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Preliminary results of adjuvant image-guided vaginal brachytherapy alone for early stage endometrial carcinoma

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ABSTRACT

Objective: This retrospective study evaluated the preliminary outcomes of image-guided vaginal brachytherapy (IG-VBT) in the adjuvant treatment of high intermediate risk endometrial cancer.

Materials and Methods: Data were collected from 48 patients who underwent adjuvant IG-VBT between 2019 and 2022 at the Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University. The vaginal cuff clinical target volume (CTV-VC) is composed of a 4-mm-thick band around vaginal cylinder at the upper 3 cm of the vaginal cuff. A total dose of 21 Gy in three fractions was delivered to the CTV-VC, and the dose to the bladder and rectum were evaluated. Treatment details, patient characteristics, and outcomes were analyzed. Descriptive statistics were used for analysis, and Kaplan-Meier method was employed for survival analysis.

Results: The mean age was 62 years, with mainly endometrioid carcinoma pathology (96 %). All patients were at stage I, with 87.5 % receiving complete surgical staging. Mean total treatment time was 10 days with mean D90 of CTV-VC was 29.7 Gy, and D2cc of bladder, rectum, and sigmoid were 24.6 Gy, 21.0 Gy, and 7.7 Gy, respectively. At a median follow-up of 37 months, 3-year local control, disease-free survival, and overall survival rates were 100 %, 100 %, and 97.9 %. respectively. Two patients (4.2 %) experienced grade 1–2 gastrointestinal toxicity, while no genitourinary toxicity or serious adverse events were observed.

Conclusions: The preliminary results of IG-VBT in endometrial cancer demonstrated favorable outcomes in terms of vaginal control and toxicity. Further studies with larger cohorts and longer follow-up durations are warranted.

1. Introduction

Endometrial cancer is one of the most common gynecological cancers in the female population. According to the FIGO cancer report for 2021, the global incidence of endometrial cancer was 382,000 new cases in 2018 (Koskas et al., 2021).

Simple hysterectomy alone or with pelvic lymph node dissection or with sentinel lymph node biopsy is the standard modality to remove the tumor and achieve complete pathological evaluation. Adjuvant radiotherapy, including external beam radiotherapy (EBRT) and vaginal brachytherapy (VBT), is tailored according to the pathological aggressiveness of the disease, with VBT utilized as monotherapy for high intermediate-risk cases; and EBRT with or without VBT and adjuvant chemotherapy employed for high-risk stage I and advanced stages. (Koskas et al., 2021; Colombo et al., 2016).

For high intermediate risk endometrial cancer, adjuvant VBT is the standard of care based on the results from the PORTEC II study. The study compared EBRT versus VBT and reported that VBT yielded better quality of life with comparable local control rate (Nout et al., 2009).

Our institution has been using VBT for over a decade as routine practice by using point-based conventional approach in which the brachytherapy dose is prescribed to the reference point 0.5 cm from the

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surface of cylinder. In 2019, we transitioned to image-guided brachytherapy (IGBT) using computed tomography (CT), which included VBT in endometrial cancer. The prescription and dose limitations for organs at risk have been converted to a volume-based approach. In this study, we aim to report on our preliminary experiences with image-guided VBT (IG-VBT) in the treatment of endometrial cancer.

2. Materials and methods

This is a retrospective study to evaluate the use of the adjuvant IG-VBT treatments for high intermediate risk endometrial cancer in Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Chiang Mai University between 2019 and 2022. The institutional review board (IRB) has approved the study with approval number 192/2023. This study was conducted according to the Declaration of Helsinki. Patients included in this study were aged over 20 years, diagnosed with endometrial cancer, and underwent surgery followed by adjuvant VBT as a monotherapy. The data was obtained from hospital's medical records and the division's information system with staging evaluated using FIGO staging 2018 criteria.

Following surgery, an interdisciplinary conference was set to discuss the adjuvant treatment. The criteria for adjuvant VBT were patients with FIGO 2018 stage I with 2 in 3 risk factors including age more than 60-year-old, tumor invasion more than half of myometrium, or grade 3 endometrial cancer; or stage II with less than half of myometrial invasion and without grade 3 tumor according to the high intermediate risk group established from PORTEC study (Nout et al., 2009). Starting in 2021, we have implemented the ESGO/ESTRO/ESP guidelines (Concin et al., 2021). According to these guidelines, patients with substantial LVSI would be switched to external beam radiation.

