

# Salvage computed tomography-guided brachytherapy for patients with postoperative vaginal recurrence of endometrial cancer

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## Research Article

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# Abstract

## Background

This study retrospectively analyzed the treatment outcomes of computed tomography (CT)-guided brachytherapy (BT) for vaginal recurrence after endometrial cancer surgery.

## Methods

Patients with vaginal recurrence after endometrial cancer surgery who underwent CT-guided BT between were retrospectively analyzed. The primary endpoint was local control (LC). Secondary endpoints included regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), overall survival (OS), and late toxicities.

## Results

50 patients were included. External beam radiotherapy (EBRT) with a median total dose of 50 Gy was administered to 30 patients. The median number of BT fractions was five for patients with superficial recurrence and three for those with visible recurrence, respectively. The median total dose delivered to the high-risk clinical target volume (HR-CTV) (equivalent dose in 2 Gy fractions; EQD2) was 70.5 Gy. The median follow-up period was 44.8 months. The 3-year LC, RRFS, DMFS, DFS, and OS rates were 85.6%, 82.9%, 65.1%, 46.0%, and 87.1%, respectively. In the univariate analysis, HR-CTV D90 was a significant prognostic factor for LC ( $p = 0.009$ ). The 3-year LC rate was significantly higher in patients with HR-CTV D90  $\geq 67.3$  Gy than in those with  $< 67.3$  Gy (100% vs. 64.2%). In the multivariate analysis, tumor visibility and postoperative risk classification were significant prognostic factors for DMFS ( $p < 0.011$  and  $p = 0.033$ , respectively).

## Conclusions

CT-guided BT provides favorable local control in patients with vaginal recurrence after endometrial cancer surgery. However, distant metastases remain a major site of failure.

## Clinical trial number

Not applicable.

## Introduction

The first-line treatment for endometrial cancer is generally surgical management. Postoperative adjuvant therapy is administered considering the risk of recurrence determined by postoperative pathological findings. Considering the results of previous clinical trials on adjuvant therapy after surgery [1, 2], adjuvant chemotherapy after surgery has been widely adopted in Japan to reduce the risk of distant metastasis [3]. Although some patients who undergo postoperative radiotherapy (RT) experience vaginal recurrence [2, 4, 5], vaginal recurrence is associated with a

more favorable prognosis than recurrence at other metastasis sites [4, 6]. RT is recommended as a treatment option for postoperative vaginal recurrence of endometrial cancer in patients without a prior history of RT [7].

Postoperative vaginal recurrence is often treated with brachytherapy (BT). Recently, image-guided brachytherapy (IGBT) using magnetic resonance imaging (MRI) and computed tomography (CT) has been increasingly adopted in clinical practice. Several reports have described the outcomes of RT for postoperative vaginal recurrence of endometrial cancer, demonstrating favorable local control rates [8, 9]. However, there are few reports on the use of IGBT for vaginal recurrence after endometrial cancer surgery. Furthermore, until recently, the definition of the high-risk clinical target volume (HR-CTV) for BT in postoperative vaginal recurrence of endometrial cancer remained unclear. Although MRI-guided BT target definition guidelines for recurrent endometrial and cervical tumors were published in 2023 [10], CT-guided BT continues to be used for gynecologic cancers at some institutions.

Therefore, this study aimed to retrospectively analyze the treatment outcomes of CT-guided BT for vaginal recurrence after endometrioid cancer surgery and to establish future treatment strategies.

## Methods

### Patients and eligibility

Patients with vaginal recurrence after surgery for endometrial cancer who underwent BT at least once at our institution between January 2014 and June 2024 were retrospectively analyzed. Patients who underwent external beam radiotherapy (EBRT) before BT at hospitals related to our institution were included. The main eligibility criteria were as follows: age 20 years or more; histological diagnosis of endometrioid carcinoma, clear cell carcinoma, or serous carcinoma; no distant metastases other than para-aortic and inguinal lymph node metastasis at the time of vaginal recurrence diagnosis; and no history of pelvic radiotherapy.

### The detection of vaginal recurrence at imaging examination

Vaginal recurrence identified by visual examination was confirmed by cytology or histological evaluation in the present study. However, recurrent tumors were detectable on imaging examinations, such as CT and MRI, in some patients, but not in others. Because the RT strategy differed considerably according to whether the recurrent tumor was detectable on imaging, patients were categorized as having non-visible recurrence when the tumor was not detectable on imaging and visible recurrence when the tumor was detectable. Therefore, the primary focus of this analysis was the imaging detectability of recurrent tumors.

### External beam radiotherapy

In some patients, a combination of EBRT and BT was administered at the discretion of the clinician. Three-dimensional conformal radiotherapy (3DCRT) or volumetric modulated arc therapy (VMAT) was administered. Depending on the treatment indication, either whole pelvic (WP) irradiation or localized vaginal irradiation was performed. For WP irradiation, the clinical target volume included the vagina, paracolpium, and regional lymph node regions (internal iliac, external iliac, common iliac, and presacral lymph nodes). No patient received concomitant chemotherapy in this study.

## Brachytherapy

High-dose-rate (HDR) brachytherapy was delivered using an iridium-192 remote afterloading system following referral to the Radiation Oncology Department or after completion of EBRT. HDR brachytherapy was performed once or twice weekly for a total of 2–6 fractions, depending on the EBRT dose. BT was performed with patients in the lithotomy position. Regarding intracavitary brachytherapy (ICBT), vaginal cylinder or ovoid applicators were used. In some patients, a combination of ICBT and interstitial brachytherapy (ISBT) was employed when ICBT alone was unlikely to provide adequate dose coverage, such as in cases of bulky tumors and irregularly shaped lesions. Additional needle catheters were inserted via the perineal or vaginal route into regions not expected to be sufficiently covered by ICBT, using transrectal ultrasound guidance under sacral anesthesia, transvenous sedation, and/or local anesthesia. Planning CT images were acquired using a large-bore CT (Aquilion LG; Toshiba, Tokyo, Japan) with a slice thickness of 2.0 mm. No intravenous contrast medium was administered for tumor visualization. Treatment planning was performed using a brachytherapy planning system (Oncentra Nucletron, Veenendaal, Netherlands). The HR-CTV and organs at risk (OARs), such as the bladder, rectum, and sigmoid colon, were contoured. Based on findings from the internal examination and MRI performed before diagnosis and before BT, HR-CTV delineation was modified with reference to the MRI-guided BT target delineation guidelines for recurrent endometrial and cervical tumors involving the vagina [10]. For patients with non-visible recurrence, the HR-CTV was defined as a 3–5 mm thickness extending from the vaginal mucosa, based on previous literature [11]. An example of contouring is shown in Fig. 1a. The bladder, rectum, and sigmoid colon were delineated according to the normal pelvic tissue contouring guidelines of the Radiation Therapy Oncology Group [12]. The methods for setting the dose distribution during BT planning were as follows. First, the prescription dose for ICBT applicators was set at 6 Gy per fraction at a depth of 5 mm from the vaginal mucosa. Second, when combined ICBT/ISBT was performed, dwell times for the inserted needles included in the HR-CTV were set at approximately 3–5s. Third, the dose distribution was manually adjusted to ensure adequate coverage of the recurrent tumor while minimizing the dose to OARs. The RT strategy was determined at the discretion of the radiation oncologists according to the patient's condition, tumor response, and dose constraints for normal tissues. Examples of HR-CTV contouring and dose distribution during brachytherapy for vaginal recurrence are shown in Fig. 1b.

