Tumor size before image-guided brachytherapy is an important factor of local control after radiotherapy for cervical squamous cell carcinoma: analysis in cases using central shielding

Kotaro Yoshio1,2,*, Hiroki Ihara2, Kazuhiro Okamoto3, Etsuji Suzuki4, Takeshi Ogata5, Soichi Sugiyama1,2, Keiichiro Nakamura3, Shoji Nagao3, Hisashi Masuyama3 and Takao Hiraki2

1Department of Proton Beam Therapy, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
2Department of Radiology, Faculty of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
3Department of Obstetrics and Gynecology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
4Department of Epidemiology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
5Department of Radiology, Tsuyama Central Hospital, 1756 Kawasaki, Tsuyama, 708-0841, Japan
*Corresponding author. Department of Proton Beam Therapy, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Tel: 81-(86)223-7151; Fax: 81-(86)235-7316; Email: ko.taro1201@gmail.com

(Received 21 March 2022; revised 4 May 2022; editorial decision 6 June 2022)

ABSTRACT

We analyzed the local control (LC) of cervical squamous cell carcinoma treated by computed tomography (CT)-based image-guided brachytherapy (IGBT) using central shielding (CS). We also examined the value of tumor diameter before brachytherapy (BT) as a factor of LC. In total, 97 patients were analyzed between April 2016 and March 2020. Whole-pelvic (WP) radiotherapy (RT) with CS was performed, and the total pelvic sidewall dose was 50 or 50.4 Gy; IGBT was delivered in 3–4 fractions. The total dose was calculated as the biologically equivalent dose in 2 Gy fractions, and distribution was modified manually by graphical optimization. The median follow-up period was 31.8 months (6.3–63.2 months). The 1- and 2-year LC rates were 89% and 87%, respectively. The hazard ratio was 10.11 (95% confidence interval: 1.48–68.99) for local recurrence in those with a horizontal tumor diameter ≥4 cm compared to those with <4 cm before BT. In CT-based IGBT for squamous cell carcinoma, favorable LC can be obtained in patients with a tumor diameter <4 cm before BT. However, if the tumor diameter is ≥4 cm, different treatment strategies such as employing interstitial-BT for dose escalation may be necessary.

Keywords: cervical cancer; tumor size; squamous cell carcinoma; image-guided brachytherapy (IGBT); central shielding (CS)

INTRODUCTION

In cervical cancer, improving local control (LC) of the primary lesion is considered to have a direct effect on disease control and survival [1]. The standard radiation therapy regimen for patients with cervical cancer consists of external beam radiotherapy (EBRT) and brachytherapy (BT) [2]. Accordingly, 3-dimensional image-guided brachytherapy (3D-IGBT) using computed tomography (CT) or magnetic resonance imaging (MRI) is widely employed [3,4]. The 2017 Japan Society of Gynecologic Oncology guidelines for the treatment of uterine cervical cancer differs from those of Europe and the United States. These guidelines indicate the use of central shielding (CS) [5–7]. In previous studies of LC after 3D-IGBT based on the Japanese treatment schedule, histological type, tumor diameter, and dose have been reported to be important factors associated with LC [8–11]. However, these
Importance of tumor size for local control

Fig. 1. The horizontal tumor diameters were measured based on the axial T2-weighted MRI.

reports analyzed LC among various histological types which impact LC. Moreover, no report has evaluated whether the tumor diameter before the start of treatment or BT is a significant factor of LC in the Japanese treatment schedule. Here, we retrospectively analyzed the LC of cervical squamous cell carcinoma from a treatment schedule employing CS and examined the value of pre-BT tumor diameter as a factor of LC.

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Ethics Committee (No. 2112–024) of the Okayama University Hospital, Okayama, Japan. In total, 97 patients with pathologically proven, previously untreated cervical squamous cell carcinoma treated at our hospital with high-dose-rate (HDR) CT-based 3D-IGBT between April 2016 and March 2020 were included in this study. All patients underwent a pelvic examination, CT scan, MRI, and blood test, including patients with the 2008 International Federation of Gynecology and Obstetrics (FIGO) stage IB1–IVB disease and those with para-aortic nodal metastasis. All radiotherapy (RT) and concurrent chemoradiotherapy (CCRT) were performed as definitive treatments. The horizontal tumor diameters were measured based on the axial T2-weighted MRI images for analysis in this study (Fig. 1).

