

# Outcomes and dose–volume parameters for computed tomography-based brachytherapy planning for vaginal recurrence of uterine cancer primarily treated with surgery

Keiko Nemoto Murofushi<sup>1,2,\*</sup>, Reiko Tanaka<sup>1</sup>, Ayako Ohkawa<sup>1</sup>, Haruko Numajiri<sup>1</sup>, Toshiyuki Okumura<sup>1</sup>, Hideyuki Sakurai<sup>1</sup>

<sup>1</sup>Faculty of Medicine, Department of Radiation Oncology & Proton Medical Research Center, University of Tsukuba, Tsukuba, 305-8576 Ibaraki, Japan

<sup>2</sup>Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku, 113-8677 Tokyo, Japan

\*Correspondence: [murofushi@pmrc.tsukuba.ac.jp](mailto:murofushi@pmrc.tsukuba.ac.jp) (Keiko Nemoto Murofushi)

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**Background:** This study aimed to evaluate the clinical outcomes and dose–volume parameters of computed tomography CT-based brachytherapy for the vaginal recurrence of uterine cancer after hysterectomy. **Methods:** We evaluated 22 uterine cancer patients treated with CT-based brachytherapy for vaginal recurrence between December 2010 and August 2015. Interstitial brachytherapy (ISBT) was used when the vaginal tumor was thicker than 5 mm and/or located at extended extravaginal tissue, whereas intracavitary brachytherapy was performed if it was 5 mm or thinner. **Results:** Overall, 11 patients had cervical cancer, and 11 had endometrial cancer. The median pretreatment tumor size on magnetic resonance imaging was 17 mm (range, 0–45 mm). Four patients had vaginal recurrence recognized only in the gynecological examination. The primary location of recurrence was the vagina, with extravaginal extension observed in 9 patients. Seventeen patients (77%) received external beam radiotherapy and brachytherapy. ISBT was performed in 12 patients (55%). The median clinical target volume (CTV) D90 was 69.2 Gy (62.6–72.8 Gy). The median D2cc of the bladder, sigmoid, and rectum were 70.2 (63.8–77.6), 37.4 (30.0–43.6), and 52.8 Gy (38.6–63.5 Gy), respectively. Complete response was reached in all patients. The 5-year overall survival rate and local control rate (LC) were 84.8 and 95.5%, respectively. No patient experienced grade  $\geq 3$  complications. **Conclusions:** CT-based brachytherapy has the potential to become an essential treatment for vaginal recurrences of uterine cancer after hysterectomy as it can achieve good LC without increasing the rate of late complications for selected patients with less recurrences.

## Keywords

Vaginal recurrence; High-dose-rate brachytherapy; Intracavitary brachytherapy; Interstitial brachytherapy; Image-guided adaptive brachytherapy

## 1. Introduction

Patients with uterine cancer, other than early-stage disease, such as stage IA (G1), often experience a recurrence in their pelvic region after radical surgery, with the most frequent being vaginal recurrence [1]. Several studies have reported that salvage 2-dimensional (2D) brachytherapy for uterine cancer patients with vaginal recurrence leads to good

local control (LC). However, the incidence of late complications was high in these cases [2, 3]. Computed tomography (CT)- or magnetic resonance imaging (MRI)-based image-guided adaptive brachytherapy (IGABT), which could enable dose evaluation for the clinical target volume (CTV) and organs at risk (OARs), has been increasingly used in recent years [4], and has led to improved LC and low incidence of late complications among patients with locally advanced cervical cancer [5]. However, few studies have reported on the outcomes of IGABT for uterine cancer patients with vaginal recurrence [6, 7].

Thus, this study aimed to evaluate the outcomes and feasibility of IGABT in uterine cancer patients with vaginal recurrence after being managed by surgery.

## 2. Materials and methods

### 2.1 Study design and patients

This retrospective study evaluated 22 uterine cancer patients treated with CT-based IGABT between December 2010 and August 2015 for vaginal recurrence confirmed by biopsy after being primarily managed by surgery. Patients receiving postoperative radiotherapy were excluded from analysis. As an adjuvant treatment after surgery, chemotherapy was administered to patients with either International Federation of Gynecologists and Obstetricians (FIGO) stage III endometrial cancer, FIGO Ib2 or greater cervical cancer. Patients with distant metastases at the time of vaginal recurrence diagnosis were excluded. Vaginal recurrence was defined according to the following criteria: (1) tumor recurrence at the vaginal stump and/or wall without extravaginal extension and (2) tumor recurrence with extravaginal extension, with the tumor continuously invading extravaginal tissue. The extension of the vaginal recurrence was determined by the gynecological examination findings and/or imaging techniques, such as CT and MRI.