## Evaluation of dose calculation

HR-CTV D90, Bladder D2cc, Rectum D2cc, and Sigmoid D2cc were measured as dose-volume parameters of brachytherapy in the present study. The minimum dose covering 90% of the HR-CTV (HR-CTV D90), expressed as the equivalent dose in 2-Gy fractions (EQD2), was used as the representative tumor dose. Bladder D2cc, Rectum D2cc, and Sigmoid D2cc were defined as the doses delivered to the most highly exposed 2.0 cc of the bladder, rectum, and sigmoid, respectively, and were evaluated as representative doses of brachytherapy for the OARs. For the calculation of the cumulative dose from EBRT and brachytherapy parameters, the EQD2 was calculated using the linear-quadratic dose model [13–15].  $\alpha/\beta$  ratios of 10 Gy and 3 Gy were assumed for tumor tissue and OARs, respectively. The dose constraints for OARs in the combined EBRT and brachytherapy treatment were as follows: Bladder D2cc < 90 Gy, Rectum D2cc < 75 Gy, and Sigmoid D2cc < 75 Gy.

## Follow-up

Patients were followed up every 2–3 months during the first 2 years after RT and every 3–6 months during the subsequent 3–5 years. Vaginal cytopathology, blood examination, and CT imaging were performed as part of

routine posttreatment examinations. If local recurrence was suspected, a biopsy and MRI were performed. When locoregional recurrence or distant metastasis could not be definitively assessed using these examinations, positron emission tomography was performed. Moreover, late toxicities occurring later than 90 days after the initiation of RT were examined during outpatient follow-up visits.

## Endpoints

The primary endpoint was local control (LC). LC was calculated from the start of RT to the date of local recurrence and was censored at the last follow-up for patients without recurrence. Local recurrence was defined as tumor progression confirmed in the vagina or paracolpium. Secondary endpoints included regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), overall survival (OS), and late toxicities. RRFS was measured from the start of RT to the date of pelvic or paraaortic lymph node metastasis. DMFS was measured from the start of RT to the date of distant metastasis. DFS was measured from the start of RT to the date of first relapse or was censored at the last follow-up for patients without relapse. OS was measured from the start of RT to the date of death from any cause and was censored at the last follow-up for surviving patients. Late toxicities were evaluated using the Common Terminology Criteria for Adverse Events, version 5.0. Symptoms associated with post-RT recurrence were not defined as late toxicities.

## Statistical analysis

Differences in patient and treatment characteristics between patients with non-visible and visible recurrence were investigated using the Mann-Whitney U test or the  $2 \times 2$  chi-square test.

LC, RRFS, DMFS, DFS, and OS were estimated using the Kaplan-Meier method. To identify the HR-CTV D90 threshold associated with local control, the cutoff values were determined using the Youden index derived from the receiver operating characteristic (ROC) curve based on local recurrence [16]. Differences in LC, RRFS, DMFS, DFS, and OS between patient subgroups were analyzed using the log-rank test in the univariate analysis. The following variables were evaluated as potential prognostic factors: age, the International Federation of Gynecology and Obstetrics (FIGO) 2023 classification (IA vs other), pathology (endometrioid [EM] G1-2 vs G3, clear cell, serous), postoperative risk classification of endometrial cancer proposed by the Japan Society of Gynecologic Oncology (JSGO) [17], postoperative chemotherapy (yes vs no), interval from surgery to recurrence, tumor visibility (non-visible vs visible), tumor location (vaginal stump vs other vaginal walls) and lymph node metastasis at recurrence. Multivariate analysis was performed using a Cox proportional hazards regression model. To ensure an adequate number of events per variable, multivariate analyses were restricted to endpoints with at least 20 events. Based on previous studies, approximately one variable was included for every 10 events [18, 19]. Factor selection was based on prognostic factors shown in previous studies and factors that were significant in the univariate analysis in our study. We also examined whether correlations existed between selected factors.

All statistical tests were two-sided, and statistical significance was defined as  $p < 0.05$ . Statistical analyses were performed using JMP16 software (SAS Institute, Cary, NC, USA).

## Results

50 patients who underwent salvage CT-guided brachytherapy for patients with postoperative vaginal recurrence of endometrial cancer were included in the present study. Patient and treatment characteristics are shown in Table 1.

Considering the risk of recurrence after surgery, postoperative adjuvant chemotherapy centered on the regimen of paclitaxel plus carboplatin or doxorubicin plus cisplatin was administered to 33 patients. Vaginal tumors were detected on imaging examinations such as CT and MRI in 30 patients (visible recurrence), but were not detected in 20 patients (non-visible recurrence). The proportion of patients with stage IA disease was significantly higher in the non-visible recurrence group than in the visible recurrence group ( $p = 0.035$ ).

Table 1  
Patient Characteristics and Treatment characteristics

| Factor                                                                                                                                                                                                                                                                                         |                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Age                                                                                                                                                                                                                                                                                            | Median 65.5 year<br>(IQR, 60–76 year)        |
| FIGO 2023 at diagnosis                                                                                                                                                                                                                                                                         |                                              |
| IA                                                                                                                                                                                                                                                                                             | 21                                           |
| IB                                                                                                                                                                                                                                                                                             | 13                                           |
| II                                                                                                                                                                                                                                                                                             | 3                                            |
| IIIA                                                                                                                                                                                                                                                                                           | 4                                            |
| IIIB                                                                                                                                                                                                                                                                                           | 5                                            |
| IIIC                                                                                                                                                                                                                                                                                           | 4                                            |
| IVB                                                                                                                                                                                                                                                                                            | 1                                            |
| Histology                                                                                                                                                                                                                                                                                      |                                              |
| EM G1                                                                                                                                                                                                                                                                                          | 21                                           |
| EM G2                                                                                                                                                                                                                                                                                          | 10                                           |
| EM G3                                                                                                                                                                                                                                                                                          | 7                                            |
| Serous or Clear                                                                                                                                                                                                                                                                                | 12                                           |
| Risk classification                                                                                                                                                                                                                                                                            |                                              |
| Low recurrence risk                                                                                                                                                                                                                                                                            | 13                                           |
| Middle recurrence risk                                                                                                                                                                                                                                                                         | 12                                           |
| High recurrence risk                                                                                                                                                                                                                                                                           | 25                                           |
| Postoperative adjuvant chemotherapy                                                                                                                                                                                                                                                            |                                              |
| Yes                                                                                                                                                                                                                                                                                            | 33                                           |
| No                                                                                                                                                                                                                                                                                             | 17                                           |
| Interval from initial surgery to recurrence                                                                                                                                                                                                                                                    | Median 14.5 months<br>(IQR, 8.3–25.3 months) |
| Tumor visibility                                                                                                                                                                                                                                                                               |                                              |
| non-visible recurrence                                                                                                                                                                                                                                                                         | 20                                           |
| visible recurrence                                                                                                                                                                                                                                                                             | 30                                           |
| Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; ICBT = intracavitary brachytherapy; ISBT = interstitial brachytherapy; HR-CTV = high-risk clinical target volume; EQD2 = the equivalent dose in 2 Gy fractions IQR = interquartile range. |                                              |