Chemotherapy

Concurrent chemotherapy of cisplatin (40 mg/m²) and nedaplatin (35 mg/m²) was administered weekly in 73 (75%) patients with FIGO Stage IB2, IIA2, and IIB-IV, or pelvic and para-aortic lymph node metastases. However, chemotherapy was not performed on patients with impaired organ function or those aged ≥ 80 years. Nedaplatin was selected when patients with impaired renal function were observed with para-aortic lymph node metastasis. Supportive treatments, such as blood transfusions, were performed during RT/CCRT. Postponement of chemotherapy was considered when grade 3 or higher adverse events in Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 appeared.

External beam radiotherapy

Radiation therapy was delivered using 10-MV photons from a linear accelerator (Primus; Canon Medical Systems, Tochigi, Japan). A superposition dose calculation algorithm with heterogeneity correction was used (Xio version 4.8.0; Elekta, Stockholm, Sweden) with a radiation therapy planning system. The clinical target volume (CTV) for EBRT included sites such as the primary tumor, whole uterus, bilateral parametrium, the upper half of the vagina, and pelvic lymph nodes (common, internal, external iliac, obturator, and presacral). The planning target volume (PTV) was defined as the CTV plus a margin of 2 cm for the primary tumor and uterus body. Three-dimensional conformal RT with an anterior–posterior parallel-opposed field or a 4-field box was used for whole pelvic (WP) irradiation. After WP irradiation, the anterior–posterior parallel-opposed field with CS of 4 cm in width was delivered according to the Japanese guideline treatment schedule [5]. CS position was set to the S2/3 level to cover the presacral area. The total pelvic dose (WP-dose plus CS-dose) administered was 50 Gy in 25 fractions or 50.4 Gy in 28 fractions.

Brachytherapy

BT was initiated after WP-EBRT and performed weekly for three or four sessions. An HDR 192Ir source was used for BT, and all patients were treated by intracavitary (IC) BT. MicroSelectron digital (HDR-V3) BT afterloader (Elekta Inc., Stockholm, Sweden) with a combination of either tandem and ovoid or tandem and vaginal cylinder applicators was used to administer and perform ICBT. CT-based 3D-IGBT was performed in each BT session. The high-risk CTV (HR-CTV) and organs at risk (OARs) were contoured on the planning CT with Oncentra® (Elekta Inc.) according to several guidelines [12–14] using MRI images acquired at diagnosis and within one week of the first BT session. The HR-CTV included the entire cervix and the macroscopic residual tumor at the time of the BT. All radiation doses were biologically converted to equivalent doses in 2 Gy (EQD2) by a linear-quadratic model using an alpha/beta ratio of 10 Gy for the HR-CTV and 3 Gy for OARs. The dwell times and dose distributions were modified manually using graphical optimization to meet our dose constraints as follows: (i) for each BT session, the HR-CTV D90 (minimum dose administered to 90% of the volume with the highest irradiation) was ≥ 6 Gy, and bladder and rectum D2 cc (minimum dose to the most irradiated 2 cm³) was < 7 Gy; and (ii) the total HR-CTV D90 was ≥ 60 Gy, bladder D2 cc was < 90 Gy, and rectum D2 cc was < 75 Gy.

In calculating the total HR-CTV and OAR doses, all EQD2 values of whole pelvic external beam radiotherapy (WP-EBRT) (not including central shielding external beam radiotherapy (CS-EBRT)) and HDR-BT were summed according to previous reports [6, 11].

Follow-up

Gynecologists followed up with each patient every one to three months for the first two years and every three to six months from the third year after completion of treatment. Tumor status and adverse events were
assessed using patient interviews, physical and gynecological examinations, and blood tests. Patients generally underwent MRI and 18F-fluorodeoxyglucose positron emission tomography one to two months after treatment to evaluate the therapeutic effects and every six to 12 months after that. The recurrence was determined when a lesion was observed on CT or MRI findings and was confirmed through biopsy. LC duration was defined as the period between the initiation of RT and a diagnosis of local recurrence or the date of the last follow-up. Late adverse events were defined as adverse events emerging ≥ 90 days after completion of RT and were graded according to the CTCAE version 4.0.

