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Phase I/II prospective clinical trial for the hybrid of intracavitary and interstitial brachytherapy for locally advanced uterine cervical cancer

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ABSTRACT

Objective: The purposes of this trial were to demonstrate the feasibility and effectiveness of the hybrid of intracavitary and interstitial brachytherapy (HBT) for locally advanced cervical cancer patients in the phase I/II prospective clinical trial.
Methods: Patients with FIGO stage IB2-IVA uterine cervical cancer pretreatment width of which was ≥5 cm measured by magnetic resonance imaging were eligible for this clinical trial. The protocol therapy included 30–30.6 Gy in 15–17 fractions of whole pelvic radiotherapy concurrent with weekly CDDP, followed by 24 Gy in 4 fractions of HBT and pelvic radiotherapy with a central shield up to 50–50.4 Gy in 25–28 fractions. The primary endpoint of phase II part was 2-year pelvic progression-free survival (PPFS) rate higher than historical control of 64%.
Results: Between October 2015 and October 2019, 73 patients were enrolled in the initial registration and 52 patients proceeded to the secondary registration. With the median follow-up period of 37.3 months (range, 13.9–52.9 months), the 2- PPFS was 80.7% (90% confidence interval [CI]=69.7%–88%). Because the lower range of 90% CI of 2-year PPFS was 69.7%, which was higher than the historical control ICBT data of 64%, therefore, the primary endpoint of this study was met.
Conclusion: The effectiveness of HBT were demonstrated by a prospective clinical study. Because the dose goal determined in the protocol was lower than 85 Gy, there is room in improvement for local control. A higher dose might have been needed for tumors with poor responses.

Keywords: Cervical Cancer; Image Guided Adaptive Brachytherapy; Intracavitary and Interstitial Brachytherapy; IC/IS

Synopsis
This is a phase I/II prospective clinical trial on IC/IS for advanced cervical cancer. Between October 2015 and October 2019, 52 patients were enrolled. The primary endpoint was met and effectiveness of IC/IS was demonstrated. A higher dose might have been needed for tumors with poor responses.

INTRODUCTION

After the first publication of the GEC-ESTRO working group recommendation of image-guided adaptive brachytherapy (IGABT) for uterine cervical cancer in 2005 [1], a landmark outcome of the EMBRACE-I study was published in 2021 with favorable local control (LC) of >90% regardless of T-stage when adequate doses were delivered to the clinical target volume (CTV) [2]. To deliver an adequate dose, the hybrid of intracavitary and interstitial brachytherapy (HBT) has been introduced and favorable clinical outcomes have been reported [3], in which, along with intracavitary applicators, additional interstitial needles are inserted to facilitate dose delivery, particularly for tumors extending lateral parametrium where it is difficult to deliver higher doses only with intracavitary brachytherapy (ICBT). Although such favorable clinical outcomes have already been presented, they are all retrospective studies, and the HBT's superiority over ICBT has not been validated by any prospective clinical trials. Because HBT is a more invasive new treatment method requiring additional interstitial needle insertion, but is a potentially promising treatment method with

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Conflict of Interest
Dr. Itami reports personal fees from HekaBio, grants and personal fees from Itochu, grants from Elekta, personal fees from AlphaTAU, personal fees from ViewRay, personal fees from Palette Science, outside the submitted work.
Dr. Igaki reports personal fees from HekaBio, personal fees from AstraZeneca, personal fees from Itochu, outside the submitted work.
The data management performed by EPS Corporation was supported by Itochu grant.
Dr. Yoshida reports personal fees from Chiyoda Technol, outside the submitted work
Dr. Inaba reports personal fees from Boston Scientific Japan, outside the submitted work.
Dr. Okonogi reports grants and other from AstraZeneca, outside the submitted work.
Data Availability Statement
All data generated and analyzed during this study are included in this published article and its supplementary information files (Data S1).

Author Contributions
Conceptualization: M.N., W.M., S.S., T.K., M.Y., A.T., K.S., H.H., K.Y., N.T., I.H., A.K., M.M., Y.K., Y.H., M.K., O.T., O.N., T.K., S.H., Y.R., Y.Y., Y.A., K.N., O.H., I.K., K.T., I.H., I.J.; Funding acquisition: I.J.; Investigation: M.N., U.T., S.S., T.K., K.T., M.Y., A.T., K.S., K.Y., I.H., A.K., M.M., Y.K., Y.H., M.K., O.T., O.N., S.A..I., I.M., T.K., S.H., Y.R., Y.Y., Y.A., K.N., O.H., I.K., K.T., I.H., I.J.; Methodology: M.N., U.T., S.S., T.K., K.T., M.Y., A.T., K.S., K.Y., I.H., A.K., M.M., Y.K., Y.H., M.K., O.T., O.N., S.A..I., T.K., S.H., Y.R., Y.Y., Y.A., K.N., O.H., I.K., K.T., I.H., I.J.; Project administration: M.N., W.M., U.T., S.S., T.K., K.T., M.Y., A.T., K.S., H.H., K.Y., N.T., I.H., A.K., M.M., Y.K., Y.H., M.K., O.T., O.N., S.A..I., I.M., O.T., T.K., S.H., Y.R., Y.Y., Y.A., K.N., O.H., I.K., K.T., I.H., I.J.; Resources: I.H., A.K., I.M., O.T., T.K., S.H., Y.R., I.H., I.J.; Supervision: K.Y., I.H., I.J.; Validation: M.N., W.M., U.T., S.S., T.K., K.T., M.Y., A.T., K.S., H.H., K.Y., N.T., I.H., A.K., M.M., Y.K., Y.H., M.K., O.T., O.N., S.A..I., O.T., T.K., S.H., Y.R., Y.Y., Y.A., K.N., O.H., I.K., K.T., I.H., I.J.; Visualization: M.N.; Writing – original draft: M.N.; Writing – review & editing: M.N., I.H.

superior LC than ICBT, we planned to demonstrate its feasibility and effectiveness over ICBT with a prospective multi-institutional clinical trial. The purposes of this trial were to show its feasibility in the phase I part and to show its effectiveness compared to historical ICBT data in the phase II part for cervical cancer patients who underwent concurrent chemoradiation therapy (cCRT). Because the results of the phase I part of this study were described in a separate publication [4], this article reports the results of the phase II part of this study.

