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# Selection Criteria and Clinical Outcomes of Patients With Asymmetrical Cervical Cancer Treated With Various High-dose-rate Brachytherapy Techniques

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**Abstract.** *Background/Aim: We aimed to evaluate the efficacy of high-dose-rate brachytherapy techniques selected according to pre-brachytherapy magnetic resonance imaging (MRI) findings in asymmetrical cervical cancer (ACC). Patients and Methods: We analyzed 33 ACC patients. Asymmetric tumors were defined as those in which the difference between the distance from the cervical canal to the farthest end of the tumor [long distance (LD)] and the distance from the cervical canal to the contralateral tumor edge [short distance (SD)] is equal to or greater than 2 cm on the basis of MRI prior to treatment. On pre-treatment and pre-brachytherapy MRI, the median LDs were 40 mm and 21 mm, respectively. Patients with LD≥2 cm and LD – SD≥1 cm on pre-brachytherapy MRI received non-conventional intracavitary brachytherapy (ICBT). Results: Sixteen patients (48%) received non-conventional ICBT. There was no significant difference in 3-year local control between the two treatment groups (100% vs. 81.2%, p=0.07); two patients had grade 2 radiation proctitis. Conclusion: Brachytherapy techniques selected according to pre-brachytherapy MRI findings were effective for ACC treatment.*

Brachytherapy is an essential component of radiotherapy for the improvement of overall survival (OS) and local control (LC) in patients with cervical cancer (1, 2). Excellent LC has been observed in patients with early cervical cancer treated with radical radiotherapy, including conventional intracavitary brachytherapy (ICBT), which delivers a pear-shaped dose distribution; dose is prescribed at point A using the Manchester method (3). However, the dose distribution of conventional ICBT is inadequate for encompassing bulky, extensive, and irregular-shaped tumors, resulting in poor LC (4, 5). Asymmetrical tumor shape is an important factor associated with local recurrence. Since conventional ICBT provides inadequate tumor coverage in these cases, a technique ideally suited for the treatment of symmetrical tumors needs to be employed (6).

The American Brachytherapy Society (ABS), and Groupe Européen de Curiethérapie - European Society for Radiotherapy and Oncology have recommended the optimal prescription doses for the clinical target volume (CTV) and organs at risk (OARs) (7, 8). The use of image-guided adaptive brachytherapy (IGABT) allows the delivery of sufficient doses to the CTV, while respecting dose constraints of the OARs (9). Therefore, IGABT offers better LC than conventional ICBT, which delivers the prescribed dose to point A (10). In patients with bulky parametrial extension, both interstitial brachytherapy (ISBT) and combined intracavitary brachytherapy with interstitial techniques (IC/ISBT) provide good LC (11, 12). However, ISBT and IC/ISBT cause higher mental and physical stress to patients compared with conventional ICBT. Therefore, the appropriate selection of brachytherapy techniques is of considerable importance. At present, the eligibility criteria for the selection of patients for ICBT *vs*. ISBT or IC/ISBT, are unclear.

In this study, we aimed to evaluate the clinical outcomes of patients with asymmetrical cervical cancer treated with

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*Key Words:* Cervical cancer, high-dose-rate brachytherapy, pre-brachytherapy magnetic resonance imaging, radiotherapy.

ICBT, IC/ISBT, or ISBT, selected according to findings on pre-brachytherapy magnetic resonance imaging (MRI).

## Patients and Methods

*Patients' characteristics*. We retrospectively analysed the data from 33 patients with asymmetrical tumors on pre-treatment MRI (Figure 1), who received radical radiotherapy between July 2009 and January 2016. Asymmetric tumors were defined as those in which the difference between the distance from the cervical canal to the farthest end of the tumor [long distance (LD)] and the distance from the cervical canal to the contralateral tumor edge [short distance (SD)] is equal to or greater than 2 cm on the basis of MRI prior to treatment. The tumor distance was measured in the largest dimension. For instance, the tumors shown in Figures 2 (a) and (b) were defined as asymmetrical tumors, but the tumor in Figure 2 (c) was described as bulky; it was symmetrical in nature. Figures 2 (d) and (e) show the typical MRI findings in asymmetrical tumors invading in the antero-posterior (AP) and lateral directions, respectively. This study was approved by the ethical review committee of our institution as per the institutional policy.

*Radiotherapy*. For all patients, radiotherapy consisted of a combination of external beam radiotherapy (EBRT) and high-dose-rate (HDR) brachytherapy. EBRT was delivered by the three-dimensional conformal technique with a linear accelerator (Clinac IX; Varian Medical System, Palo Alto, CA, USA) using 15-MV photon beams. For patients treated with ICBT and IC/ISBT, whole pelvic EBRT was initially administered to a dose of 30.6-39.6 Gy in 17-22 fractions with the standard box technique; additional 10.8-19.8 Gy were delivered in 6-11 fractions by EBRT using a 4-cm wide midline block (MB) and antero-posterior/posterior-anterior (AP/PA) parallel-opposed fields. For patients treated with ISBT, an MB was placed along the 50% isodose line, as determined during ISBT planning. When the shortest diameter of the pelvic lymph nodes exceeded 1 cm, an EBRT boost dose of 6-10 Gy in 3-5 fractions was added. All patients underwent a pre-brachytherapy MRI 7 days prior to the first brachytherapy session.