**Statistical analysis**

Descriptive analysis was performed for patient and tumor characteristics, as well as treatment details according to tumor size before BT (≥ 4 cm vs < 4 cm). The Shapiro–Wilk normality test was used to examine the normality. To compare the characteristics of the groups, we used Fisher’s exact test (categorical variables), Student’s t-test (normally distributed continuous variables), and Mann–Whitney U test (non-normally distributed continuous variables). The 1- and 2-year LC rates were analyzed using the Kaplan–Meier method. We also examined LC by pre-treatment and pre-BT tumor diameter using the Kaplan–Meier method. Hazard ratios and their 95% confidence intervals for local recurrence were estimated through Cox proportional hazard regression analysis. Although the cut-off value was determined using median values (age, D90–100, body mass index, SCC-antigen, overall treatment time), the cut-off value of tumor size before treatment and BT was intentionally determined from the results of the receiver operating characteristic (ROC) analysis, the value of previous reports [6, 7, 11], and the ease of use in daily clinical practice. The Multivariable Cox regression analyses examined the association between the tumor sizes and local recurrence, adjusting for total HR-CTV D90 and age at diagnosis. These variables were selected based on the previous reports [6, 11, 15]. A two-sided P-value < 0.05 was identified to be statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16].

**RESULTS**

Patient and tumor characteristics and treatment details are summarized in Tables 1 and 2, respectively. The median follow-up period was 31.8 months (range 6.3–63.2 months). Additionally, 12 patients (12%) developed local recurrence. The 1- and 2-year LC rates were 89% and 87%, respectively (Fig. 2). Table 3 shows the baseline data comparison between tumor size groups. As shown in Table 4, tumor size before treatment (≥ 5 cm) (P = 0.002) and before BT (≥ 4 cm) (P < 0.001) were significant factors in simple Cox hazard regression analysis. When LC by pre-treatment and pre-BT tumor diameter was evaluated, no recurrence was observed in those whose tumor diameter was ≥ 5 cm before treatment and shrank to < 4 cm before BT (n = 13) (Fig. 3).

Only tumor size before BT was a significant factor of LC in multiple regression analysis (Table 5). The hazard ratio was 10.11 (95% confidence interval: 1.48–68.99) for local recurrence in those with a tumor diameter ≥ 4 cm compared to those with a tumor diameter < 4 cm before BT. Figure 4 shows a scatter plot of tumor diameter before BT and D90. When the tumor diameter before BT was ≥ 4 cm, recurrence was observed regardless of D90. Here, two cases of recurrence were described despite the tumor diameter being < 4 cm before BT. One

| Table 1. Patient and tumor characteristics (n = 97) |
|-----------------------------|
| Characteristics            |
| Median age at diagnosis (years) (IQR) | 57 (47–68) |
| Median body mass index (IQR) | 22.1 (20–25.1) |
| FIGO 2008 (%)              |
| IB1                        | 13 (14%)     |
| IB2                        | 12 (12%)     |
| IIA1                       | 6 (6%)       |
| IIA2                       | 2 (2%)       |
| IIB                        | 44 (45%)     |
| IIA                        | 1 (1%)       |
| IIIB                       | 17 (18%)     |
| IVA                        | 1 (1%)       |
| IVB                        | 1 (1%)       |
| Histologic type (%)        |
| SCC                        | 97 (100%)    |
| Median value of tumor marker: SCC-antigen (ng/ml) (IQR) | 6.4 (3–15.9) |
| Median tumor size before treatment (mm) (IQR) | 41 (32–54) |
| Median tumor size before BT (mm) (IQR) | 29 (21–37) |
| Median HR-CTV at initial BT (ml) (IQR) | 51 (38.5–66.5) |

Abbreviations: IQR = interquartile range, SCC = squamous cell carcinoma, FIGO = International Federation of Gynecology and Obstetrics, BT = brachytherapy, HR-CTV = high-risk clinical target volume