All patients received IG-VBT with a dose of 21 Gy in 3 fractions. Patients were placed in the lithotomy position. Foley's catheter was inserted with 7 cc of NSS in the balloon. Intravaginal cylinders with appropriate sizing were utilized, followed by transfer to computed tomography (CT) for imaging. Bladders were filled with 100 cc of contrast diluted in normal saline solution. Pelvic CT was performed with a slice thickness of 3 mm, and the image dataset was transferred to the treatment planning software (Oncentra brachytherapy treatment planning system version 4.5.3). The regions of interest (ROIs) included the clinical target volume of the vaginal cuff (CTV-VC), bladder, sigmoid, and rectum. The CTV-VC was contoured by the 4-mm strip around the cylinder cover to upper 3-cm of the VC with subsequent contouring of the outer walls of the bladder, sigmoid, and rectum.

The planning aim was to keep the dose at 90 % of CTV-VC received a dose of 7 Gy per fraction. The dwell position covered the whole length of CTV-VC with extra 1 cm below the CTV-VC. Then, the dwelling time was adjusted to ensure the coverage of isodose of 7 Gy to cover 90 % of CTV-VC while limit dose D2cc < 6.5 Gy for bladder, D2cc < 6 Gy for rectum, D2cc < 5.5 Gy for sigmoid and D2cc < 5 Gy for small bowel.

The doses to the CTV-VC, bladder, rectum, and sigmoid were converted to equivalent dose in 2 Gy fractions (EQD_2) using $\alpha/\beta = 10$ for CTV-VC and $\alpha/\beta = 3$ for the organs, and were then recorded. Target, organs at risk delineated in this study, and dose distribution are illustrated in Fig. 1. After completing the treatment, patients were evaluated by per vaginal examination every 3 months for 1 year, every 4 months for 1 year, every 6 months for 2 years, and then annually. Imaging studies were scheduled based on symptoms. Late gastrointestinal and genitourinary toxicities were evaluated by using CTCAE version 5 (U.S. Department of Health and Human Service, Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017).