## 2.2 Radiotherapy

All patients received high-dose-rate (HDR) brachytherapy. If the patients (1) did not undergo lymph node dissection at the initial surgery, (2) had the tumor invading their extravaginal tissue, or (3) had pelvic lymph node metastasis at the time of vaginal recurrence, radiotherapy consisted of a combination of external beam radiotherapy (EBRT) and HDR brachytherapy.

EBRT was delivered using the three-dimensional conformal technique with a linear accelerator (Clinac iX; Varian Medical System, Palo Alto, CA) with a 10 MV photon beam. The EBRT field included pelvic lymph node regions, such as common, internal and external iliac lymph nodes, as well as obturator lymph nodes. Whole pelvic EBRT was initially administered at 30.0–50.0 Gy in 15–25 fractions using the four-field technique, and a further 0–20 Gy in 0–10 fractions was administered along with the insertion of a 3-cm wide midline block (MB) using the anterior-posterior/posterior-anterior technique.

The first HDR-ICBT or ISBT was performed within 7 days after MB insertion. Brachytherapy was performed using an iridium 192 (<sup>192</sup>Ir) remote afterloading system (MicroSelectron HDR™; Nucletron, Veenendaal, the Netherlands). For all patients, planning was based on CT images of 2.5-mm slice thickness, and dose calculations were performed using Oncentra (Nucletron, Veenendaal, the Netherlands).

The type of brachytherapy was selected according to the initial extent of the disease and the tumor thickness, measured via MRI, CT, or gynecological examination just before brachytherapy. For patients with vaginal stump and/or wall recurrence, intracavitary brachytherapy (ICBT) was selected if the tumor thickness just before brachytherapy was  $\leq 5$  mm. Cylinder application was used for the patients with vaginal wall recurrence (Fig. 1A), while the ovoid application was used for those with recurrence at only the vaginal stump (Fig. 1B). If the tumor was thicker than 5 mm just before brachytherapy and/or extended to extravaginal tissue, interstitial brachytherapy (ISBT) was selected (Fig. 1C). The Martinez Universal Perineal Interstitial Template was used during ISBT. The stainless needles were inserted with CT guide under spinal anesthesia, and irradiation was performed twice a day for 2–3 days. For the patients with recurrence at the vaginal wall, the CTV included the (1) macroscopic tumor identified on gynecological examination, CT, and/or T2-weighted MRI and (2) the entire vagina. If patients had recurrence at the vaginal stump or extravaginally, CTV included the macroscopic tumor only. For the patients with recurrence at the vaginal wall and stump, CTV included the original extent of the disease. For patients with extravaginal recurrence, CTV included the tumor remaining at the time of brachytherapy. The vaginal wall, including the muscular layer, was contoured as the CTV, even if the recurrence was mucosal tumor. For ICBT, a dose of 18–35 Gy in 3–5 fractions was prescribed to a 5-mm depth from the vaginal mucosa. For ISBT, a dose of 18–30 Gy in 3–5 fractions/2–3 days

was prescribed to CTV. CTV D90 was evaluated for ICBT and ISBT.

## 2.3 Chemotherapy

A weekly regimen of cisplatin (40 mg/m<sup>2</sup>) was administered during the radiotherapy period if the patients were treated with EBRT and brachytherapy had cervical cancer as a primary tumor, pelvic lymph node metastasis, and/or a large tumor. Concurrent chemoradiotherapy (CCRT) was not performed in patients with a history of difficult chemotherapy administration or those aged  $\geq 75$  years.