![Fig. 2. Kaplan–Meier curves for LC. The LC rate was 89% for 1 year and 87% for 2 years.](image-url)
Table 2. Treatment details and histogram parameters (n = 97)

| Characteristics                                      | Median overall treatment time (days) (IQR) | Chemotherapy (%) |
|-------------------------------------------------------|------------------------------------------|------------------|
|                                                       |                                          | Without          |
|                                                       |                                          | 49 (45–52)       |
|                                                       |                                          | 24 (25%)         |
|                                                       |                                          | wCDDP            |
|                                                       |                                          | 58 (60%)         |
|                                                       |                                          | wCDGP            |
|                                                       |                                          | 15 (15%)         |
| EBRT (%)                                              |                                          | wp               |
| WP dose (Gy)                                          | 19.8/20                                  | 19 (20%)         |
|                                                       | 30/30.6                                  | 69 (71%)         |
|                                                       | 39.6/40                                  | 9 (9%)           |
| CS dose (Gy)                                          | 10/10.8                                  | 9 (9%)           |
|                                                       | 19.8/20                                  | 69 (71%)         |
| Brachytherapy                                         | 30/30.6                                  | 19 (20%)         |
| Median number of fractions                            | 3                                        | 10 (10%)         |
|                                                      | 4                                        | 87 (90%)         |
| Applicator (%)                                        | Tandem + Ovoids                          | 85 (88%)         |
|                                                       | Tandem + Cylinder                        | 12 (12%)         |
| Histogram parameters calculated by EQD2               | Median total HR-CTV D90 (Gy) (IQR)       | 66.3 (62–70.4)   |
|                                                       | Median total HR-CTV D95 (Gy) (IQR)       | 61 (57.7–65.8)   |
|                                                       | Median total HR-CTV D100 (Gy) (IQR)      | 50.5 (47.2–53.7) |
|                                                       | Median rectum D2 cc (Gy) (IQR)           | 66.9 (60.9–72)   |
|                                                       | Median bladder D2 cc (Gy) (IQR)          | 80.4 (73.5–87.2) |

Abbreviations: IQR = interquartile range, WP = whole pelvis, CS = central shielding, EBRT = external beam radiotherapy, CDDP = cisplatin, CDGP = nedaplatin, HR-CTV = high-risk clinical target volume, EQD2 = equivalent dose in 2 Gy, D90–100 and D2 cc = minimum dose received by the 90–100% and 2 cc volume with highest irradiation.

DISCUSSION

Clinical outcomes regarding the LC of CT-based 3D-IGBT for squamous cell carcinoma were analyzed in this study. The LC rate was 89% at 1 year and 87% at 2 years. Furthermore, multivariate analysis showed that pre-BT tumor diameter was a significant factor of LC and had a higher hazard ratio than pre-treatment tumor diameter. Several studies have reported factors of LC from treatment schedules with CS. For example, Murakami et al. [8] reported a 3-year LC of 91.7% in an analysis of 51 cases (48 cases of squamous cell carcinoma and three cases of adenocarcinoma). In contrast to the current study, their analysis included cases with and without CS and non-squamous cell carcinoma. As a result of univariate analysis, they reported that an HR-CTV D90 ≥ 60 Gy was a significant factor of LC. However, in their report, the effect of tumor diameter before BT on LC was not fully investigated. Moreover, Kawashima et al. [11] reported a 3-year LC of 89% in an analysis of 84 cases (71 cases of squamous cell carcinoma and 13 cases of adenocarcinoma). Their report, like ours, analyzed only cases of IC irradiation and those with CS. Multivariate analysis in their study identified histological type (adenocarcinoma) and pre-treatment tumor diameter (≥4.5 cm) to be risk factors for local recurrence. However, they analyzed the HR-CTV as a variable, not the tumor diameter at the time of the first BT.

In the current study, we considered the tumor diameter before BT and the HR-CTV at the first BT as potential factors of LC. However, pre-BT tumor diameter was evaluated as it can be measured by MRI, making it a more reproducible variable since these factors as correlated. Moreover, the effect of histological type on LC has already been reported [11,17]. The analysis that included adenocarcinoma was considered problematic as adenocarcinoma is a risk factor for local recurrence. This study examined only squamous cell carcinoma and performed MRI analysis before BT in all cases to increase reliability.

Dimopoulos et al. [6] reported that cases with tumor diameters > 5 cm at the time of diagnosis had different control rates depending on whether they were 2–5 or > 5 cm at BT. They performed MRI-based treatment without CS for a group of subjects with various histological types. They reported that an HR-CTV D90 ≥ 87 Gy is required to achieve 95% LC. Our results showed an LC rate of 97% in the group with a pre-BT tumor diameter < 4 cm. Even if the tumor diameter is 5 cm or more before the start of treatment, excellent results can be obtained if the tumor responds well to EBRT. The reason is that the tumor diameter before BT reflects the radiosensitivity and
Table 3. Summary of baseline data comparison between tumor size group ≥ 4 cm and < 4 cm