The first HDR-ICBT, ISBT, and IC/ISBT session was performed within 7 days after placement of the MB. EBRT with MB was administered 4 times a week, while ICBT or IC/ISBT was performed once a week. Brachytherapy was performed using an iridium 192 ($^{192}$Ir) remote afterloading system (microSelectron HDRTM; Nucletron, Veenendaal, the Netherlands). Radiography was usually employed for conventional ICBT planning according to the Manchester system; the prescription dose was administered to point A. For all patients treated with brachytherapy, except for those receiving conventional ICBT, planning was performed based on computed tomography (CT) images of 2-mm slice thickness, using the PLATO v 3 (Nucletron) and Oncentra v4.0 (Nucletron) treatment planning systems till October 2011 and between November 2011 and September 2015, respectively. Since planning CT equipment is not installed in the brachytherapy room at our institute, patients treated with non-conventional ICBT were shifted to the CT room to acquire the planning CT images after applicator insertion. The high-risk CTV (HR-CTV) included the macroscopic residual tumor [identified on high T2-weighted images (T2WI) on pre-brachytherapy MRI] and the entire cervix. The bladder, sigmoid colon, and rectum, in the region between 2 cm cranially from the uterine fundus to the upper border of the anal canal, were delineated as OARs. Conventional ICBT was performed once a week under mild sedation; the dose to point A was 20-24 Gy in 4 fractions. In cases receiving IC/ISBT, a D90 (dose reported as percentage of the prescription dose received by 90% of the CTV) of 20-24 Gy in 4 fractions was administered as to the HR-CTV once a week, using tandem/ovoid applicators and a few (1-3) transvaginal needles under local anaesthesia and mild sedation. The Martinez Universal Perineal Interstitial Template was used to deliver ISBT to a dose of 24-30 Gy in 4-5 fractions for 2-3 consecutive days to the HR-CTV D90. All ISBT procedures were performed under general anaesthesia, and epidural anaesthesia was administered for pain control until needle removal.

*Chemotherapy*. Weekly paclitaxel (TP) and cisplatin (CDDP) were administered at doses of 50 mg/m$^2$ and 30 mg/m$^2$, respectively, during the entire period of radiotherapy. In patients aged 70 years or older, or in those who wanted to avoid the alopecia caused by paclitaxel, single-agent weekly CDDP was administered at a dose of 40 mg/m$^2$. Patients with insufficient renal function or those aged 75 years or older did not receive concurrent chemoradiotherapy. Overall, 4, 29, and 24 patients received radiotherapy alone, concurrent chemoradiotherapy, and weekly TP+CDDP, respectively.

*MRI protocol*. A 3.0-T superconductive scanner was used for the MRI scans. Transaxial T1-weighted imaging (T1WI) sequences [repetition time (TR): 300-600 ms; echo time (TE): 10-20 ms] were obtained with 5-mm slice thicknesses, 1.0-mm section gaps, and 384×256 matrix sizes; transaxial T2-weighted sequences (TR: 2500-5000 ms; TE: 100-110 ms) were obtained with 5-mm slice thicknesses, 1.0-mm section gaps, and 448×288 matrix sizes. Sagittal T2-weight images (TR: 3000-5000 ms; TE: 100-120 ms) were obtained with 5-mm slice thicknesses, 1.0-mm section gaps, and 416×288 matrix sizes.

*MRI assessment and brachytherapy technique selection*. Asymmetrical tumors assessed during pre-brachytherapy MRI were defined on the basis of the following criteria (Figure 1):
1) LD>2 cm (* in Figure 3)
2) LD (* in Figure 3) − SD († in Figure 3) =1 cm or greater
The tumor distance was measured in the largest dimension. Tumors fulfilling both criteria on pre-brachytherapy MRI were defined as asymmetrical tumors. A typical asymmetrical tumor on pre-brachytherapy MRI is shown in Figure 3 (a). However, the tumors described in Figure 3 (b, c, and d) were not categorized as asymmetrical tumors on pre-brachytherapy MRI. At pre-brachytherapy MRI, 16 patients had an asymmetrical tumor, for which non-conventional ICBT was selected.

Conventional ICBT was performed only in patients with symmetrical tumors; other brachytherapy techniques were employed in those with asymmetrical tumors on pre-brachytherapy MRI. IC/ISBT using few needles was selected for asymmetrical tumors with total vaginal invasion depths of 5 mm or less. ISBT using multiple needles was selected for tumors with vaginal invasion depths exceeding 5 mm. However, in patients with tumors extending to the iliac artery or sigmoid colon, the insertion of brachytherapy needles was not deemed safe; these patients received ICBT with an intensity-modulated radiotherapy (IMRT) boost (Figure 1).

