Long-term Result of High Dose-rate Afterloading Brachytherapy in Squamous Cell Carcinoma of the Cervix: Relationship between Facility Structure and Outcome

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Objective: To compare outcome results for squamous cell carcinoma of the uterine cervix between patients treated in a single facility [single facility therapy: (SFT)] and others combined with external beam irradiation (EBRT) in a small facility and intracavitary brachytherapy in a central facility (combined facilities therapy: CFT).

Methods: This is a retrospective analysis of 155 patients with histologically proven squamous cell carcinoma of the cervix radically treated by EBRT and high dose-rate (HDR) intracavitary brachytherapy from August 1995 to May 2000. The overall survival and cause-specific survival rates were calculated by using the Kaplan–Meier method. The endpoint was defined as death due to cervical cancer for the cause-specific survival. The log-rank test and the generalized Wilcoxon test were used to compare the survival curves between the two treatment groups.

Results: Nine patients were lost, so 146 patients were retrospectively analyzed. There were 22 patients (15%) in stage I, 21 (14%) stage IIA, 51 (35%) stage IIB, 41 (28%) stage III, 11 (8%) stage IVA. The median age was 72 years (range, 30–89 years). The median follow-up time was 58 months. The proportion of patients treated with SFT was 23% (33/146) and CFT 77% (113/146). The overall survival rate was 62.3% and the cause-specific survival rate was 71.3%. The cause-specific survival rates for SFT and CFT were 87.9% and 66.4%, respectively; the difference between these two treatments was statistically significant (P = 0.024). The difference in the survival rate between these two treatments for stage III and IVA patients was also statistically significant (P = 0.021). However, no significant difference between these treatments was seen in the cause-specific survival rate for each stage. There was a significant difference between SFT and CFT in the incidence rate of severe late complications (grade 3–5) (P = 0.038). There was no significant difference in overall treatment times and total dose between the two groups; the applied photon beam energy showed a significant difference.

Conclusion: Our results suggest that the survival outcome will be aggravated by CFT. If the treatment process of using a lower photon beam energy were to be improved by the installation of a high-energy linear accelerator, CFT can be applied to patients with cervical cancer.

Key words: cervical cancer – squamous cell carcinoma – intracavitary brachytherapy

INTRODUCTION

Cervical cancer is the most common gynecological cancer in Japan, with an estimated 15 new cases per 100 000 females every year. High dose-rate (HDR) intracavitary brachytherapy in combination with external beam irradiation (EBRT) has become an acceptable treatment for carcinoma of the cervix (1).

The Patterns of Care Study (PCS) of American College of Radiology (ACR) was originally developed in 1973 to study the structure, process and outcome of radiation therapy (2–4). It has been an important process in defining the standard of practice for radiation oncology. During the past decade, a number of studies including several from the PCS have emphasized the importance of adhering to radiobiological principles. These are time, dose and treatment volume and others, which remain the cornerstones for the successful management of this disease (5–7).

A structure survey of the Japanese Society for Therapeutic Radiation and Oncology (JASTRO) was started in 1990. A
subsequent comparative study between the USA and Japan showed that >60% of the institutions in Japan were staffed by part-time radiation oncologists and their structure was immature and still developing (8–10). To improve the quality of radiation oncology throughout Japan, PCS was introduced. It showed that radiation therapy in Japan is sufficiently sophisticated only in a few large centers (11). Moreover, outcome analyses of early PCS surveys (for 1973 and 1978) suggested a relationship between facility structure and outcome (2,12). One of the most important prognostic factors associated with improved survival for carcinoma of the uterine cervix was the use of intracavitary brachytherapy (13). There was a 30% difference in the utilization of brachytherapy between large facilities and the others, because in Japan many hospitals have only a Linac system, and not a brachytherapy unit. Some of the Japanese radiation oncologists in small facilities sent their patients to an appropriate facility in the neighborhood (14). Therefore, there have been two groups of patients with cervical carcinoma treated with EBRT and intracavitary brachytherapy. One is the group in a single facility [single facility therapy (SFT)] and the other is combined with EBRT in a small facility and intracavitary brachytherapy in a central facility [combined facilities therapy (CFT)]. In this study, we compared the survival outcomes of SFT and CFT.