| Variable                        | Tumor size before BT | P     |
|---------------------------------|----------------------|-------|
|                                 | ≥ 4 cm (n = 23)      | < 4 cm (n = 74) |
|                                 |                      |       |
| Age at diagnosis (years)        | median 51 years      | 59.5  |
|                                 | IQR 44.5–66 years    | 47.3–67.8 |
|                                 | 0.2*                 |       |
|                                 |                      |       |
| Body mass index (kg/m²)         | median 21.8 kg/m²    | 22.5  |
|                                 | IQR 13.2–37.2 kg/m²  | 15.9–42.4 |
|                                 | 0.38*                |       |
|                                 |                      |       |
| Tumor size before EBRT (%)      | < 5 cm ≥ 13%         | 61 (82%) |
|                                 | ≥ 5 cm 20 (87%)      | 13 (18%) |
|                                 | < 0.001*             |       |
|                                 |                      |       |
| Chemotherapy (%)                | With 19 (83%)        | 54 (73%) |
|                                 | Without 4 (17%)      | 20 (27%) |
|                                 | 0.42*                |       |
|                                 |                      |       |
| Total HR-CTV D90 (Gy)           | median 63.5 Gy       | 67.7  |
|                                 | IQR 60.7–66.8 Gy     | 63–71.4 |
|                                 | 0.011†               |       |
|                                 |                      |       |
| Total HR-CTV D95 (Gy)           | median 59 Gy         | 62.6  |
|                                 | IQR 57.2–63.3 Gy     | 58.3–66.4 |
|                                 | 0.031†               |       |
|                                 |                      |       |
| Total HR-CTV D100 (Gy)          | median 49.6 Gy       | 51.1  |
|                                 | IQR 47.4–52.6 Gy     | 46.7–54.6 |
|                                 | 0.23†                |       |
|                                 |                      |       |
| Overall treatment time (days)    | median 49 days       | 47.5  |
|                                 | IQR 47–51 days       | 45–52 |
|                                 | 0.77†                |       |

Abbreviations: BT = brachytherapy, EBRT = external beam radiotherapy, HR-CTV = high-risk clinical target volume, IQR = interquartile range, D90–100 = minimum dose received by the 90–100% volume with highest irradiation

* = Mann–Whitney U test  † = Fisher’s exact test  ‡ = Student’s t-test

This study had several limitations. The retrospective and single institutional nature of this study is a limitation. In addition, while our outcomes are based on a larger number of cases than those previously reported, our report is limited to cases of CT-based treatment schedules using CS of 3 cm wide, squamous cell carcinoma, and IC-BT. Furthermore, CS hinders the accurate evaluation of the dose to the tumor and normal organs. Although Tamaki et al. [19, 20] reported measuring the effects of CS on tumors and normal organs using a phantom, the dose contribution of EBRT with the CS technique to the HR-CTV is unclear.

In this study, the pre-BT tumor diameter (≥ 4 cm) was the most important factor of LC. Favorable results are obtained from the current treatment using IC-BT for patients with a pre-BT tumor diameter < 4 cm. However, if the tumor diameter is ≥ 4 cm before BT, it may
### Table 4. Simple regression analysis for LC (n = 97)