## 2.4 Follow-up

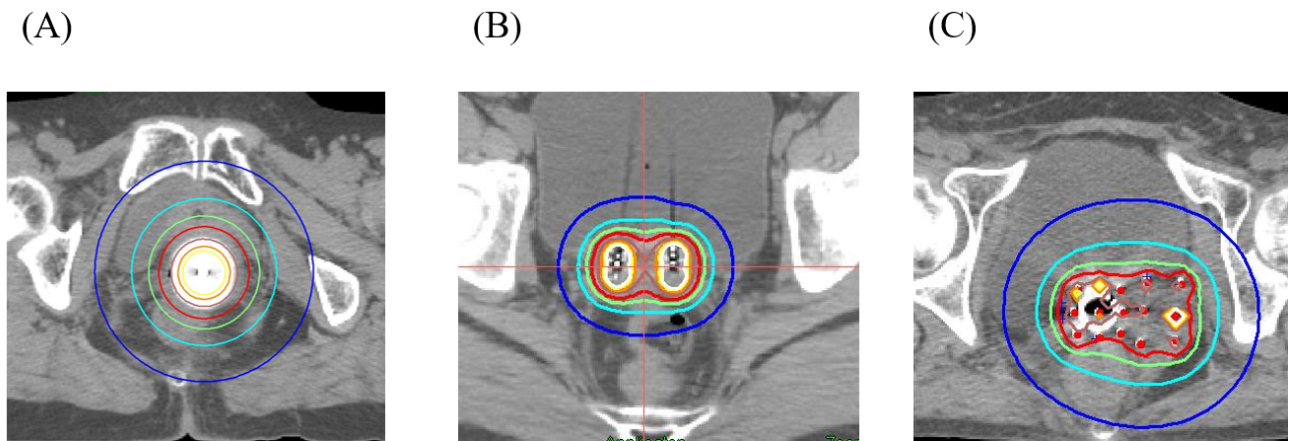
Treatment responses were assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST) at 2–3 months after radiotherapy completion using histopathology and/or MRI [8]. Late adverse events were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. The follow-up comprised of gynecological examinations, cytology, blood tests, and imaging by CT or MRI, every 2–6 months for 5 years.

## 2.5 Statistical analysis

For the dose summation of brachytherapy plus EBRT prior to MB insertion, the equivalent dose in 2 Gy fractions was calculated based on the linear-quadratic model [9]. The tumor dose was calculated using an  $\alpha/\beta$  ratio of 10 Gy. The  $\alpha/\beta$  ratio was assumed to be 3 Gy when calculating the dose-volume parameters of the OAR (i.e., D2cc) [10]. The CTV and bladder volume, CTV D90, and OAR dose-volume parameters were compared between the ICBT and ISBT groups using the Mann-Whitney U test. The 5-year rates of overall survival (OS), disease-free survival (DFS), and LC were estimated using the Kaplan-Meier method. Differences in the outcomes were compared using the log-rank test. All statistical analyses were performed using the SPSS Base System software program version 24.0.0.0 (SPSS, Chicago, IL) and the SAS software version 9.4 (SAS Institute, Cary, NC). Statistical significance was set at  $p < 0.05$ .

## 3. Results

The patient characteristics are shown in Table 1. All patients were operated by laparotomy. Initial International Federation of Gynecologists and Obstetricians stage III endometrial cancer was observed in 2 patients who received total abdominal hysterectomy and bilateral salpingo-oophorectomy as initial surgery and adjuvant chemotherapy. The median tumor size at the time of vaginal recurrence diagnosis and as measured by MRI was 17 mm (range, 0–45 mm). Vaginal recurrence was identified through gynecological examination and was not detected using MRI in 4 of the 22 patients. Overall, 15 patients received radiotherapy alone, and 7 patients received CCRT. There were 12 patients (55%) treated with ISBT and 10 patients (45%) with ICBT. ISBT was administered to all 9 patients with extravaginal recurrence and to 3 of the 13 patients with recurrence at the vaginal stump and/or wall. At the time of recurrence, 3 patients



**Fig. 1.** Dose distributions of (A) ICBT using cylinder application, (B) ICBT using ovoid application, and (C) of ISBT. Isodose line: blue line: 25% of prescribed dose; light blue line: 50%; green line: 75%; red line: 100%; brown line: 150%; orange line: 200%; yellow line: 250%; white line: 300%.

