Preliminary Results of Magnetic Resonance Imaging-aided High-dose-rate Interstitial Brachytherapy for Recurrent Uterine Carcinoma after Curative Surgery

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Recurrent uterine carcinoma/Magnetic resonance imaging (MRI)/Image-based brachytherapy/High-dose-rate brachytherapy.

This report presents initial experience with imaging-aided high-dose-rate interstitial brachytherapy (HDR-ISBT) for post-operative recurrence of uterine carcinoma. Fourteen patients presenting with post-operative recurrence of uterine carcinoma (nine cervix and five corpus) between July 2005 and October 2008 were enrolled in this study (median follow-up: 37 months, range: 6–59 months). We implanted magnetic resonance imaging (MRI)-compatible plastic applicators using our own ambulatory technique. HDR-ISBT treatment consisted of twice-a-day irradiation of 6 Gy each with at least a six-hour interval to provide the total prescribed dose. Treatment was based on treatment planning-computed tomography with MRI as a reference. Seven patients were treated with a combination of ISBT (median 30 Gy/5 fractions; range: 27–33 Gy) and external beam radiation therapy (EBRT), and the other seven with brachytherapy only (median 54 Gy/9 fractions; range: 48–54 Gy), one of whom had previously received pelvic EBRT. The three-year estimates of local control and overall survival rates were 77.9% (95% confidence interval (CI): 55.8–100%) and 77.1% (95% CI: 54.2–100%), respectively. Two patients, who had received combined treatment with EBRT showed untoward reactions, including a grade 3 subileus and grade 2 constipation. Another patient, who had been treated with ISBT alone, developed grade 2 urinary constriction. Our imaging-aided HDR-ISBT for post-operative recurrence of uterine carcinoma was found to be practical with promising preliminary results.

INTRODUCTION

Interstitial brachytherapy (ISBT) is a valuable treatment method for gynecological cancer. In cases of previously untreated uterine cervical carcinoma, the American Brachytherapy Society recommends that ISBT be used for problem situations such as bulky lesion, narrow vagina, inability to enter the cervical os, extension to the lateral parametrium or pelvic side wall, and lower vaginal extension. Moreover, several clinical studies have reported good local control results using low-dose-rate (LDR) or high-dose-rate (HDR) ISBT. Locally recurrent uterine carcinoma is also a good candidate for ISBT. Interstitial implantation is an effective approach for massive vaginal or parametrial tumor lesions when an intrauterine applicator for operative recurrence cannot be used, and several favorable results have been reported. Weitmann et al. reviewed the results from six institutes and found local control rates of 29–100% and overall survival rates of 56–63%.

Image guidance has potential to improve treatment results because the post-operative recurrent tumor is often large and its complex shape makes it difficult to achieve a satisfactory implant with non-image guidance. For applicator implantation, the applicability of ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) has been investigated.

For our patients, we introduced our transrectal ultrasonography (TRUS) guided implantation and MRI-assisted CT treatment planning combined with our previously reported...
novel ambulatory implantation technique for prostate cancer. \textsuperscript{15} We used flexible applicators with our own removable template so that patients could walk during the treatment. As a result, no metallic treatment items were used for our patients so that they could receive MRI examination. We have also suggested this method for previously untreated uterine cervical carcinoma. \textsuperscript{16} Free-hand implantation without a template was used because it is easier to implant into a parametrial extension without pubic arch interference. Imaging modality guidance proved to be very useful for effective free-hand implantation. We report here preliminary results obtained with our imaging-aided ISBT technique for post-operative locally recurrent uterine carcinoma.

**MATERIALS AND METHODS**

**Patient characteristics**

All 14 patients enrolled in this trial underwent hysterectomy between January 2003 and September 2006 at the time of initial diagnosis of uterine carcinoma, and subsequently experienced vaginal recurrence. These patients (median age: 54.5 years; range: 27–82 years) were treated between July 2005 and October 2008. The primary site of nine patients was the uterine cervix, and that of the other five was the uterine corpus. Tumor size was determined by means of pelvic examination and transrectal ultrasonography (median: 2.7 cm; range: 1–8 cm). Superficial disease cases that could be cured with intracavitary brachytherapy were excluded from this study. In addition, patients with distant metastases were considered ineligible. Histologic findings showed three squamous cell carcinomas, nine adenocarcinomas (including all uterine corpus carcinomas), and two adenosquamous carcinomas. All patients underwent hysterectomy as initial treatment, 11 patients were treated with bilateral salpingo-oophorectomy (BSO) and 10 patients with pelvic lymph node dissection (PLND). One patient received postoperative pelvic irradiation (50 Gy). Table 1 summarizes patient characteristics in this study.