| Factors                              | Total | Local failure, n (%) | Hazard ratio | 95% CI      | P       |
|--------------------------------------|-------|----------------------|--------------|-------------|---------|
| Tumor size before BT                 |       |                      |              |             |         |
| ≥ 4 cm                               | 23    | 10 (43%)             | 19.44        | 4.25–88.87  | < 0.001 |
| < 4 cm                               | 74    | 2 (3%)               |              |             |         |
| Tumor size before EBRT               |       |                      |              |             |         |
| ≥ 5 cm                               | 33    | 10 (30%)             | 11.33        | 2.48–51.76  | 0.002   |
| < 5 cm                               | 64    | 2 (3%)               |              |             |         |
| Age at diagnosis (years)             |       |                      |              |             |         |
| ≥ 58 years                           | 48    | 3 (6%)               | 0.31         | 0.08–1.13   | 0.075   |
| < 58 years                           | 49    | 9 (18%)              |              |             |         |
| Total HR-CTV D90 (EQD2)              |       |                      |              |             |         |
| ≥ 66.3 Gy                            | 49    | 5 (10%)              | 0.73         | 0.23–2.31   | 0.6     |
| < 66.3 Gy                            | 48    | 7 (15%)              |              |             |         |
| Total HR-CTV D95 (EQD2)              |       |                      |              |             |         |
| ≥ 61.0 Gy                            | 49    | 5 (10%)              | 0.73         | 0.23–2.31   | 0.6     |
| < 61.0 Gy                            | 48    | 7 (15%)              |              |             |         |
| Total HR-CTV D100 (EQD2)             |       |                      |              |             |         |
| ≥ 50.5 Gy                            | 50    | 7 (10%)              | 0.71         | 0.22–2.22   | 0.55    |
| < 50.5 Gy                            | 47    | 7 (15%)              |              |             |         |
| Body mass index                      |       |                      |              |             |         |
| ≥ 22.1                               | 49    | 6 (12%)              | 0.92         | 0.3–2.87    | 0.89    |
| < 22.1                               | 48    | 6 (13%)              |              |             |         |
| FIGO stage                           |       |                      |              |             |         |
| IIB–IV                               | 64    | 11 (17%)             | 5.96         | 0.77–46.19  | 0.087   |
| I–IIA                                | 33    | 1 (3%)               |              |             |         |
| Tumor marker: SCC-antigen            |       |                      |              |             |         |
| ≥ 6.4 ng/ml                          | 49    | 7 (14%)              | 1.35         | 0.43–4.26   | 0.61    |
| < 6.4 ng/ml                          | 48    | 5 (10%)              |              |             |         |
| Applicator                           |       |                      |              |             |         |
| T + O                                | 85    | 11 (13%)             | 1.63         | 0.21–12.65  | 0.64    |
| T + C                                | 12    | 1 (8%)               | 1.7          | 0.37–7.77   | 0.49    |
| Chemotherapy                         |       |                      |              |             |         |
| With                                 | 73    | 10 (14%)             | 1.7          | 0.37–7.77   | 0.49    |
| Without                              | 24    | 2 (8%)               |              |             |         |
| Number of BT                         |       |                      |              |             |         |
| 3 fractions                          | 10    | 7 (20%)              | 1.78         | 0.39–8.11   | 0.46    |
| 4 fractions                          | 87    | 7 (11%)              |              |             |         |
| Overall treatment time               |       |                      |              |             |         |
| ≥ 49 days                            | 49    | 7 (14%)              | 1.38         | 0.44–4.33   | 0.59    |
| < 49 days                            | 48    | 7 (10%)              |              |             |         |

**Abbreviations:** BT = brachytherapy, HR-CTV = high-risk clinical target volume, EBRT = external beam radiotherapy, FIGO = International Federation of Gynecology and Obstetrics, SCC = squamous cell carcinoma, D90–100 = minimum dose received by the 90–100% volume with highest irradiation, CI = confidence interval

### Table 5. Hazard ratios for local recurrence (n = 97)

| Variables                                      | Hazard ratio | 95% CI | P       |
|------------------------------------------------|--------------|--------|---------|
| Tumor size before BT, ≥ 4 cm vs < 4 cm         | 10.11        | 1.48–68.99 | 0.018   |
| Tumor size before EBRT, ≥ 5 cm vs < 5 cm       | 2.56         | 0.4–16.32  | 0.32    |
| Total HR-CTV D90 (Gy)                          | 1            | 0.89–1.12  | 0.98    |
| Age at diagnosis (years)                       | 0.98         | 0.94–1.03  | 0.48    |

**Abbreviations:** BT = brachytherapy, EBRT = external beam radiotherapy, HR-CTV = high-risk clinical target volume, CI = confidence interval, D90 = minimum dose received by the 90% volume with highest irradiation

### Table 6. Number of patients with late complications (Graded according to CTCAE version 4.0)

| Grade | 0    | 1    | 2    | 3    | 4    | 5 | 6 | 7 | 8 | 9 | 10 |
|-------|------|------|------|------|------|---|---|---|---|---|----|
| Rectum (%)   | 70 (72%) | 18 (19%) | 3 (3%) | 5 (5%) | 0 | 1 (1%) | 0 | 0 | 0 | 0 |    |
| Sigmoid (%)  | 92 (95%) | 1 (1%) | 1 (1%) | 3 (3%) | 0 | 0 | 0 | 0 | 0 | 0 |    |
| Bladder (%)  | 89 (92%) | 6 (6%) | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 | 0 | 0 |    |

**Abbreviations:** CTCAE = Common Terminology Criteria for Adverse Events
CONFLICT OF INTEREST
The authors declare they have no conflicts of interest.

