# A Clinical Evaluation of American Brachytherapy Society Consensus Guideline for Bulky Vaginal Mass in Gynecological Cancer

# A Clinical Evaluation of American Brachytherapy Society Consensus Guideline for Bulky Vaginal Mass in Gynecological Cancer

*Keiko Nemoto Murofushi, MD,\*† Nozomi Kitamura, MS,\* Yasuo Yoshioka, MD, PhD,\* Minako Sumi, MD, PhD,\* Hitoshi Ishikawa, MD, PhD,† Masahiko Oguchi, MD, PhD,\* and Hideyuki Sakurai, MD, PhD†*

**Objectives:** American Brachytherapy Society (ABS)-recommended interstitial brachytherapy (IBT) should be considered for bulky vaginal tumor thicker than 5 mm. The aim of this study was to evaluate the ABS consensus guideline for patients with severe vaginal invasion based on our long-term follow-up results.

**Methods/Materials:** The study included 7 patients with vaginal cancer and 14 patients with cervical cancer invading to the lower vagina. Based on prebrachytherapy magnetic resonance imaging findings, patients received intracavitary brachytherapy (ICT) for vaginal tumors 5 mm or less or IBT for vaginal tumors less than 5 mm. Nine patients received ICT and the remaining 12 patients received IBT. For dosimetric comparison, an experimental recalculation as the virtual IBT for patients actually treated by ICT, and vice versa, was performed.

**Results:** The 5-year local control rate for all tumors was 89.4%. No differences in local control between ICT- and IBT-treated groups were observed ($P = 0.21$). One patient experienced a grade 3 rectal complication. There were no significant differences in the CTV D90 and rectum D2cc between the 2 groups ($P = 0.13$ and 0.39, respectively). In the dosimetric study of ICT-treated patients, neither the actual ICT plans nor the experimental IBT plans exceeded the limited dose for organs at risk, which were recommended in the guideline published from the ABS. In the IBT-treated patients, D2cc for bladder and rectum of the experimental ICT plans was significantly higher than for the actual IBT plans ($P < 0.001$ and $<0.001$, respectively), and 11 experimental ICT plans (92%) exceeded the limited dose for bladder and/or rectum D2cc.

**Conclusions:** Tumor control and toxicity after selected brachytherapy according to vaginal tumor thickness were satisfactory; IBT instead of ICT is recommended for patients with vaginal tumor thickness greater than 5 mm to maintain bladder and/or rectum D2cc.

**Key Words:** Cervical cancer with severe vaginal invasion, Vaginal cancer, Dose-volume histogram parameter, Image-guided brachytherapy

\*Radiation Oncology Department, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo; and †Department of Radiation Oncology and Proton Medical Research Center, University of Tsukuba, Ibaraki, Japan.
Address correspondence and reprint requests to
Keiko Nemoto Murofushi, MD, Department of Radiation Oncology and Proton Medical Research Center, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki, 305–8576, Japan.
E-mail: murofushi@pmrc.tsukuba.ac.jp.
The authors declare no conflicts of interest.

Brachytherapy as a dose escalation method improves survival in patients undergoing definitive radiotherapy for cervical cancer,[1,2] and appropriate applicators for brachytherapy should be selected to adapt to the shape and extent of the tumor.[3] Intracavitary brachytherapy (ICT) with the tandem and cylinder applicators is mostly used for FIGO IIIA cervical cancer and vaginal cancer to irradiate the entire vagina. In the American Brachytherapy Society (ABS) guideline, however, for a vaginal tumor thicker than 5 mm, interstitial brachytherapy (IBT) is recommended.[4]

Image-guided adaptive brachytherapy (IGABT) improved pelvic control and severe late complications, compared with conventional brachytherapy.[5,6] However, few previous reports evaluated the advantage on dose volume histogram (DVH) parameters of selected brachytherapy based on the vaginal tumor thickness.

The aim of this study was to evaluate the ABS consensus guideline when administering the treatments, ICT or IBT, according to vaginal tumor thickness measured by using magnetic resonance imaging (MRI) just before brachytherapy. We also report DVH parameters in ICT and IBT for this patient category using computed tomography (CT)-based treatment planning.

## MATERIALS AND METHODS

### Characteristics of the Patients

We analyzed patients with vaginal cancers thicker than 5 mm, and patients with cervical cancer with the lower half of vaginal invasion thicker than 5 mm. Vaginal invasion was measured by MRI obtained just before brachytherapy. Between July 2010 and June 2013, 21 of 178 patients treated with definitive radiotherapy for cervical cancer and vaginal cancer were eligible for this study. The primary cancers were cervical cancer in 14 patients and vaginal cancer in 7 patients. Table 1 shows the details of the patients' characteristics. This study was approved by the ethical review committee at our institution.