MATERIALS AND METHODS

1. Study patients

The detailed trial protocol is described in the previously published protocol paper [5]. Patients between the ages of 20 and 75 years with previously untreated stage IB2, IIA2, IIB, IIIB, and IVA (bladder invasion) uterine cervical carcinoma (2009 version of the FIGO) with a maximum tumor diameter >5 cm measured by magnetic resonance imaging (MRI) were eligible for the initial registration. As well as showing the efficacy of HBT, one of the main purposes of this study was to demonstrate the safety of HBT. Therefore, because patients with IVA (rectal invasion) are highly likely to develop rectovaginal fistula even after successful tumor control, they were excluded from this study. In contrast, because the tolerance dose for the bladder is higher than the rectum, patients with IVA (bladder invasion) were allowed to be enrolled. Histopathology should be either squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. Patients with kidney or bone marrow dysfunction who could not tolerate cCRT, patients with para-aortic lymph node metastasis, and those taking anticoagulant or antiplatelet medication were ineligible. The reason for excluding patients with para-aortic lymph node metastasis was that such patients required extended-field pelvic irradiation, which potentially resulted in myelosuppression and systemic chemotherapy could not be adequately administered as intended. This could potentially affect the primary endpoint; therefore, such patients were excluded. While chest, abdominal, and pelvic computed tomography (CT) and pelvic MRI were mandatory for staging, PET-CT was arbitrary. Tumor width (gross tumor volume) was measured again with MRI within one week before the first HBT, and if it was >4 cm, patients were referred to the secondary registration. At the secondary registration, IIIA patients whose thickness of vaginal involvement was > 5 mm or patients with too large tumors to be adequately covered by HBT were excluded because multi-catheter interstitial brachytherapy (ISBT) should be performed instead of HBT in such cases. Because tumor measurement with MRI both before primary and secondary registration was mandatory, a tumor shrinkage ratio calculated with the following equation was performed:

$$\text{Tumor Shrinkage Ratio} = \frac{(\text{Baseline Tumor Diameter} - \text{Tumor Diameter Prior to HBT})}{(\text{Baseline Tumor Diameter})}$$

2. Treatment procedures

An overview of the protocol treatment is shown in **Fig. S1**.

3. External beam radiation therapy (EBRT)

Whole pelvic radiation therapy (WPRT) was delivered by CT-based three-dimensional conformal radiation therapy (3D-CRT) with four portals encompassing the whole uterus, the upper part of the vagina, and regional pelvic lymph node drainage. No intensity-modulated radiation therapy was permitted. According to the Japanese guidelines for the treatment

of uterine cervical cancer [6], following 30-30.6 Gy in 15-17 fractions of WPRT, 24 Gy in 4 fractions of brachytherapy, and 3–4 cm width of central shielded pelvic irradiation (CS) up to 50-50.4 Gy in 25–28 fractions has started. If clinically enlarged regional pelvic lymph nodes were present, boost EBRT of 6–10 Gy in 3–5 fractions was administered. Dose was prescribed to a certain reference point; an isocenter in WPRT without CS and boost lymph node irradiation and an off-center reference point in WPRT with CS.

4. Brachytherapy

A total of four fractions of 6 Gy of brachytherapy were performed. In HBT, additional needles could be inserted either through the vaginal wall or the perineum under sedation and local anesthesia. The dose calculation was based either on MRI or CT. Two institutions routinely obtain MRI during the first brachytherapy, while the remaining institutions use CT-based IGABT with MRI obtained immediately prior to initiating brachytherapy as a reference. The equivalent dose in 2 Gy fractions (EQD_2) based on the linear-quadratic model was used in calculating the total dose of EBRT and brachytherapy [7]. No point dose prescription, such as the traditional point A, was performed, but the dose was prescribed to a volume, CTV_{HR}. Dose constraints for CTV_{HR} and organs at risk (OARs) were as follows: CTV_{HR} D_{90} delivered by brachytherapy >24 Gy/4 f, total rectum D_{2cc}<75 Gy, total bladder D_{2cc}<90 Gy, and total sigmoid D_{2cc}<75 Gy. At least HBT should be performed at the time of the first brachytherapy. When adequate tumor shrinkage has been obtained, ICBT can be used after the second brachytherapy. Based on the experience of head and neck interstitial brachytherapy [8,9], the diameter of the hyperdose sleeve around the interstitial needles outside of the uterus, which represents the isodose line of 200% of the prescribed dose, was advised to be smaller than 1 cm and should be kept smaller than 1.5 cm. Because the uterus is primarily composed of smooth muscle tissue, a diameter of the hyperdose sleeve greater than 1.5 cm inside of the uterus was permitted.