**EBRT**

One patient had undergone postoperative pelvic EBRT, and she was treated with ISBT alone this time. Another patient 82 years of age was treated with ISBT alone due to advanced age (all 13 remaining patients in this study were 71 years of age or younger). Another patient with simultaneous local and nodal recurrence was treated with EBRT and ISBT. For the other 11 patients, indication of EBRT was determined according to whether the interval exceeded 12 months. Five patients with a longer interval (median: 31 months, range: 12–40 months) were treated with ISBT alone, while six with a shorter interval (median: seven months, range: 5–12 months) underwent combination therapy with EBRT and ISBT for pelvic control in view of the possibility of simultaneous subclinical nodal recurrence. The patients received EBRT to the whole pelvis with the median prescribed dose of 30 Gy (range, 20–30 Gy) or 2 Gy per fraction. In addition, they underwent center-shielded (CS) EBRT (20 Gy) with 2 Gy per fraction. Neither additional boost irradiation nor expansive irradiation of para-aortic lymph nodes was performed. ISBT was performed after whole pelvic EBRT and before CS EBRT. In principle, the midline block of CS EBRT was decided depending on the ISBT treatment volume. No patient received chemotherapy.

**Applicator implantation**

We performed multifractionated HDR irradiations with a single implant session for all patients. Implantation was per-

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<th>Table 1. Patient Characteristics</th>
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<td><strong>Age (y)</strong></td>
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<td><strong>Follow-up period (mo)</strong></td>
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<td><strong>Primary origin (no. of patients)</strong></td>
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<td>Cervix</td>
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<td><strong>Histology (no. of patients)</strong></td>
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<td><strong>Modality (no. of patients)</strong></td>
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<td>ISBT+EBRT</td>
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<td><strong>Tumor size (cm)</strong></td>
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<td><strong>Nodal metastasis (no. of patients)</strong></td>
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<td><strong>Whole pelvic EBRT (Gy)</strong></td>
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<td><strong>ISBT (Gy)</strong></td>
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Abbreviations: EBRT, external beam radiotherapy; ISBT, interstitial brachytherapy; SCC, squamous cell carcinoma; Ad, adenocarcinoma; AdSq, adenosquamous carcinoma
formed in the operating room with lumbar anesthesia and continuous epidural anesthesia. The implantation was monitored with the aid of TRUS (Aloka, Tokyo, Japan) and flexible needles (ProGuide Sharp Needle; Nucletron, Veenendaal, The Netherlands) were used for all patients. First, a single flexible needle applicator (anchor needle) was inserted through the center of the vaginal stump. A button stopper was then affixed to the anchor needle and placed in contact with the stump. After implantation of the anchor needle, a silicon cylinder was inserted into the vagina. This cylinder is custom-made from silicon rubber with the size depending on the patient’s vaginal size and it has five implant holes, with the center hole used for the anchor needle. The concept of ambulatory technique has been described in detail elsewhere.\textsuperscript{15} Briefly, the anchor needle and cylinder complex was sutured to the uterine cervix with silk thread. After inserting the cylinder, we attached a custom-made vinyl template to the patient’s perineum. This template has holes for flexible needle applicators. The positions of the holes for freehand implantation are determined by consulting preimplantation TRUS, CT, and MRI images. We implanted four cylinder-guided needles into the holes of both the cylinder and the vinyl template. Next, we implanted the other applicators by free-hand implantation using the holes other than the cylinder’s holes. The objective of the implantation was to cover the clinical target volume (CTV) with TRUS guidance. After implantation was complete, we fixed all needles to the vinyl template and the perineum with silk thread affixed to a color bead-button complex. The color beads, but not the anchor needles, were then affixed to the applicator with an adhesive before implantation. This fixation of the bead-button complex determined the needle length, and the beads were color coded for identification of the needle length. Finally, the protruding connector end of the applicator was cut off (Fig. 1).

\textit{Treatment planning and treatment}

All patients underwent CT and MRI immediately after implantation was finished for the purpose of treatment planning. MRI examinations included T2-weighted and T1-weighted axial images and T2-weighted sagittal images using a pelvic surface coil. Both CT and MRI images were obtained with 3-mm thick sections (Fig. 2(a), 2(b)).