### Radiotherapy

External beam radiotherapy (EBRT) was delivered by the three-dimensional (3D)-conformal technique with a linear accelerator (Clinac IX; Varian Medical System, Palo Alto, CA) using a 15 MV photon beam. For patients treated by ICT, whole pelvic EBRT was initially administered at 30.6 to 39.6 Gy in 17 to 22 fractions with the 4-field technique, and a further 10.8 to 19.8 Gy in 6 to 11 fractions were irradiated by EBRT with a 4-cm wide midline block (MB) and the anterior-posterior/posterior-anterior technique. For patients treated using IBT, an MB was inserted along the 50% isodose line, as determined by IBT planning. Within 7 days before brachytherapy, all patients underwent MRI.

The first high dose rate-ICT or IBT was performed within 7 days after MB insertion. Brachytherapy was performed using an iridium 192 (192Ir) remote after loading system (MicroSelectron HDRTM; Nucletron, Veenendaal, the Netherlands). Brachytherapy planning was based on CT images of 2-mm slice thickness, and calculated using PLATO ver3 (Nucletron) from July 2010 to October 2011 and Oncentra v4.0 (Nucletron) from November 2011 to June 2013. The clinical

**TABLE 1.** Patient and tumor characteristics

| Characteristics | | n |
|---|---|---|
| Age, median (range), y | 60 (34–78) | |
| Primary cancer | | |
| Cervical cancer (n = 14) | FIGO IIIA | 5 |
| Vaginal cancer (n = 7) | IIIB | 8 |
| | IVA | 1 |
| | I | 1 |
| | II | 6 |
| Vaginal tumor site (n = 21) | Upper 2/3 | 8 |
| | Lower 1/3 | 1 |
| | Entire vagina | 12 |
| Lymph node metastasis (n = 21) | Yes | 16 |
| | No | 5 |
| Histology (n = 21) | Squamous cell carcinoma | 18 |
| | Other | 3 |
| Vaginal tumor thickness | Pretreatment | Median, 20 mm (10–40 mm) |
| | Prebrachytherapy | Median, 8 mm (0–33 mm) |

FIGO indicates International Federation of Gynecologists and Obstetricians.

target volume (CTV) included the macroscopic residual tumor (ie, high T2-weighted imaging [T2WI] area on MRI just before brachytherapy), the entire cervix, and the entire vagina. The ICT with tandem and cylinder applicators was administered once weekly to achieve a total dose of 20 to 24 Gy in 4 fractions prescribed at point A and a depth of 5 mm from the surface of the vaginal mucosa. The source dwell patterns were determined using the Manchester system and modified to deliver the prescribed dose to the CTV and to adjust the dose to the organs at risk (OAR). The Martinez Universal Perineal Interstitial Template was used in IBT to deliver a total dose of 24 to 42 Gy in 4 to 7 fractions over 2 to 4 days to the CTV D90.

### Magnetic Resonance Imaging Protocol

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

### Selection of the Type of Brachytherapy

A high-T2WI area indicated the vaginal tumor. The median vaginal tumor thickness by MRI at the stance of the

treatment was 20 mm (range, 10–40 mm). The median vaginal tumor thickness by MRI just before brachytherapy was 8 mm (range, 0–33 mm). Selection of the type of brachytherapy was based on ABS guideline.[4] The ICT was principally used for patients with a vaginal tumor thickness of 5 mm or less on MRI just before brachytherapy. The IBT was used for patients with a vaginal tumor thickness more than 5 mm. Actually, 9 patients were treated by using ICT and 12 patients using IBT. On MRI just before brachytherapy, as a result, the median vaginal tumor thickness was 5 mm (range, 0–8 mm) for 9 patients treated by ICT and 14 mm (range, 6–33 mm) for 12 patients treated by IBT.

In our institution, IBT was principally used not only for vaginal tumor thicker than 5 mm, but also for bulky cervical tumor and tumor with severe parametrial invasion. In this study, none of the 9 patients treated with ICT had bulky cervical tumor or tumor with severe parametrial invasion at the time of the first brachytherapy.

## Chemotherapy

A weekly regimen of TP including paclitaxel (PT; 50 mg/m$^2$) plus cisplatin (CDDP; 30 mg/m$^2$) was principally administered during the radiotherapy period. Weekly CDDP at a dose of 40 mg/m$^2$ was used for patients aged 70 years or older or for patients who did not want alopecia caused by paclitaxel. Concurrent chemoradiotherapy was not performed in patients with stage I vaginal cancer, with insufficient renal function, or aged 75 years or older. Four patients ultimately received radiotherapy alone. Seventeen patients received concurrent chemoradiotherapy, and 13 of these patients received weekly TP.

