Clinical results of external beam radiotherapy alone with a concomitant boost program or with conventional fractionation for cervical cancer patients who did not receive intracavitary brachytherapy

Kanji MATSUURA1,*, Tomoyuki OKABE1, Kazushi FUJITA2, Hiroshi TANIMOTO3, Yukio AKAGI4,5 and Masayuki KAGEMOTO1

1Department of Radiation Oncology, Hiroshima City Hospital, 7-33 Moto-machi, Naka-ku, Hiroshima 730-8518, Japan
2Department of Radiology, Higashi-Hiroshima Medical Center, 513 Jige, Saijo-cho, Higashi-Hiroshima 739-0041, Japan
3Department of Obstetrics and Gynecology, Hiroshima City Asa Hospital, 2-1-1 Kabe-minami, Asakita-ku, Hiroshima 731-0293, Japan
4Department of Radiation Oncology, Hiroshima City Asa Hospital, 2-1-1 Kabe-minami, Asakita-ku, Hiroshima 731-0293, Japan
5Hiroshima Heiwa Clinic, State of the Art Treatment Center, 1-31 Kawara-machi, Hiroshima 730-0856, Japan

*Corresponding author. Tel: +81(82)221-2291; Fax: +81(82)223-5514; Email: mkanji@fg8.so-net.ne.jp

A combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is well established as the standard radical radiotherapy (RT) for cervical cancer. However, it is sometimes necessary to perform EBRT alone for patients where ICBT is not feasible. For these patients, we initiated EBRT alone with three-dimensional conformal radiotherapy (3DCRT). The purpose of this study is to evaluate the results of EBRT alone without ICBT for patients with cervical cancer. Sixteen patients were treated with EBRT alone between 2002 and 2009. There were three stage IIB, six stage IIIB and seven patients with stage IVA disease. A total of 10 patients were treated with a median dose of 66 Gy with a median overall treatment time (OTT) of 40 days delivered by a concomitant boost (CCB), and a median dose of 60 Gy with a median OTT of 47 days was administered for six patients by conventional fractionation (CF). The 3-year overall survival (OAS) and local control (LC) rates were 43.8% and 75.0%, respectively. The 3-year LC rate was 90.0% for the CCB group, 50.0% for the CF group ($P = 0.0692$); 100% for OTT $\leq 42$ days, 42.9% for OTT $\geq 43$ days ($P = 0.0095$). No severe acute and late adverse effects were encountered for any of the patients. These outcomes suggest that EBRT with a CCB program may be a promising radical treatment for cervical cancer that provides better LC with minimal complications, especially in cases where ICBT cannot be performed.

Keywords: cervical cancer; external beam radiotherapy (EBRT); three-dimensional conformal radiotherapy (3DCRT); concomitant boost (CCB)

INTRODUCTION

A combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is well established as the standard radical radiotherapy (RT) for cervical cancer. The use of ICBT was a factor significantly associated with decreased local failure according to results of a pattern of care study [1–3], and therefore it has been thought that the local control (LC) rate of EBRT alone without ICBT was poor.

However, in the actual clinical setting it is sometimes necessary to perform EBRT alone for patients where ICBT is not feasible. For these patients, from 2002 we have initiated EBRT alone with three-dimensional conformal radiotherapy (3DCRT) in order to improve LC. We previously reported the early clinical results of EBRT alone with the concomitant boost (CCB) program in 2007 [4]. These early results suggested that 3DCRT with the CCB program is a feasible treatment modality. This present work updates the results from our experience in performing EBRT for cervical cancer.
cancer, thereby extending the follow-up period. In addition, it is therefore important to clarify what type of fractionation is most suitable when EBRT alone is chosen as a radical treatment.

