High-dose-rate Interstitial Brachytherapy with Computed Tomography-based Treatment Planning for Patients with Locally Advanced Uterine Cervical Carcinoma

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Interstitial brachytherapy/High dose rate/Computed tomography/Image based treatment planning/Cervical carcinoma.

The aims of this study were to carry out a dose volume analysis of high-dose-rate interstitial brachytherapy with computed tomography-based treatment planning and to investigate the treatment outcome of patients with locally advanced bulky and/or irregularly shaped uterine cervical carcinoma. Between July 2003 and December 2007, 15 patients were treated with external beam radiation therapy and high-dose-rate interstitial brachytherapy with or without intracavitary brachytherapy. Seven patients were treated with interstitial brachytherapy alone, and 8 were treated with combined use of intracavitary and interstitial brachytherapy. A comparison of the volume and dose parameters with intracavitary and interstitial brachytherapy in patients who received both treatments showed that the median D90 of the high-risk clinical target volume per fraction was 4.4 Gy with intracavitary brachytherapy and 5.6 Gy with interstitial brachytherapy, and the median V100 was 66% with intracavitary brachytherapy and 85% with interstitial brachytherapy. The median D2cc of the bladder with intracavitary and interstitial brachytherapy per fraction was 5.5 Gy and 4.7 Gy, respectively, and the median D2cc of the rectum with intracavitary and interstitial brachytherapy was 5.9 Gy and 4.1 Gy, respectively. The median follow-up time was 37 months, and the overall and progression-free survival rates for all patients at 3 years were 78% and 51%, respectively. The actuarial 2-year and 3-year locoregional control rates were 80% and 71%, respectively. Dose distribution was improved with image-based interstitial brachytherapy, and satisfactory local control was achieved for patients with locally advanced uterine cervical carcinoma in which intracavitary brachytherapy may result in a suboptimal dose distribution.

INTRODUCTION

Radiation therapy plays an important role in the management of patients with uterine cervical carcinoma. The curative potential of radiation therapy in the treatment of uterine cervical carcinoma depends on the delivery of a high radiation dose to the tumor with the combination of external beam radiation therapy (EBRT) and brachytherapy. Intracavitary brachytherapy (ICBT) is an established treatment method in the management of cervical carcinoma. However, routine ICBT has a limitation in source arrangement and may not deliver an adequate dose for the treatment of locally advanced or irregularly shaped disease. In those cases, interstitial brachytherapy (ISBT) has the potential to achieve a better dose distribution. The American Brachytherapy Society (ABS) recommends that ISBT should be used in situations such as bulky lesions, narrow vaginal apex, inability to enter the cervical os, extension to the lateral parametria or pelvic side wall, and lower vaginal extension.1

Some reports have shown good local control in the treatment of locally advanced gynecologic malignancies with high-dose-rate (HDR) ISBT, but relatively severe complications have also been reported.2–4 The ABS has recommended the use of three-dimensional (3-D) isodose calculations using computed tomography (CT) or magnetic resonance imaging (MRI) with ISBT, if available.1 Some studies on 3-D image-based brachytherapy using HDR sources for cervi-
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Cervical cancer have been reported. However, dose volume analysis of HDR ISBT remains insufficient.

We performed HDR ISBT with CT-based treatment planning combined with EBRT for the initial treatment of patients with locally advanced uterine cervical carcinoma in which ICBT may result in a suboptimal dose distribution and analyzed the clinical outcomes and dose and volume parameters of brachytherapy retrospectively.