| Factor                                                                                                                                                                                                                                                                                         |                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Tumor location                                                                                                                                                                                                                                                                                 |                              |
| Vaginal stump                                                                                                                                                                                                                                                                                  | 35                           |
| Other vaginal walls                                                                                                                                                                                                                                                                            | 15                           |
| Lymph node metastasis at recurrence                                                                                                                                                                                                                                                            |                              |
| Yes                                                                                                                                                                                                                                                                                            | 5                            |
| No                                                                                                                                                                                                                                                                                             | 45                           |
| External beam radiotherapy                                                                                                                                                                                                                                                                     |                              |
| Yes                                                                                                                                                                                                                                                                                            | 30                           |
|                                                                                                                                                                                                                                                                                                | (Visible: 26, Non-visible:4) |
|                                                                                                                                                                                                                                                                                                | (WP: 16, Local: 14)          |
| No                                                                                                                                                                                                                                                                                             | 20                           |
| The number of brachytherapy                                                                                                                                                                                                                                                                    |                              |
| Visible recurrence                                                                                                                                                                                                                                                                             | Median 3fr (IQR:2-4fr)       |
| Non-visible recurrence                                                                                                                                                                                                                                                                         | Median 5fr (IQR:5-5fr)       |
| ICBT Applicator type                                                                                                                                                                                                                                                                           |                              |
| Cylinder                                                                                                                                                                                                                                                                                       | 43                           |
| Ovoid                                                                                                                                                                                                                                                                                          | 5                            |
| None                                                                                                                                                                                                                                                                                           | 2                            |
| The use of ISBT                                                                                                                                                                                                                                                                                |                              |
| Yes                                                                                                                                                                                                                                                                                            | 22                           |
|                                                                                                                                                                                                                                                                                                | (Advanced: 22, Supercial: 0) |
| No                                                                                                                                                                                                                                                                                             | 28                           |
|                                                                                                                                                                                                                                                                                                | (Advanced:8, Superficial 20) |
| HR-CTV at initial brachytherapy                                                                                                                                                                                                                                                                |                              |
|                                                                                                                                                                                                                                                                                                | Median 1.59 cc               |
|                                                                                                                                                                                                                                                                                                | (IQR: 0.98–3.93 cc)          |
| Visible recurrence                                                                                                                                                                                                                                                                             |                              |
|                                                                                                                                                                                                                                                                                                | Median 3.51 cc               |
|                                                                                                                                                                                                                                                                                                | (IQR:1.86–7.70 cc)           |
| Non-visible recurrence                                                                                                                                                                                                                                                                         |                              |
|                                                                                                                                                                                                                                                                                                | Median 0.94 cc               |
|                                                                                                                                                                                                                                                                                                | (IQR: 0.85–1.13 cc)          |
| Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; ICBT = intracavitary brachytherapy; ISBT = interstitial brachytherapy; HR-CTV = high-risk clinical target volume; EQD2 = the equivalent dose in 2 Gy fractions IQR = interquartile range. |                              |

| Factor                                                                                                                                                                                                                                                                                         |                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| HR-CTV D90 in EQD2                                                                                                                                                                                                                                                                             | Median 70.5 Gy      |
| Visible recurrence                                                                                                                                                                                                                                                                             | Median 75.1 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR:69.6–77.1 Gy)  |
| Non-visible recurrence                                                                                                                                                                                                                                                                         | Median 57.8 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 53.0-69.6 Gy) |
| Dose of bladder D2cc in EQD2                                                                                                                                                                                                                                                                   | Median 64.9 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 50.1–72.3 Gy) |
| Visible recurrence                                                                                                                                                                                                                                                                             | Median 67.9 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 63.7–73.2 Gy) |
| Non-visible recurrence                                                                                                                                                                                                                                                                         | Median 50.5 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 40.2–65.2 Gy) |
| Dose of Rectum D2cc in EQD2                                                                                                                                                                                                                                                                    | Median 59.6 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 50.8–66.0 Gy) |
| Visible recurrence                                                                                                                                                                                                                                                                             | Median 63.5 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 58.6–71.2 Gy) |
| Non-visible recurrence                                                                                                                                                                                                                                                                         | Median 52.0 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 46.4–60.4 Gy) |
| Dose of Sigmoid D2cc in EQD2                                                                                                                                                                                                                                                                   | Median 46.2 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 11.9–52.0 Gy) |
| Visible recurrence                                                                                                                                                                                                                                                                             | Median 50.4 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 44.2–53.3 Gy) |
| Non-visible recurrence                                                                                                                                                                                                                                                                         | Median 10.5 Gy      |
|                                                                                                                                                                                                                                                                                                | (IQR: 6.7–45.6 Gy)  |
| Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; ICBT = intracavitary brachytherapy; ISBT = interstitial brachytherapy; HR-CTV = high-risk clinical target volume; EQD2 = the equivalent dose in 2 Gy fractions IQR = interquartile range. |                     |

EBRT with a median total dose of 50 Gy (range, 30–60 Gy) was delivered to 30 patients. Whole pelvic irradiation was performed in 16 patients, whereas localized vaginal irradiation was performed in 14 patients.

The median number of BT fractions was 5 (interquartile range [IQR], 5–5 fractions) in patients with non-visible recurrence and 3 fractions (IQR, 2–4 fractions) in those with visible recurrence, respectively. The median total dose of the HR-CTV D90 (EQD2) was 70.5 Gy (IQR, 60.9–76.2 Gy).

