Shimane J. Med. Sci., Vol.30 pp.77-86, 2014

Initial Evaluation on the Safety and Efficacy of Accelerated Hyperfractionated Radiotherapy for Locally Advanced Cervical Cancer: A Pilot Study

Yukihisa TAMAKI[1], Rika YOSHIDA[2], Satoru TAKAHASHI[3], Tetsuya KAWABE[4], Masao MURAKAMI[4], Yasushi KAJI[4], Masanori NAKAZAWA[3], Kazuo FUKAZAWA[5], Takeshi YOSHIZAKO[2], Hajime KITAGAKI[2], Kazumasa SEKIHARA[1], Yoko HIEDA[1] and Taisuke INOMATA[1]

[1]*Department of Radiation Oncology, Shimane University School of Medicine, Izumo, Shimane, Japan*
[2]*Department of Radiology, Shimane University School of Medicine, Izumo, Shimane, Japan*
[3]*Department of Radiotherapy, Jichi Medical University Hospital, Shimotuke, Tochigi, Japan*
[4]*Department of Radiology, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan*
[5]*Department of Obsterics and Gynecology, Dokkyo Medical University School of Medicine, Mibu, Tochigi, Japan*
（Received December 6 2013; Accepted January 30, 2014）

We used the accelerated hyperfractionated radiotherapy of locally advanced cervical cancer and assessed the initial treatment efficacy and safety. This study enrolled three patients. Using a field-in-field technique, the whole pelvic region was set as a large irradiated field and received a dose of 35.2-39.6 Gy, whereas small field irradiation targeting only the tumor and parametrium was performed at 9.6-10.8 Gy. We then performed center shield field irradiation of the pelvic lymph node area, which were irradiated at 50 Gy in sum total. Intracavitary radiotherapy was added two to three times. Two patients received chemotherapy. In all patients, treatments were completed with overall treatment time（OTT）of 37-40 days. All patients were in complete response. Acute adverse events included two cases of grade 3 leukopenia, one case of grade 3 neutropenia. In conclusion, this treatment was effective and safet with good outcomes, acceptable adverse events, and greatly reduced OTT.

Key words: cervical cancer, hyperfractionated radiotherapy, safety, efficacy, accelerated repopulation

Corresponding to: Yukihisa Tamaki. MD, PhD
Department of Radiation Oncology, Shimane University School of Medicine, 89-1, Enya-cho, Izumo, Shimane, Japan
Tel: +81-853-20-2582
Fax: +81-853-20-2582
E-mail: ytamaki@med.shimane-u.ac.jp

INTRODUCTION

Curative treatment for cervical cancer（CC）can be divided mainly into surgical treatment and radiotherapy, in the latter of which concurrent chemoradiotherapy（CCRT）is regarded a most important treatment option in present. The efficacy of CCRT and its high levels of evidence have been shown in randomised control trials（RCT）in 1999［1, 2］and two meta-analyses.［3, 4］Although surgical treatment has long been the standard treatment method for CC in Japan, CCRT is performed more often in present especially in patients with the International Federation of Gynecology and Obsterics（FIGO）classification stage IIIA, IIIB, and IV. But the outcome of CCRT has not yet been satisfactory.

Predictable prognostic factors, which can be used as key points in the prevention of locally advanced CC, are clinical stage, tumor size, and tumor geometry.［5, 6］In addition, radiosensitivity of tumors is an important factor for local control［7, 8］, and Ohara *et al*. reported that this factor was the most strong one.［9］Prolonged overall treatment time（OTT）is known to negatively affect treatment outcomes in radiotherapy of CC relating to the above.［10］This is not however limited to CC but seen in head and neck cancer and esophageal cancer［11］as well as squamous cell carcinoma（SCC）. This association appears to be more significant with head and neck cancer in young generations of patients, such as those younger than 50［12］or 60［13］years of age. In addition to SCC, similar results

have been obtained with bladder cancer which is transitional cell carcinoma. [14, 15] One of the factors contributing to this phenomenon is accelerated repopulation (AR). [16] AR of SCC in head and neck cancer appears 21-28 days after the initiation of radiotherapy. [17] Furthermore, the risk of tumor recurrence has been shown to increase linearly if treatment time extends over 28 days. [18] The 5-year local control rate of patients who receive a total dose of 64 Gy over a period of 31-60 days is estimated to decrease by 1.0-1.25% every time the treatment period is extended by one day.