MATERIALS AND METHODS

Patients

Between July 2003 and December 2007, 15 newly diagnosed patients with locally advanced cervical cancer were treated with EBRT and HDR ISBT as an initial treatment at the Department of Radiation Oncology of Gunma University Graduate School of Medicine (Table 1). The patients’ ages ranged from 35–84 years, with a median of 62 years. Fourteen patients had a good performance status of 0 or 1, and 1 had a poor performance status of 3. Histologic findings showed 14 squamous cell carcinomas and 1 adenosquamous carcinoma. The patients were classified according to the International Federation of Gynecology and Obstetrics (FIGO) stages: 4 patients had stage IIB disease, 1 had stage IIIA disease, 6 had stage IIIB disease and 4 had stage IVA disease. The median tumor diameter at initial diagnosis was 7.0 cm (range, 4.6–8.7 cm). Eight patients (53%) had radiographic evidence of lymph node metastasis prior to therapy. Five patients were treated with radiation therapy alone, and 10 were treated with concurrent chemoradiotherapy.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>35–84 (Median: 62)</th>
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<tbody>
<tr>
<td>PS</td>
<td>0–1</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>FIGO stage</td>
<td>IIB</td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
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<tr>
<td></td>
<td>IIIB</td>
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<tr>
<td></td>
<td>IVA</td>
</tr>
<tr>
<td>Lymph node</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>positive</td>
</tr>
<tr>
<td>Indications for ISBT</td>
<td>Bulky lesion</td>
</tr>
<tr>
<td></td>
<td>Irregularly shaped lesion</td>
</tr>
<tr>
<td>Histology</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Adenosquamous carcinoma</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>+</td>
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<tr>
<td></td>
<td>−</td>
</tr>
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</table>

PS: performance status ISBT: interstitial brachytherapy

Radiation therapy

All patients were treated with EBRT combined with HDR ISBT. Initially, the external irradiation was delivered with 10-MV photons to the whole pelvis using antero-posterior parallel opposed beams with a fractional dose of 2 Gy in 5 fractions per week. A center shield (width of 3 cm at the central axis) was inserted when the whole pelvic irradiation dose reached 30 Gy, and then center-shielded EBRT was continued to a total dose of 50 Gy in principle (median total dose, 50 Gy; range 49–50 Gy). Three patients who had a positive node in the pelvic region received an additional external beam boost to the metastatic nodes at a total dose of 56 to 58 Gy.

Brachytherapy was started after completion of whole pelvic EBRT. At first, 8 patients were treated with HDR ICBT, and the therapeutic measures were changed to ISBT for the modification of dose distribution. Seven patients were treated with HDR ISBT from the start. The indications for ISBT were as follows: 13 patients (87%) had bulky lesions with lateral and/or anteroposterior extension; 2 patients had irregularly shaped lesions, and typical ICBT resulted in a suboptimal dose distribution.

Treatment schedule of HDR ISBT was adjusted mainly according to tumor response or recovery status from myelo-suppression owing to concurrent chemotherapy. Transperineal implantation of applicators for ISBT was done under general or spinal anesthesia. An epidural catheter was maintained for intraoperative and postoperative pain management, and intravenous patient-controlled analgesia was also used for enhancing the analgesic effect in some cases. The perineal and vaginal areas were sterilized, and a tandem was inserted into the uterine cavity. Then, an endovaginal cylinder with a template (The Martinez Universal Perineal Interstitial Template, Nucletron) was arranged, and trocar point needle applicators were inserted under CT image guidance through the template. After implantation was complete, the template was fixed to the perineal skin with sutures, and all needles were fixed to the template. The number of implanted needle applicators ranged from 9 to 18, with a median of 14.

Next, CT scans were generated again for treatment planning. Dose distribution was confirmed on CT images for the high-risk clinical target volume (HR-CTV), which was defined as the parameter of ICBT in the Gynaecological (GYN) Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendation for organs at risk (OARs), such as the bladder and rectum.8,9 The planning was performed using diagnostic MRI as a reference to contour the HR-CTV and OARs. Treatment planning was carried out using the PLATO Brachytherapy Planning System (software version 14.2.6 or 14.3.6, Nucletron) with computer optimization and manual modification (Fig. 1). The treatment source was 192Ir, and the median fractional dose of ISBT prescribed to the
HR-CTV was 6 Gy (range, 5–6 Gy). Twice daily fractions were delivered with a minimum interval of 6 hours between the two fractions. The median total prescribed dose for patients treated with ISBT alone was 30 Gy/5 fractions (range, 27.5–30 Gy). For patients treated with the combination of ICBT and ISBT, each ICBT session delivered a dose of 6 Gy at point A, and the median total prescribed dose of ICBT and ISBT was 30 Gy/5 fractions (range, 27–42 Gy). Two poor responders received 42 Gy/7 fractions. The implant was removed after completion of ISBT. Throughout the treatment period, adequate antibiotic coverage was given, and hydration of the patient was maintained. The median overall treatment duration was 45 days (range, 38–68 days).