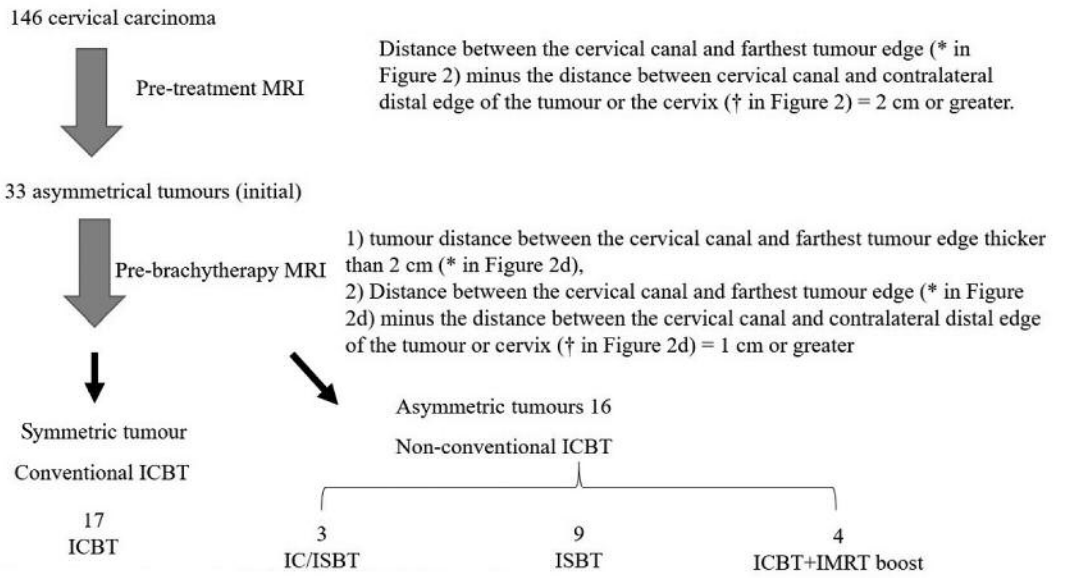


Figure 1. *Patient selection. Selection of patients with asymmetric tumors according to the pre-treatment MRI. Dotted lines delineate the tumor. Asymmetrical tumors were defined as those with differences of ≥2 cm between the distance from the cervical canal to the farthest tumor edge and the distance from the cervical canal to the contralateral distal edge of the tumor (c) or cervix (d). The tumor in figure (e) was bulky but symmetrical. The tumors invading in the antero-posterior (AP) and lateral directions are shown in figures a and b, respectively. *Distance between the cervical tube and farthest tumor edge. †Distance between the cervical tube and contralateral distal edge of the tumor or cervix. MRI: Magnetic resonance imaging; ICBT: intracavitary brachytherapy; IC: intracavitary; ISBT; interstitial brachytherapy; IMRT: intensity-modulated radiotherapy.*

*Follow-up*. The treatment response was evaluated on MRI at 2-3 months after the completion of radiotherapy, according to the Response Evaluation Criteria in Solid Tumors. Follow-up cytology, blood tests, and imaging were performed every 2-6 months for 5 years. The median duration of follow-up was 44.2 months (range=8.8-81.5 months).

*Dose calculation and measurements*. For patients treated with ISBT or IC/ISBT, the doses to the CTV and OARs were calculated as the uniform dose summation of brachytherapy with EBRT before the insertion of the MB. Furthermore, the equivalent dose in 2 Gy fractions (EQD2) was calculated on the basis of the linear-quadratic model (13). The tumor dose was calculated using an $\alpha/\beta$ ratio of 10 Gy. To calculate the dose-volume parameters of the OAR [D2.0 ml (dose in Gray received by 2 ml of the organ)], the $\alpha/\beta$ ratio was assumed to be 3 Gy.

To estimate the response to radiation therapy in each of the cases, the LDs were measured based on the pretreatment and pre-brachytherapy MRI findings (* in Figures 2 and 3), and the volume reduction ratio was defined using the following formula:

$$100 - \frac{\text{LD in pre – brachytherapy MRI (mm)}}{\text{LD in pretreatment MRI (mm)}} \times 100\ (\%)$$

The volume reduction ratios were calculated according to the direction of tumor extension.

*Statistical analysis*. The 5-year OS, disease-free survival (DFS), distant metastasis-free survival and LC rates were estimated using the Kaplan–Meier method. Differences in the outcomes were compared using a log-rank test. A Student's *t*-test was used to compare the differences in LD and volume reduction rates between the pre-treatment and pre-brachytherapy MRI scans. Statistical significance was at $p<0.05$. All statistical analyses for this study were performed using the SPSS Base System software program (SPSS, Chicago, IL, USA). Late adverse events were graded based on the Common Terminology Criteria for Adverse Events, version 4.0. of the National Cancer Institute.

## Results

The median age of the cohort was 57 years (range=27-75 years). Overall, 2, 8, 16, and 7 patients had International Federation of Gynecology and Obstetrics (FIGO) stages IB2, II, III, and IVA disease, respectively. The histologies in 29 and 4 patients were squamous cell carcinoma and adenosquamous or adenocarcinoma, respectively. The asymmetrical tumor extended in the AP direction (Figure 2d), lateral direction (Figure 2e), and in both directions in 16, 12, and 4 patients, respectively. In the remaining patient, the tumor developed in the anterior cervical wall and extended in the cranial direction to invade the sigmoid colon. The median tumor size, defined as the maximum tumor size measured on pre-treatment MRI, was 54 mm (range=30-85 mm). Table I summarizes patient characteristics.