The definition of high-risk clinical target volume (CTV_{HR}) contouring was defined in the protocol paper [5], which was modified from the CT-based CTV_{HR} contouring guidelines proposed by Viswanathan et al. [10] While the rectum, sigmoid colon, and bladder were filled in from the inside, the vagina was contoured as a 4 mm thick donut-like wall structure [11].

5. Chemotherapy

Along with WPRT, concurrent weekly cisplatin (CDDP, 40 mg/m^2) was administered. If ≥grade 3 neutropenia or thrombocytopenia or ≥grade 2 creatinine elevation was observed, dosage was reduced to 30 mg/m^2.

6. Definition of initial response and follow-up

Three months after the completion of the treatment, chest X-ray or CT, pelvic CT, MRI, and cytology from the uterine cervix were taken to assess clinical response. No apparent tumor on the imaging studies and pathological disappearance of malignancy assessed three months after the completion of the protocol treatment was defined as a complete response (CR), and the others were defined as non-CR. Patients were followed every three months for the first year after treatment and every six months thereafter.

7. Statistical analysis

The contemporary approach of image-guided ISBT for locally advanced cervical cancer was found to have a 6.9% rate of grade ≥3 acute non-hematologic adverse effects [12]. Therefore, if the rate of grade ≥3 acute non-hematologic adverse events related to HBT (non-Hem-

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AE-HBT) was >10%, HBT was deemed unfeasible, and the study will not proceed to the phase II part. This decision was made based on the initial 20 patients who proceeded to the secondary registration. When the 20th patient was registered on the secondary registration, the patient accrual was temporarily halted to assess the feasibility of HBT based on the decision definition described above [4]. In the phase II part, it is expected that HBT has superior local effects than ICBT for locally advanced cervical cancer. Pötter et al. [13] reported a 2-year pelvic progression-free survival (PPFS) rate of 64% for patients with uterine cervical cancer whose initial tumor size was >5 cm and were treated with standard ICBT. This report was used as a historical control, and if the lower margin of 90% confidence interval (CI) of the HBT trial's 2-year PPFS is more than 64%, the HBT is deemed to be more effective than ICBT and this was the primary endpoint of this study. With an estimated HBT's 2-year PPFS of 80%, a one-sided alpha error of 0.05, and a beta effort of 0.2, the calculated sample size for the phase II part was 55 patients, including 20 patients enrolled in the phase I part. The initial planned patient accrual period was two years.

The overall survival (OS) rate was estimated from the primary registration date to the date of death from any cause, or censored at the last follow-up date. The progression-free survival (PFS) rate was estimated from the primary registration date to the date of any disease progression or the date of death from any cause, or censored at the last follow-up date. The PPFS rate was estimated from the primary registration date to the date of disease progression within the WPRT field or the date of death from any cause, or censored at the last follow-up date. The LC rate was estimated from the primary registration date to the date of disease progression within the uterus or the date of death from any cause, or censored at the last follow-up date. Survival curves were calculated using the Kaplan-Meier method and analyzed using the log-rank and Cox regression hazard model. Clinical factors in the regression model were selected by the backward elimination method with a threshold of p=0.1. A p-value ≤0.05 was considered statistically significant. In both univariate and multivariate Cox regression analyses, the median was generally used to determine a value for dichotomizing patient cohorts. If the median did not perform well, then a number around the median in an increment of 5 was selected. The statistical analysis was performed using the SAS Institute's statistical software version 9.4.

8. Ethics

The study protocol was approved by the institutional review board at each participating center in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The trial is registered with the UMIN (University Hospital Medical Information Network in Japan) Clinical Trials Registry, number UMIN000019081. Written informed consent was obtained from all patients before the enrollment of the clinical study.

RESULTS

1. Patients

Between October 2015 and October 2019, 73 patients were enrolled from in the initial registration from 18 Japanese institutions, and 52 patients (71.2%) proceeded to the secondary registration. The planned patient number for this study was 55, however, because of slow patient accrual, patient enrollment was closed when the 52nd patient proceeded to the secondary registration in October 2019 (**Fig. 1**).

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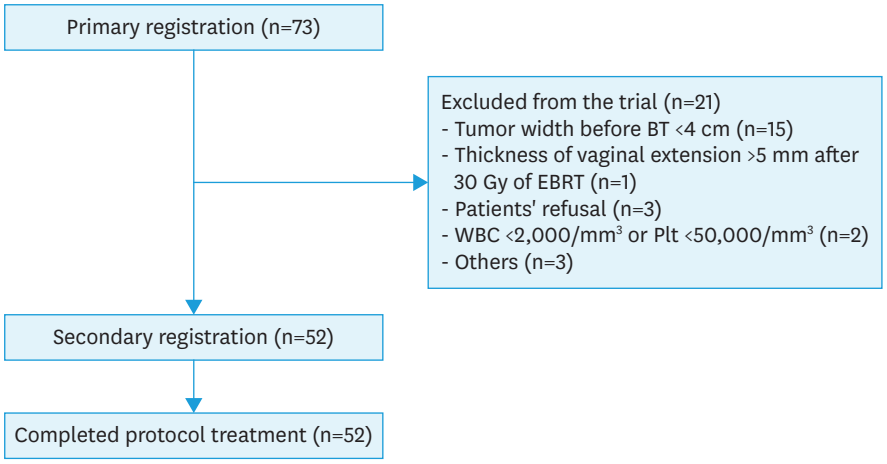

Fig. 1. The study's CONSORT flow diagram is depicted in Fig. 1. This diagram shows the patient flow throughout the trial.
BT, brachytherapy; EBRT, external beam radiation therapy; Plt, platelet ;WBC, white blood cell.