Chemotherapy
Ten patients received chemotherapy concurrently with EBRT. Patients received an infusion of cisplatin of 40 mg/m² once a week. Three patients received 3 cycles of chemotherapy, and 7 patients received 4 cycles.

Statistical analysis
All statistical analyses were performed with commercial statistical software (StatView 5.0, SAS Institute Inc.). The survival time was measured from the first day of treatment to the date of death or last follow-up time. The Kaplan-Meier method was employed to determine the actuarial survival rate and the locoregional control rate.

RESULTS

Analysis of the dose volume histogram
The dose volume histogram (DVH) was calculated for the HR-CTV and the OARs (Table 2). The median volume of the HR-CTV at the time of ISBT was 103 cc (range, 33–174 cc). The median D100 and D90 were 3.3 Gy (range, 2.3–4.0 Gy) and 5.7 Gy (range, 4.7–6.4 Gy), respectively. The median V100 was 87% (range, 72–94%). The median D2cc of the bladder was 4.9 Gy (range, 4.1–5.7 Gy) and D2cc of the rectum was 4.7 Gy (range, 2.7–7.4 Gy).

Table 2. Volume and dose parameters at the time of interstitial brachytherapy

<table>
<thead>
<tr>
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<th>Median</th>
<th>Range</th>
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<tbody>
<tr>
<td>HR-CTV volume</td>
<td>103</td>
<td>(33–174)</td>
</tr>
<tr>
<td>D100 (Gy)</td>
<td>3.3</td>
<td>(2.3–4.0)</td>
</tr>
<tr>
<td>D90 (Gy)</td>
<td>5.7</td>
<td>(4.7–6.4)</td>
</tr>
<tr>
<td>V100 (%)</td>
<td>87</td>
<td>(72–94)</td>
</tr>
<tr>
<td>D2cc of the bladder (Gy)</td>
<td>4.9</td>
<td>(4.1–5.7)</td>
</tr>
<tr>
<td>D2cc of the rectum (Gy)</td>
<td>4.7</td>
<td>(2.7–7.4)</td>
</tr>
</tbody>
</table>

HR-CTV: high-risk clinical target volume, D100; minimal target dose, D90; dose received by > 90% of volume, V100; volume treated to > 100% of prescribed dose, D2cc; minimum dose to maximally irradiated 2 cc.

Table 3. Comparison of volume and dose parameters with interstitial brachytherapy and the latest session of intracavitary brachytherapy

<table>
<thead>
<tr>
<th></th>
<th>ISBT</th>
<th>ICBT</th>
</tr>
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<tbody>
<tr>
<td>HR-CTV D100 (Gy)</td>
<td>3.3 (2.3–4.0)</td>
<td>2.9 (1.8–4.0)</td>
</tr>
<tr>
<td>D90 (Gy)</td>
<td>5.6 (4.7–6.2)</td>
<td>4.4 (3.0–7.3)</td>
</tr>
<tr>
<td>V100 (%)</td>
<td>85 (72–92)</td>
<td>66 (41–97)</td>
</tr>
<tr>
<td>D2cc of the bladder (Gy)</td>
<td>4.7</td>
<td>(4.1–5.6)</td>
</tr>
<tr>
<td>D2cc of the rectum (Gy)</td>
<td>4.1</td>
<td>(2.7–6.9)</td>
</tr>
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</table>

ICBT: intracavitary brachytherapy
ISBT: interstitial brachytherapy
HR-CTV: high-risk clinical target volume, D100; minimal target dose, D90; dose received by > 90% of volume, V100; volume treated to > 100% of prescribed dose, D2cc; minimum dose to maximally irradiated 2 cc.
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(range, 72–92%) with ISBT, and 66% (range, 41–97%) with ICBT. The median D2cc of the bladder and rectum with ISBT was 4.7 Gy (range, 4.1–5.6 Gy) and 4.1 Gy (range, 2.7–6.9 Gy), respectively, and the median D2cc of the bladder and rectum with ICBT was 5.5 Gy (range, 4.6–9.1 Gy) and 5.9 Gy (range, 4.6–7.7 Gy), respectively. The median duration between the treatment day with the latest session of ICBT and that with ISBT was 7 days (range, 5–13 days).