For CT-based planning, MRI was used as a reference to outline the CTV and organs at risk (OAR: rectum, bladder, sigmoid colon, small intestine). Clinical examination findings and information from the marker seed, which was implanted at the edge of the CTV, were also used for delineation. All contours were drawn on CT images (CT-MRI fusion was not used). Applicator positions were easily defined on both CT and MRI, and helped contouring as landmarks. For CTV-based dose prescription, the PLATO planning system (software version 14.2; Nucletron) was used with manual modification to cover CTV by the 100\% isodose line on every slice after computer optimization using a geometrical optimization algorithm.\textsuperscript{17} We did not use any single reference point for dose prescription. We kept the doses to the OAR below the 100\% prescribed dose except in cases where the OAR were adhering to or invaded by the tumor.

HDR-ISBT treatment consisted of twice-daily irradiation of 6 Gy each time, with at least a six-hour interval to provide the total prescribed dose. Seven patients were treated with a

\textbf{Fig. 1.} The vinyl template-applicator was sutured to the perineum. The anchor needle was fixed with a button only (arrow), and the other needles were fixed with the button-bead complex.

**Fig. 2.** (a) Magnetic resonance image of a patient obtained just after implantation. The flexible applicator is shown as a black dot (arrow). (b) Isodose curves on computed tomography image of the patient in Fig. 2(a). CTV is outlined with a thick red line based on the MRI image. CTV was almost covered by the 100\% isodose line (thin red line).
combination of ISBT (median 30 Gy/5 fractions; range: 27–33 Gy) and external beam radiation therapy (EBRT). Brachytherapy only was used for six patients, five of whom received 54 Gy/9 fractions. The remaining patient was treated with 48 Gy/8 fractions because pelvic EBRT had previously been administered. We used the microSelectron-HDR (Nucletron) for treatment and 192Ir as the treatment source.

Follow-up and statistics
Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE-ver 3.0). As a rule, patients were monitored by means of monthly medical examinations both during and after treatment. All statistical calculations were performed with the aid of JMP8.0 statistical software (SAS Institute Japan Inc., Tokyo, Japan). We calculated local control, progression-free survival (PFS), and overall survival (OS) rates with the Kaplan-Meier method. Follow-up times for local control and survival were calculated from the start of radiotherapy (EBRT or BT).

RESULTS
The median follow-up for all patients was 37 months (range: 6–59 months). Three patients died of carcinoma and four cancer-bearing patients were alive at the time of writing. The three-year overall survival rate was 77.1% for all patients (95% confidence interval (CI): 54.2–100%) (Fig. 3).

Of the seven patients showing disease progression, three presented local failure (local only: one, local and distant: two), three developed distant metastasis only and one nodal and distant metastasis. The three-year progression-free survival rate was 50% (95% CI: 23.8–76.2%) for all patients, and the three-year local control rate was 77.9% (95% CI: 55.8–100%) (Fig. 4). The three patients who developed local recurrences had adenocarcinoma of the uterine cervix. One patient who developed local recurrence outside the initial CTV after one year of observation underwent another ISBT (48 Gy/8 fractions) as salvage therapy. However, local control could not be achieved.

Severe grade 3 adverse events developed in one patient treated with EBRT and ISBT. She experienced intestinal obstruction and needed total parenteral nutrition. Grade 2 adverse events were observed in two patients. One patient treated with a combination of EBRT and ISBT experienced neuroconstipation and neuralgia of the lower extremities. Another patient treated with ISBT alone developed urethral stricture and was treated with dilation.

DISCUSSION
Early-stage uterine carcinoma has a high cure rate for radical surgery. However, radical treatment becomes difficult if the tumor recurs locally because indication for salvage pelvic exenteration is limited.\(^{18}\) EBRT with or without chemotherapy is a well-tolerated modality, but treatment outcome is not satisfactory.\(^{19}\)

ISBT is an effective treatment option for locally-recurring uterine carcinoma after radical surgery. Charra et al. reported that 78 patients with upper-third vaginal recurrence attained five-year local control and overall survival rates of 70.4% and 56%, respectively.\(^{7}\) In their study, LDR-ISBT with or without EBRT was used and eight of 78 patients (10.2%) showed grade 3 complication. Nag et al. reported their treatment results for 13 previously non-irradiated patients with isolated vaginal recurrences of endometrial carcinoma with a local control rate of 100%.\(^{20}\) The cause-specific survival rate was 77% and two of the 13 patients (15%) showed grade 3–4 complications. Tewari et al. treated 30 vaginal recurrences of endometrial carcinoma and achieved a local control rate of 77%\(^{21}\). Five-year cause-specific survival rate was 65% and the severe complication rate was 17%. Jensen et al. treated 34 gynecological cancer patients (22 pelvic recurrences and 12 primary locally advanced diseases) for a local control rate of 53% and a 2-year survival rate of 63%.\(^{22}\) Five of the 34 patients (15%) incurred acute major complications and 17 (50%) chronic complication. To summarize the above-mentioned reports, local control rates ranged from 53 to 100% and severe complication rates from 10.2 to 50% at 2–8 years. The authors emphasize that they used a template on implantation but they did not utilize an imaging modality. CT might have been used only for treatment planning but never for implantation.
guidance.