MATERIALS AND METHODS

From May 2002 to September 2009, 16 patients with cervical cancer were treated with EBRT alone without ICBT and with either the CCB program or the conventional fractionation (CF) schedule at Higashi-Hiroshima Medical Center and Hiroshima City Asa Hospital. A remote after loading system for ICBT had not been installed at these two hospitals. These 16 patients were evaluated in this study. The reasons for not performing ICBT included the following: (i) patient’s refusal prior to start of treatment: 13 patients; (ii) stump carcinoma: 3 patients. The main causes of refusal for the 13 patients were refusal due to a lack of up-to-date medical knowledge, personal preference and a desire to avoid pain. With regard to pain, some patients hated even the minor pain of the vaginal examination. Although we explained that it is possible to control pain by using analgesics and with sedative treatment, they refused to potentially experience further pain and did not want to receive ICBT. In all these patients, chemotherapy was not combined because of the patient’s refusal, comorbidity or renal impairment. Before the start of treatment, we carefully explained that EBRT alone was not the standard treatment and suggested that a combination of EBRT and ICBT is well established as the gold standard course of RT. Additionally, we decided to perform EBRT alone only in patients who indicated a clear intention of refusing ICBT following our explanation. All patients signed a written informed consent form.

The patients’ ages ranged from 39 to 89 years and median age was 72 years. All patients had a good Eastern Cooperative Oncology Group performance status (PS), PS was zero in eight patients, one in five patients and two in three patients. The histology was squamous cell carcinoma in 15 patients, and adenocarcinoma in one. All 16 patients were diagnosed and staged by a radiation oncologist and a gynecological oncologist, based on the results of gynecological examination, cytological and/or histopathological studies, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the pelvis and abdomen and/or fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification and the stage was IIB in three (19%), IIIB in six (38%), and IVA in seven patients (43%). Two patients had regional lymph node metastasis detected by CT, MRI or FDG-PET (both patients had internal iliac node metastasis). The tumor characteristics according to the fractionation schedule are shown in Table 1.

External radiotherapy (EBRT)

The patients were treated with EBRT alone administered by a combination of whole pelvic irradiation (WPI) and local irradiation (LI) (Fig. 1). All patients underwent CT simulation, and EBRT was administered with 3DCRT. EBRT was delivered using a linear accelerator with an X-ray energy of

| Table 1. Tumor characteristics according to the fractionation schedule |
|-------------------------|--------|--------|---|
| Characteristics         | CCB program | CF schedule | P |
| FIGO stage              |         |         |   |
| IIB                     | (n = 10) | (n = 6) | NS |
| IIIB                    |          |         |  |
| IVA                     |          |         |  |
| Maximum tumor diameter  |         |         |   |
| ≤5 cm                   | 6       | 1       | NS |
| >5 cm                   | 4       | 5       |   |
| Regional lymph nodes    |         |         |   |
| Metastasis (+)          | 2       | 0       |   |
| Metastasis (–)          | 8       | 6       |   |

FIGO, International Federation of Gynecology and Obstetrics; NS, not significant.

Fig. 1. A schematic diagram of the ideal concomitant boost program and dose distribution. A circle signifies whole pelvic irradiation of 45 Gy in 1.8-Gy fractions; a triangle signifies local irradiation of 12 Gy in 1.2-Gy fractions for concomitant boost, given at 6 h after whole pelvic irradiation; a square signifies local boost to final target volume of 9–15 Gy in twice-daily 1.5-Gy fractions. Total dose of 66–72 Gy is delivered in 5.5–6 weeks. A cervical tumor on a CT slice is shown by the light blue line.
The clinical target volume (CTV) of WPI included the gross tumor volume of the primary tumor, uterine cervix, uterus corpus, vagina, parametrical tissue and regional nodes (common iliac, internal iliac, external iliac, hypogastric, obturator and presacral nodes). For primary tumor delineation, we referred to T2-weighted axial MRI images. The primary tumor, uterine cervix and uterine corpus are subject to internal motion, which is individual and unpredictable. We generally set an internal margin of 5–10 mm around the primary tumor, cervix and corpus. For contouring of the nodal areas for CTV, an 8-mm margin was set around the vessels for nodal coverage. The CTV of WPI was expanded uniformly by 1 cm in all directions to produce a planning target volume (PTV). The CTV of LI included primary tumor, parametrium invasion area and metastatic regional nodes. Additionally, the CTV was expanded uniformly by 5–10 mm in all directions to produce an internal target volume (ITV) for LI. In creating the PTV of LI, a margin of 1 cm was circumferentially added around the ITV, and a 1.5-cm margin was added both superiorly and inferiorly. A four-field technique by 3DCRT was used to irradiate the whole pelvis sparing the small bowel. For LI, multiple fields or dynamic conformal arc fields were used to reduce the total dose to the surrounding tissue, especially to the rectum and bladder.