Table 1 summarizes the patients' characteristics. All 52 patients completed the planned protocol treatment. **Table 2** summarizes the treatment details. Sixteen patients were treated by MRI-based IGABT, and the remaining patients were treated by CT-based IGABT.

Fig. S2 shows a typical case treated by HBT. MRI before the treatment, MRI one week prior to the first HBT, and dose distribution of the first HBT are shown.

All patients completed the protocol treatment. Acute toxicities of the study were reported in the previous publication [4]. While only one grade 3 uterine hemorrhage was reported

Table 1. Patients' characteristics

Characteristics	Secondary registration (n=52)
PS	
0	37
1	15
2	0
Age (yr)	48 (26–74)
FIGO stage (2008)	
IB2	10
IIA2	2
IIB	20
IIIA	0
IIIB	20
IVA (bladder inv.)	0
Tumor width before primary registration (cm)	5.7 (4.3–9.2)
Tumor diameter before primary registration (cm)	6.0 (5.1–9.5)
Tumor width before secondary registration (cm)	4.6 (4.0–6.8)
Pelvic lymph node metastasis	
No	29
Yes	23
Histopathology	
SCC	47
ACC	4
ASC	1
Others	0

Values are presented as number or median (range).
AC, adenocarcinoma; ASC, adenosquamous carcinoma; FIGO, International Federation of Gynecology and Obstetrics; PS, performance status; Scc: squamous cell carcinoma.

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Table 2. Treatment details

Variables	Median (range)	SD
Whole pelvic radiation therapy (Gy)	30.0 (30.0–32)	0.3
Central Shield (Gy)	20.0 (18–20)	0.3
Lymph node boost (Gy)	6.0 (5.4–10.0)	1.8
CTV_{HR} (mL) at the first brachytherapy	38.2 (16.3–113.2)	21.7
CTV_{HR} (mL) at the secondary brachytherapy	34.6 (15.2–101.4)	19.1
CTV_{HR} (mL) at the third brachytherapy	29.6 (14–86.6)	16.8
CTV_{HR} (mL) at the forth brachytherapy	28.8 (9–75.6)	14.8
CTV_{HR} V_{100} (%)	98.5 (42.7–100)	9.1
Cumulative CTV_{HR} D_{90} (Gy, EQD_2, α/β=10 Gy)	71.9 (60.2–81.0)	3.9
Cumulative Rectum D_{2cc} (Gy, EQD_2, α/β=3 Gy)	54.3 (39.0–80.4)	8.8
Cumulative Sigmoid colon D_{2cc} (Gy, EQD_2, α/β=3 Gy)	53.8 (38.8–70.7)	7.2
Cumulative Bladder D_{2cc} (Gy, EQD_2, α/β=3 Gy)	69.8 (50.0–84.9)	7.0
Cumulative Vagina D_{2cc} (Gy, EQD_2, α/β=3 Gy)	131.7 (92.4–252.1)	34.2
The median number of needles inserted	2 (0–6)	1.5
The mean maximum hyper-dose sleeve diameter (mm)	8.5 (2.6–23.8)	3.9
CDDP cycles	6 (4–7)	0.8
Total CDDP dose (mg/m^2)	204.0 (128.4–278.5)	33.8
Total treatment time (wk)	6.6 (5.6–7.6)	0.5
Clinical response assessed 3 months after treatment		
CR	40 (76.9%)	
Non-CR	12 (23.1%)	

The total doses for the target and organs at risk were calculated by combining external beam radiation therapy and all brachytherapy (EQD_2).
CDDP, cisplatin; CR, complete response; CTVHR, high-risk clinical target volume; EQD_2, equivalent doses delivered in 2 Gy fractions; SD, standard deviation.

(1.9%), 18 grade 1–2 minor troubles were reported, including local infection, vaginal/uterine bleeding, or hematuria. It was found that CTV_{HR} ≥35 mL was associated with an increased risk of any grade of acute non-hematologic adverse events related to HBT [4].

2. Efficacy

The median follow-up period was 37.3 months (range, 13.9–52.9 months). The 2- and 3-year PPFS were 80.7% (90% CI=69.7%–88% and 95% CI=67.1%–89.1%) and 75.9% (95% CI=61.3%–85.6%), respectively. The 2- and 3-year LC were 86.5% (95% CI=73.7%–93.3%) and 81.4% (95% CI=67.1%–90.0%), respectively. The 2- and 3-year PFS were 73.1% (95% CI=58.8%–83.1%) and 70.6% (95% CI=55.9%–81.1%), respectively. The 2- and 3-year OS were 90.2% (95% CI=78.1%–95.8%) and 87.6% (95% CI=74.2%–94.3%), respectively (**Fig. 2**).

Multivariate analysis with the Cox regression analysis found that initial tumor size ≥6 cm (HR=0.14; 95% CI=0.03–0.60; p<0.01), CDDP>200 mg/m^2 (HR=0.12; 95% CI=0.03–0.49; p<0.01), and CR (HR=0.15; 95% CI=0.04–0.60; p<0.01) were found to be a significant clinical factor for better PPFS (**Table 3**). Tumor size before treatment ≥6 cm (HR=0.24; 95% CI=0.07–0.83; p=0.02), tumor shrinkage ratio >15% (HR=0.27; 95% CI=0.09–0.81; p=0.02), CDDP>200 mg/m^2 (HR=0.26; 95% CI=0.08–0.80; p=0.02) and CR assessed three months after the completion of the protocol treatment (HR=0.22; 95% CI=0.07–0.69; p=0.01) were found to be a significant clinical factor for better PFS (**Table S1**). Histopathology of Scc (HR=0.12; 95% CI=0.02–0.81; p=0.03, presence of pelvic lymph node(s) (HR=0.16; 95% CI=0.03–0.92; p=0.04), CDDP >200 mg/m^2 (HR=0.13; 95% C= 0.03–0.65; p=0.01), and CR (HR=0.10; 95% CI=0.02–0.45; p<0.01) were found to be a significant clinical factor for better LC (**Table S2**). Tumor shrinkage ratio >15% (HR=0.04; 95% CI=0.01–0.55; p=0.02), CR (HR=0.01; 95% CI=0.01–0.19; p<0.01), and CDDP>200 mg/m^2 (HR=0.05; 95% CI=0.01–0.54; p=0.02) was associated with better OS (**Table S3**).