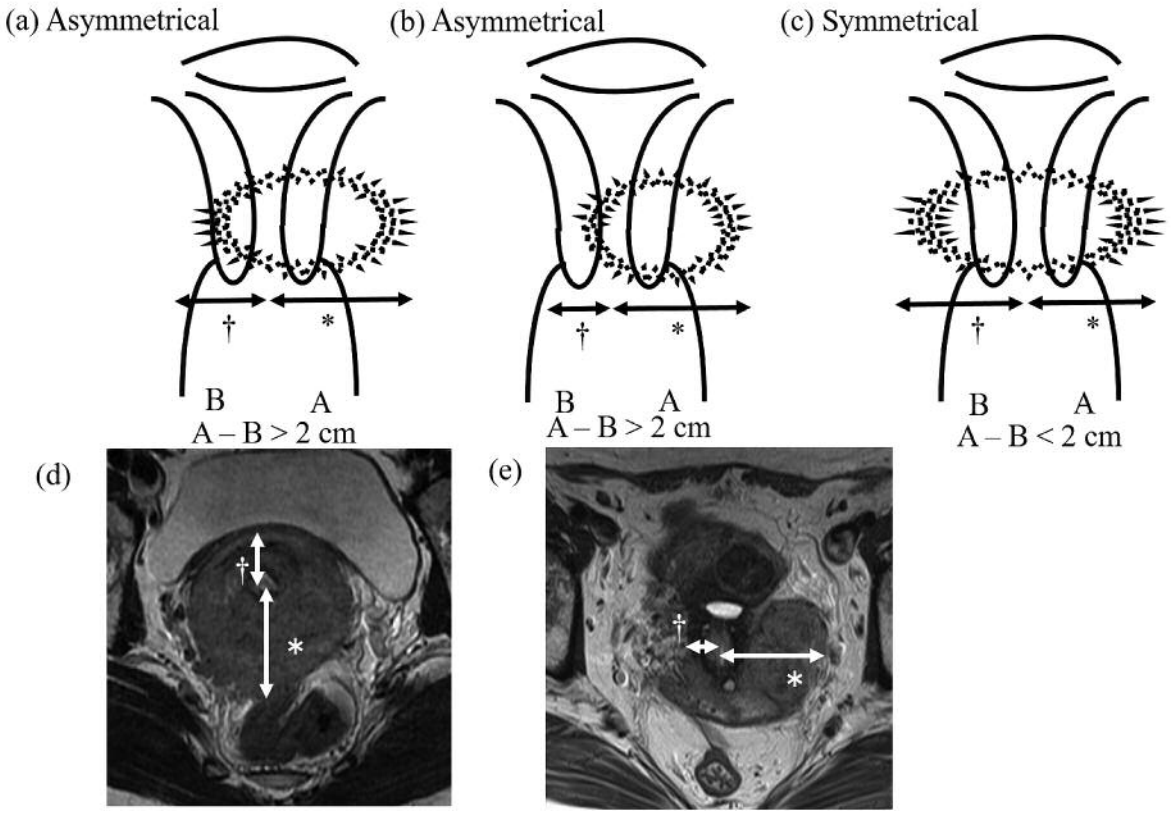


Figure 2. *Asymmetric tumors on pre-treatment MRI. (a, b) Typical asymmetrical tumors. (c) Bulky but symmetrical tumor. (d) Tumor extending in the anterior or posterior direction on pre-treatment MRI. (e) Tumor extending in the lateral direction on pre-treatment MRI. *Distance between the cervical canal and farthest tumor edge. †Distance between the cervical canal and contralateral distal edge of the tumor or cervix.*

In the pre-treatment period, the median LDs for the patients with tumor invasion in the AP and lateral directions were 34 mm (range=28-52 mm) and 45 mm (range=29-51 mm), respectively ($p$=0.20) (Figure 2); the corresponding values on pre-brachytherapy MRI were 18 mm (range=10-42 mm) and 27 mm (range=15-48 mm), respectively ($p$=0.02) (Figure 3). The median tumor distance reduction rates in all patients, those with tumor invasion in the AP direction, and those with tumor invasion in the lateral direction were 37.5% (range=5.9-68.0%), 48.6% (range=18.9-68.0%), and 32.7% (range=5.9-57.1%), respectively ($p$=0.01 for AP *vs*. lateral). At pre-treatment MRI, no significant differences were observed in LDs between patients with tumor invasion in the AP and lateral directions. However, the tumor reduction rates after EBRT were poor in patients with tumor invasion in the lateral direction.

A total of 17 patients (51.5%) received conventional ICBT, while the remaining 16 (48.5%) received non-conventional ICBT, of whom 9 (27.3%), 3 (9.1%), and 4 (12.1%) received ISBT, IC/ISBT, and ICBT with an IMRT boost, respectively (Table II). IMRT boost was required in 3 and 1 patients for the parametrial component extending to the internal iliac artery and for the tumor invading the sigmoid colon, respectively. Twelve of 16 patients with tumor invasion in the lateral direction (75%) received non-conventional ICBT. Patients with tumors extending in the lateral direction were more likely to receive non-conventional ICBT than those with tumors extending in the AP direction.