PATIENTS AND METHODS

PATIENT POPULATION

From August 1995 to May 2000, 155 patients with squamous cell carcinoma of the cervix were treated with radical intent by a combination of EBRT and HDR intracavitary brachytherapy in Nagoya University Hospital and its affiliated facilities. Nine patients were lost, hence 146 patients were the subjects of this analysis. Thirty-three patients were treated with SFT and compared with 113 patients treated with CFT.

The median age was 72 years (range, 30–89 years), the median age was 70 years (range, 45–87 years) and for the CFT patients it was 73 years (range, 30–89 years). The patient age distribution was not significantly different between SFT and CFT (Student's t-test; P = 0.751).

Follow-up examinations consisted of a review of the institutional medical records, telephone interview and occasional direct communication with the patients or their relatives. All patients who survived were followed up for more than 2 years with a median follow-up time of 58 months.

The patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Gynecologists and radiation oncologists jointly performed routine clinical staging at each institution. An MRI scan was not routinely done during the staging. All patients were examined by chest X-ray, computed tomography (CT) and blood chemistry. There were 22 patients (15%) in stage I, 21 (14%) in stage IIA, 51 (35%) in stage IIB, 41 (28%) in stage III and 11 (8%) in stage IV. As shown in Table 1, most of the patients in this series were in stages IIB and III. The proportion of patients treated with SFT was 23% (33/146) and CFT 77% (113/146) (Table 2). The patient FIGO stage distributions showed no significant difference between these two treatment groups (chi-squared test; P = 0.342).

The performance status (PS) of the patients showed no significant difference between the two treatment groups (P = 0.752) (Table 2).

HISTOPATHOLOGY

All patients had histology proven for malignancy and this study was limited to squamous cell carcinoma, except for the marginal recurrence and multiple carcinomas.

EXTERNAL BEAM IRRADIATION

Irradiation to the whole pelvis was administered with 4–10 MV photons through individually shaped portals using the AP/PA technique. The AP and PA field borders generally extended superiorly to the top of the fifth lumbar vertebra to cover all

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Table 1. Patients' characteristics

<table>
<thead>
<tr>
<th>Total No. of patients</th>
<th>146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: median (range) (years)</td>
<td>72 (30–89)</td>
</tr>
<tr>
<td>Follow-up: median (range) (months)</td>
<td>58.0 (0.4–82.7)</td>
</tr>
</tbody>
</table>

Table 2. Comparison of patients' characteristics for single institution and combined institutions

<table>
<thead>
<tr>
<th></th>
<th>Single</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>33</td>
<td>113</td>
</tr>
<tr>
<td>Age: median (range) (years)</td>
<td>70 (45–87)</td>
<td>73 (30–89)</td>
</tr>
<tr>
<td>PS (No. of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (12%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>1</td>
<td>26 (79%)</td>
<td>90 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (9%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Follow-up: median (range) (months)</td>
<td>42.5 (3.0–80.0)</td>
<td>36.2 (0.4–82.7)</td>
</tr>
</tbody>
</table>
Squamous cell carcinoma of the cervix

of the common iliac nodes and inferiorly to the obturator foramina distally. A 2 cm margin lateral to the bony pelvis is adequate as the lateral border. The usual field is about $16 \times 16$ cm at the midplane. When there is vaginal involvement, the entire length of the vagina should be treated down to the introitus. A multileaf collimator should be used for all fields to exclude normal tissue as far as possible.

Central shielding is usually at least five half-value layers thick. Since the pelvic geometry of the applicator changes considerably during intracavitary irradiation, a simple shielding block, such as straight shields 4 cm wide at the axis of the beams, is often used.