The patients were treated with either the CCB program or CF schedule. In principle the CCB program was instituted using a fractionation schedule. For patients who had difficulty in visiting a hospital for treatment twice a day, the CF schedule was used. The CCB program was used for 10 patients, and the CF program was used for six patients. The CCB program was typically delivered according to a previously described schedule [4]. The CCB program included WPI of 45 Gy at 1.8 Gy per fraction, LI of 12 Gy at 1.2 Gy per fraction administered over 10 concomitant days during weeks 4–5, and boost LI of 9–15 Gy in twice-daily 1.5-Gy fractions (Fig. 1). The median total dose was 66 Gy (range: 66–73 Gy) with a median overall treatment time (OTT) of 40 days (range: 36–46 days) on the CCB program. The CF schedule typically included WPI of 40 Gy and LI of 20 Gy in once-daily 2.0-Gy fractions. The median total dose was 60 Gy (range: 60–66.2 Gy) with a median OTT of 47 days (range: 42–57 days) on the CF schedule.

Follow-up
The follow-up evaluations were performed at 1-month intervals for the first year, at 3-month intervals for the second year and at 6-month intervals thereafter. At the time of the follow-up visits, we prospectively collected data regarding the locoregional and distant status and late toxicities. The follow-up evaluation routinely included a physical examination, diagnostic imaging and toxicity assessment. The median follow-up time was 40 months (range: 6–93 months) for all patients.

Statistical analysis
The actuarial curves of LC and overall survival (OAS) rates were calculated using the Kaplan–Meier method, with the first day of treatment as the starting point. The Log-rank test was used to compare important treatment variables and tumor characteristics on a univariate analysis, and the results were considered to be statistically significant with  \( P \leq 0.05 \). The evaluated RT variables and tumor characteristics included fractionation, OTT, FIGO stage and maximum tumor diameter (MTD).

RESULTS
Clinical response and outcome
The clinical response rate was evaluated at 2 months after the completion of treatment, according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [5]. Of 16 patients, 12 achieved complete response (CR), two achieved partial response (PR) and two had stable disease (SD). Of 12 CR patients, seven patients are alive without disease (one patient in whom para-aortic and supra-clavicular recurrence occurred at 25 months and who was successfully treated by EBRT alone is included) and one patient who had stage IIB disease with 5.5 cm of MTD was alive with local recurrence. In three patients with CR, distant metastasis occurred and they died of disease without pelvic recurrence. The remaining patient with CR died of intracerebral hemorrhage. Of the four patients with PR or SD, one patient with PR was successfully locally controlled, however, she eventually died of para-aortic, supra-clavicular recurrence and bone metastasis. The remaining three patients with PR or SD died of various types of recurrence (local recurrence; local recurrence; local recurrence and liver metastasis).

Local control and overall survival
The 3-year LC and OAS rates for all patients were 75.0% and 43.8%, respectively. The 3-year LC curves according to the RT variables and tumor characteristics are shown in Fig. 2, 3, 4 and 5. The 3-year LC of the CCB group tended to improve in comparison with the CF group (90.0% vs. 50.0%,  \( P = 0.0692 \), Fig. 2). The 3-year LC of the OTT ≤42 days group showed a significant statistical increase in comparison with the OTT >42 days group (100% vs. 42.9%,  \( P = 0.0095 \), Fig. 3). No significantly statistical difference was observed in the 3-year LC between the FIGO Stage IIB/IIB group and Stage IVA (88.9% vs. 57.1%,  \( P = 0.1242 \), Fig. 4). The 3-year LC of the MTD ≤5 cm group
tended to be improved in comparison with the MTD >5 cm group (100% vs. 55.6%, \( P = 0.0513 \), Fig. 5). In the OAS there was no significant statistical difference depending on the RT variables and tumor characteristics.