The median follow-up period was 44.8 months (IQR, 31.1–68.0 months), and 9 patients died after RT. Recurrence after RT was detected in 27 patients. Local recurrence, regional recurrence, and distant metastasis were observed in 7, 9, and 21 patients, respectively. Regarding the details of the distant metastasis, lung metastasis (13 patients), extra-regional lymph node metastasis (4 patients), and peritoneal dissemination (2 patients) were frequently detected. The 3-year LC, RRFS, DMFS, DFS, and OS rates in all patients were 85.6% (95% confidence interval [CI] 71.0–93.5%), 82.9% (95%CI, 69.3–91.3%), 65.1% (95%CI, 50.8–77.1%), 46.0% (95% CI 32.3–60.2%), and 87.1% (95% CI 73.9–94.1%), respectively (Fig. 2A).

The ROC curves analysis identified an HR-CTV D90 cutoff value of 67.3 Gy (area under the curve [AUC], 0.786). In the univariate analysis, HR-CTV D90 was the only significant prognostic factor for LC. The 3-year LC rates were 100% in patients with an HR-CTV D90  $\geq$  67.3 Gy and < 67.3 Gy and 64.2% (95% CI, 39.7–83.0%), respectively ( $p = 0.009$ ). Local recurrence occurred more commonly in patients with non-visible recurrence (four patients) than in those with visible recurrence (three patients), likely because the HR-CTV D90 was lower in the non-visible recurrence group. All patients with non-visible recurrence who developed local recurrence had been treated with ICBT alone. Kaplan-Meier curves stratified by HR-CTV D90 are shown in Fig. 2B.

The results of the univariate analysis are presented in Table 2. Tumor visibility was a significant prognostic factor for RRFS ( $P = 0.037$ ), DMFS ( $p < 0.001$ ), DFS ( $p = 0.004$ ), and OS ( $p = 0.005$ ). FIGO stage was a significant prognostic factor for DMFS ( $p < 0.001$ ), DFS ( $p = 0.014$ ), and OS ( $p < 0.001$ ). Histology was a significant prognostic factor for DMFS ( $p = 0.01$ ). Risk classification was a significant prognostic factor for DMFS ( $p = 0.004$ ), DFS ( $p = 0.048$ ), and OS ( $p = 0.026$ ). Postoperative chemotherapy was a significant prognostic factor for OS ( $p = 0.014$ ). Lymph node metastasis at recurrence was a significant prognostic factor for DFS ( $p = 0.031$ ) and OS ( $p = 0.018$ ). The results of the multivariate analysis are presented in Table 3. Based on the number of events, the univariate analysis results, and the relationships between each factor, multivariate analysis was performed for DMFS (distant metastasis: 21 patients, risk classification, and tumor visibility) and DFS (disease progression: 27 patients, risk classification, tumor visibility, and lymph node metastasis). Because the number of local recurrence events was small (7 patients), only univariate analysis was performed for LC. The factors used in the multivariate analysis were tumor visibility and risk classification for DMFS, and tumor visibility, risk classification, and lymph node metastasis for DFS. Tumor visibility remained a significant prognostic factor for DMFS ( $p = 0.011$ ), whereas tumor visibility and lymph node metastasis remained significant prognostic factors for DFS ( $p = 0.005$  and  $0.024$ , respectively). Kaplan-Meier curves for patients with non-visible and visible recurrences are shown in Fig. 3.

Table 2  
The results of univariate analysis

| Factor                           | LC                        |            | RFFS                      |            | DMFS                      |                   | DFS                       |              | OS                        |                   |
|----------------------------------|---------------------------|------------|---------------------------|------------|---------------------------|-------------------|---------------------------|--------------|---------------------------|-------------------|
|                                  | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value        | 3-year<br>(95%<br>CI)     | p<br>value   | 3-year<br>(95%<br>CI)     | p<br>value        |
| Age                              |                           | 0.207      |                           | 0.678      |                           | 0.819             |                           | 0.645        |                           | 0.909             |
| > 65 year                        | 80.5%<br>(57.5–<br>92.7%) |            | 81.3%<br>(59.3–<br>92.9%) |            | 67.0%<br>(46.6–<br>82.6%) |                   | 45.3%<br>(26.8–<br>65.3%) |              | 86.3%<br>(64.7–<br>95.6%) |                   |
| ≤ 65 year                        | 90.9%<br>(69.9–<br>97.8%) |            | 83.8%<br>(63.9–<br>93.8%) |            | 62.8%<br>(42.3–<br>79.5%) |                   | 47.1%<br>(28.7–<br>66.4%) |              | 88.0%<br>(68.7–<br>96.1%) |                   |
| FIGO 2023                        |                           | 0.688      |                           | 0.091      |                           | <<br><b>0.001</b> |                           | <b>0.014</b> |                           | <<br><b>0.001</b> |
| IA                               | 80.0%<br>(57.0–<br>92.3%) |            | 90.2%<br>(68.2–<br>97.5%) |            | 90.4%<br>(68.9–<br>97.6%) |                   | 60.7%<br>(38.8–<br>79.2%) |              | 100%                      |                   |
| other                            | 91.6%<br>(71.5–<br>97.9%) |            | 77.5%<br>(57.9–<br>89.6%) |            | 46.1%<br>(28.7–<br>64.4%) |                   | 36.1%<br>(20.7–<br>55.0%) |              | 76.3%<br>(55.3–<br>89.3%) |                   |
| Histology                        |                           | 0.308      |                           | 0.379      |                           | <b>0.01</b>       |                           | 0.077        |                           | 0.086             |
| EM G1-2                          | 81.8%<br>(62.7–<br>92.3%) |            | 87.1%<br>(70.3–<br>95.1%) |            | 77.1%<br>(59.1–<br>88.7%) |                   | 53.6%<br>(35.6–<br>70.4%) |              | 89.7%<br>(72.2–<br>96.7%) |                   |
| EM3, serous<br>clear cell        | 94.4%<br>(69.3–<br>99.2%) |            | 74.9%<br>(48.1–<br>90.6%) |            | 45.3%<br>(24.7–<br>67.7%) |                   | 34.2%<br>(16.3–<br>58.0%) |              | 83.3%<br>(59.1–<br>94.5%) |                   |
| Risk<br>classification           |                           | 0.416      |                           | 0.451      |                           | <b>0.004</b>      |                           | <b>0.048</b> |                           | <b>0.026</b>      |
| Low-Middle<br>recurrence<br>risk | 82.8%<br>(61.8–<br>93.5%) |            | 88.0%<br>(68.7–<br>96.1%) |            | 83.8%<br>(63.9–<br>93.8%) |                   | 59.1%<br>(39.0–<br>76.5%) |              | 91.4%<br>(71.3–<br>97.9%) |                   |
| High<br>recurrence<br>risk       | 90.2%<br>(67.7–<br>97.6%) |            | 77.8%<br>(56.1–<br>90.6%) |            | 46.3%<br>(27.9–<br>65.8%) |                   | 33.8%<br>(18.0–<br>54.5%) |              | 83.3%<br>(63.1–<br>93.6)  |                   |

Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; LC =local control; RFFS = regional recurrence-free survival ; DMFS = distant metastasis-free survival; DFS = disease-free survival; OS = overall survival; CI = confidence interval.

| Factor                                                                                                                                                                                                                                                                                    | LC                        |            | RFFS                      |              | DMFS                      |                   | DFS                       |              | OS                        |              |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------|---------------------------|--------------|---------------------------|-------------------|---------------------------|--------------|---------------------------|--------------|
|                                                                                                                                                                                                                                                                                           | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value   | 3-year<br>(95%<br>CI)     | p<br>value        | 3-year<br>(95%<br>CI)     | p<br>value   | 3-year<br>(95%<br>CI)     | p<br>value   |
| Postoperative chemotherapy                                                                                                                                                                                                                                                                |                           | 0.714      |                           | 0.349        |                           | 0.168             |                           | 0.299        |                           | <b>0.014</b> |
| Yes                                                                                                                                                                                                                                                                                       | 89.6%<br>(72.1–<br>96.6%) |            | 81.0%<br>(63.5–<br>91.2%) |              | 57.3%<br>(40.1–<br>72.8%) |                   | 57.3%<br>(40.1–<br>72.8%) |              | 80.3%<br>(62.2–<br>91.1%) |              |
| No                                                                                                                                                                                                                                                                                        | 79.5%<br>(51.8–<br>93.4%) |            | 87.1%<br>(60.3–<br>96.8%) |              | 80.8%<br>(54.3–<br>93.7%) |                   | 80.8%<br>(54.3–<br>93.7%) |              | 100%                      |              |
| Interval from initial surgery to recurrence                                                                                                                                                                                                                                               |                           | 0.891      |                           | 0.816        |                           | 0.856             |                           | 0.745        |                           | 0.261        |
| ≥ 12 months                                                                                                                                                                                                                                                                               | 83.6%<br>(63.0–<br>93.8%) |            | 81.7%<br>(62.7–<br>92.2%) |              | 65.1%<br>(46.3–<br>80.1%) |                   | 43.5%<br>(26.6–<br>62.1%) |              | 81.8%<br>(63.0–<br>92.3%) |              |
| < 12 months                                                                                                                                                                                                                                                                               | 89.1%<br>(65.0–<br>97.3%) |            | 84.4%<br>(61.2–<br>94.9%) |              | 65.1%<br>(42.7–<br>82.4%) |                   | 50.3%<br>(29.6–<br>70.8%) |              | 95%<br>(71.8–<br>99.3%)   |              |
| Tumor visibility                                                                                                                                                                                                                                                                          |                           | 0.495      |                           | <b>0.037</b> |                           | <b>&lt; 0.001</b> |                           | <b>0.004</b> |                           | <b>0.005</b> |
| Non-visible recurrence                                                                                                                                                                                                                                                                    | 77.2%<br>(52.1–<br>91.3%) |            | 94.7%<br>(70.6–<br>99.3%) |              | 89.5%<br>(66.3–<br>97.3%) |                   | 67.0%<br>(43.0–<br>84.5%) |              | 100%                      |              |
| visible recurrence                                                                                                                                                                                                                                                                        | 93.2%<br>(76.6–<br>98.3%) |            | 74.3%<br>(54.7–<br>87.4%) |              | 48.9%<br>(31.6–<br>66.5%) |                   | 32.5%<br>(18.1–<br>51.1%) |              | 78.7%<br>(59.6–<br>90.2%) |              |
| Tumor location                                                                                                                                                                                                                                                                            |                           | 0.937      |                           | 0.201        |                           | 0.264             |                           | 0.504        |                           | 0.85         |
| Vaginal stump                                                                                                                                                                                                                                                                             | 86.0%<br>(67.6–<br>94.7%) |            | 78.6%<br>(61.3–<br>89.5%) |              | 70.4%<br>(53.1–<br>83.3%) |                   | 48.8%<br>(32.2–<br>65.6%) |              | 84.5%<br>(72.5–<br>95.5%) |              |
| Other                                                                                                                                                                                                                                                                                     | 84.8%<br>(55.0–<br>96.3%) |            | 93.3%<br>(64.8–<br>99.1%) |              | 53.3%<br>(29.3–<br>75.9%) |                   | 40.0%<br>(19.2–<br>65.2%) |              | 93.3%<br>(64.8–<br>99.1%) |              |
| Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; LC =local control; RFFS = regional recurrence-free survival ; DMFS = distant metastasis-free survival; DFS = disease-free survival; OS = overall survival; CI = confidence interval. |                           |            |                           |              |                           |                   |                           |              |                           |              |

| Factor                                                                                                                                                                                                                                                                                    | LC                        |            | RFFS                      |            | DMFS                      |            | DFS                       |            | OS                        |            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------|---------------------------|------------|---------------------------|------------|---------------------------|------------|---------------------------|------------|
|                                                                                                                                                                                                                                                                                           | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value | 3-year<br>(95%<br>CI)     | p<br>value |
| Lymph node metastasis                                                                                                                                                                                                                                                                     |                           | 0.466      |                           | 0.087      |                           | 0.068      |                           | 0.031      |                           | 0.018      |
| Yes                                                                                                                                                                                                                                                                                       | 100%                      |            | 60.0%<br>(20.0–<br>90.0%) |            | 40.0%<br>(10.0–<br>80.0%) |            | 20.0%<br>(2.72–<br>69.1%) |            | 60.0%<br>(20.0–<br>90.0%) |            |
| No                                                                                                                                                                                                                                                                                        | 84.5%<br>(69.3–<br>93.0%) |            | 85.8%<br>(71.7–<br>93.5%) |            | 68.2%<br>(53.2–<br>80.2%) |            | 49.0%<br>(34.4–<br>63.8%) |            | 90.3%<br>(76.8–<br>96.3%) |            |
| Abbreviations: FIGO = The International Federation of Gynaecology and Obstetrics; EM = endometrioid; LC =local control; RFFS = regional recurrence-free survival ; DMFS = distant metastasis-free survival; DFS = disease-free survival; OS = overall survival; CI = confidence interval. |                           |            |                           |            |                           |            |                           |            |                           |            |

Table 3  
The results of multivariate analysis

| DMFS                                                                                                           | Hazard ratio | 95%CI     | p value |
|----------------------------------------------------------------------------------------------------------------|--------------|-----------|---------|
| Risk classification                                                                                            |              |           | 0.033   |
| Low-Middle                                                                                                     | Ref          | -         | -       |
| High                                                                                                           | 2.88         | 1.09–7.6  |         |
| Tumor visibility                                                                                               |              |           | 0.011   |
| non-visible recurrence                                                                                         | Ref          | -         | -       |
| visible recurrence                                                                                             | 6.96         | 1.56-31.0 |         |
| DFS                                                                                                            |              |           |         |
| Risk classification                                                                                            |              |           | 0.277   |
| Low-Middle                                                                                                     | Ref          | -         | -       |
| High                                                                                                           | 1.55         | 0.70–3.44 |         |
| Tumor visibility                                                                                               |              |           | 0.005   |
| non-visible recurrence                                                                                         | Ref          | -         | -       |
| visible recurrence                                                                                             | 3.84         | 1.49–9.91 |         |
| Lymph node metastasis                                                                                          |              |           | 0.024   |
| No                                                                                                             | Ref          | -         | -       |
| Yes                                                                                                            | 3.9          | 1.20–12.8 |         |
| Abbreviations: DMFS = distant metastasis-free survival; DFS = disease-free survival; CI = confidence interval. |              |           |         |

Grade 3 late toxicities were detected in 3 patients (6.0%). All three patients developed vaginal inflammation after receiving lenvatinib for post-RT recurrence. Two of those patients received Hyperbaric oxygen therapy. Grade 2 proctitis was detected in two patients.