## Dosimetric Study

For dosimetric comparisons, we performed an experimental recalculation as the virtual IBT for patients who actually been treated by ICT and a virtual ICT for patients who actually been treated by IBT. In particular, for IBT-treated patients, the experimental ICT plans involved the use of tandem and cylinder applicators without interstitial needles in the planning CT. For ICT-treated patients, the experimental IBT plans involved the virtual insertion of needles. Experimental plans were created that obtained the same CTV D90 as the actual plans, and the doses to OAR were compared (Fig. 1).

Two patients who underwent the actual ICT were not used for this dosimetric study. One patient refused IBT, even though her vaginal tumor thickness was 8 mm. The other patient had internal iliac arterial invasion, which was difficult to be treated by IBT, although the tumor thickness was beyond 5 mm; she was treated by ICT and an EBRT boost to the right parametrium using the intensity-modulated radiotherapy technique of administering a dose of 20 Gy in 10 fractions.

## Follow up

Treatment responses, based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, were assessed at 2 to 3 months after the completion of radiotherapy using MRI. Every 2 to 6 months for 5 years, patients were followed with cytology, blood tests, and imaging. The median follow-up duration was 58.9 months (range, 20.9–80.1 months).

## Statistical Analysis

For the dose summation of brachytherapy plus EBRT before the insertion of the MB, the equivalent dose in 2 Gy
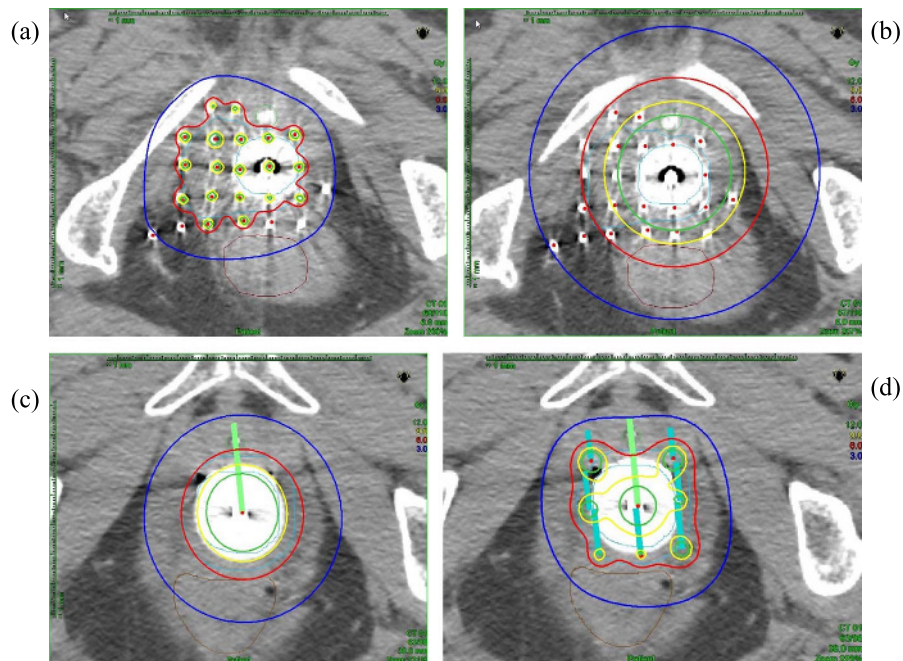


**FIGURE 1.** Dose distribution curves of actual brachytherapy plan and the experimental brachytherapy plan (the red line indicates the prescribed dose). The dose distribution curves of the actual IBT (A), experimental ICT (B), actual ICT (C), and experimental IBT (D).

fractions (EQD2) was calculated, based on the linear-quadratic (LQ) model.[7] The tumor dose was calculated using an $\alpha/\beta$ ratio of 10 Gy. For calculating the dose-volume parameters of the OAR (ie, D2.0 cc), the $\alpha/\beta$ ratio was assumed to be 3 Gy.

The 5-years rates of overall survival (OS), disease-free survival, and local control (LC) were estimated using the Kaplan-Meier method. Differences in the outcomes were compared using the log-rank test. Late adverse events were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. The $\chi^2$ test and the Student $t$ test were used to compare incidence of adverse events and DVH data, respectively. The differences in CTV D90 and doses to organs at risk between the actual IBT plans and the experimental ICT and between the actual ICT plans and the experimental IBT were also examined by the Student $t$ test. The paired $t$ test was used to compare total EQD2 of the CTV D90 and the OARs between the actual IBT plan and the experimental ICT plan and between the actual ICT plan and the experimental IBT plan. Statistical significance was at $P < 0.05$. Statistical analyses were performed by using the SPSS Base System software program (SPSS, Chicago, IL).

