Brachytherapy for cervical cancer in septate uterus: Dose-volume differences with tandem implant placement in right vs. left uterine canal: A case report

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Abstract. Brachytherapy is a standard treatment modality for locally advanced cervical cancer. In patients with uterine anomalies, the radiation dose to the target volume and the organs at risk can vary depending on the positioning of the brachytherapy tandem implant. However, there have been few reports concerning the use of brachytherapy in patients with uterine anomalies. The present study reports the case of a 55-year-old woman with locally advanced squamous cell carcinoma of the cervix and complete septate uterus. The patient was treated with external-beam radiation therapy, cisplatin chemotherapy, and brachytherapy. Computed tomography-based planning was performed for image-guided brachytherapy with the tandem implant alternately in the right and left uterine canals and using the right and left point A. A comparison of the resulting dose-volume histograms revealed wide variations in the projected dose to the clinical target volume and organs at risk. Tandem implant positioning for brachytherapy was chosen to optimize the dose-volume distribution. At the point of writing, the patient has not experienced local recurrence.

Introduction

The standard treatment for locally advanced cervical cancer is pelvic external beam radiation therapy (EBRT) with concurrent cisplatin chemotherapy and brachytherapy (BT) (1-3). Recently, 3D image-guided brachytherapy (IGBT), which uses computed tomography (CT) or magnetic resonance imaging (MRI) to obtain images of inserted applicators, has come into widespread use (4-6). The present study reports the use of BT in a patient with locally advanced cervical cancer involving a complete septate uterus with right and left uterine canals. Prior to treatment, CT images were obtained with a tandem implant inserted alternately into the right and left uterine canals. A treatment-planning system was used to compare the resulting dose volumes; the uterine canal that was associated with optimal distribution of the dose volume was chosen for BT. There have been only a few reports of BT in patients with uterine anomalies. To the best of our knowledge, this is the first case in which the dose-volume difference between tandem implant placement in the right versus left uterine canal was examined.

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Abbreviations: EBRT, external beam radiation therapy; BT, brachytherapy; IGBT, image-guided brachytherapy

Key words: brachytherapy, cervical cancer, septate uterus, dose volume

Case report

Patient presentation and diagnosis. A 55-year-old woman presented with a 1-month history of general malaise. A high creatinine level of 2.26 mg/dl (normal range, 0.46-0.79 mg/dl) was found upon hematological examination; CT revealed that a cervical tumor was causing bilateral hydronephrosis involving the bilateral ureters. Therefore, bilateral ureteral stents were inserted. Tissue biopsy of the cervical tumor led to a diagnosis of squamous cell carcinoma. MRI revealed that the endometrial cavity was separated into right and left canals by a septum on the cranial side of the cervical tumor (Fig. 1A and B). The septum reached the level of the internal cervical os, indicating a complete septate uterus corresponding to class V of the American Society of Reproductive Medicine classification (7) and class U2 of the European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy classification (8). The patient exhibited hydronephrosis at presentation, indicating disease stage IIIB, according to the uterine cervical cancer staging system of the International Federation of Gynecology and Obstetrics (FIGO) (9). CT and MRI revealed no lymph node metastasis; endoscopy revealed no abnormalities of the mucosa in the rectum or the bladder. Thus, combined EBRT and concurrent chemotherapy with 5 courses

of intravenously administered weekly cisplatin (40 mg/m^2) and high-dose-rate BT were planned with hospitalization. For EBRT, whole-pelvic irradiation, covering the cervical tumor, uterus, parametrium, vagina, and the pelvic lymph node regions as the clinical target volume, was performed using the box technique (6). Irradiation was applied at 2 Gy per fraction five times per week until 30 Gy was reached. Thereafter, a central shield (3 cm wide) was added and irradiation was administered until a total dose of 50 Gy was reached.