## Discussion

We reported the treatment outcomes of CT-guided brachytherapy in patients with postoperative vaginal recurrence of endometrial cancer. Previous studies have reported LC rates of approximately 90% with a total dose of around 75 Gy [8, 9]. Kamran et al. reported that CT-guided BT was inferior to MRI-guided BT in terms of local control [20], whereas other studies demonstrated favorable LC with MRI-guided BT [21, 22]. We believe that the HR-CTV was delineated with reasonable accuracy despite the use of CT-based planning. Overall, our treatment results suggest that salvage CT-guided brachytherapy, with or without EBRT, is an effective treatment option for achieving LC in patients with postoperative vaginal recurrence of endometrial cancer. Interestingly, LC was significantly poorer in patients with non-visible recurrence than in those with visible recurrence. Consistent with this finding, the total HR-CTV D90 dose was significantly lower in patients with non-visible recurrence (median, 57.8 Gy) than in those with visible recurrence (median, 75.1 Gy). When vaginal BT is administered as postoperative adjuvant treatment to prevent recurrence, dose schedules such as 21 Gy in 3 fractions or 30 Gy in 5 fractions are administered [23, 24]. Owing to their small size, most patients with non-visible recurrence received doses similar to those of postoperative vaginal BT for patients with positive surgical margins. However, our results suggest that even non-visible recurrence requires adequate dose escalation to achieve optimal LC. Sekii et al. investigated the treatment outcomes of ICBT and ISBT for isolated vaginal recurrence of endometrial cancer [25]. Although tumor size was smaller in the ICBT group than that in the ISBT group, the 4-year LC rates were 75.3% and 87.3%, respectively. In addition, the cumulative RT dose was significantly higher in the ISBT group than in the ICBT group (70 vs. 56 Gy,  $p < 0.001$ ). The recommended dose for patients who received prior EBRT is 75–79 Gy [8], although this has not yet been established. In the present study, some patients with visible recurrence received ISBT despite the HR-CTV not being particularly large. The American Brachytherapy Society (ABS) consensus guidelines recommend ISBT for patients with vaginal tumors of more than 0.5 cm thickness [26]. Furthermore, several studies have reported favorable results with ISBT [20, 22, 25, 27]. Therefore, achieving adequate dose coverage through the appropriate use of ISBT should be considered, even in selected patients with relatively small visible recurrences.

In the present study, combined EBRT and BT were administered mainly to patients with visible recurrence. Jhingran et al. reported that the combination of EBRT and BT provides excellent LC for isolated vaginal recurrence of endometrial carcinoma [28]. Furthermore, previous recommendations suggest administering 45–50 Gy to the pelvis before BT [8]. Therefore, in patients without a prior history of RT, combined EBRT and BT may be desirable to facilitate dose escalation while considering the potential risks of microscopic disease. The joint guidelines of the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) recommend EBRT plus IGBT for vaginal cuff recurrence [7]. One possible reason for the poorer LC observed in patients with non-visible recurrence is the less frequent use of combined EBRT and BT in this group. Whether WP irradiation, including the pelvic lymph node regions, should be incorporated into EBRT remains controversial. Beak et al. reported that none of the 17 patients treated with WP irradiation and BT developed nodal failure, whereas 6 of 26 (23%) patients treated with BT developed nodal recurrence [29]. In the present study, regional lymph node metastasis was observed mainly in patients with visible recurrence, regardless of prophylactic irradiation. Curran et al. reported that pelvic recurrence after treatment was detected in 29 of 55 (57%), whereas no pelvic recurrence was observed in patients with tumors confined to the mucosa. [30] Based on these results, WP irradiation may be beneficial for patients with visible recurrence. Recent

studies have shown that WP irradiation with intensity-modulated radiotherapy reduces the frequency of gastrointestinal complications [31, 32]. Previous reports have shown that the frequency of locoregional recurrence varies according to the postoperative recurrence risk classification [33]. Therefore, decisions regarding WP irradiation should be individualized based on the patient's postoperative recurrence risk. For example, localized irradiation may be a good option for postoperative low-risk patients with non-visible recurrence.

Our study demonstrates that local control can be achieved when an adequate radiation dose is delivered to recurrent lesions. However, distant metastases were observed in a substantial proportion of patients following RT. Previous studies also demonstrated distant metastasis after salvage RT for postoperative vaginal recurrence [9, 34]. One possible explanation is that patients with a high risk of postoperative recurrence are more likely to develop distant metastases. Previous studies have shown that, regardless of whether pelvic irradiation is performed, patients with a high risk of postoperative recurrence have a higher frequency of distant metastasis, and the time between surgery and the onset of distant metastasis is also shorter [33]. Furthermore, distant metastases have been reported even in clinical trials evaluating adjuvant chemotherapy after surgery [1, 2]. Although patients with a high risk of postoperative recurrence frequently showed distant metastases in the present study, previous studies have also identified FIGO stage and histologic subtype as significant prognostic factors for distant metastasis [27, 29, 35, 36]. Chapman et al. reported that FIGO stage IA and grade 1–2 disease at initial diagnosis were prognostic factors for distant metastasis after RT [27]. Similarly, Lindemann et al. reported that patients with stage I high-risk disease and Stage II-III disease at diagnosis had a significantly increased risk of second relapse [35]. Another reason for distant metastasis after RT is the progression of vaginal recurrence to a stage at which it becomes detectable on imaging examination. In the present study, patients with macroscopic lesions were significantly more likely to develop distant metastases. Previous studies have also identified tumor size as a prognostic factor for outcomes after salvage RT for vaginal recurrence [25, 37]. Moreover, patients with both vaginal lesions and lymph node metastases remain at increased risk of developing distant metastasis [34, 36]. Therefore, careful surveillance is essential to identify vaginal recurrence at an early stage. Previous studies have also demonstrated that the interval from surgery to vaginal recurrence is also the important prognostic factor [25, 34], although no statistically significant difference was observed in the present study. The median interval between initial surgery and vaginal recurrence was 14.5 months. Therefore, frequent internal examinations during the first two years after surgery may be warranted to facilitate early detection of recurrence. In the Study309/KEYNOTE-775, lenvatinib plus pembrolizumab improved OS and PFS compared to chemotherapy in patients with previously treated advanced endometrial cancer [38]. Lenvatinib may be administered when distant metastases are confirmed after definitive RT for vaginal recurrence. However, vaginal ulceration requiring treatment was observed in patients who received lenvatinib in the present study. A previous case report also described lenvatinib-associated vaginal necrosis after BT for postoperative vaginal recurrence [39]. Because angiogenesis inhibitors, such as lenvatinib, may impair normal tissue healing after high-dose BT, their use may increase the risk of severe complications, including fistula formation and tissue necrosis. Therefore, careful consideration should be given not only to OAR dose constraints during RT planning but also to the selection of subsequent treatments. Because all patients in the present study received RT alone, the addition of concurrent chemotherapy may represent a potential strategy for reducing the risk of distant metastasis. However, based on the results of previous clinical trials, the usefulness of concurrent chemotherapy could not be demonstrated [40], and further investigation is needed.