## RESULTS

Complete response was obtained from all patients. The 5-year OS rates for all patients, ICT-treated patients, and IBT-treated patients were 85.2%, 88.9% and 81.8%, respectively ($P = 0.54$ for ICT vs IBT) (Fig. 2a). The 5-year disease-free survival and LC rates for all patients, ICT-treated patients, and IBT-treated patients were 80.7% and 89.4%, 88.9% and 100%, and 74.1% and 81.5%, respectively ($P = 0.47$ and $P = 0.21$) (Fig. 2b). At the time of the analysis, local recurrence was observed in 2 patients who were treated with IBT. In these patients, 1 had local recurrence at the peripheral external orifice of the urethra (outside the irradiated field), whereas local recurrence at the cervix (within the irradiated field) was observed in another patient with a large tumor with poor response.

Table 2 lists the late adverse rectal events. Radiation proctitis (RP) developed in 5 (23.8%) patients. Among them, grade 3 RP was observed in 1 patient treated with IBT, and hyperbaric oxygen therapy was required. There were no significant differences in incidence of RP between ICT and IBT groups ($P = 0.45$).

The mean EQD2 of the CTV D90 was $67.2 \pm 5.8$ Gy for all patients. There was no significant difference in the CTV D90 between ICT- and IBT-patients ($P = 0.13$) (Fig. 3). There were also no significant differences in the actual D2cc for the sigmoid and rectum between the ICT- and IBT-treated patients ($P = 0.13$ and 0.39, respectively), although the bladder D2cc ($66.4 \pm 9.8$ Gy) in the IBT-treated patients was significantly lower than that ($78.8 \pm 10.1$ Gy) in the ICT-treated patients ($P = 0.04$).

In dosimetric study, the EQD2 of D2cc for bladder, rectum, and sigmoid of the experimental ICT plans was significantly higher than those of the actual plans in the IBT-treated patients (Fig. 4). Similarly, the EQD2 of D2cc for bladder and rectum of the experimental IBT plans was significantly lower than those of the actual plans in the ICT-treated patients, ($P = 0.001$ and 0.006, respectively).

When each CTV D90 of the experimental plan was set to almost equal to actual plan, individual data of D2cc for the OARs were plotted in Figure 4. Although D2cc of the bladder and rectum of ICT plans was significantly reduced by use of IBT in both ICT-treated and IBT-treated patients, the differences between the actual IBT and the experimental ICT plans in IBT-treated patients were larger than those between the actual ICT and the experimental IBT plans in ICT-treated patients.

In the ICT-treated patients, the EQD2 of D2cc for all OARs of both the actual ICT plans and the experimental IBT plans did not exceed the limited doses determined by the ABS consensus guideline; bladder D2cc less than EQD2 90 Gy, and rectum and sigmoid D2cc less than EQD2 75 Gy (3). In the IBT-treated patients, rectum D2cc in 1 actual IBT plan (8%) exceeded 75 Gy (Fig. 3). However, bladder D2cc and/or rectum D2cc in 11 experimental ICT plans (94%) were higher than the limited dose.

## DISCUSSION

Frank et al[8] obtained excellent pelvic control after administering definitive radiotherapy without IGABT to 143 patients with vaginal stage I and II cancers but recommended a tailored radiotherapy using EBRT, ICT, or IBT based on tumor size, site, and circumferential location. Manuel et al[9] showed that image-based IBT significantly improved LC compared with non–image-based IBT. Recent studies reported that the
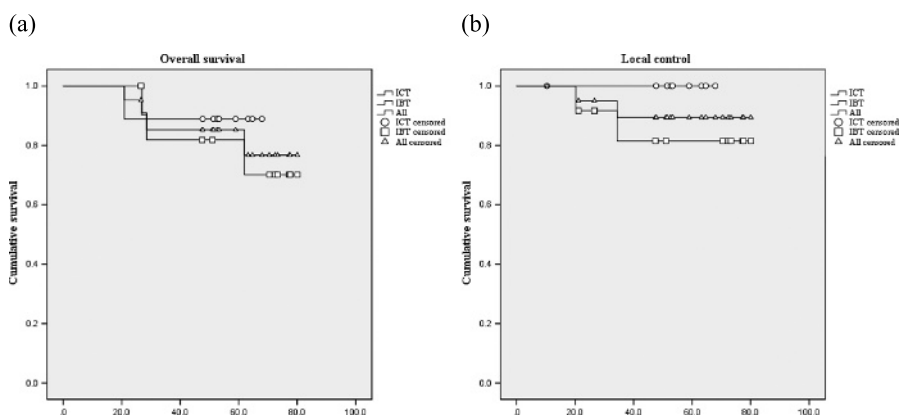
(a)