**Toxicity**

The acute and late toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). No acute treatment-related toxicities of Grade 3 or worse were observed. However, acute toxicity of grade 1 diarrhea was seen in seven patients and acute toxicity of grade 1 and grade 2 urinary frequency were seen in six patients and in one patient, respectively. With a median follow-up time of 67 months (range: 16–93 months) for the surviving patients, grade 2 rectal hemorrhage in two patients, grade 2 bladder hemorrhage in one patient and grade 2 vaginal stenosis in one patient were observed as late toxicities. No late Grade 3 or worse toxicities were observed.

**DISCUSSION**

This report updates the results from early clinical reports of 3DCRT with CCB program for cervical cancer in 2007, and we have ascertained that the encouraging initially observed LC rate after EBRT with CCB is durable in this present study. Our outcome suggests that EBRT with CCB is promising as a radical treatment for cervical cancer, although the present study is a retrospective analysis of a small number of patients. Regarding treatment with EBRT alone for cervical cancer, LI with highly precise EBRT is needed in place of ICBT. We believe that the merits of LI with 3DCRT compared with ICBT are as follows: (i) the uniformity of high dose distribution to primary tumors and the cervix avoiding surrounding normal tissues; (ii) the lack of physical pain for patients; and (iii) low emotional stress for patients. However, this does not mean that EBRT alone is recommended for radical intent by our low-level evidence. The gold standard course of radical RT for cervical cancer is a combination of EBRT and
ICBT. We believe that EBRT with CCB is an alternative radical therapy to be used when ICBT cannot be administered. So far we have abandoned the use of radical RT halfway without giving adequately high doses with EBRT in cases where ICBT would not be suitable, although EBRT was started as a combination radical RT. However, it is possible that we can also offer radical treatment with highly precise EBRT alone with CCB as an alternative radical RT under such circumstances.

On radical treatment with EBRT alone for cervical cancer, when 2D treatment planning with an X-ray simulator was mainstream, anterior–posterior parallel opposing fields or four box fields were mostly used. However, using this irradiation technique brought with it the problem that most portions of the rectum and bladder were irradiated with an equal dose to the target volume. Therefore it has been thought so far that we could not irradiate at a high dose to the target with EBRT alone because we could not obtain a dose distribution which resembles that of ICBT. However, we believe that this rationale does not apply to the present conditions as highly precise EBRT can be performed due to the 3D treatment planning system. With 3D treatment planning, we can grasp the relationship of the position of the target lesion and the surrounding normal tissue, and we can set an adequate field that agrees with the target volume shape, excluding the surrounding normal tissue. As a result we obtain an improvement of spatial dose distribution, and are able to perform highly precise EBRT, and we expect improvements in local control. However for better LC of cervical cancer, an improvement in temporal dose distribution is also indispensable. On the occasion of the initiation of radical treatment with EBRT alone, we referred to the results of the altered fractionation schedule for head and neck squamous cell carcinoma. When head and neck squamous cell carcinoma were treated with RT alone, the LC rate declined in patients who received over 6 weeks of OTT [6]. This suggests that the mechanism for this effect is the accelerated repopulation of tumor cells during fractionated RT [7]. It is well known that the accelerated repopulation of tumor cells in head and neck squamous cell carcinoma occurs from 3–4 weeks after the start of RT [8]. Moreover, the local control improved by shortening the OTT [9, 10], and it is very important to avoid an unnecessary prolongation of OTT. In RT for cervical cancer, it is well known that the ‘prolongation of OTT’ diminishes the LC rate [6, 11–14] and that the ‘shortening of OTT’ improves the OAS rate in the same manner as that observed in patients with head and neck squamous carcinoma [15]. Nishimura et al. reported that RT must be delivered in the range of 66–70 Gy in 6 weeks to obtain optimal LC with minimum adverse effects for head and neck cancer and cervical cancer [6]. Based on these rationales, we planned our original CCB program to enhance treatment intensity by local boost from the fourth week and to deliver 66–72 Gy in 5.5–6 weeks. The current results showed the 3-year LC rate for patients treated by the CCB program with a high dose to be significantly higher than that of patients treated by the CF program with 60 Gy, and we were able to obtain good LC after the CCB program, with minimum adverse effects, being a match for a combination of EBRT and ICBT, even EBRT alone. There was a difference in the median OTT between the CCB program with a high dose and the CF program with 60 Gy. Therefore, it is difficult to discuss the effects of shortening OTT. However, we have the impression that shortening OTT is important, and evaluating the shortening of OTT is thus considered to be an appropriate subject for future investigations.