**Table 1. Patient and tumor characteristics.**

Characteristic		Value		
		All	Cervical cancer patients	
			n = 11	Endometrial cancer patients n = 11
Age at the time of vaginal recurrence years, median, (range)		63 (33–78)	59 (33–78)	63 (33–74)
Initial FIGO stage	0	2 (9)	2 (18)	0 (0)
	I	16 (73)	7 (64)	9 (82)
	II	2 (9)	2 (18)	0 (0)
	III	2 (9)	0 (0)	2 (18)
Histology	Squamous cell carcinoma	4 (18)	4 (36)	0 (0)
	AdSqcc or Adenocarcinoma	5 (23)	5 (45)	0 (0)
	Endometrioid adenocarcinoma (G1)	9 (41)	0 (0)	9 (82)
	Others	4 (18)	2 (18)	2 (18)
Initial surgery	Radical hysterectomy	5 (23)	5 (45)	0 (0)
	Modified radical hysterectomy	5 (23)	2 (18)	3 (27)
	Abdominal total hysterectomy	12 (54)	4 (36)	8 (73)
Initial pelvic lymph node dissection	Yes	13 (59)	7 (64)	6 (55)
	No	9 (41)	4 (36)	5 (45)
Location of vaginal recurrence	Vaginal stump and/or wall	13 (59)	6 (55)	7 (64)
	Extravaginal extension	9 (41)	5 (45)	4 (36)
Size of vaginal recurrence mm, mean (range)		17 (0–45)	12 (0–36)	20 (0–45)
Pelvic lymph node metastasis at the time of recurrence	Yes	3 (14)	2 (18)	1 (9)
	No	19 (86)	9 (82)	10 (91)

Abbreviations: FIGO, International Federation of Gynecologists and Obstetricians; AdSqcc, adenosquamous cell carcinoma.

had pelvic node metastasis detected by CT and/or MRI. Table 2 shows the clinical and treatment features of the ICBT and ISBT groups. The size of vaginal recurrence was significantly larger in patients treated with ISBT than those treated with ICBT ( $p < 0.01$ ).

The volume and dose-volume parameters for CTV and OARs are also shown in Table 2. The CTV D90 was significantly higher for the ISBT group than for the ICBT group ( $p < 0.01$ ). Meanwhile, there were no significant differences in the D2cc for the bladder and intestine between the two groups ( $p = 0.79$  and  $p = 0.34$ , respectively). However, the rectum D2cc was significantly lower in the ICBT group than

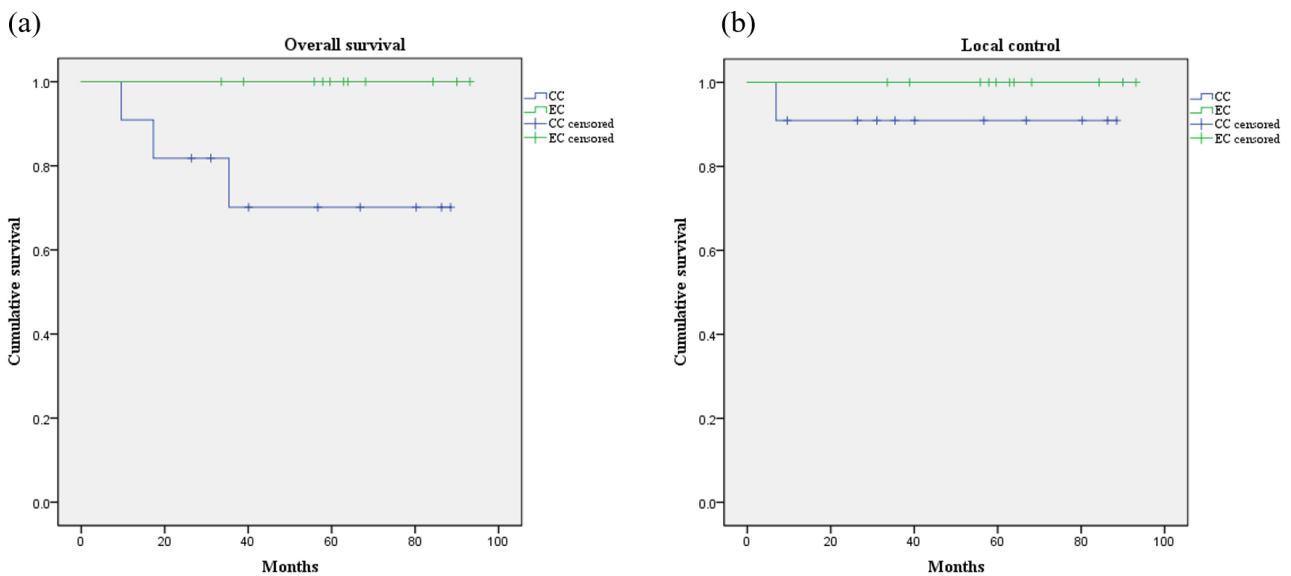
in the ISBT group ( $p < 0.01$ ).