(b)

**FIGURE 2.** The Kaplan-Meier curves of overall survival (A) and pelvic recurrence-free survival (B).

**TABLE 2.** Late rectal toxicity

|  |  | All | ICT | IBT |
|---|---|---|---|---|
| RP | Grade 0 | 16 (76.2%) | 6 (66.7%) | 10 (83.4%) |
|  | 1 | 2 (9.5%) | 2 (22.2%) | 0 (0%) |
|  | 2 | 2 (9.5%) | 1 (11.1%) | 1 (8.3%) |
|  | 3 | 1 (4.8%) | 0 (0%) | 1 (8.3%) |
|  | ≥4 | 0 (0%) | 0 (0%) | 0 (0%) |
| Hematuria | Grade 0 | 21 (100%) | 9 (100%) | 12 (100%) |

sufficient irradiation doses to CTV using IGABT are very important to control advanced vaginal tumor, but the indication to use IBT remains unknown. Furthermore, it is also unclear whether improved DVH parameters by selected brachytherapy according to vaginal tumor thickness make better tumor control or not.[9–11] In the ABS consensus guideline, IBT is recommended for bulky vaginal cancers thicker than 5 mm.[4] The present study evaluated the clinical outcomes for cervical cancer patients who required irradiation of the entire vagina. According to vaginal tumor thickness assessed by MRI images obtained just before brachytherapy, we selected IBT in case of tumor thickness beyond 5 mm. As results, a total EQD2 dose of 65 Gy for mean CTV D90 was delivered for all patient, and no significant difference in the mean CTV D90 between ICT- and IBT-treated patients was observed ($P = 0.13$) (Fig. 3), and selected brachytherapy yielded good 3-year OS and LC rates for both IBT and ICT group without any differences ($P = 0.54$ and $0.47$, respectively). Grade 3 RP was observed in 1 patient treated with IBT (Table 2). There was no significant difference in incidence of RP between ICT and IBT groups ($P = 0.45$).

Although the incidence of RP tends to increase in patients who required irradiation for the entire vagina, in this study, the incident rate of severe RP was acceptable in patients treated with both ICT and IBT.

Concurrent chemoradiotherapy (CCRT), including weekly CDDP has an important role in the definitive standard treatment for locally advanced cervical cancer patients.[12,13] However, it has been reported that PT increased the radiation sensitivity of squamous cell carcinoma in vitro, whereas the combination of TP caused synergistic effects.[14,15] In Japan, phase I study of CCRT recommended a weekly dose of CDDP 30 mg/m$^2$ and PT 50 mg/m$^{2.16}$ The Japan Clinical Cancer Research Organization GY-01 trial was a multicenter phase II prospective study, aimed at evaluating the efficacy of CCRT including weekly TP, as well as ICT, delivering a prescription dose to point A for stage III to IVA cervical cancer.[17] The 2-year cumulative pelvic disease progression-free rate was 89.6%. On the other hand, in Japanese Gynecologic Oncology Group 1066, which evaluated the efficacy of CCRT including weekly CDDP (40 mg/m$^2$) and ICT, delivering a prescription dose to point A for stage III to IVA cervical cancer, the 2-year pelvic disease progression-free rate was 73%.[13] In Japan Clinical Cancer Research Organization GY-01, 60 of 68 patients (88%) received chemotherapy for 5 cycles or more, whereas planned radiotherapy was completed in 63 patients (93%).[17] The incidence of grade 3 or more leukopenia was 54.4%, and tended to be less, compared with that (83%) in Japanese retrospective study including triweekly CDDP.[18] The CCRT, including weekly TP, is not a standard treatment; however, it demonstrated favorable antitumor activity and acceptable adverse effects in Japanese clinical trials.[17]