The pelvic doses prescribed ranged from 45 to 60 Gy with or without an appropriate shielding block (center splitter) according to the tumor stage. Five fractions of 1.8–2.0 Gy per day (total weekly dose of 9–10 Gy) were used. We made an agreement with the above treatment protocol (field, fraction and dose) in advance between the two groups.

**BRACHYTHERAPY**

Brachytherapy was performed using a single high-intensity Ir-192 source with an activity of 370 GBq, which was remotely afterloaded into a Manchester system applicator (Nucletron microSelectron HDR source). The dose distribution was calculated for each individual patient and placement. Applicator placement and radiation treatment were performed in the lithotomy position to maintain an accurate position of the applicators. Three to five intracavitary placements with a fraction size of 6.0 Gy to point A were given at weekly intervals (Table 3). This fractionation scheme was based on the policy regarding irradiation for carcinoma of the uterine cervix recommended by the Japanese Society of Gynecology and Obstetrics (15).

**FOllow-up**

After completion of irradiation, the patients were assessed every 1–3 months for 2 years and every 6 months thereafter. Late complications were graded in accordance with the Radiation Therapy Oncology Group (RTOG) criteria, especially for bladder and bowel complications.

**Table 3. Initial University of Nagoya fractionation protocols for cervical cancer**

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>External irradiation</th>
<th>Intracavitary irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WP (Gy)</td>
<td>CS (Gy)</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>II</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>20–30</td>
<td>20–30</td>
</tr>
<tr>
<td>Large</td>
<td>30–40</td>
<td>15–25</td>
</tr>
<tr>
<td>IVA</td>
<td>40–50</td>
<td>10–15</td>
</tr>
</tbody>
</table>

WP, whole-pelvis; CS, pelvis field with central shielding; DR, dose rate.

**Statistical Analysis**

The overall survival and cause-specific survival rates were calculated by using the Kaplan–Meier method. Here, for the cause-specific survival, the endpoint was defined as death due to cervical cancer. The log-rank test and the generalized Wilcoxon test were used to compare the survival curves between the two treatment groups.

The statistical significance of the overall treatment times and total doses of the external beam and the brachytherapy was tested by means of a $t$-test and that of the energies of the external beam was tested by Fishers exact test.

We used SPSS software (SPSS, Chicago, IL) for all statistical analyses and adopted 5% as a significance level for the statistical test.
RESULTS

SURVIVAL

A Kaplan–Meier plot of the 6.9 year overall survival and cause-specific survival rates for all patients is shown in Fig. 1. The overall survival rate was 62.3% and the cause-specific survival rate was 71.3%.

The overall survival rate was 77.2, 55.6, 65.5, 40.0 and 55.6% for stage I, IIA, IIB, III and IV A, respectively. The cause-specific survival rate was 91, 95, 76, 55 and 36 for stage I, IIA, IIB, III and IVA, respectively (Fig. 2).

The cause-specific survival rates for SFT and CFT were 87.9 and 66.4%, respectively; this difference between these two treatments was statistically significant ($P = 0.024$) (Fig. 3). The difference in cause-specific survival rate between these two treatments for stage III and IVA patients was also statistically significant ($P = 0.021$) (Fig. 4). However, no significant difference between these treatments was seen in the cause-specific survival rate for each stage.

Table 4. Complications (RTOG grading for late complications)

<table>
<thead>
<tr>
<th>Stage</th>
<th>0</th>
<th>1/2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IIA</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>IIB</td>
<td>21</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>14</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IVA</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>28</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>63</td>
<td>30.4</td>
<td>3.3</td>
<td>1.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Table 5. Comparison of late complications for single facility and combined facilities

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1/2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFT</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CFT</td>
<td>46</td>
<td>16</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>28</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>63</td>
<td>30.4</td>
<td>3.3</td>
<td>1.1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

COMPlications

Regarding the occurrence of complications, 91 patients (62%) were confirmed and 34 patients had some complications. The overall incidence rate of late complications for bowel (these were grade 1–5 according to the RTOG criteria) was 37.0% (Table 4). The six patients in stage II developed moderate to severe complications (grade 3–5); all were in the CFT. There was a significant difference between SFT and CFT in the incidence rate of severe late complications (grade 3–5) ($P = 0.038$) (Table 5).