Complete response was reached in all patients. At the time of analysis, pelvic recurrence or distant metastasis were observed in 5 of 7 cervical cancer patients treated with ISBT. In contrast, there was no incidence of pelvic recurrence and distant metastasis in either endometrial cancer patients or cervical cancer patients treated with ICBT. Local recurrence was observed in one cervical cancer patient treated with ISBT at 6.9 months from radiotherapy, despite no residual tumor was observed on MRI and negative cytology was reported 2 months after radiotherapy. Although the sufficient dose (71.8 Gy) was administered to the CTV D90 in this patient

**Table 2. Clinical and treatment features and the volume and dose-volume parameters for CTV and OARs in the ICBT and ISBT groups.**

Clinical/treatment features	ICBT group (n = 10)	ISBT group (n = 12)	p value
Age at the time of vaginal recurrence (years), median (range)	61 (33–74)	65 (33–78)	0.31
Primary disease	Cervical cancer	4	0.69
	Endometrioid cancer	6	
Size of vaginal recurrence (cm), median (range)	0.6 (0.0–1.7)	2.7 (1.2–4.5)	<0.01
Site of vaginal recurrence	Vaginal stump and/or wall	10	<0.01
	Extravaginal extension	0	
Treatment	Radiotherapy alone	9	0.13
	Chemoradiotherapy	1	
EBRT	Yes	5	0.02
	No	5	
Dose of WPI without midline block (Gy), median (range)	15 (0–40)	30 (30–50)	0.01
Volume for CTV (cc), median (IQR)	6.6 (5.8–10.5)	25.7 (16.9–53.4)	<0.01
CTV D90 (Gy), median (IQR)	60.9 (52.9–66.8)	72.8 (71.9–75.7)	<0.01
Bladder D2cc	69.8 (50.3–81.9)	70.2 (66.8–74.8)	0.79
Intestine D2cc	33.6 (6.8–39.3)	36.1 (30.0–41.2)	0.34
Sigmoid D2cc	25.7 (1.7–33)	42.8 (38.9–47.5)	<0.01
Rectum D2cc	36.4 (32.4–45.8)	61.1 (53.8–66.0)	<0.01

Abbreviations: IQR, interquartile range; CTV, clinical target volume; OAR, organs at risk; ICBT, intracavitary brachytherapy; ISBT, interstitial brachytherapy; EBRT, external beam radiotherapy; WPI, whole pelvic irradiation.



**Fig. 2. Kaplan-Meier curve describing overall survival (a) and local control (b).** Blue line: cervical cancer patients; green line: endometrial cancer patients. Abbreviations: CC, cervical cancer patients; EC, endometrial cancer patients.

with local recurrence, a part of the tumor edge adjacent to the pelvic wall enlarged. Inguinal lymph node metastasis and distant metastasis (i.e., lung, bone and peritoneal dissemination) were observed in 1 and 3 patients, respectively. The median follow-up duration was 58.7 months (range, 9.6–93.1 months). The 5-year OS, DFS and LC rates in the overall cohort were 84.8, 77.3 and 95.5%, respectively. Specifically, the 5-year OS rates (Fig. 2a) in cervical cancer patients and endometrial cancer patients were 70.1 and 100%, respectively (cervical cancer vs. endometrial cancer,  $p = 0.06$ ), whereas

the 5-year LC rates (Fig. 2b) were 90.9 and 100%, respectively ( $p = 0.32$ ). There were no significant differences in OS and LC between the cervical cancer and endometrial cancer patients. Finally, the ICBT and ISBT groups reported 5-year LC rates of 100 and 90.9%, respectively (ICBT vs. ISBT,  $p = 0.36$ ).

Grade 2 late rectal complications occurred in 2 patients (9%) who received ISBT. No patients experienced grade  $\geq 3$  late rectal complications and grade  $\geq 2$  late gastrointestinal and urinary complications at the time of analysis.



## 4. Discussion

Data on the outcomes of IGABT for uterine cancer patients with vaginal recurrence are scarce. In this study, IGABT for vaginal recurrence could deliver a sufficient CTV dose, with the OAR doses maintained within those recommended by the American Brachytherapy Society (ABS) [11]. Therefore, an excellent 5-year LC (95.5%) was obtained, while no patients experienced grade  $\geq 3$  late adverse events.