Dimopoulos et al reported that the LC rate was 92% for patients with advanced vaginal cancer treated by IGABT at
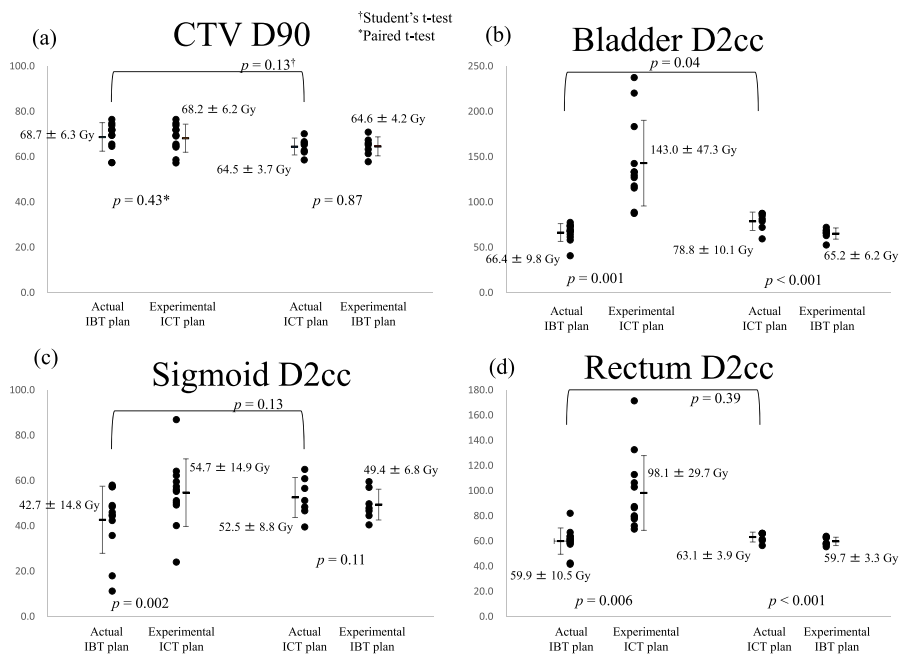


**FIGURE 3.** EQD2 of the CTV D90 (A) and organs at risk [ie, bladder D2.0 cc (B), sigmoid D2.0 cc (C), and rectum D2.0 cc (D)] in the actual and experimental plans.
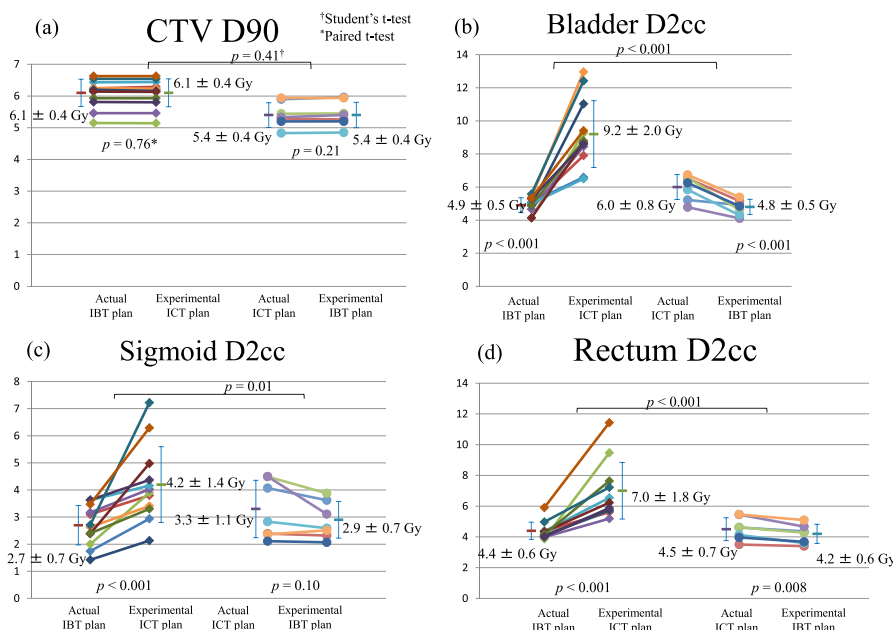
**FIGURE 4.** The comparison between the actual brachytherapy plan and the simulated brachytherapy plan of the dose-volume histogram parameters for CTV D90 (A) and OAR [ie, bladder D2.0 cc (B), sigmoid D2.0 cc (C), and rectum D2.0 cc (D)].

the mean total dose of 86 Gy to 90% volume for CTV.[9] The Groupe Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC–ESTRO) and ABS recommend delivery of a cumulative dose of approximately 80 to 90 Gy for the target volume.[3,19] However, the protocols in Japanese studies traditionally have used lower doses in a shorter overall treatment time, compared with the protocols in these countries.[20,21] Actually, Japanese Gynecologic Oncology Group 1066 demonstrated comparable outcomes of concurrent chemoradiotherapy delivering an EQD2 of 62 to 65 Gy to point A for stage III/IVA cervical cancer to results from studies at the United States and European countries.[13] In this study, at the time of the analysis, 2 patients had local recurrence while receiving a total EQD2 dose of 65 Gy for mean CTV D90; then, 1 patient, who experienced local recurrence within the irradiated field, had a large tumor with poor response. In future, we should try to escalate the dose to the CTV for large tumors with poor response while reducing the dose to OARs by using IBT.