Some limitations of this study should be acknowledged. First, because HR-CTV delineation was based on CT rather than MRI, the contoured target volumes may have been larger than those that would have been defined using MRI images. Consequently, the HR-CTV D90 values may have been underestimated. Moreover, HR-CTV delineation in patients with non-visible recurrence is inherently uncertain, which may have further contributed to the

underestimation of the D90 values. Second, because of the retrospective study design, the RT schedule varied greatly among patients. Furthermore, treatment approaches differed between patients with visible and non-visible recurrence, including variations in the use of EBRT and BT as well as the incorporation of ISBT. These differences may have introduced treatment-related heterogeneity and influenced the observed outcomes.

## Conclusions

Our study demonstrated that CT-guided BT provides favorable local control for vaginal recurrence after surgery for endometrial cancer when an adequate radiation dose is delivered. These findings suggest that dose escalation using EBRT plus BT may be beneficial even in patients with non-visible recurrence. However, distant metastases remain a major pattern of failure after RT. Therefore, careful follow-up is necessary, especially for patients with visible recurrence on imaging or those with high-risk postoperative factors.

## Abbreviations

3DCRT Three  
dimensional conformal radiotherapy

## Declarations

### Ethics approval and consent to participate

This study was approved by Ethics Committee Tohoku University Graduate School of Medicine (2025-1-955) and was conducted according to the tenets of the Declaration of Helsinki. Because of the retrospective nature of the study, the requirement for written informed consent from each patient was waived. Instead, an opt-out method was provided on our institutional website at Tohoku University Graduate School of Medicine to allow patients the opportunity to decline participation.

### Competing interests

The authors declare no competing interests in this study.

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The authors declared no financial disclosures in this study.

## Author Contribution

RU; Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft and Writing – review & editing. SS; Conceptualization, Data curation, Formal analysis, Methodology and Writing – review & editing. TY; Conceptualization, Data curation and Writing – review & editing. NT; Conceptualization, Data curation and Writing – review & editing. YS; Conceptualization, Data curation and Writing – review & editing. KK; Conceptualization, Data curation and Writing – review & editing. SO; Conceptualization, Data curation and Writing – review & editing. HH; Conceptualization, Data curation and Writing – review & editing. NK; Conceptualization, Data curation and Writing – review & editing. MS; Conceptualization, Formal analysis, Methodology and Writing – review

& editing. KJ; Conceptualization, Formal analysis, Methodology, Writing – original draft and Writing – review & editing. All authors read and approved the final manuscript

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## Data Availability

The datasets supporting the conclusions of this article are included within the article.