To sum up the doses of EBRT and brachytherapy, the biologically equivalent dose was calculated in equivalent 2 Gy fractions (EQD2) considering \( \alpha/\beta \) ratios equal to 10 for tumors and 3 for OARs. The median D90 of the HR-CTV for all treatments was 67.6 Gy10 (range, 60.1–77.1 Gy10) in EQD2. The median D2cc of the bladder and rectum for all treatments was 76.7 Gy3 (range, 62.0–83.6 Gy3) and 68.6 Gy3 (range, 54.4–110.4 Gy3), respectively.

Survival and local control

Of all 15 patients, 11 were alive at the last follow-up time. The follow-up duration of 11 living patients ranged from 25–83 months, and the median follow-up duration was 37 months. The Kaplan-Meier overall and progression-free survival curves from the initial treatment are shown in Fig. 2. The overall survival rates at 2 years and 3 years were 93% and 78%, respectively, and the progression-free survival rates at 2 years and 3 years were 67% and 51%, respectively.

The locoregional control rate during the follow-up period is shown in Fig. 3. The actuarial 2-year and 3-year locoregional control rates were 80% and 71%, respectively. Four patients had locoregional failure, local-only progression was seen in two patients, regional lymph node recurrence without local progression was observed in one patient, and local and regional lymph node recurrence was seen in one patient. Three patients who experienced local failure had very large tumors with a median HR-CTV at ISBT of 140 cc. As for DVH parameters in these 3 patients, the D90 of the HR-CTV per fraction in each patient was 5.9 Gy, 6.2 Gy, and 6.4 Gy, and the V100 of the HR-CTV was 89%, 93%, and 94%, respectively. Extrapelvic recurrences without locoregional failure were seen in 3 patients.

Complications

Toxicities were assessed with the National Cancer Institute CTCAE version 4.0. Insertion and removal of the applicators was performed without serious bleeding. Acute Grade 3 hematologic toxicities were observed in 4 patients who received concurrent chemotherapy, and a Grade 3 non-hematologic toxicity (diarrhea) was observed in one patient. Acute toxicity greater than or equal to Grade 4 was not observed. Late adverse events greater than or equal to Grade 3 were experienced in three patients. Grade 3 rectal bleeding was seen in 2 patients, and Grade 3 urogenital bleeding was seen in one patient. The D2cc of the rectum at ISBT of the 2 patients who experienced Grade 3 rectal bleeding was 4.8 Gy and 3.7 Gy per fraction, and 87.5 Gy3 and 64.1 Gy3 for all treatments. These patients needed a blood transfusion temporarily, but bleeding had stopped by the last follow-up time. The patient who experienced Grade 3 urogenital bleeding had intrapelvic recurrence at that time, and the D2cc of the bladder at ISBT of this patient was 5.6 Gy per fraction and 77.7 Gy3 for all treatments.

DISCUSSION

Local control rates of uterine cervical carcinoma with radiation therapy have been reported to be 80–90% for early-stage disease. However, those for advanced-stage disease range from 67–75%, and further improvement is needed. One of the reasons for local failure is thought to be inadequate dose coverage to bulky and/or irregularly shaped tumors. In order to achieve adequate dose coverage for the treatment of locally advanced uterine cervical carcinoma, CT image-based ISBT was adopted at Gunma
University.