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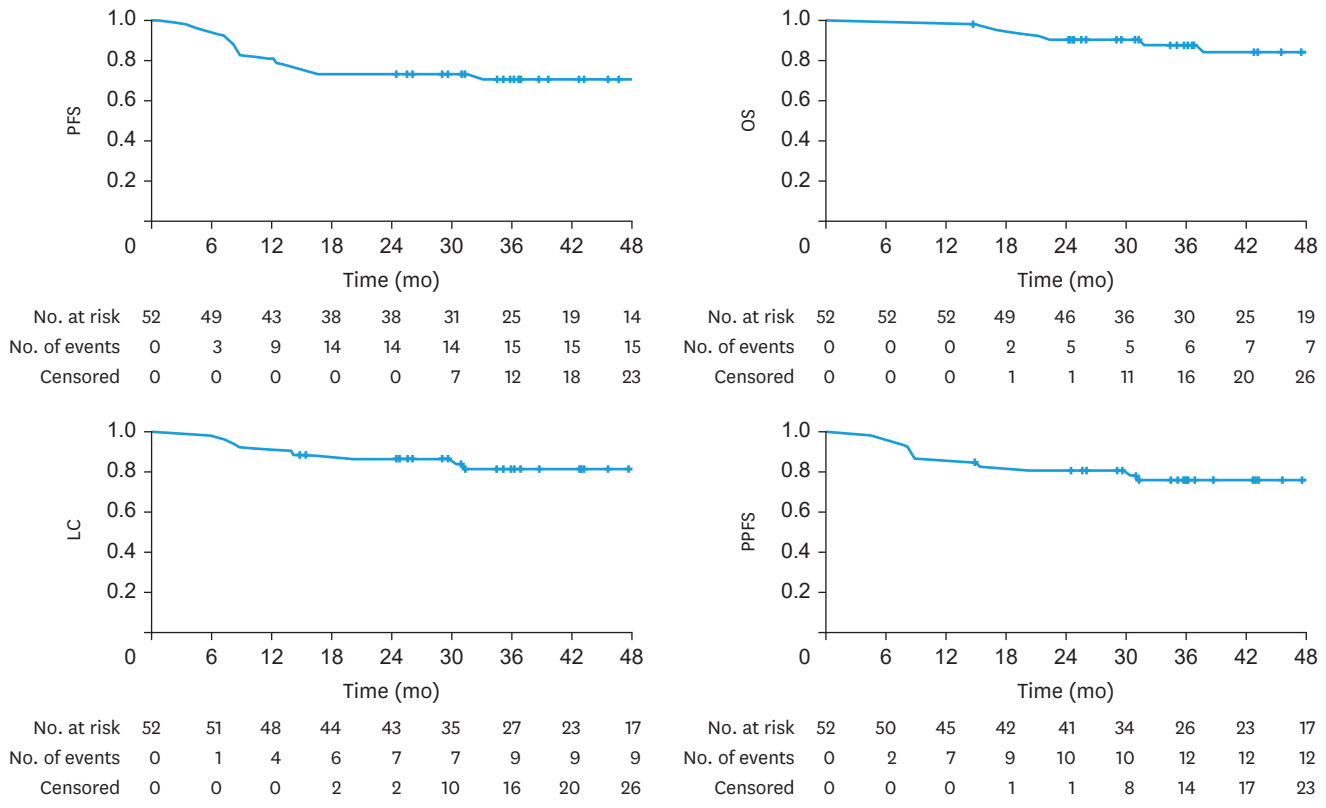

Fig. 2. Figure 2 shows progression-free survival, overall survival, local control, and pelvic progression-free survival curves.

3. Late toxicity

While 31 late gastrointestinal toxicities at all grades were observed, only two ≥ grade 3 late gastrointestinal toxicities were recorded (3.8%, grade 3 abdominal pain and grade 3 ileus). While six late bladder toxicities at all grades were observed, no ≥ grade 3 late bladder toxicities were recorded. While ten late vaginal toxicities at all grades were observed, only two ≥ grade 3 late vaginal toxicities were recorded (3.8%, grade 3 vaginal pain and grade 3 vaginal inflammation). **Table 4** summarizes the results of the logistic regression analysis on the relationship between clinical factors and late toxicities. Late vaginal toxicities were related to rectal D_{2cc}≥55.18 Gy (HR=14.62; 95% CI=1.69–126.48; p=0.015) and vagina D_{2cc}≥140.85 Gy (HR=4.23; 95% CI=1.00–17.84; p=0.05). The association between late toxicities and the diameter of the hyperdose sleeve around interstitial needles outside of the uterus was investigated with the logistic regression analysis. It was found that the size of the hyperdose sleeve around interstitial needles outside of the uterus did not influence the incidence of late toxicities (**Table 4**).