On the other hand, image-guided implantation has been adopted in some other studies as follows. Eisbruch et al. visualized tumor and template by using preplanning CT to determine implant position and distance by “cylinder’s eye view”.[11] Twenty gynecological cancer patients including six recurrent cancer patients were treated in this manner. Local control rate was 55% and the slight to moderate late complication rate was 10%. Sharma et al. used implantation guided by TRUS monitoring, which enabled them to prevent accidental entry of the applicator into OAR.[23] The 25 uterine cervical cancer patients they treated included nine recurrent patients and the local control rate was 64% (56% for the recurrent patients), while 12% suffered severe late complications. Weitmann et al. also used TRUS-guided implantation and treated 23 recurrent uterine carcinoma patients. The five-year cause-specific survival and local control rates were 43% and 47%, respectively. Grade 3 gastrointestinal and urinary late complications occurred in five of 23 patients (22%). Corn et al. introduced endorectal-coil MRI guidance. Three of the first five patients they treated could be controlled locally even though the maximum diameter of the tumors was 4–7 cm. Popowski et al. developed a titanium-zirconium applicator for open MRI-guided implantation and reported their experience with six patients.[25] Finally, Viswanathan et al. reported their results for 10 recurrent endometrial carcinoma patients who underwent MR-guided interstitial brachytherapy and one (10%) showed grade 3 complication.[24] In summary, the rates of severe late complication, reported as 10–22% in the above-mentioned literature, seemed considerably lower than non-image guidance ISBT. However, it should be noted that the background of each report, such as the proportion of re-irradiated cases, differed.

The Image-Guided Brachytherapy Working Group recommended T2-weighted MRI with image-based intracavitary brachytherapy for cervical cancer.[26] The value of MRI in imaging gynecologic malignancies lies in its superior contrast resolution, which enables visualization of tumor size and volume, and discrimination of the tumor from normal tissue. Although these recommendations were originally aimed at intracavitary brachytherapy, the advantage of MRI seems apparently applicable to ISBT. That is why we have decided to utilize MRI on ISBT.

Just after the initial installation of the microSelectron-HDR at Osaka University Hospital in 1991, we tried several dose-fractions for recurrent cancers in the pelvic area. A total dose of 24 to 50 Gy with a fraction dose of 5 to 7.5 Gy was administered for eleven patients from 1991 to 1994.[27] After the first experience, the fraction dose was fixed at 6 Gy. From 1995 to 1997 we treated 15 patients of recurrent carcinoma of the uterus with 42 Gy in seven fractions or 48 Gy in eight fractions. In this study we established the principle that non-irradiated cases receive 48 Gy while re-irradiated cases receive 42 Gy; this principle is still ongoing at Osaka University Hospital.[28]

We started using MRI-assisted treatment planning in 2005 at Osaka National Hospital. At the same time, we escalated the total dose to 54 Gy for non-irradiated cases and to 48 Gy for re-irradiated cases by adding one fraction of 6 Gy, to improve local control rate with the expectation that we can reduce the complication rate by MRI-assisted planning. On the other hand, for EBRT-combined cases, we used the same dose-fractionation as the one for fresh (previously untreated) cases of cervical cancer. We have reported a local control rate of 83% (15/18) even though all patients had advanced T3–4 stage tumors.[16]

In the current study, although we have treated only 14 patients, we achieved a three-year local control rate of 77.9% (95% CI: 55.8–100%), evidently an equivalent or better result than previously reported outcomes. The authors would like to emphasize that only 7.1% (one patient) experienced grade 3 complication, which seemed even lower than elsewhere in the literature. These results lead us to regard imaging-aided ISBT as useful for satisfactory delivery of prescribed doses to the CTV and, at the same time, for reducing the dose to the OAR. To determine the actual utility of our treatment, more patients and longer follow-up are necessary, and a comparison of outcomes for this novel treatment with those obtained with metal needles era will also be warranted. In conclusion, imaging-aided HDR-ISBT for the treatment of post-operative recurrence of uterine carcinoma was found to be practical, with promising preliminary results.

REFERENCES


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