1920s and 1930s, three classical dosimetry systems of ICBT for cervical cancer were formed, namely the Stockholm, Paris, and Manchester systems. Point A determined by the Manchester system is still used as the reference point for prescription. In the 1960s, Chassagne et al. developed the Paris System of ICBT, which used three applicators (one in the cervix and two in the vagina fornix) (Park et al., 2013). At present, the design of applicators for 2D-ICBT against cervical cancer is mostly based on the prototype of the Paris system.

Park et al. reported that ICBT requires precise dose coverage of the target area shape, and the selection of applicators greatly influences this process. Compared with single-channel applicators, multi-channel applicators offer better dose-line coverage of the target area and can reduce the exposure of OARs (Tarn et al., 1988).

Brachytherapy for advanced cervical cancer with uterine malformation, especially uterus didelphys, requires the use of multi-channel individualized applicators. However, due to the limited number of reported cases, there are currently no appropriate applicators for uterine malformation. Placement of the applicators in the bilateral uterine cavity for uterus didelphys is not uniform, and most solutions are based on the classic Paris system of three-channel applicators with one tandem and two ovoids.

Among the eight cases reported in this review, the placement method of the applicator was unknown for one patient. Platta et al. reported that a Rotte-Y tandem and two CT-compatible ovoids were successfully placed in the bilateral uterine cavity and vaginal fornices, respectively, for the treatment of one patient using 3D-ICBT. The Rotte-Y applicator consists of two individual uterine tandems that lock together after placement of the applicator. But insertion of Rotte-Y tandem is challenging (Platta et al., 2014).

Lee et al. reported one case treated with 2D-ICBT by inserted two stainless-steel catheters through the bilateral uterine cavity, with two vaginal cylinders (diameter: 3 cm) on either side of the vaginal septum (Lee et al., 2000). Loo and Locks also reported another case treated with the same approach. They inserted an intrauterine catheter into the right uterine canal and a radio-opaque marker to the left uterine canal with a

vaginal cylinder (diameter: 3 cm). This process was repeated for the opposite canals on the second fraction (Loo and Locks, 2010).

Cordoba et al. reported a case in which the vaginal mold technique was adopted to place the multi-channel applicators for 3D-ICBT (Cordoba et al., 2017). Ishibashi et al. reported using tandem for insertion into the right and left uterine canals separately, with two ovoids implanted on vaginal fornices (Ishibashi et al., 2018). Using the same method of applicator placement, Kaneyasu et al. reported a case treated with 2D-ICBT (Kaneyasu et al., 2019).

Yavas reported a case (the tumor was located predominantly on the right side) treated with 3D-ICBT using tandem for insertion into the right side of the uterus, with two ovoids implanted on vaginal fornices (Yavas et al., 2017).

This study reported six cases treated in our hospital. Four cases were treated with 3D-ICBT, using a tandem and flexible intrauterine catheter in each side of the uterine cavity combined with two ovoids and/or interstitial needles for large tumors. The remaining two cases were treated with 2D-ICBT using tandem in one side of the uterine cavity alternately combined with ovoids on vaginal fornices.

The dose reference point used in traditional 2D-ICBT is the anatomical location. In 1985, point A was defined by the International Commission on Radiation Units as the point 2 cm lateral and superior to the cervical os. There are numerous uncertainties regarding the location of point A due to changes in the anatomical structure of the cervix, especially in cases with uterus didelphys. Tam et al. proposed that for patients with cervical cancer with uterine anomalies, the traditional point A dose would deviate and cannot accurately reflect the radiation dose (Gao et al., 2010).

Lee et al. stated that the use of traditional point A for 2D-ICBT with uterine malformation would result in a markedly wider prescription isodose surface with a risk for overdosage of the midline structures. They used modified A points defined at the midline between the two intrauterine tubes, 2 cm superior to the mean position of the small metallic flanges located at each os cervix (Lee et al., 2000). In 2005, the Groupe Européen de Curiethérapie–European Society for Radiotherapy & Oncology and the American Brachytherapy Society recommended using 3D-ICBT for the treatment of advanced cervical cancer. The DVH parameters of HR-CTV D90 and D1cc, D2cc of rectum, bladder, and other concepts were adopted (Pötter et al., 2006).

Gao et al. retrospectively analyzed the DVH of 2D-ICBT in eight patients. They found that, compared with 3D-ICBT, the cervical dose coverage rate was not satisfactory, and the coverage rate was negatively correlated with the cervical shape and size (Ha et al., 2018). Ha et al. corroborated these findings by retrospectively analyzing 20 cases treated with 3D-ICBT. They found that the dose coverage of the target area was better and exposure the OARs was lower than those noted with 2D-ICBT (Kang et al., 2010). Kang et al. reported that the 3-year local control rate with 3D-ICBT was 98% higher than that of 2D-ICBT in the treatment of advanced cervical cancer, and the incidence of severe radiation toxicity was markedly reduced [24].

In this study, the 3D brachytherapy plan for four patients at our hospital was achieved by contouring the HR-CTV based on the reconstruction CT image; the plan was designed and optimized using the PLATO system. Considering that the fixed point A dose was not completely referenced, the accuracy of the target dose was slightly affected by the anatomical deformity of the uterine. In clinical practice, we realized that 3D-ICBT is more suitable for the treatment of uterine malformations in terms of the accuracy and individualization of dosimetric design and evaluation.

In summary, the use of radiotherapy for advanced cervical cancer with uterine malformation is rare, and there is no standard treatment at present. Individualized radiotherapy is required due to uterine malformation. In concurrent chemoradiotherapy, the use of IMRT combined with 3D ICBT is recommended. Nevertheless, further clinical practice evidence is warranted to verify the present findings.

5. Ethics statement

The studies involving human participants were reviewed and approved by the Cancer Hospital, Chinese Academy of Medical Sciences. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CL and MH conceived the study and wrote the manuscript. NL, JA and SX collected and analyzed the data. YX provided expert clinical knowledge. All authors critically reviewed the manuscript for intellectual content.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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