In patients treated with ISBT or IC/ISBT, the mean EQD2 of the CTV D90 was 69.6±3.6 Gy. The D2cc for the bladder, sigmoid, and rectum were 70.6±8.4 Gy, 45.6±6.0 Gy, and 62.3±2.5 Gy, respectively. None of the patients received more than the recommended OAR doses as per the ABS guidelines (8).

A total of 31 (93.9%) patients achieved complete response. At the time of analysis, residual tumor or local recurrence was observed in 3 patients who received ISBT. The 3-year OS rates in the entire cohort, patients who received conventional ICBT, and those who received non-conventional ICBT, were 83.5%, 100%, and 63.2%, respectively ($p$=0.01 for conventional ICBT *vs*. non-conventional ICBT) (Figure 4a). The overall 3-year DFS and distant metastasis-free survival rates were 77.9% and 78.3%, respectively. The 3-

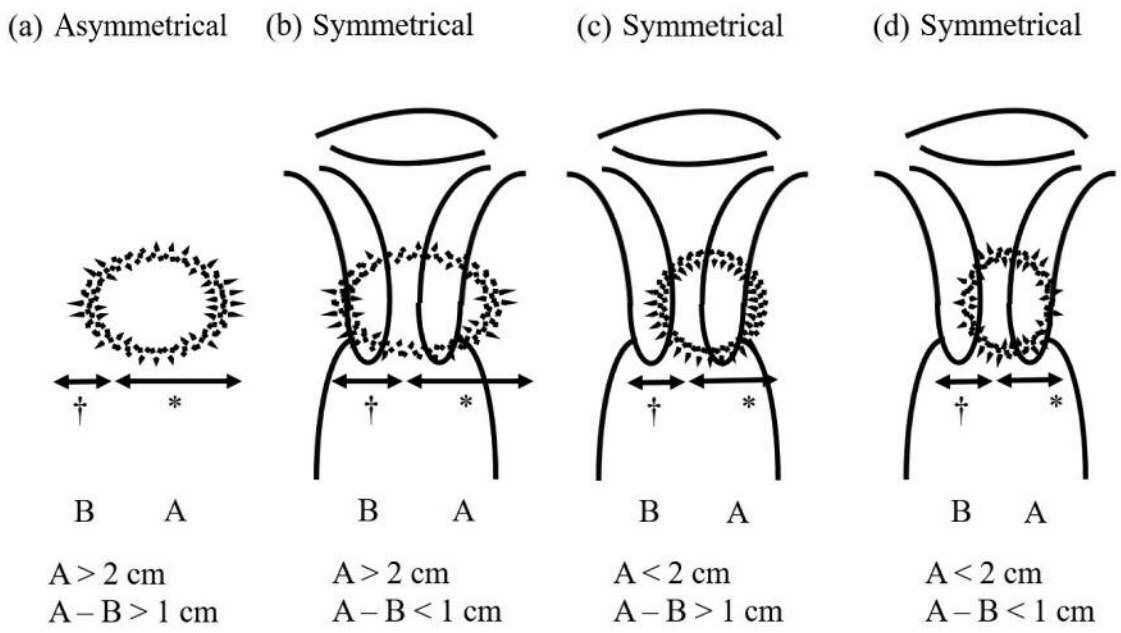


Figure 3. *Asymmetric tumors on pre-brachytherapy MRI. (a) Typical asymmetrical tumor. (b) Bulky but symmetrical tumor. (c) Asymmetrical but not bulky tumor. (d) Small symmetrical tumor. *Distance between the cervical canal and farthest tumor edge. †Distance between the cervical canal and contralateral distal edge of the tumor or cervix.*

Table I. *Patient and tumor characteristics.*

| | | |
|---|---|---|
| Age | | Median: 57 years (range=27-80 years) |
| FIGO stage | IB2 | 2 (6%) |
| | II | 8 (24) |
| | III | 16 (48) |
| | IVA | 7 (21) |
| Pelvic lymph node metastasis | Negative | 13 (39) |
| | Positive | 20 (61) |
| Para-aortic lymph node metastasis | Negative | 29 (88) |
| | Positive | 4 (12) |
| Histology | Squamous cell carcinoma | 29 (88) |
| | AdSqcc or Adenocarcinoma | 4 (12) |
| Main tumor location | Antero-posterior direction | 16 (48) |
| | Lateral direction | 12 (36) |
| | Both directions | 4 (12) |
| Median tumor size (range) | Pretreatment MRI | 54 mm (30-85 mm) |
| | Pre-brachytherapy MRI | 35 mm (15-74 mm) |
| LD* (range) | Pretreatment MRI | 40 mm (28-52 mm) |
| | Pre-brachytherapy MRI | 21 mm (10-48 mm) |

FIGO: International Federation of Gynecologists and Obstetricians; AdSqcc: adenosquamous cell carcinoma; MRI: magnetic resonance imaging; LD: long distance. *Maximum diameter measured from the cervical canal to the lateral border of the tumor.

year LC rates for the entire cohort, patients who received conventional ICBT, and patients who received non-conventional ICBT, were 90.9%, 100%, and 81.2%, respectively ($p$=0.07) (Figure 4b).