To overcome this problem, altered fractionated radiotherapy, in which irradiation is performed multiple times a day, is considered more effective than commonly used conventional fractionated (CF) radiotherapy (approximately 1.8-2 Gy per fraction, once a day, five days a week, and a total dose of 60-70 Gy). Altered fractionated radiotherapy is classified into hyperfractionated radiotherapy (HF), accelerated fractionated radiotherapy (AF), and accelerated hyperfractionated radiotherapy (AHF). Among these, AF is not commonly used because of the high incidence of severe acute adverse events. HF can minimize the late adverse events by reducing an irradiation dose per fraction and increase the total dose. This also enhances antitumor effects by facilitating redistribution about the cell cycle and increasing radiosensitivity. Advantages of AHF are those mentioned above for HF plus its inhibitory effect on accelerated repopulation of tumors. Even though acute adverse events may appear more severe in AHF, they are milder than those seen with AF. Therefore, AHF was widely used.

In head and neck SCC, the use of HF and AHF have improved the local control rates [19-21] and the survival rate in meta-analysis. [12] Good treatment outcomes were also shown in bladder cancer. [22] Furthermore, altered fractionated radiotherapy improved survival rates in non-small cell lung cancer as well as SCC group compared with the CF radiotherapy. However, other histological types such as adenocarcinoma didn't show significant differences. [23] There were very few studies investigated the efficacy of AHF or HF radiotherapy in CC, which was made up of a majority of SCC. Therefore, we have developed a novel treatment strategy for CC, in which AHF is used to enhance antitumor effects by minimizing AR of tumors. Because AHF of the whole pelvic region will affect a wide area

Table 1. Patient Characteristics

	Case 1	Case 2	Case 3
Age (year-old)	68	62	64
PS (ECOG)	0	0	0
FIGO Stage	IIIA	IIIA	IIIB
Histology	SCC	SCC	Adeno ca
tumor size	36mm	40mm	28mm
vaginal invasion	(+)	(+)	(+)
pelvic wall invasion	(-)	(-)	(+)
lymph node metastasis	(-)	(-)	(-)
distant metastasis	(-)	(-)	(-)

PS ; performance status, ECOG ; Europe Clinical Oncology Group, FIGO ; International Federation of Gynecology and Obstetrics, SCC ; Squamous cell carcinoma, Adeno ca ; Adenocarcinoma

including the bowels and bladder and thus increase adverse events, the whole pelvic region was treated in HF radiotherapy (1.1 Gy per fraction, twice daily) in an effort to minimize adverse events and increase antitumor effect by facilitating tumor cycle redistribution. To achieve this, we used the field-in-field technique in HF radiotherapy. The aim of this study was to report our first experience with this treatment method and evaluate the initial treatment outcome, safety, and adequacy.

MATERIAL AND METHODS

Patients

This study investigated three patients who were pathologically diagnosed with CC and underwent curative radiotherapy at Dokkyo Medical University Hospital (DMUH) between October 2011 and January 2012. The patients provided written informed consent after hearing detailed explanation about HF radiotherapy and being informed of their right to reject the therapy. Table 1 shows patient attributes, and the age of patients ranged from 62 to 68 years. They were all in the Europe Clinical Oncology Group performance status (PS) 0 and the International Federation of Gynecology and Obstetrics (FIGO) stage IIIA or IIIB.

Radiotherapy and Chemotherapy

All patients received external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) in this study. In EBRT, the field-in-field technique was used to irradiate two fields: large field (LF) and small field (SF). In LF-EBRT, the whole pelvic region was chosen as the irradiated field, i.e., whole pelvis radiotherapy (WPRT), and irradiation of 2.2 Gy per day (1.1 Gy per fraction, twice daily) was performed from four directions (anterior, posterior, left, and right). In SF-EBRT, the area of tumor and parametrium with the potential to develop tumor was set as an irradiated field and irradiated at a dose of 0.6 Gy per day (0.3 Gy per fraction, twice daily) from two directions (right and left). Taken irradiation in both LF and SF-EBRT into consideration, tumor and parametrium received 2.8 Gy per day (1.4 Gy per fraction, twice daily). These procedures were followed by another radiotherapy with a dose of 1.8 Gy/fraction/day using a center shield (CS), a shield used routinely in our country and Asian countries to protect the colon. Table 2 shows