DISCUSSION

To the best of our knowledge, this is the first prospective clinical trial focusing on HBT in locally advanced uterine cervical cancer. The 2- and 3-year PPFS were 80.7% (90% CI=69.7%–88% and 95% CI=67.1%–89.1%) and 75.9% (95% CI=61.3%–85.6%), respectively. The lower range of 90% CI of 2-year PPFS was 69.7%, which was the primary endpoint of this study, and the even stricter end point of the lower range of 95% CI of 67.1 was higher than the prespecified historical control ICBT data of 64%. Therefore, the primary endpoint of phase

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Table 3. Cox regression analysis on the relationship between clinical factors and pelvic progression-free survival rate

Clinical factors	No.	Events (%)	Univariate analysis			Multivariate analysis†		
			Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Histopathology								
SCC	47	10 (21.3%)	Reference	-	-	-	-	-
AC+ASC	5	2 (40.0%)	2.04	(0.45–9.33)	0.36	-	-	-
FIGO stage								
IB2+IIA2+IIB	32	7 (21.9%)	Reference	-	-	-	-	-
IIIA+IIIB	20	5 (25.0%)	1.16	(0.37–3.65)	0.80	-	-	-
Tumor diameter before treatment (cm)								
<6	24	9 (37.5%)	Reference	-	-	Reference	-	-
≥6	28	3 (10.7%)	0.25	(0.07–0.92)	0.04*	0.14	(0.03–0.60)	0.01*
Tumor diameter before BT (cm)								
<5	32	8 (25.0%)	Reference	-	-	-	-	-
≥5	20	4 (20.0%)	0.83	(0.25–2.75)	0.76	-	-	-
Tumor shrinkage ratio (%)‡								
<15	12	5 (41.7%)	Reference	-	-	-	-	-
≥15	40	7 (17.5%)	0.33	(0.10–1.04)	0.06	-	-	-
CTV_{HR} D_{90} (a total of 4 BTs)								
<29 Gy	24	6 (25.0%)	Reference	-	-	-	-	-
≥29 Gy	28	6 (21.4%)	0.78	(0.25–2.41)	0.66	-	-	-
Pelvic lymph node metastasis								
No	29	7 (24.1%)	Reference	-	-	-	-	-
Yes	23	5 (21.7%)	0.891	(0.28–2.81)	0.85	-	-	-
A total amount of CDDP (mg/m^2)								
≤200	17	7 (41.2%)	Reference	-	-	Reference	-	-
>200	35	5 (14.3%)	0.27	(0.09–0.87)	0.03*	0.12	(0.03–0.49)	<0.01*
CR or not§								
Non-CR	12	5 (41.7%)	Reference	-	-	Reference	-	-
CR	40	7 (17.5%)	0.32	(0.10–1.00)	0.05*	0.15	(0.04–0.60)	<0.01*

AC, adenocarcinoma; ASC, adenosquamous carcinoma; BT, brachytherapy; CDDP, cisplatin; CR, complete response; CTV_{HR} D_{90}, the minimal dose delivered to 90% of the high-risk clinical target volume; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.
*Statistical significance was defined as a p-value of ≤0.05.
†Clinical factors in the regression model were selected by the backward elimination method with a threshold of p=0.1.
‡Tumor Reduction Ratio = {(Tumor Diameter Before Treatment)−(Tumor Diameter Before the First Brachytherapy)}/(Tumor Diameter Before Treatment).
§A complete response was assessed three months after protocol treatment according to the findings of histology, physical examination, and magnetic resonance imaging.

Table 4. Logistic regression analysis on relationship between clinical factors and late toxicities

Variables	No.	Events	Univariate analysis		
			Odds ratio	95% CI	p-value
Rectum D_{2cc} (EQD_2)*1					
<55.18 Gy	27	5 (18.5%)	Reference	-	
≥55.18 Gy	25	8 (32.0%)	2.07	0.57–7.48	0.27
Rectum D_{2cc} (EQD_2)*2					
<55.18 Gy	27	1 (3.7%)	Reference	-	
≥55.18 Gy	25	9 (36.0%)	14.62	1.69–126.48	0.02*
Bladder D_{2cc} (EQD_2)*3					
<68.97 Gy	24	3 (12.5%)	Reference	-	
≥68.97 Gy	28	3 (10.7%)	0.84	0.15–4.61	0.84
Vagina D_{2cc} (EQD_2)*2					
<140.85 Gy	35	4 (11.4%)	Reference	-	
≥140.85 Gy	17	6 (35.3%)	4.23	1.00–17.84	0.05*
The mean maximum hyper-dose sleeve diameter					
≤10 mm	36	13 (36.1%)	Reference	-	
>10 mm	16	4 (25.0%)	0.59	0.16–2.21	0.43
The mean maximum hyper-dose sleeve diameter					
≤15 mm	46	16 (34.8%)	Reference	-	
>15 mm	6	1 (16.7%)	0.38	0.04–8.87	0.39

EQD_2, equivalent doses delivered in 2 Gy fractions; *1, rectal late adverse events were included as events; *2, vaginal late adverse events were included as events; *3, bladder late adverse events were included as events.
*Statistical significance was defined as a p-value of ≤0.05.

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II part was met, and it can be concluded that HBT is superior to conventional ICBT in terms of LC. In addition, although the direct comparison is impossible, the 2-year PPFS of 80.7% observed in the current study appeared to be better than the 2-year PPFS of 72% for tumors 50–70 mm treated with 2D-ICBT with a similar typical Japanese dose schedule involving CS conducted in a prospective phase II study in Japan [14], indicating a better LC effect of HBT for locally advanced diseases.