Grade 2 late rectal complications were reported in 2 (6.1%) patients who received conventional ICBT. However, no grade 3 late rectal complications were observed at the time of analysis. No grade 2 or higher-grade late urinary adverse

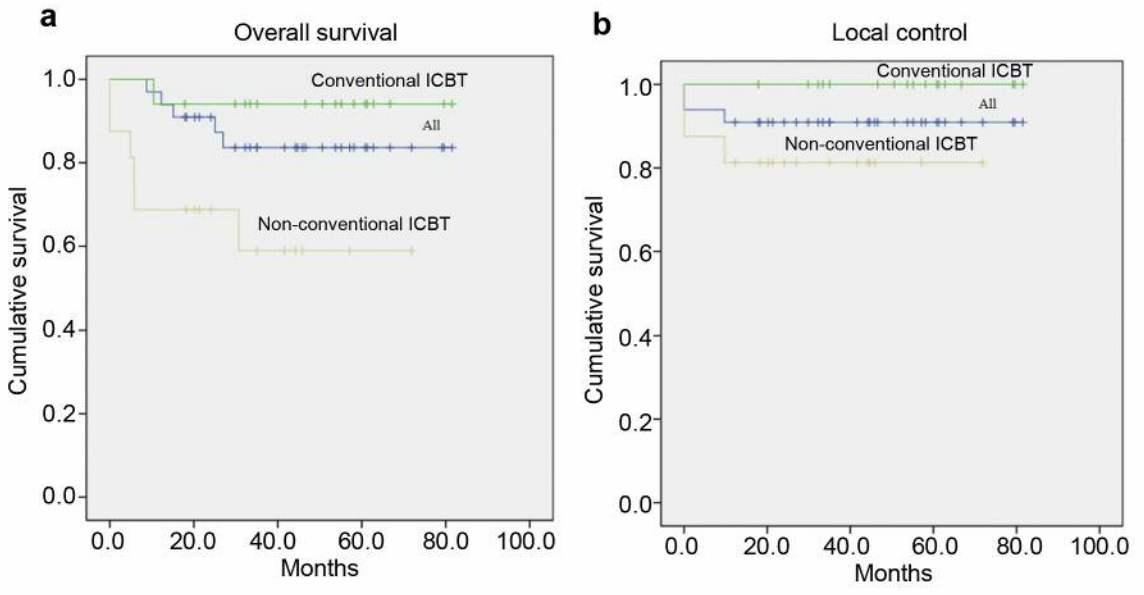


Figure 4. *Kaplan–Meier curves showing: (a) Overall survival, (b) local control. ICBT: Intracavitary brachytherapy.*

Table II. *Direction of tumor extension on pretreatment magnetic resonance imaging and brachytherapy techniques.*

| | All | AP direction | Lateral direction | Both AP and lateral directions | Cranial direction |
|---|---|---|---|---|---|
| Conventional ICBT | 17 (52%) | 13 (81) | 4 (33) | 0 (0) | 0 (0) |
| Brachytherapy except for conventional ICBT | 16 (48) | 3 (19) | 8 (67) | 4 (100) | 1 (100) |
| ISBT | 9 | 3 | 5 | 1 | 0 |
| IC/ISBT | 3 | 0 | 1 | 2 | 0 |
| ICBT with IMRT boost | 4 | 0 | 2 | 1 | 1 |

AP: Antero-posterior; ICBT: intracavitary brachytherapy; ISBT: interstitial brachytherapy; IMRT: intensity-modulated radiotherapy.

events were reported at the time of the analysis. A grade 2 insufficient fracture was reported in 1 patient (3%).

## Discussion

Previous studies have shown that the pelvic control rate among patients with locally advanced cervical cancer having severe parametrial invasion was about 50%-70% following conventional ICBT (6, 14). In this study, one of the eligibility criteria for non-conventional ICBT was LD–SD=1 cm or greater. Kirisits *et al*. have reported that when 1 needle is loaded in the 3 o'clock position of a ring applicator with a diameter of 34 mm, IC/ISBT could deliver the prescribed dose at a distance of 31 mm lateral to the tandem axis; the dose on the contralateral side could still be normalized at 20 mm from the tandem at the level of point A (15). This finding suggests that IC/ISBT offers greater advantage in terms of CTV dose coverage if the difference in width is 1 cm or larger. Although it is unclear whether the eligibility criteria were correctly defined, there was no significant difference in the 3-year LC rate between the conventional ICBT and non-conventional ICBT groups (100% *vs*. 81.2%, $p$=0.07). In patients treated with ISBT or IC/ISBT, the adequate EQD2 of the CTV D90 (mean 69.6±3.6 Gy) was delivered according to the Japanese treatment schedule (16). None of the patients received more than the recommended OAR doses as per the ABS guidelines (8). In addition, the 3-year LC rate among patients treated with brachytherapy selected according to the pre-brachytherapy MRI findings was 90.9%; no grade 3 or higher late complications were observed at the time of analysis. Recent studies have shown that the LC rate in patients with locally advanced cervical cancer treated with IGABT, including IC/ISBT and ISBT was 85%-94% (12, 17, 18). Although these results concur with those of our study,

this study only included patients with asymmetrical cervical cancer who were likely to achieve poor LC with conventional ICBT treatment. Ohno *et al*. have reported that 14 of 80 patients (17.5%) with stages IB-IVA cervical cancer in their cohort received IC/ISBT with a 5-year LC of 94% (17). In the RetroEMBRACE study, 168 of 731 patients with locally advanced cervical cancer (23%) received IC/ISBT with excellent LC (91% at 3 years) (18). The proportion of non-conventional ICBT use in this study (48.5%) was higher than that of recent studies that evaluated the efficacy of IGABT against stages IB-IVA cervical cancer (17, 18).