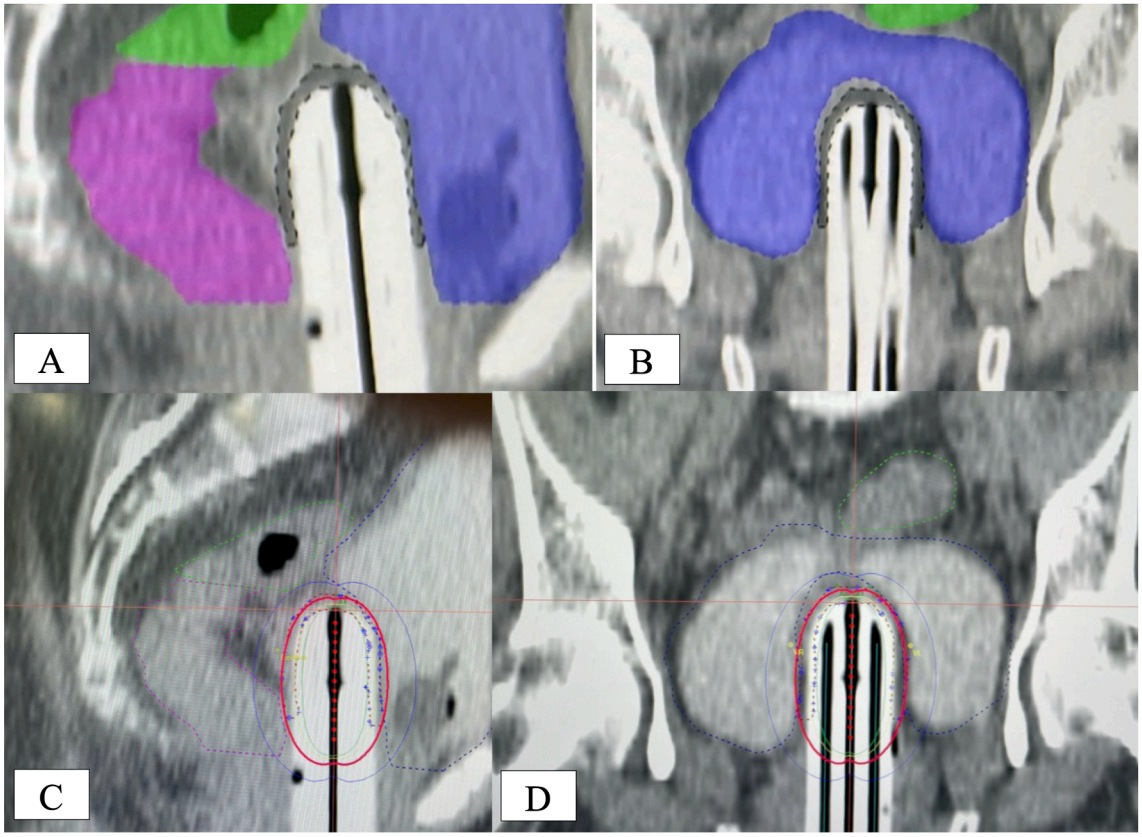

Fig. 1. (A) and (B): Sagittal and coronal view of the regions of interest, including CTV-VC (black), bladder(blue), rectum(purple), and sigmoid(green). (C) and (D): Sagittal and coronal view of dose distribution, with the red line indicating the dose of 7 Gy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.1. Statistical analysis

Patient characteristics, radiotherapy details, and toxicities were analyzed by using descriptive analysis. Quantitative data were presented as median with standard deviation (SD) or medians with interquartile ranges (IQR), while categorical data were expressed as numbers with corresponding percentages. Local control, disease-free survival, and overall survival were calculated from the initiation of brachytherapy to the occurrence of events or censoring using the Kaplan-Meier method. All analyses were conducted using STATA software version 16 (Stata Corp LLC, Texas, USA).

3. Results

3.1. Patient characteristics

From 2019 to 2022, IG-VBT was performed in 51 patients. This study only included data from 48 patients due to missing data for three individuals. The mean age was 62 years old (range; 36–87). The pathology was endometrioid carcinoma in 46 patients (96 %), and clear cell carcinoma in the other 2 patients. All patients were stage I. Among these, 42 patients (87.5 %) received complete surgical staging (CSS). Substantial lymphovascular invasion was present in seven patients (14.6 %). Myometrial invasion of greater than 50 % was present in 27 patients. Among endometrial carcinoma, grade 1, grade 2, and grade 3 differentiation were observed in 19 patients (41.3 %), 19 patients (41.3 %), and 8 patients (17.4 %), respectively. However, no stage IB G3 was presented in this cohort. All data pertaining to patient characteristics is shown in Table 1.

3.2. Treatment outcomes

The median total treatment time was 10 days and median volume of CTV-VC was 8.2 cc (range 5–21 cc). The mean EQD_2 of D90 of CTV-VC was 29.7 Gy, and D2cc of bladder, rectum, and sigmoid were 24.6 Gy, 21.0 Gy, and 7.7 Gy, respectively. The EQD_2 of dose parameters (D90/D98 for target and D2cc/D0.1 cc for OARs) are shown in Table 2.

At a median follow-up time of 37 months (range 13–61 months), no local recurrence was detected. One patient had died without recurrence. The 3-year local control, disease-free survival, and overall survival rates were 100 %, 100 %, and 97.9 %. respectively. Throughout the follow-up period, late gastrointestinal toxicity was reported in two patients (4.2 %), with one patient experienced grade 1 and the other patient developed grade 2 toxicity. No late genitourinary toxicity was observed during this period. No grade 3–4 adverse events were observed during the follow-up period.

Table 1
Patient characteristics.

Parameters	Numbers (%)
Stage	
– IA	23 (48)
– IB	25 (52)
Pathology	
– Endometrioid carcinoma	46 (96)
– Clear cell carcinoma	2 (4)
Surgery	
– Complete surgical staging	42 (87.5)
– Incomplete surgical staging	6 (12.5)
Myometrial invasion	
– Inner half myometrial invasion	21 (43.7)
– Outer half myometrial invasion	27 (56.3)
Lymphovascular invasion	
– No and focal lymphovascular invasion	33 (68.7)
– Substantial lymphovascular invasion	7 (14.6)
– Positive without counting	8 (16.7)

Table 2
Dose parameters.

ROIs	Dose in EQD2 (Gy; mean ± SD)
Clinical Target Volume of Vaginal Cuff (D90)	29.7 ± 0.3
Clinical Target Volume of Vaginal Cuff (D98)	26.4 ± 0.6
Bladder (D2cc)	24.6 ± 4.6
Bladder (D0.1 cc)	37.5 ± 8.8
Rectum (D2cc)	21.0 ± 4.7
Rectum (D0.1 cc)	36.1 ± 7.2
Sigmoid (D2cc)	7.7 ± 4.8
Sigmoid (D0.1 cc)	14.2 ± 10.4

EQD2 = equivalent dose of 2 Gy; ROI = regions of interest.