In the treatment of locally advanced cervical cancer, improvement of survival and variable controls by concurrent chemoradiotherapy (CCRT) has been demonstrated [16, 17], and CCRT is a standard radical treatment for cervical cancer at present. No patients who were evaluated in this study received any concurrent chemotherapy. Our results suggested the possibility that a CCB program produces a high LC rate for non-bulky volume tumors of cervix without concurrent chemotherapy, whereas it is not easy to control a bulky tumor by EBRT alone with a CCB program. We recently started a CCB program combined with concurrent chemotherapy for patients with bulky tumor volumes to improve the LC when ICBT cannot be performed. However, it is necessary to pay heed to the increase of the incidence of toxicity on CCRT. With WPI, which is delivered using a four-field box technique encompassing the macroscopic and microscopic disease, a large volume of pelvic bone marrow (BM) is also irradiated in addition to rectum, bowel and bladder, and therefore hematologic toxicity would occur with a high frequency compared with RT alone. Nowadays, intensity-modulated radiation therapy (IMRT), whose conformality is better than 3DCRT, is coming to be applied for WBI of cervical cancer in order to spare the BM [18–20]. BM sparing IMRT for WPI has been reported to possibly reduce the occurrence of acute hematologic toxicity in comparison with 3DCRT [18–20]. We plan to introduce IMRT for WPI, and to try and establish a suitable fractionation schedule for CCRT with a CCB program.

On target volume setting for LI of 3DCRT, cervix position influenced by the contours of rectum, bowel and bladder are important factors in treatment planning. We especially think that a countermeasure to rectal movement is important, because rectal movement with an increased bowel peristalsis induced by WBI is not easy to control. If there is an unstable status of rectal contour and shape, then we need a large internal margin in order to establish the target volume. We therefore instructed the patients to void as a countermeasure of an unstable cervix position, which is influenced by rectal and bladder shape just before CT
scanning and irradiation, thereby minimizing the interfraction variations of rectal and bladder contour influenced by the filling. Besides the contour of the surrounding organ, the contour of the cervix, which is influenced by regression and movement, is also an important factor [21]. In addition, the interfractional variations in the cervix position are large [22], and therefore it is sometimes important to evaluate the cervix contour during the period with LI to determine whether we must shrink the field or not. We recently started to perform image-guided radiation therapy with cone beam CT (CBCT) to improve the treatment accuracy of 3DCRT for cervical cancer. If a marked tumor reduction is recognized on the CBCT findings, then we shrink the field to keep the irradiated volume of the surrounding organs as small as possible.

In conclusion, our updated outcome suggests that the 3-year LC of EBRT with a CCB for cervical cancer was better than that of CF, and we also ascertained that the encouraging initial outcome that was reported in 2007 was therefore both valid and reproducible. At present, the gold standard course of RT for cervical cancer is therefore considered to be a combination of EBRT and ICBT. However, EBRT with CCB is deemed to be a promising and feasible modality as an alternative radical therapy in cases where ICBT cannot be administered.

REFERENCES