In this study, there was no significant difference in the tumor width between patients with invasion in the lateral and AP directions on the pre-treatment scans ($p$=0.20). However, the median reduction rate among the tumors spreading in the lateral direction (32.7%) was significantly lower than that of tumors spreading in the AP direction (48.6%) ($p$=0.01). In patients with large tumors at the time of brachytherapy, the RetroEMBRACE study demonstrated that the use of IC/ISBT significantly increased the LC rate without increasing the morbidity (19). In the RetroEMBRACE study, volumetric analyses were performed to divide patients into 6 groups according to the following parameters: a) gross tumor volume ($GTV_D$), which was obtained from the pre-treatment MRI, b) HR-CTV to $GTV_D$ ratio, and c) extent of residual parametrial disease at the time of brachytherapy (20). IC/ISBT was used more frequently in patients with large tumors with moderate or poor response (59% and 89%, respectively) than in patients with stage IB tumors with good tumor response. In this study, 12 of 16 patients (75%) with tumor invasion in the lateral direction were treated with non-conventional ICBT; the results were similar to those observed in patients with moderate or poor tumor response in the RetroEMBRACE study. Compared with tumors spreading in the AP direction, when a tumor invaded laterally, a poorer response was observed.

In patients with asymmetrical cervical cancer, our criteria based on pre-brachytherapy MRI findings are of value in the selection of the appropriate brachytherapy technique (conventional ICBT *vs*. non-conventional ICBT), and may lead to good OS and LC. Unlike tumors spreading in the AP direction, non-conventional ICBT should be preferred for tumors invading laterally.

The impact of the findings of our study has been limited by the small number of patients, and the lack of dose-volume histogram data on the CTV and OARs in patients treated with conventional ICBT. Further prospective studies are needed on larger patient numbers with dosimetric data for the CTV and OARs, to evaluate and confirm the utility of our eligibility criteria.

The use of our pre-brachytherapy MRI-based criteria for the selection of appropriate brachytherapy techniques in patients with asymmetrical cervical cancer was useful, and may improve the LC and OS in these patients.

## Conflicts of Interest

None of the Authors have any conflicts of interest to declare regarding this study.

## Authors' Contributions

Keiko Murofushi designed the study, and wrote the initial draft and the manuscript. Yasuo Yoshioka contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other Authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All Authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## References

1 Lanciano RM, Won M, Coia LR and Hanks GE: Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys *20(4)*: 667-676, 1991. PMID: 2004942. DOI: 10.1016/0360-3016(91)90007-q

2 Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL and Gersell D: Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med *340(15)*: 1154-1161, 1999. PMID: 10202166. DOI: 10.1056/NEJM199904153401503

3 Goksedef BP, Kunos C, Belinson JL and Rose PG: Concurrent cisplatin-based chemoradiation International Federation of Gynecology and Obstetrics stage IB2 cervical carcinoma. Am J Obstet Gynecol *200(2)*: 175 e1-5, 2009. PMID: 19091305. DOI: 10.1016/j.ajog.2008.08.055

4 Werner-Wasik M, Schmid CH, Bornstein L, Ball HG, Smith DM and Madoc-Jones H: Prognostic factors for local and distant recurrence in stage I and II cervical carcinoma. Int J Radiat Oncol Biol Phys *30(5)*: 1309-1317, 1995. PMID: 7635770. DOI: 10.1016/0360-3016(94)00613-P

5 Syed AM, Puthawala AA, Abdelaziz NN, el-Naggar M, Disaia P, Berman M, Tewari KS, Shama A, Londrc A, Juwadi A, Cherlow JM, Damore S and Chen YJ: Long-term results of low-dose-rate interstitial–intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol Phys *54(1)*: 67-78, 2002. PMID: 12182976. DOI: 10.1016/s0360-3016(02)02900-0

6 Perez CA, Grigsby PW, Nene SM, Camel HM, Galakatos A, Kao MS and Lockett MA: Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer *69(11)*: 2796-2806, 1992. PMID: 1571911. DOI: 10.1002/1097-0142(19920601)69:11<2796::aid-cncr2820691127>3.0.co;2-o

7 Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, Dumas I, Erickson B, Lang S, Nulens A, Petrow P, Rownd J and Kirisits C; GEC ESTRO Working Group: Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol *78(1)*: 67-77, 2006. PMID: 16403584. DOI: 10.1016/j.radonc.2005.11.014