4. Discussion

This study investigated the preliminary outcomes of IG-VBT in 48 patients with endometrial cancer in our hospital. The outcomes of our study on the application of IG-VBT by CT are promising. With a median follow-up time of 37 months, no vaginal recurrence was observed, and one patient died without recurrence. Two patients developed grade 1–2 late gastrointestinal toxicity, with no late genitourinary toxicity. No serious adverse events were observed in the follow-up period.

Adjuvant VBT as a monotherapy is recommended for treatment of high intermediate risk endometrial cancer due to lower toxicity and better quality of life compared to EBRT. The adjuvant VBT is also endorsed by international guidelines such as SGO (Hamilton et al., 2021), ASTRO (Harkenrider et al., 2023), and ESGO/ESTRO/ESP (Concin et al., 2021). The PORTEC-2 study established important evidence supporting the use of VBT in high intermediate risk endometrial cancer. The study compared whole pelvic radiotherapy (WPRT) with a dose of 46 Gy in 23 fractions versus 21 Gy in 3 fractions of VBT were compared and evaluated in terms of treatment results, toxicity, and quality of life. The first report at 5 years showed the equivalent outcomes of recurrence at the vaginal cuff, with VBT showed superior the quality of life. The 5-year local control rate in the VBT arm was 98 %, with less than 1 % incidence of grade 3 + toxicity (Nout et al., 2009; Nout et al., 2010). From the ten-year results of the PORTEC-2 study, the patients who received VBT had a 10-year survival rate of 69.5 % with a vaginal recurrence rate of 3.4 %. These results did not differ significantly from the outcomes observed in patients who underwent WPRT (Wortman et al., 2018).

Numerous international publications also confirm these findings by demonstrating good local control, less than 5 % of vaginal recurrence and more than 80 % of overall survival rates have been observed following the use of VBT as monotherapy (Nout et al., 2010; Alektiar et al., 2005; Atahan et al., 2008; Sorbe et al., 2012; Diavolitsis et al., 2012; Eldredge-Hindy et al., 2014). Table 3 summarizes the findings of selected studies of VBT as a monotherapy for high intermediate risk endometrial cancer.

The current standard treatment for adjuvant VBT typically follows a point-based system, where the dose is prescribed either at the surface or at 5 mm from the surface of the applicator (Albuquerque et al., 2019; Glatzer et al., 2022). However, there is a growing trend towards volume-based prescription in clinical practice. Although the PORTEC 4a protocol specifies prescribing the dose to 5 mm from the surface of the applicator, it also outlines the use of 3-mm strip contours around the upper 3.5 cm of the cylinder (Wortman et al., 2021). Kim et al. reported CT-based IG-VBT and defined CTV-VC by expanding 2.5 cm uppermost of cylinder 5 mm and excluded bladder and rectal wall. The study revealed that IG-VBT can reduce the dose to surrounding organs without compromising the dose to CTV-VC (Kim et al., 2012). Hashemi et al compare 2D and 3D Cobalt-60 HDR treatment planning. In 3D planning, CTV-VC was contoured by using 5 mm strip around cylinder with narrowing or expanding the thickness based on the thickness of vagina on each CT slide or the adjacent organs. The result showed 3D planning can deliver suitable dose to the target while reduce the dose to organs at risk

Table 3
Selected studies of VBT as a monotherapy for intermediate risk endometrial cancer.

Study	N	VBT schedule	FU	OS (%)	Vaginal recurrence (%)
Alektiar et al (Alektiar et al., 2005)	382	7 Gy x 3F	5 yr	93	0.8
Atahan et al (Atahan et al., 2008)	128	7 Gy x 3F	5 yr	96	0
Nout et al (Nout et al., 2010)	213	7 Gy x 3F	5 yr	84.8	1.8
Sorbe et al (Sorbe et al., 2012)	263	3Gy x 6F or 5.9 Gy x 3F	5 yr	90	0.7
Diavolitsis et al. (Diavolitsis et al., 2012)	169	7 Gy x 3F or 5.5 Gyx 4F or 70 Gy (LDR)	5 yr	95.5	0.6
Eldredge-Hindy et al (Eldredge-Hindy et al., 2014)	31	7 Gy x 3F or 6 Gy x 5F	3 yr	83	3.2
Our study	48	7 Gy x 3F	3 yr	97.9	0

FU: follow-up; F: fraction; OS: overall survival; VBT: vaginal brachytherapy.