Intracanal brachytherapy. A second MRI performed prior to BT revealed that the cervical tumor had shrunk, allowing the tandem insert to be inserted into the right and left uterine canals separately. The right canal lumen was 7 cm long and the left was 6 cm, according to MRI findings. In the BT room, a standard tandem implant (LAR 04-01; Eckert & Ziegler BEBIG, Berlin, Germany) with a 15˚ angle was inserted in the left uterine canal to a distance of 6 cm from the external cervical os under X-ray fluoroscopy; ovoid implants were inserted into the right and left vaginal fornices. Following X-ray imaging, the patient was transferred to a CT room, where CT images with a 2-mm slice thickness were obtained and tandem implant insertion in the left uterine canal was confirmed (Fig. 2A). The patient was returned to the BT room, where a standard tandem implant (LAR 06-01; Eckert & Ziegler BEBIG) with a 30˚ angle was inserted in the right uterine canal at a distance of 7 cm under X-ray fluoroscopy; ovoid implants were placed into the right and left vaginal fornices. After X-ray imaging, CT images were obtained that confirmed tandem implant insertion in the right uterine canal (Fig. 2B). At Nihon University School of Medicine (Tokyo, Japan), high-dose-rate BT was performed with a ^{60}Co remote afterloading system (MultiSource; Eckert & Ziegler BEBIG). The CT images were uploaded to the treatment planning system (HDR plus; Eckert & Ziegler BEBIG), and the high-risk clinical target volume (HR-CTV) and organs at risk (OARs; the rectum and bladder) were contoured according to the Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology guidelines (10,11). The gross tumor volume was determined using pretreatment contrast-enhanced CT images and second MRI images prior to BT for reference. At Nihon University School of Medicine, positional checks for BT are performed with X-ray films alone; Manchester point A (12) was used for treatment planning. On CT, the left and right Manchester point A were set 2 cm superior to the line connecting the superior aspects of the ovoid implants and 2 cm to the right and left of the intrauterine source train. Calculation of the 90% target dose (D_{90}) for HR-CTV, the minimum dose delivered to the highest irradiated 2-cm^3 area ($D_{2\ cm^3}$) for the rectum, and the $D_{2\ cm^3}$ for the bladder per fraction at a dose of 6 Gy to the right and left of point A with the tandem implant inserted into the right and left uterine canals in succession revealed the presence of wide variations in the isodose lines for the OARs (Fig. 3). When the dose-volume histograms of these four treatment plans were compared, there were variations in each item; there was a particularly wide variation in $D_{2\ cm^3}$ for the bladder, ranging from 7.49 to 12.41 Gy per fraction (Table I). A total of four irradiations (two irradiations based on the treatment plan at the right point A with the tandem implant inserted into the right uterine canal, which was associated with the lowest dose for OARs, and two irradiations based on the treatment plan at the left point A with the tandem implant inserted into the right uterine canal, which was associated with the highest dose for HR-CTV) were applied at a dose of 6 Gy per fraction. Prior to each BT session, X-ray films were obtained and compared with X-ray images obtained at the time of CT for positional checks, and tandem implant insertion in the right uterine canal was confirmed. To reproduce the treatment plan developed with CT imaging as accurately as possible, the patient's legs were extended during BT in the same manner as during CT imaging. The total dose of EBRT and BT was ~61.76 Gy [2 Gy per fraction-equivalent dose; (EQD2)] for D_{90} for HR-CTV, 61.73 Gy (EQD2) for $D_{2\ cm^3}$ for the rectum and 115.5 Gy (EQD2) for $D_{2\ cm^3}$ for the bladder, with α/β=10 for HR-CTV and α/β=3 for the OARs. The cisplatin dose was reduced to 30 mg/m^2 because of renal function impairment, as was administered once a week for five courses. As acute complications, grade 2 diarrhea and grade 2 cystitis (according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.03 (13) were noted; which resolved spontaneously. No local recurrence has occurred at the time of writing, 1.5 months after the completion of radiation therapy.

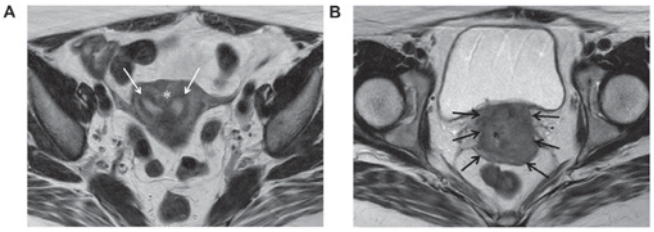

Figure 1. Magnetic resonance imaging axial image depicting (A) complete septate uterus (indicated with an asterisk), with right and left uterine canals (white arrows). (B) A large tumor (black arrows) involving the cervix and bilateral ureters.