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## Figures

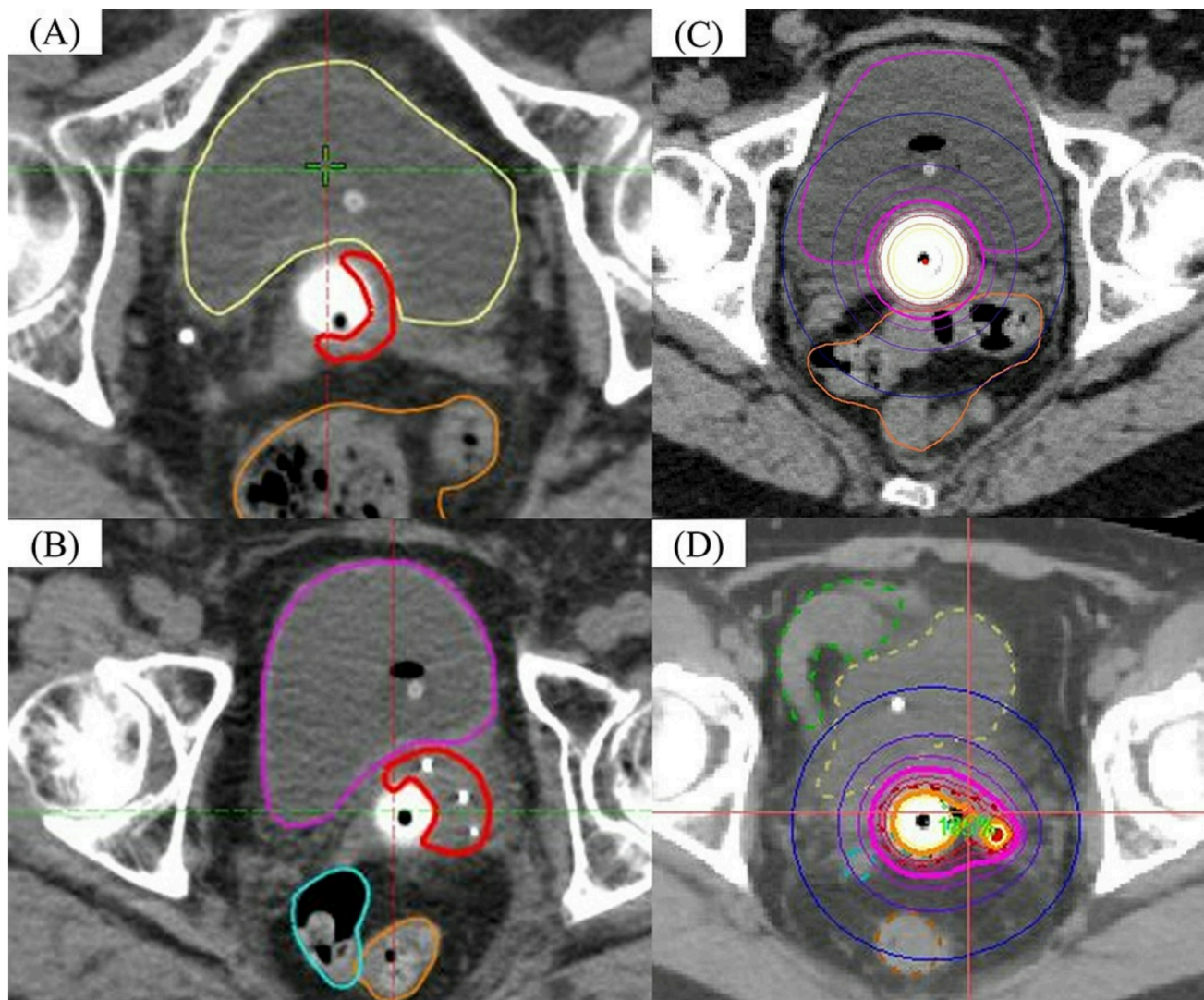


**Figure 1**

Axial images showing high-risk clinical target volume contouring for non-visible recurrence (A) and visible recurrence (B), and axial images of dose distribution using a cylinder applicator for intracavitary brachytherapy (C) and intracavitary and interstitial brachytherapy (D).

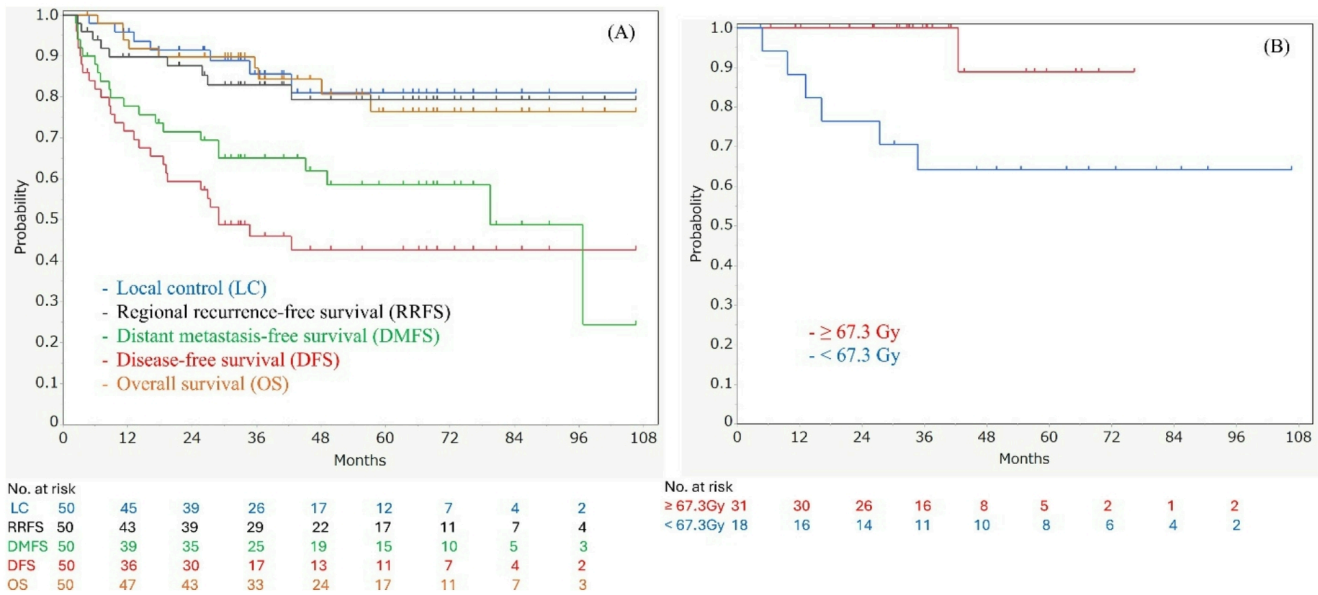


**Figure 2**

Results of local control, regional recurrence-free survival, distant metastasis-free survival, disease-free survival, and overall survival in all patients (A), and local control in HR-CTV D90  $\geq 67.3$  Gy and  $< 67.3$  Gy (B).

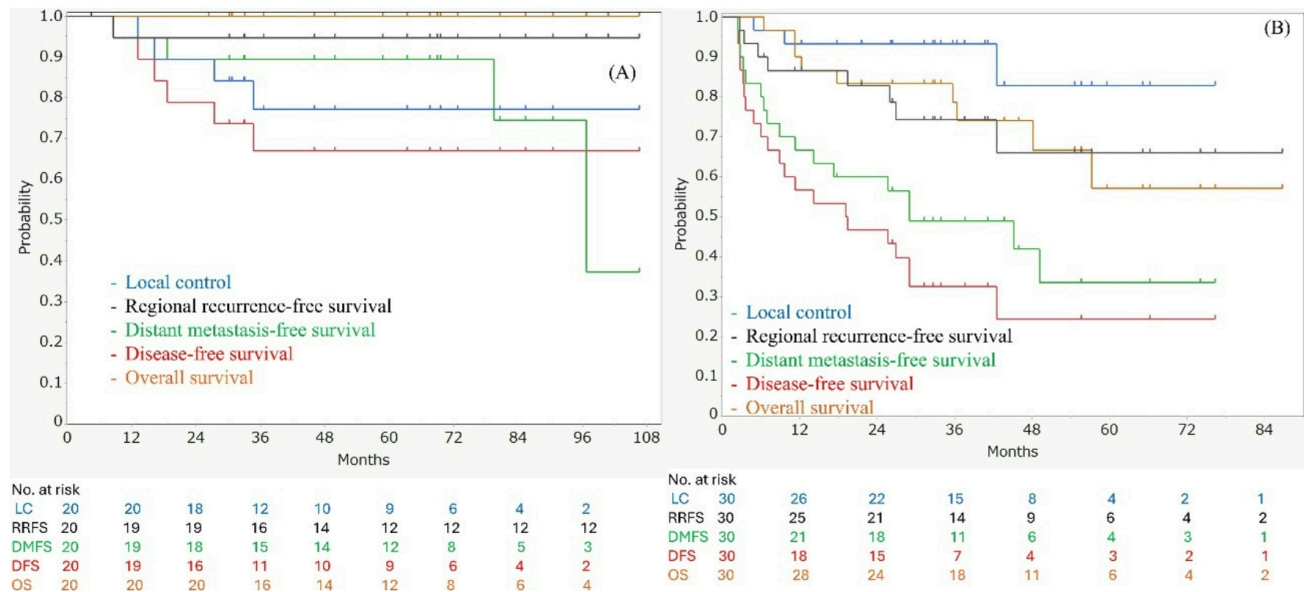


**Figure 3**

Results of local control, regional recurrence-free survival, distant metastasis-free survival, disease-free survival, and overall survival in patients with non-visible (A) and visible recurrence (B).