It has been demonstrated that when >85 Gy is delivered to the CTV_{HR} D_{90}, >90% LC will be expected regardless of T-stage, but it is at the cost of high rate of ≥grade 3 late severe radiation-related toxicities in more than 10% of patients [2], which is considered unacceptable from the Japanese point of view. In contrast, Japanese treatment guidelines adopt response-based dose delivery, but as the results of this study showed, pelvic control is under 90% and there is room for improvement. In other words, the Japanese strategy was effective in approximately 80% of patients. As shown in our previous work, there is a group of patients who responded well to the treatment and were cured by a lower dosage [15]. However, in 20% of patients, it did not work, and a higher dosage of >85 Gy should have been needed. Finding tumors with radioresistant features before the initiation of treatment is the next step we must take. While the etiology of the majority of cervical cancer patients is human papillomavirus (HPV) infection, some tumors are HPV-independent, and it has been reported that such HPV-independent tumors are associated with lymph node metastasis in the early stage, more distant metastasis, and poorer prognosis [16]. Consequently, investigating the relationship between HPV status and radioresistant features is an interesting topic; unfortunately, HPV testing was not mandatory in this study, but this should be elucidated by future studies.

As shown in **Table 3** and **Tables S1–S3**, larger tumor size prior to treatment or BT was associated with better clinical outcomes, which is clinically unreasonable. Unlike nodules in lung parenchyma, some uterine cervical tumors with blurred tumor boundaries are difficult to precisely measure. Uncertainties regarding the gross target volume contouring during MRI-based IGABT have been previously reported [17]. In addition, central review of all MRIs before treatment or BT was not performed in this trial. These points are possible explanations for why such clinically implausible outcomes were observed in this study.

In line with the previous reports [18], it was demonstrated that a total amount of CDDP >200 mg/m^2 was associated with better LC (HR=0.13; 95% CI=0.03–0.65; p=0.01), PFS (HR=0.26; 95% CI=0.08–0.80; p=0.02), and OS (HR=0.05; 95% CI=0.01–0.54; p=0.02, **Tables S1–S3**). This means that, similar to head and neck cancer chemoradiotherapy [19], it is recommended to administer >200 mg/m^2 of CDDP (>5 cycles) to obtain an adequate effect to eradicate systemic micro-metastasis also in advanced cervical cancer. In the era of IGABT, the main patterns of recurrence are distant metastasis, and novel agents for systemic control are warranted. In eradicating micro-metastasis, prophylactic extended-field pelvic irradiation has a role [20], however, it will increase the toxicities and can only cover para-aortic lymph node region. Immunotherapy may hold the promise of improving distant control. However, the CALLA trial [21], in which durvalumab, an anti-PD-L1 antibody, was used concurrently and adjuvantly with CCRT was compared to CCRT, and favorable results were anticipated, did not result in a statistically significant improvement in PFS [22]. The Keynote-A18 adding Pembrolizumab, an anti-PD-1 antibody, to CCRT is still ongoing [23], and if positive results are obtained, the combination of improved radiation technique and new systemic agents will further improve patients' outcomes.

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A major strength of this study was that it demonstrated an acceptable 3-year LC rate of 81% with very low late severe toxicity rates. Because the usage of CS was mandatory in the protocol treatment, both the median CTV_{HR} D_{90} and OARs were lower than those reported by the EMBRACE-I study. While the dose contribution from CS was ignored in this study, it was reported that 13%–35% of the dose from CS with a 4 cm width would have been delivered both to the CTV depending on the size of the tumor [24]. Therefore, in reality, these doses would have been slightly higher than what was presented in this study. Nonetheless, the median CTV_{HR} D_{90} and OARs were still lower than in the EMBRACE-I study. Consequently, 5-y LC of 92% was achieved in the EMBRACE-I study, while the current study had 3-y LC of 81% [2]. Similarly, the retroEMBRACE study, in which 610 patients were retrospectively analyzed, demonstrated 5-y LC of 89% with CTV_{HR} D_{90} 88 Gy [3]. The reason why relatively favorable outcomes were observed in this study despite the lower CTV_{HR} D_{90} were supposed to be partly attributable to the shorter TTT in this study, in which the median TTT was 6.6 weeks (range 5.6–7.6) (**Table 2**) compared to other studies using European and American treatment guidelines [25,26]. Shortening TTT may potentially decrease the dose to overcome the effect of repopulation [27], and this could be the possible explanations for the lower CTV_{HR} D_{90} with favorable LC. Besides the lower CTV_{HR} D_{90} doses, the lower LC in the current study compared to other studies was partly because all the patients enrolled in this study had an initial tumor width larger than 5 cm. Even so, due to the lower rate of severe radiation-related toxicities in this study, it is possible that we could give another fraction of HBT, namely WPRT 30 Gy + CS 20 Gy + HBT 6 Gy x 5 fractions for patients with poor response, which should be investigated in future studies.

The treatment schedule of the current study is different from that most commonly used worldwide in that CS was used after 30 Gy of pelvic irradiation and brachytherapy was started. Therefore, it is possible that maximal tumor regression could not be obtained because brachytherapy was initiated before the full course of pelvic radiotherapy of 45–50 Gy. As written in the exclusion criteria, patients having too large tumor to be adequately covered by HBT were excluded from this study: as shown in **Fig. 1**, one patient was excluded due to having a vaginal extension that was thicker than 5 mm. If this patient received the full dose of 45–50 Gy of pelvic irradiation, it would be possible to offer HBT. However, this comes at the cost of doses to the OARs. Therefore, the pros and cons of whether to deliver a full dose of pelvic irradiation followed by HBT or incorporate CS and apply multi-catheter ISBT should be considered on a case-by-case basis and institutions-by-institution basis. It was found in the current study that CR assessed three months after protocol treatment was associated with better LC (HR=0.10; 95% CI=0.02–0.45; p<0.01, **Table S2**). However, such information can only be obtained three months after treatment. To select patients who really need >85 Gy much earlier, not only tumor shrinkage ratio [15], but tumor pathological characteristics [28] or image texture [29] would be an alternative way to distinguish patients, and such a more sophisticated and personally tailored treatment strategy would be an imaginable future direction of management of radiation therapy for cervical cancer patients.