TREATMENT

Overall treatment times varied between 31 and 80 days (median, 45 days) for the SFT and between 14 and 85 days (median, 43) for the CFT. There was no significant difference between the two groups ($P = 0.756$). For stage III and IVA patients, there was also no significant difference ($P = 0.879$) (Fig. 5).

The median total dose of external beam and the brachytherapy was 74.4 Gy (range, 30.0–84.0 Gy). For SFT patients the median total dose was 74.4 Gy (range, 50.0–84.0 Gy) and for CFT patients 74.4 Gy (range, 30.0–80.4 Gy). There was no significant difference between the two groups ($P = 0.503$). For stage III and IVA patients, there was also no significant difference ($P = 0.697$) (Fig. 6).
For external beam equipment, the applied photon beam energy was significantly different between the two groups. Accelerators of 10 MV were generally used in SFT (88%), but 49% of patients underwent lower energy treatment in CFT (Fishers exact test: $P < 0.0001$). Similarly, there was a significant difference for stage III and IVA patients ($P < 0.0001$) (Fig. 7). There were no patients treated with a telecobalt unit in SFT, whereas one patient underwent telecobalt therapy in CFT.

**DISCUSSION**

The PCS has documented the status of the practice of radiation therapy in the USA since 1972. Several publications have pointed out the relationship between outcome and various treatment parameters such as dose and technique. One of the most important prognostic factors associated with improved survival for carcinoma of the uterine cervix was the use of intracavitary brachytherapy. The American Brachytherapy Society (ABS) recommended that brachytherapy must be included as a component of the definitive radiation therapy for cervical carcinoma (13), based on the PCS that showed that recurrences and complications were decreased when brachytherapy was used in addition to EBRT.

On the other hand, the PCS in Japan has shown that institutions became less resourced with equipment and personnel and that fewer brachytherapy units became installed when they are stratified based on the structure survey by JASTRO (10). These
data indicate that >60% of the institutions in Japan were staffed by part-time radiation oncologists, and those physicians in unfavorable institutions sent their patients to an appropriate facility in their neighborhood (11,14). Such situations are seen almost universally outside the metropolitan areas.

Our treatment results were comparable to those in other radiation therapy centers for each stage and all stages combined (16–20). However, on comparison between SFT and CFT, our study demonstrated a significant difference in survival outcome, especially, for stage III and IVA patients. If we are to improve the survival outcome for patients treated with combined facilities under the present circumstances, we need to search for a way to treat patients for advanced stages.

Only two-thirds of the patients were identified with late complications after completion of radiotherapy. We suppose that this is due to the lack of regular communication with patients by the medical staff in the facilities. Furthermore, because there are few full-time equivalent radiation oncologists in these facilities, most patients are followed up only by gynecological oncologists. It is therefore also supposed that these patients’ complications might not be treated appropriately.

This study showed that the survival outcome would be aggravated by CFT. It is clearly shown that total dose (21), overall treatment duration (22) and the applied photon beam energy of the treatment machine (10) are important factors for the treatment outcome. For a constant total dose there was a decrease in the probability of local control associated with prolongation of overall treatment duration (23). Utilization of a higher photon beam energy was recommended and resulted in an improvement in survival rates. Delaying the start of the brachytherapy and using non-standard treatment schedules, including radiation dose, adversely affect the treatment outcome for cervical cancer.

Our research showed no difference in overall treatment duration and total dose between SFT and CFT, when the two groups kept strictly to the standard treatment schedules. However, there is one problem, namely that a lower energy of the external beam of the treatment machine is applied in CFT. It was a concern that treatment outcome was aggravated because of this factor. If this factor can be resolved by the installation of a high-energy linear accelerator, CFT can be applied to patients with cervical cancer.

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References