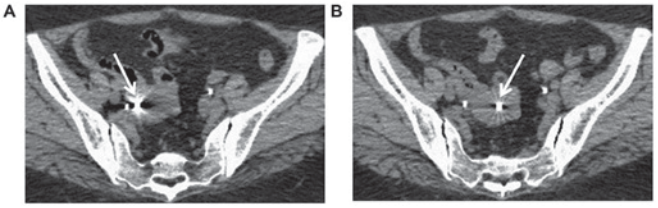

Figure 2. Computed tomography demonstrating (A) tandem implant inserted in right uterine canal (white arrow) and (B) tandem implant inserted in left uterine canal (white arrow).

Discussion

The standard treatment for locally advanced uterine cervical cancer is EBRT with concurrent cisplatin chemotherapy and BT (14,15). For BT, a prescribed dose of irradiation is traditionally applied to the Manchester point A. However, in the case of a large mass, it is possible for irradiation to this point A, administered with a uniform approach, to result in an insufficient dose to the tumor. In recent years, favorable disease control has been achieved with more efficient irradiation of cervical tumors using 3D image-guided BT (IGBT) with CT or MRI, instead of a point A prescription (4-6). However, a

Table I. Dose-volume histogram variations for high-risk clinical target volume and organs at risk at a prescribed dose of 6 Gy per fraction at point A.

GrLocation of tandem implant	Point A	HR-CTV D_{90}, Gy	Rectum $D_{2\,cm^3}$, Gy	Bladder $D_{2\,cm^3}$, Gy
Right canal	Right	5.01	4.17	7.49
Right canal	Left	6.85	5.70	10.24
Left canal	Right	4.92	5.06	10.52
Left canal	Left	5.81	5.96	12.41

HR-CTV D_{90}, minimum dose delivered to 90% of the high-risk clinical target volume; $D_{2\,cm^3}$, minimum dose delivered to the highest irradiated 2-cm^3 area.