Although when the current study was launched, the application of intensity modulated radiation therapy (IMRT) was limited supposedly due to uncertainties regarding internal organ motion and this study had to prepare two IMRT plans, WPRT with and without CS, there have been accumulated reports on the safety and efficacy of IMRT to treat locally advanced cervical cancer [30,31]. Acute and long-term consequences of bowel irradiation cannot be ignored, therefore, incorporating IMRT will potentially further improve patients 'outcomes in the future.

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Although the rate of late severe ≥grade 3 vaginal toxicities was 3.8%, when all grade late vaginal toxicities were considered as events, patients with vagina D_{2cc}≥140.85 Gy had a 4.23 times higher probability of experiencing late vaginal toxicities than patients with vagina D_{2cc}<140.85 Gy. Because this trial required contouring the vaginal wall in the same manner for all the patients, the obtained results can be highly reliable. It was in line with the previous report that D_{2cc} ≥ 145 Gy was associated with an increased risk of vaginal ulcer development [11]. Susko et al. [32] also reported an association between vaginal dose and its toxicities. In addition, as retro-EMBRACE studies demonstrated that vaginal toxicities were associated with the ICRU-recto-vaginal reference point [33,34], rectal D_{2cc}≥55.18 Gy was associated with an increased risk of late vaginal toxicities in this study (**Table 4**).

Based on the lessons learned from head and neck interstitial brachytherapy [8,9], it was assumed that the diameter of the hyperdose sleeve around the additionally inserted interstitial needles should be kept under 1–1.5 cm for safety reasons, and this limit was set in the protocol of this study. However, it was found that the size of the hyperdose sleeve around interstitial needles outside of the uterus did not influence the incidence of late severe toxicities at least up to 1.5 cm (**Table 4**), which is important information, especially for those who want to start HBT.

While 81.4% of 3-year LC was observed in this study, out-of-field metastases were observed in about 30% of patients at three years, which should be improved in further treatment development. Previous studies have shown the potential utility of circulating tumor DNA (ctDNA) in selecting appropriate patients for adjuvant treatment for rectal or colon cancer [35]. Such ctDNA detection has also been demonstrated in locally advanced cervical cancer during chemoradiotherapy [36]. In addition, recently, immune checkpoint inhibitors have demonstrated a clinical benefit for recurrent or metastatic cervical cancer [37]. Similar to locally advanced lung cancer [38], adjuvant immune checkpoint inhibitors would be beneficial for patients harboring positive ctDNA after cCRT.

The data cited as the historical control in this study was not based on IGABT, but on 2-D based ICBT. Clinical outcomes of a single institution's retrospective 2-D based ICBT could only be used as historical data due to the lack of clinical data with image-guided ICBT stratified by large tumor size at the time this protocol was developed; however, numerous studies have demonstrated excellent LC with IGABT with ICBT since then [2,39]. In accordance with the Japanese treatment guideline [6], CS was utilized in this study, despite not being recommended by the European and American treatment guidelines [1,25,26]. Due to the use of CS, the median total dose delivered to the CTV_{HR} D_{90} was less than 85 Gy recommended by the European and American guidelines. On the other hand, because of the application of CS, the doses of OARs were kept at a lower level and the rate of late severe adverse events was below 5%, which was significantly lower than the standard in Western countries. However, the LC of poorly responding tumors was insufficient and must be enhanced with higher doses. Despite the above-mentioned limitations, the authors believe the results obtained by this prospective clinical trial dedicated to HBT are valuable and should be widely shared with our society.

A direct comparison between ICBT and HBT for locally advanced tumors is desirable in the future, but, given that there are several favorable clinical outcomes with retrospective studies [3,40] and the current prospective study that support the superiority of HBT over ICBT, it is ethically difficult to perform a direct comparison.

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The feasibility and effectiveness of HBT were demonstrated by a prospective clinical study. Because the CTV_{HR} D_{90} dose goal determined in the protocol was lower than 85 Gy, there is room for improvement for LC. A higher dose might have been needed for tumors with poor responses.

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SUPPLEMENTARY MATERIALS

Table S1
Cox regression analysis on the relationship between clinical factors and progression-free survival rate

Click here to view

Table S2
Cox regression analysis on the relationship between clinical factors and local control

Click here to view

Table S3
Cox regression analysis on the relationship between clinical factors and overall survival

Click here to view

Fig. S1
An overview of the protocol treatment.

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Fig. S2
(A) MRI of a T3bN1M0 uterine cervical squamous cell cancer patient prior to treatment. The tumor had bilateral parametrial invasion to the pelvic wall and had uterine body invasion accompanied by hydrometra. The tumor had a maximum diameter in the lateral direction of 55 mm. (B) The width of the tumor was still 51 mm on an MRI taken one week prior to the first brachytherapy, and proceeded to secondary registration. (C) Dose distribution of the first brachytherapy with three needles inserted into each side of the parametrium with transperineal free-hand approach.

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