In this study, ICT with tandem and cylinder applicators principally administered a prescription to point A rather than to an MRI-defined volume, and the source dwell patterns were modified to deliver the prescribed dose to the CTV and to adjust the dose to OAR. The reason we conducted this treatment planning procedure is that we thought it could make the dose distribution for each patient more uniform and avoid unexpected high dosage area in the vaginal mucosa.

If the tumor invades to the lower vagina, ICT with tandem and cylinder applicators is more useful to irradiate the entire vagina rather than ICT with tandem and ovoid applicators, but it is difficult to deliver a sufficient dose to the parametrium while sparing OARs. In our institution, IBT was

selected if the patients had at least 1 tumor character listed as follows: 1) vaginal tumor thicker than 5 mm, 2) bulky cervical tumor, and 3) tumor with severe parametrial invasion. In this study, none of the 9 thin vaginal tumor patients treated with ICT had bulky cervical tumor or tumor with severe parametrial invasion. If patients with vaginal tumor 5 mm thick or less had simultaneously bulky cervical tumor or tumor with severe parametrial invasion, IBT is selected to deliver a sufficient dose to CTV.

To safely perform brachytherapy for cervical cancer, the GEC-ESTRO and ABS recommend calculating the dose of D0.1cc, D1cc, and D2cc to OAR such as the bladder, sigmoid, and rectum.[3,22] In ABS guideline, the D2cc for the rectum and sigmoid should be reduced to less than 70 to 75 Gy, and the D2cc for the bladder should be less than 90Gy.[3,23] Results from the EMBRACE study showed that severe rectal toxicities, with higher frequencies, occurred with D2cc value of 75 Gy or more.[24] In this study, both ICT- and IBT-treated patients received the rectum D2cc value of approximately 60 Gy, and there was no significant difference between 2 treatment groups. On the other hand, the bladder D2cc in the ICT-treated patients was significantly higher than that in the IBT-treated patients ($P = 0.04$). There were, however, no differences in complications in the urinary system because no patient received 90 Gy or more for the bladder D2cc in both ICT- and IBT-treated patients. Hence, selected brachytherapy based on the threshold of 5 mm for vaginal tumor thickness could deliver the sufficient doses to CTV while under the limited dose of OARs, such as bladder, sigmoid, and rectum.

In this study, a dosimetric evaluation as the virtual IBT for patients actually treated by ICT, and vice versa, was performed to assess whether our selection criteria of brachytherapy type

was appropriate or not. In the IBT-treated patients with their vaginal tumors thicker than 5 mm, irradiated doses and volumes of bladder, rectum, and sigmoid colon in the experimental ICT plans were higher than those in the actual IBT plans ($P < 0.001$, 0.002, and <0.001, respectively) (Fig. 4). Among them, the mean D2cc for bladder and rectum in the experimental plans was extremely high (143.0 Gy and 98.1 Gy, respectively), and 11 of 12 plans (92%) exceeded at least any one of the limited doses for bladder D2cc, rectum D2cc, and sigmoid colon D2cc (Fig. 3). Therefore, many severe complications at the bladder and rectum may occur if ICT is selected for patients with their vaginal tumor thickness beyond 5 mm.

On the other hand, in the ICT-treated patients, who had the vaginal tumor measuring 5 mm or less, D2cc for bladder and rectum of the actual ICT plans was also higher than those of the experimental IBT plans ($P = 0.001$ and 0.006, respectively). However, the D2cc for bladder, rectum, and sigmoid colon was acceptable in both of the actual ICT plans and the experimental IBT plans. The IBT has a small advantage for patients with vaginal tumor thickness less than 5 mm because no actual ICT plans exceeded the limited dose of bladder D2cc according to the ABS consensus guideline. Kirchheiner et al reported that brachytherapy with 2 fractions in 1 application under spinal/epidural anesthesia caused post-traumatic stress disorder, which occurred in 41% of patients 3 months after treatment.[25] The IBT generally carries a severe mental and physical burden on the patient compared with ICT. Taking the obtained results and the mental and physical burden on the patients into consideration, there was almost no benefit on most ICT-treated patients if they had received more invasive IBT. Based on results from dosimetric comparison in this study, the usefulness of selected brachytherapy for cervical cancer with vaginal invasion based on the guideline published from the ABS was confirmed.

The limitation of this study is that it was retrospectively analyzed and included a small number of patients. Further prospective study with a large number of patients is necessary to more accurately evaluate the ABS consensus guideline in patients with severe vaginal invasion.