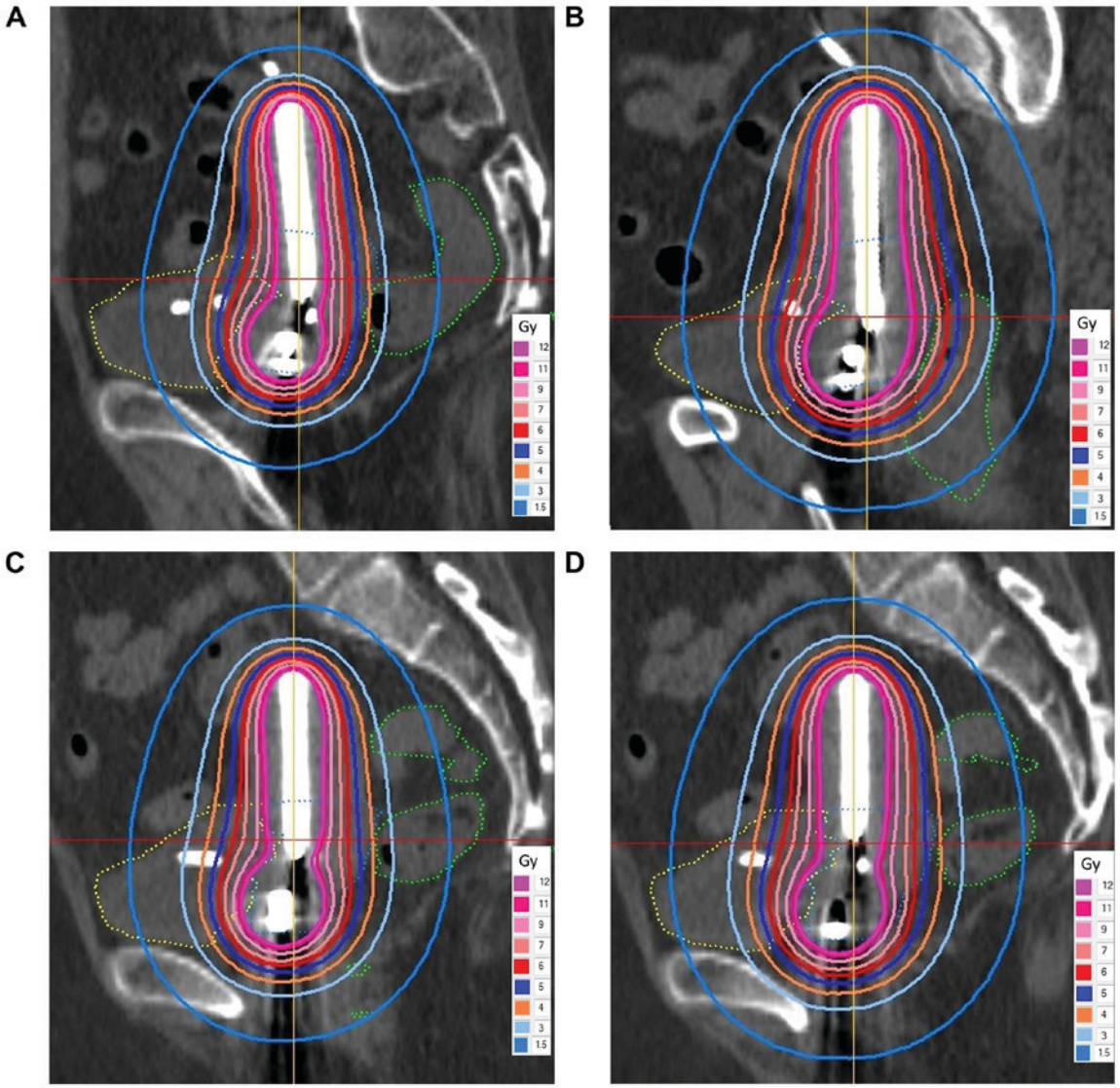

Figure 3. Computed tomography sagittal scan with brachytherapy dosimetry showing isodose lines from 12 to 1.5 Gy. (A) Right point A with tandem implant in the right uterine canal. (B) Left point A with tandem implant in the right uterine canal. (C) Right point A with tandem implant in the left uterine canal. (D) Left point A with tandem implant in the left uterine canal. Images demonstrate anatomical associations between HR-CTV (blue dotted line), rectum (green dotted line), and bladder (yellow dotted line). HR-CTV, high-risk clinical target volume.

2015 nationwide Japanese survey reported that 84% of BT treatment facilities used X-ray films during treatment (16). Until recently, position-checking and treatment-planning at Nihon University School of Medicine were performed using a 2D method that used X-ray film, as CT was not available in the treatment room, and it was therefore difficult to obtain

Table II. Patients with uterine anomaly treated with brachytherapy.

Patient	Age, years	FIGO stage	Histology	Uterine anomaly	EBRT	BT technique and dose	Chemotherapy	RFS, months	(Refs.)
1	45	IIA1	P/D squamous cell carcinoma	Uterus didelphys	Whole pelvis; 45 Gy	2 tandems in the two uterine canals; HDR; 6 Gy x 1, 6.5 Gy x 1; modified point A	Unknown	~36	(17)
2	58	IIA	M/D squamous cell carcinoma	Bicornuate uterus	Whole pelvis; 50 Gy	Vaginal mold and catheter alternately in each uterine canal; LDR; 9 Gy x 2; point A	Cisplatin	24	(18)
3	34	IIB	P/D adenocarcinoma	Septate uterus	Whole pelvis; 45 Gy; metastatic iliac node; additional 9 Gy	2 tandem implants in the two uterine canals and 2 ovoid implants; HDR; 5.5 Gy x 5; point A	Cisplatin	20	(19)
4	37	IIIA	Adenocarcinoma	Uterus didelphys	Whole pelvis and para-aorta; 50.4 Gy; GTV 59.92 Gy	Vaginal mold; PDR; 20 Gy x 1; HR-CTV	Cisplatin	30	(20)
5	55	IIIB	P/D squamous cell carcinoma	Septate uterus	Whole pelvis; 50 Gy	Tandem implants in right uterine canal and 2 ovoid implants; 6 Gy x 4; point A	Cisplatin	1.5	Present case

FIGO, International Federation of Gynecology and Obstetrics; EBRT, external beam radiation therapy; BT, brachytherapy; P/D, poorly differentiated; RFS, relapse-free survival; HDR, high dose rate; PDR, pulsed dose rate; GTV, gross tumor volume; HR-CTV, high-risk clinical target volume; M/D, moderately differentiated; LDR, low dose rate.