Historically, low-dose-rate or high-dose-rate ISBT has been performed with free hand-placement, ultrasound-guided, CT-guided and template-guided needles for locally advanced gynecologic malignancies.2–7,16–19 The ABS recommended the use of CT or MRI for producing true 3-D isodose calculations and delineating the relationship of the implant to the tumor and normal anatomical structures.3 In the current series, needle applicators were inserted under CT image guidance through the template, and treatment planning was also carried out with 3-D CT image-based planning. There were no problems with implantation, and a better dose distribution was obtained by increasing the HR-CTV while keeping the bladder and rectal dose at tolerable levels, even in the cases of bulky and/or irregularly shaped cervical carcinomas. A comparison of the dose distribution of ICBT with that of ISBT in patients who received both treatments showed that the median D90 of the HR-CTV improved from 4.4 Gy to 5.5 Gy on the dose volume histogram by changing from ICBT to ISBT. In addition, the median D2cc of the bladder was reduced from 5.5 Gy to 4.6 Gy, and the median D2cc of the rectum was reduced from 5.9 Gy to 3.8 Gy. The 5-year local control rates in patients with advanced cervical carcinoma with tumors > 6 cm were reported to be 36–48%.20,21 In the current series, 13 patients (87%) had bulky lesions > 6 cm at initial diagnosis, and an actuarial 3-year locoregional control rate of 71% was achieved for patients who had a very large HR-CTV with a median volume of 103 cc at the time of ISBT. Late adverse events greater than or equal to Grade 3 were observed in three patients. However, one patient who experienced Grade 3 urogenital bleeding had intrapelvic recurrence of disease, and the cause of bleeding was considered to be due to tumor invasion. Two patients experienced Grade 3 rectal bleeding, and the D2cc of the rectum of ISBT was 4.8 Gy and 3.7 Gy per fraction and 87.5 Gy3 and 64.1 Gy3 for all treatments. Isohashi et al. reported the results of an analysis of volume and dose parameters according to rectal bleeding with EBRT and HDR ICBT.22 In that report, the median D2cc of the rectum was 72 Gy3 for all patients, and 85 Gy3 for patients who experienced rectal bleeding. In the current series, a D2cc of the rectum over 85 Gy3 was observed in 3 patients, and all 3 developed late rectal bleeding, including 2 with Grade 1 toxicity and 1 with Grade 3 toxicity.

As a source for imaging the female pelvis, MRI is recognized to be the best modality for the delineation of gross tumor volume in the treatment planning of uterine cervical carcinoma. Viswanathan AN et al. reported the results of comparing the contours and DVHs with CT vs. MRI in cervical cancer brachytherapy.23 They concluded that no significant difference was seen between CT and MRI in volume or dose to the OARs, but that the width of the HR-CTV was greater on CT, resulting in a decrease in the D100 and D90.23 Yoshida et al. reported the experience of HDR image-based ISBT using MRI available applicators for uterine cervical cancer.7 They reported that the median volume of the HR-CTV was 29.8 cc, the median D90 of the HR-CTV per fraction was 6.8 Gy, and the median V100 of the HR-CTV was 98.4%. They also reported that the D2cc of the bladder per fraction was 4.2 Gy, and the D2cc of the rectum per fraction was 4.4 Gy. These results seem to be better in dose coverage of the HR-CTV and similar in the exposed doses of the OARs compared to our outcomes. However, the median volume of the HR-CTV at ISBT was 103 cc and was much larger in the current series. These results might be due to how the diagnostic imaging modalities were used or real differences in tumor sizes. We performed CT image-guided implantation of applicators and CT image-based treatment planning using diagnostic MRI as a reference to contour the HR-CTV and OARs. Although MRI provides superior soft tissue resolution, MRI image-based brachytherapy requires special nonmagnetic applicators and usually requires much time and effort. A CT scanner was installed in the brachytherapy treatment room at Gunma University, so that implantation of applicators and CT image-based treatment planning can be performed on the same treatment table without patient transfer. CT image-based ISBT may become a useful option for the treatment of locally advanced uterine cervical carcinoma.

We have presented the treatment results of image-based HDR ISBT for patients with locally advanced uterine cervical carcinoma. When the dose distribution of image-based ISBT was compared with that of typical ICBT, the dose administered to the target was improved, and the exposure of the bladder and rectum was markedly reduced.

REFERENCES


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