In the dose-volume parameters of this study, CTV D90 in the ISBT group was higher than that in the ICBT group. This could be considering that 5 out of 10 patients who received ICBT underwent ICBT alone. Moreover, the CTV D90 for patients with thinner vaginal recurrence could have been underestimated due to the contouring in the vaginal stump or wall. In the ICBT group, all 10 patients presenting a small CTV obtained local control, in spite of lower dose of CTV D90 compared to those in ISBT group. This may be caused by underestimation of actual delivered dose to CTV. Furthermore, the rectum and sigmoid D2ccs were higher in the ISBT group compared to the ICBT group (both with  $p < 0.01$ ), as all 12 patients treated with ISBT received EBRT. For these ISBT-treated patients, the whole pelvic irradiation dose without MB was higher than that with ICBT ( $p = 0.01$ ). However, for all ISBT-treated patients, the rectum and sigmoid D2ccs were lower than the doses recommended by ABS [11, 12]. Thus, in this study, excellent LC was obtained, while no patients experienced grade  $\geq 3$  late complications.

Salvage 2D planning brachytherapy for endometrial cancer patients with vaginal recurrence after radical surgery has reportedly led to 5-year LC rates of 65–100%, but also with high rates of grade 3 or 4 adverse effects (9–18%) [2, 3, 13, 14]. Over the last two decades, IGABT, which could evaluate the doses for CTV and OARs, had been increasingly preferred over 2D planning brachytherapy (Tan, 2011 [4]; WPI). Previous studies reported that IGABT for vaginal recurrence could deliver higher doses to the CTV while being within the recommended doses for OARs, hence leading to good LC (about 95%) and low rate of grade  $\geq 3$  late severe complications (0–4%) [5, 15].

Whyllie *et al.* [14] reported that large vaginal recurrence predicted poor LC and that 2D planning ICBT led to a 5-year LC of 65% in 49 endometrial cancer patients whose median vaginal recurrence size was 2.0 cm. Furthermore, Ito *et al.* [16] showed that for patients without palpable vaginal recurrence, 2D planning ICBT achieved cumulative local failure of only 10%, compared to the 49 and 63% for median- ( $< 3$  cm), and large- ( $\geq 3$  cm) sized vaginal stump recurrence, respectively. The ABS guideline recommends ISBT for a vaginal tumor thicker than 5 mm [11, 12]. In previous 3D planning brachytherapy reports for vaginal recurrence, 27–74% of the patients received ISBT, and their median size of vaginal recurrence was 1.9–2.6 cm. Moreover, about 95% LC was achieved [6, 7, 15]. Sekii *et al.* [17] also showed that in patients treated with 2D or 3D planning ICBT and 3D planning ISBT, the 4-year LC were 75.3 and 85.7%, respectively. Fur-

thermore, although the patients who received 3D planning ISBT had significantly larger vaginal recurrence than those who received ICBT ( $p < 0.001$ ), there was no significant difference in LC between the ICBT- and ISBT-treated patients ( $p = 0.82$ ). In the current study, ISBT was selected for patients with tumors thicker than 5 mm and/or those with extravaginal location (55%). There was no significant difference between the ISBT and ICBT groups with respect to LC ( $p = 0.36$ ) despite the vaginal recurrence size and the CTV in the ISBT-treated patients being larger than those in the ICBT-treated patients (both  $p < 0.01$ ).

The limitations of this study include its retrospective design and the small sample size. Moreover, bias was present in the patients' clinical background and the dose prescription. Thus, further multicenter studies that include a larger number of patients with uniform clinical background are needed to verify our findings. However, outcomes and dose-volume parameters evaluated in this study could encourage implementing IGABT for vaginal recurrence after being primarily managed by surgery.

## 5. Conclusions

CT-based IGABT based on the initial disease extent and tumor thickness enabled sufficient CTV dose administration, tolerable to organs at risk. CT-based brachytherapy has the potential to become essential to treat the vaginal recurrence of uterine cancer after being managed by surgery as it can achieve good LC without increasing the rate of late complications.

## Author contributions

KNM, AO and HN designed the research study. RT performed the research. TO and HS provided help and advice on the ELISA experiments. RT analyzed. KNM wrote the manuscript. All authors contributed to editorial change in the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This retrospective study was approved by the institutional review board of Tsukuba University (R01-277) and was conducted according to the tenets of the 1975 Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study.

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## Conflict of interest

The authors declare no conflict of interest.

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