8 Viswanathan AN, Beriwal S, De Los Santos JF, Demanes DJ, Gaffney D, Hansen J, Jones E, Kirisits C, Thomadsen B and Erickson B: American Brachytherapy Society: American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. Brachytherapy *11(1)*: 47-52, 2012. PMID: 22265437. DOI: 10.1016/j.brachy.2011.07.002

9 Kharouta M, Malin M, Son C, Al-Hallaq H and Hasan Y: Initial experience using superflab as intravaginal packing during interstitial brachytherapy for advanced gynecologic cancer. J Contemp Brachytherapy *10(3)*: 218-224, 2018. PMID: 3003 8641. DOI: 10.5114/jcb.2018.76522

10 Rijkmans EC, Nout RA, Rutten IH, Ketelaars M, Neelis KJ, Laman MS, Coen VL, Gaarenstroom KN, Kroep JR and Creutzberg CL: Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gynecol Oncol *135(2)*: 231-238, 2014. PMID: 25172763. DOI: 10.1016/j.ygyno.2014.08.027

11 Pötter R, Georg P, Dimopoulos JC, Grimm M, Berger D, Nesvacil N, Georg D, Schmid MP, Reinthaller A, Sturdza A and Kirisits C: Clinical outcome of protocol-based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol *100(1)*: 116-123, 2011. PMID: 21821305. DOI: 10.1016/j.radonc.2011.07.012

12 Pinn-Bingham M, Puthawala AA, Syed AM, Sharma A, Disaia P, Berman M, Tewari KS, Randall-Whitis L, Mahmood U, Ramsinghani N, Kuo J, Chen WP and McLaren CE: Outcomes of high-dose-rate interstitial brachytherapy in the treatment of locally advanced cervical cancer: long-term results. Int J Radiat Oncol Biol Phys *85(3)*: 714-720, 2013. PMID 22763030. DOI: 10.1016/j.ijrobp.2012.05.033

13 Dale RG: The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. Br J Radiol *58(690)*: 515-528, 1985. PMID: 4063711. DOI: 10.1259/0007-1285-58-690-515

14 Kovallic JJ, Perez CA, Grigsby PW and Lockett MA: The effect of volume of disease in patients with carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys *21(4)*: 905-910, 1991. PMID: 1917618. DOI: 10.1016/0360-3016(91)90728-m

15 Kirisits C, Lang S, Dimopoulos J, Berger D, Georg D and Pötter R: The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. Int J Radiat Oncol Biol Phys *65(2)*: 624-630, 2006. PMID: 16690444. DOI: 10.1016/j.ijrobp.2006.01.036

16 Toita T, Kitagawa R, Hamano T, Umayahara K, Hirashima Y, Aoki Y, Oguchi M, Mikami M and Takizawa K; Cervical Cancer (Vulva Cancer) Committee of Japanese Gynecologic Oncology Group (JGOG): Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule. Gynecol Oncol *126(2)*: 211-216, 2012. PMID: 22555110. DOI: 10.1016/j.ygyno.2012.04.036

17 Ohno T, Noda SE, Okonogi, Murata K, Shibuya K, Kiyohara H, Tamaki T, Ando K, Oike T, Ohkubo Y, Wakatsuki M, Saitoh JI and Nakano T: In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. J Radiat Res *58(4)*: 543-551, 2017. PMID: 27986859. DOI: 10.1093/jrr/rrw121

18 Sturdza A, Pötter R, Fokda LU, Haie-Meder C, Tan LT, Mazeron R, Petric P, Segedin B, Jurgenliemk-Schulz IM, Nomden C, Gillham C, McArdle O, Van Limbergen E, Janssen H, Hoskin P, Lowe G, Tharavichitkul E, Villafranca E, Mahantshetty U, Georg P, Kirchheiner K, Kirisits C, Tanderup K and Lindegaard JC: Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. Radiother Oncol *120(3)*: 428-433, 2016. PMID: 27134181. DOI: 10.1016/j.radonc.2016.03.011

19 Fokdal L, Sturdza A, Mazeron R, Haie-Meder C, Tan LT, Gillham C, Segedin B, Jürgenliemk-Schultz I, Kirisits C, Hoskin P, Pötter R, Lindegaard JC and Tanderup K: Image guided adaptive brachytherapy with combined intracavitary and interstitial technique improves the therapeutic ratio in locally advanced cervical cancer: analysis from the retroEMBRACE study. Radiother Oncol *120(3)*: 434-440, 2016. PMID: 27113795. DOI: 10.1016/j.radonc.2016.03.020

20 Jastaniyah N, Yoshida K, Tanderup K, Lindegaard JC, Sturdza A, Kirisits C, Segedin B, Mahantshetty U, Rai B, Jürgenliemk-Schultz I, Haie-Meder C, Banerjee S and Pötter R; EMBRACE Collaborative Group: A volumetric analysis of GTVD and CTVHR as defined by the GEC ESTRO recommendations in FIGO stage IIB and IIIB cervical cancer patients treated with IGABT in a prospective multicentric trial (EMBRACE). Radiother Oncol *120(3)*: 404-411, 2016. PMID: 27452409. DOI: 10.1016/j.radonc.2016.05.029

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