CT images with the patient in a proper position and with the applicators inserted properly. A standard fixed dose of 6 Gy per fraction was prescribed to the point A, according to the Japanese Gynecologic Oncology Group 1066 prospective study (15). However, the present patient had a complete septate uterus with left and right uterine canals. Therefore, it was expected that the dose distribution of the point A prescription would vary widely depending upon whether the tandem implant was inserted into the right or left uterine canal. To overcome this challenge, the tandem implant was inserted into the right and left uterine canal by turns and CT images were used to compare the resulting dose-volume histograms. As expected, the D_{90} for HR-CTV and the $D_{2\ cm^3}$ for the OARs varied according to the point A and the location of the tandem implant. The variation was particularly wide in the $D_{2\ cm^3}$ for the bladder. This finding might be explained by changes in the intensity of bladder compression by the uterus according to the position of the tandem implant. This variation in the dose to OARs cannot be assessed with X-ray films alone. The use of CT images in this case allowed us to confirm the optimal uterine canal for tandem implant insertion and the optimal point A.

To the best of our knowledge, there have been only four reported cases (17-20) of BT in patients with uterine anomalies (Table II). No dose-volume histogram comparisons with insertion of the tandem implant into the right versus left uterine canals were reported in any of those cases. Two cases of BT in patients with uterus didelphys have been reported (17,20). In one of these cases, tandem implants were inserted into the two uterine canals simultaneously, and the point A was defined according to the midline between the two tandem implants and was 2 cm superior to the mean position of the os cervix (17). In the other case, a mold was inserted vaginally and a dose was prescribed for HR-CTV according to IGBT (20). One reported case involved a bicornuate uterus. In that case, a mold was inserted vaginally, and from there a radiation source was inserted into one uterine canal, whereas a marker was inserted into the other uterine canal and the position of the marker of point A of the other side was calculated; this process was repeated for the opposite canal (18). The fourth patient had a partial septate uterus. In that case, the Rotte Y applicator, which includes two tandem implants, was used; tandem implants were inserted simultaneously into the two uterine canals and were locked together with two ovoid implants. Point A was then defined as 2 cm superior to the line connecting the superior aspect of the ovoid implants and 2 cm lateral to the line running between and parallel to the two channels of the Rotte Y applicator (19).

Uterine anomalies are found in up to 7% of women. A septate uterus is the most common of these, found in 0.9-2% of women and accounting for 55% of all mullerian anomalies (21,22). Detailed examination of CT and MRI images from patients with uterine cervical cancer reveals that a septate uterus may not be uncommon. When BT is performed in patients with a septate uterus, the optimal dose distribution can be determined without the use of special instruments by comparing dose-volume histograms with the standard tandem implant inserted alternately into the right and left uterine canals. In the present case, the approximate total dose of EBRT and BT was 61.76 Gy (EQD2) for the D_{90} for HR-CTV, 61.73 Gy (EQD2) for the $D_{2\ cm^3}$ for the rectum, and 115.5 Gy (EQD2) for the $D_{2\ cm^3}$ for the bladder. According to a previous study concerning a patient with uterine cervical cancer treated with BRT and BT with central shielding (6), the D_{90} for HR-CTV reached the necessary dose, and the patient exhibited no local recurrence. However, the $D_{2\ cm^3}$ for the bladder was high, necessitating meticulous ongoing follow-up for the possible development of late complications.

The present study shows that when cervical cancer with uterine anomalies is treated with BT, the projected dose and the clinical target volume may vary, putting organs at risk. Where possible, CT based BT should be the preferred course of action.

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Authors' contributions

NI treated the patient and analyzed the patient's data, and was a major contributor in writing the manuscript. TN biopsied the cervical tumor and performed chemotherapy. TM, TA, MS and MO treated the patient. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patient provided written informed consent.

Consent for publication

The patient provided written informed consent.

Competing interests

The authors declare that they have no competing interests.