REFERENCES
1. Elledge CR, LaVigne AW, Bhatia RK et al. Aiming for 100% local control in locally advanced cervical cancer: the role of complex brachytherapy applicators and Intraprocedural imaging. Semin Radiat Oncol 2020;30:300–10.
2. Monk BJ, Tewari KS, Koh WJ. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol 2007;25:2952–65.
3. Ohno T, Toita T, Tsujino K et al. A questionnaire-based survey on 3D image-guided brachytherapy for cervical cancer in Japan: advances and obstacles. J Radiat Res 2015;56:897–903.
4. Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American brachytherapy society. Int J Radiat Oncol Biol Phys 2010;76:104–9.
5. Ebina Y, Mikami M, Nagase S et al. Japan Society of Gynecologic Oncology guidelines 2017 for the treatment of uterine cervical cancer. Int J Clin Oncol 2019;24:1–19.
6. Dimopoulos JCA, Lang S, Kirisits C et al. Dose-volume histogram parameters and local tumor control in magnetic resonance image-guided cervical cancer brachytherapy. Int J Radiat Oncol Biol Phys 2009;75:56–63.
7. Viswanathan AN, Beriwalle S, Santos JFDL et al. American brachytherapy society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. Brachytherapy 2012;11:47–52.
8. Murakami N, Kasamatsu T, Wakita A et al. CT-based three dimensional dose-volume evaluations for high-dose rate intracavitary brachytherapy for cervical cancer. BMC Cancer 2014;14:447.
9. Kusada T, Toita T, Ariga T et al. Computed tomography-based image-guided brachytherapy for cervical cancer: correlations between dose-volume parameters and clinical outcomes. J Radiat Res 2018;59:67–76.
10. Kusada T, Toita T, Ariga T et al. Definitive radiotherapy consisting of whole pelvic radiotherapy with no central shielding and CT-based intracavitary brachytherapy for cervical cancer: feasibility, toxicity, and oncologic outcomes in Japanese patients. Int J Clin Oncol 2020;25:1977–84.
11. Kawashima A, Isoshita F, Mabuchi S et al. A 3-year follow-up study of radiotherapy using computed tomography-based image-guided brachytherapy for cervical cancer. J Radiat Res 2019;60:264–9.
12. Haie-Meder C, Pötter R, Van Limbergen E et al. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 2005;74:235–45.
13. Ohno T, Wakisaka M, Toita T et al. Recommendations for high-risk clinical target volume definition with computed tomography for three-dimensional image-guided brachytherapy in cervical cancer patients. J Radiat Res 2017;58:341–50.
Importance of tumor size for local control

14. Gay HA, Barthold HJ, O’Meara E et al. Pelvic normal tissue contouring guidelines for radiation therapy: a radiation therapy oncology group consensus panel atlas. *Int J Radiat Oncol Biol Phys* 2012;83:e353–62.

15. Horne ZD, Karukonda P, Kalash R et al. Single-institution experience in 3D MRI-based brachytherapy for cervical cancer for 239 women: can dose overcome poor response? *Int J Radiat Oncol Biol Phys* 2019;104:157–164.

16. Kanda Y. Investigation of the freely available easy-to-use software ‘EZIR’ for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.

17. Yokoi E, Mabuchi S, Takahashi R et al. Impact of histological subtype on survival in patients with locally advanced cervical cancer that were treated with definitive radiotherapy: adenocarcinoma/adenosquamous carcinoma versus squamous cell carcinoma. *J Gynecol Oncol* 2017;28:e19.

18. Ohno T, Noda SE, Okonogi N et al. In-room computed tomography-based brachytherapy for uterine cervical cancer: results of a 5-year retrospective study. *J Radiat Res* 2017;58:543–51.

19. Tamaki T, Ohno T, Noda SE et al. Filling the gap in central shielding: three-dimensional analysis of the EQD2 dose in radiotherapy for cervical cancer with the central shielding technique. *J Radiat Res* 2015;56:804–10.

20. Tamaki T, Noda SE, Ohno T et al. Dose-volume histogram analysis of composite EQD2 dose distributions using the central shielding technique in cervical cancer radiotherapy. *Brachytherapy* 2016;15:598–606.