## CONCLUSIONS

Selected ICT or IBT as an appropriate brachytherapy method according to prebrachytherapy MRI evaluation of vaginal tumor thickness based on ABS guidelines have yielded high LC rate with low complication rate. In dosimetric comparison, almost all experimental ICT plans for the IBT-treated patients with vaginal tumor thicker than 5 mm exceeded the limited doses of bladder D2cc and/or rectum D2cc. Results from the present study strongly support brachytherapy selection according to ABS consensus guidelines for vaginal tumor treatment, with an improvement seen with IBT in terms of OAR doses for all patients with gross vaginal disease, irrespective of the thickness.

## REFERENCES

1. Lanciano RM, Won M, Coia LR, et al. 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.* 1991;20:667–676.
2. Montana GS, Hanlon AL, Brickner TJ, et al. Carcinoma of the cervix: patterns of care studies: review of 1978, 1983, and 1988–1989 surveys. *Int J Radiat Oncol Biol Phys.* 1995;32:1481–1486.
3. Viswanathan AN, Beriwal S, De Los Santos JF, 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.
4. Beriwal S, Demanes DJ, Erickson B, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. *Brachytherapy.* 2012;11:68–75.
5. Potter R, Georg P, Dimopoulos JC, et al. 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.* 2011;100:116–123.
6. Rijkmans EC, Nout RA, Rutten IH, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol.* 2014;135:231–238.
7. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol.* 1985;58:515–528.
8. Frank SJ, Jhingran A, Levenback C, et al. Definitive radiation therapy for squamous cell carcinoma of the vagina. *Int J Radiat Oncol Biol Phys.* 2005;62:138–147.
9. Manuel MM, Cho LP, Catalano PJ, et al. Outcomes with image-based interstitial brachytherapy for vaginal cancer. *Radiother Oncol.* 2016;120:486–492.
10. Dimopoulos JC, Schmid MP, Fidarova E, et al. Treatment of locally advanced vaginal cancer with radiochemotherapy and magnetic resonance image-guided adaptive brachytherapy: dose-volume parameters and first clinical results. *Int J Radiat Oncol Biol Phys.* 2012;82:1880–1888.
11. Huertas A, Dumas I, Escande A, et al. Image-guided adaptive brachytherapy in primary vaginal cancers: a monocentric experience. *Brachytherapy.* 2018;6:S1538–4721(18) [Epub ahead of print].
12. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer : a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol.* 2008;26:5802–5812.
13. Toita T, Kitagawa R, Hamano T, et al. 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.* 2012;126:211–216.
14. Jaakkola M, Rantanen V, Grénman S, et al. In vitro concurrent paclitaxel and radiation of four vulvar squamous cell carcinoma cell lines. *Cancer.* 1996;77:1940–1946.
15. Jekunen AP, Christen RD, Shalinsky DR, et al. Synergistic interaction between cisplatin and taxol in human ovarian carcinoma cells in vitro. *Br J Cancer.* 1994;69:299–306.
16. Umayahara K, Takeshima N, Nose T, et al. Phase I study of concurrent chemoradiotherapy with weekly cisplatin and paclitaxel chemotherapy for locally advanced cervical carcinoma in Japanese women. *Int J Gynecol Cancer.* 2009;19:723–727.

17. Umayahara K, Takekuma M, Hirashima Y, et al. Phase II study of concurrent chemoradiotherapy with weekly cisplatin and paclitaxel in patients with locally advanced uterine cervical cancer: The JACCRO GY-01 trial. *Gynecol Oncol.* 2016;140:253–258.

18. Toita T, Moromizato H, Ogawa K, et al. Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. *Gynecol Oncol.* 2005;96:665–670.

19. Lang S, Nulens A, Briot E, et al. Intercomparison of treatment concepts for MR image assisted brachytherapy of cervical carcinoma based on GYN GEC-ESTRO recommendations. *Radiother Oncol.* 2006;78:185–193.

20. Toita T, Kodaira T, Shinoda A, et al. Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. *Int J Radiat Oncol Biol Phys.* 2008;70:788–794.

21. Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys.* 2012;82:250–255.

22. Potter R, Haie-Meder C, Van Limbergen E, et al. 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.* 2006;78:67–77.

23. Georg P, Lang S, Dimopoulos JC, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys.* 2011;79:356–362.

24. Mazeron R, Fokdal LU, Kirchheiner K, et al. Dose–volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. *Radiother Oncol.* 2016;120:412–419.

25. Kirchheiner K, Czajka-Pepl A, Ponocny-Seliger E, et al. Posttraumatic stress disorder after high-dose-rate brachytherapy for cervical cancer with 2 fractions in 1 application under spinal/epidural anesthesia: incidence and risk factors. *Int J Radiat Oncol Biol Phys.* 2014;89:260–267.