References

1. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, Rotman M, Gershenson D and Mutch DG: Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 22: 872-880, 2004.
2. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL and Insalaco S: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340: 1144-1153, 1999.
3. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration: Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: A systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 26: 5802-5812, 2008.

4. Ribeiro I, Janssen H, De Brabandere M, Nulens A, De Bal D, Vergote I and Van Limbergen E: Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. Radiother Oncol 120: 447-454, 2016.
5. Sturdza A, Pötter R, Fokdal LU, Haie-Meder C, Tan LT, Mazeron R, Petric P, Šegedin B, Jurgenliemk-Schulz IM, Nomden C, *et al*: Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol 120: 428-433, 2016.
6. Ohno T, Noda SE, Okonogi N, Murata K, Shibuya K, Kiyohara H, Tamaki T, Ando K, Oike T, Ohkubo Y, *et al*: In-room computed tomography-based brachytherapy for uterine cervical cancer: Results of a 5-year retrospective study. J Radiat Res 58: 543-551, 2017.
7. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, müllerian anomalies and intrauterine adhesions. Fertil Steril 49: 944-955, 1988.
8. Grimbizis GF, Gordts S, Di Spiezio Sardo A, Brucker S, De Angelis C, Gergolet M, Li TC, Tanos V, Brölmann H, Gianaroli L and Campo R: The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies. Hum Reprod 28: 2032-2044, 2013.
9. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105: 103-104, 2009.
10. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, Dumas I, Hellebust TP, Kirisits C, Lang S, *et al*: Gynaecological (GYN) GEC-ESTRO working group. Recommendations from Gynaecological (GYN) GEC-ESTRO working group (I): Concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 74: 235-245, 2005.
11. Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, Dumas I, Erickson B, Lang S, Nulens A, *et al*: Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 78: 67-77, 2006.
12. Dean EM, Lambert GD and Dawes PJ: Gynaecological treatments using the Selectron remote afterloading system. Br J Radiol 61: 1053-1057, 1988.
13. National cancer institute common terminology criteria for adverse events (CTCAE) 4.03. Jun 14, 2010.
14. Monk BJ, Tewari KS and Koh WJ: Multimodality therapy for locally advanced cervical carcinoma: State of the art and future directions. J Clin Oncol 25: 2952-2965, 2007.
15. Toita T, Kitagawa R, Hamano T, Umayahara K, Hirashima Y, Aoki Y, Oguchi M, Mikami M and Takizawa K; Cervical Cancer (Vulva Cancer) Committee of Japanese Gynecologic Oncology Group (JGOG): Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: Efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol 126: 211-216, 2012.
16. Ohno T, Toita T, Tsujino K, Uchida N, Hatano K, Nishimura T and Ishikura S: A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: Advances and obstacles. J Radiat Res 56: 897-903, 2015.
17. Lee CD, Churn M, Haddad N, Davies-Humphries J, Kingston RK and Jones B: Bilateral radical radiotherapy in a patient with uterus didelphys. Br J Radiol 73: 553-556, 2000.
18. Loo HW and Locks SM: Squamous cell carcinoma of the cervix: Report of an unusual case of bicornuate bicollis uterus treated with bilateral intracavity brachytherapy. Br J Radiol 83: e143-e146, 2010.
19. Platta CS, Wallace C, Gondi V, Das R, Straub M, Al-Niaimi A, Applegate G and Bradley KA: Cervical brachytherapy technique for locally advanced carcinoma of the cervix in a patient with septate uterus. J Contemp Brachytherapy 6: 76-81, 2014.
20. Cordoba A, Escande A, Comte P, Fumagalli I, Bresson L, Mubiayi N and Lartigau E: Locally advanced adenocarcinoma of the cervix on uterus didelphys: A case report. J Contemp Brachytherapy 9: 71-76, 2017.
21. Bhagavath B, Ellie G, Griffiths KM, Winter T, Alur-Gupta S, Richardson C and Lindheim SR: Uterine malformations: An update of diagnosis, management, and outcomes. Obstet Gynecol Surv 72: 377-392, 2017.
22. Troiano RN and McCarthy SM: Mullerian duct anomalies: Imaging and clinical issues. Radiology 233: 19-34, 2004.