(Hashemi et al., 2021). In term of the thickness of strip for vaginal CTV, the findings of the MRI-based IG-VBT demonstrated that the vaginal wall has a thickness of 2.16–2.24 mm (Boonyawan et al., 2014).The study of vaginal wall histology demonstrated 95 % of vaginal lymphatic channels are located within 3 mm of the vaginal surface and all vaginal lymphatic channels are located within 4 mm (Choo et al., 2005). In our institute, we chose 4-mm strip surrounding the cylinder. We believe that our practice can reduce the dose to the organs at risk without compromising the local control of vaginal cuff. However, robust evidence with longer follow-up time is needed for IG-VBT. Our protocol also involved bladder filling to aid contouring and minimize radiation exposure to the bowel. Evidence has demonstrated that bladder filling leads to increased radiation dose to the bladder while reducing the dose to the bowel, with no significant impact on other organs (del Carmen Salas et al., 2021). As the bladder can tolerate higher dose to the bowel, we believe our approach is justifiable.

The findings of our study, describing the preliminary results of IG-VBT with truly volume-based treatment utilizing a truly volume-based treatment approach, demonstrate favorable clinical results. No local recurrence was observed, and no serious adverse events were found in our study. Our volume-based approach warrants further investigation and is a potentially promising procedure for routine practice.Our study has some limitations. Firstly, this study was a retrospective study conducted at a single center, which may introduce bias and confounding factors, limiting its generalizability. Secondly, the sample size was relatively small (48 patients) and short follow-up time (31 months) may limit the robustness of our findings. For evaluating the utilizing of IG-VBT in the long term, the study with greater number of patients with a longer follow-up time, in addition to a quality-of-life assessment, is needed alongside with toxicity evaluation. Thirdly, the molecular parameters (POLE mutation, MMR, and TP53) and point-based evaluations as PORTEC 4a were not reported in our study. These indicators could add valuable information to the findings for future studies. (Wortman et al., 2021; Wortman et al., 2018).

In conclusion, our preliminary results of IG-VBT in endometrial cancer demonstrated favorable outcomes in terms of vaginal control and toxicity. Further studies with larger cohorts and longer follow-up durations are warranted to validate these findings and assess the long-term efficacy of IG-VBT.

5. Ethics approval and consent to participate

This study was approved by Research Ethic Committee, Faculty of Medicine, Chiang Mai University No. 192/2023. The data collection was authorized by the faculty. Informed consent was not required by the faculty and Research Ethic Committee due to retrospective study with anonymized patient identification. This study was carried out in accordance with the Helsinki Declaration.

6. Consent for publication

Not Applicable.

7. Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to containing information that could compromise research participant privacy.

8. Authors' contributions

Pooriwat Muangwong: Conceptualization, Investigation, Validation, Writing – Original Draft, Project administration. **Ekkasit Tharavichitkul:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – Original Draft, Project administration. **Somvilai Chakrabandhu:** Writing – Review & Editing. **Pitchayaponne Klunklin:** Writing – Review & Editing. **Wimrak Onchan:** Writing – Review & Editing. **Bongkot Jia-Mahasap:** Writing – Review & Editing. **Piyapasara Toapichattrakul:** Writing – Review & Editing. **Wannapha Nobnop:** Validation, Writing – Review & Editing, Project administration. **Anirut Watcharawipha:** Writing – Review & Editing. **Ravan M Galalae:** Writing – Review & Editing, Supervision. **Imjai Chitapanarux:** Writing – Review & Editing, Supervision.

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CRediT authorship contribution statement

Pooriwat Muangwong: Writing – original draft, Validation, Project administration, Investigation. **Ekkasit Tharavichitkul:** Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Somvilai Chakrabandhu:** Writing – original draft. **Pitchayaponne Klunklin:** Writing – original draft. **Wimrak Onchan:** Writing – original draft. **Bongkot Jia-Mahasap:** Writing – original draft. **Piyapasara Toapichattrakul:** Writing – original draft. **Wannapha Nobnop:** Writing – original draft, Validation, Project administration. **Anirut Watcharawipha:** Writing – original draft. **Razvan M. Galalae:** Writing – original draft, Supervision. **Imjai Chitapanarux:** Writing – original draft, Supervision.

Declaration of Competing Interest

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

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