Table 2. Details of chemotherapy and radiotherapy in each case

	Case 1	Case 2	Case 3
Chemotherapy			
regimen	cisplatin (weekly)	cisplatin (weekly)	not recieved
dose	40mg/m2	40mg/m2	
External beam radiotherapy			
large field (LF)	35.2Gy/32frs (1.1Gy/fraction, twice daily)	39.6Gy/36frs	39.6Gy/36frs
small field (SF)	9.6Gy/32 frs (0.3Gy/fraction, twice daily)	10.8Gy/36 frs	10.8Gy/36frs
center shield field (CS)	14.4Gy/8 frs (1.8Gy/fraction, once daily)	10.8Gy/6frs	10.8Gy/6frs
Intracacity brachytherapy (ICBT)			
number of times	three times	twice	twice
A point dose	5.5, 5.5, and 5.5Gy	5, and 5.5Gy	3.62, and 6Gy

frs: fractions

the details of radiotherapy in each case, and the actual irradiation field used in LF, SF, and CS was shown in Figs. 1, 2 and 3 respectively. All patients were transported to nearby Jichi Medical University Hospital（JMUH）for ICBT because DMUH is not equipped with the ICBT device. High dose rate ICBT, widely used in Asian countries, was performed by a radiation oncologist at JMUH and a radiation oncologist accompanying patients from DMUH. In accordance with the Manchester system, A point was set as a treatment point and treatment planning was performed in each time. Although an A point dose was basically set at 5 or 6 Gy, corrections were made, if necessary, based on the rectal or bladder dose calculated by the treatment planning system. As a result, tumor, parametrium, and the region of pelvic lymph nodes received different levels of radiation. Tumors received radiation from LF- and SF-EBRT and the A point dose in ICBT, whereas the parametrium received the sum of LF-, SF-, and CS- EBRT, because the area was in the irradiation field in all three treatments, plus the B point dose in ICBT. The region of pelvic lymph nodes received the sum of LF- and CS-EBRT, but stayed outside the irradiation field in ICBT. Cases 1 and 2 underwent concurrent weekly cisplatin chemotherapy（40 mg/m2）. The case 3 patient with stage IIIB FIGO received radiotherapy alone because of hydronephrosis with decreased renal function.

Follow-up

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events（CTCAE）Version 4.0. After the completion of therapy, closed follow-up was provided at the department of radiotherapy and gynecology, and treatment efficacy was evaluated according to the Response Evaluation Criteria In Solid Tumors（RECIST）version 1.1.［24］

RESULTS

All patients successfully completed therapy without interruption or termination of radiotherapy, and OTT was 37-40 days. The two patients who received concurrent chemotherapy completed the five courses without interruption during the course of radiotherapy. Initial assessment revealed complete response（CR）in all patients. All patients have no evidence of recurrence. Acute adverse events in patients were shown in Table 3. All patients had grade 3 or lower hematological toxicity. Grade 3 leucopenia developed in two patients, but improved soon after the administration of granulocyte-colony stimulating factor（G-CSF）. No hepatic or renal dysfunction was observed. With regard to non-hematological toxicity, one patient developed gastrointestinal disorder, i.e., grade 2 diarrhea, but none of the patients had radiation dermatitis or renal and urinary disorder.

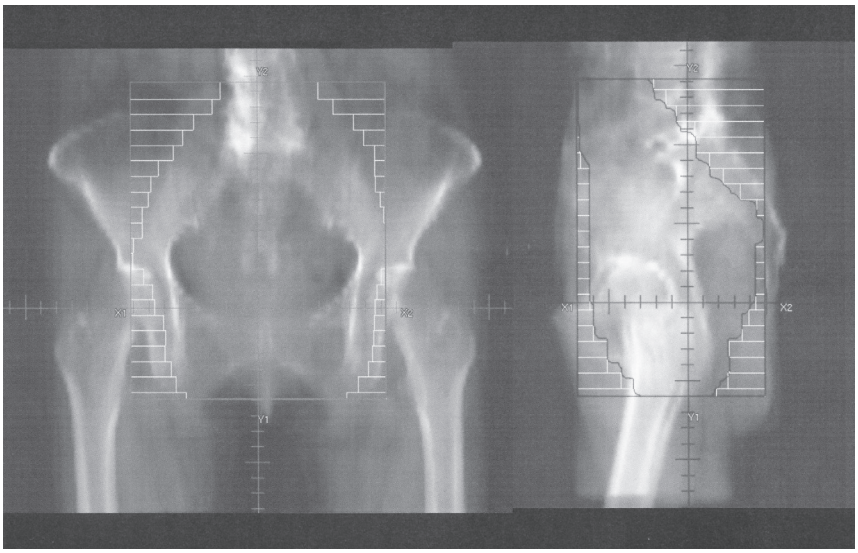

Fig. 1. Digitally reconstructed radiographic image of the whole pelvic region as the irradiation field in large field.

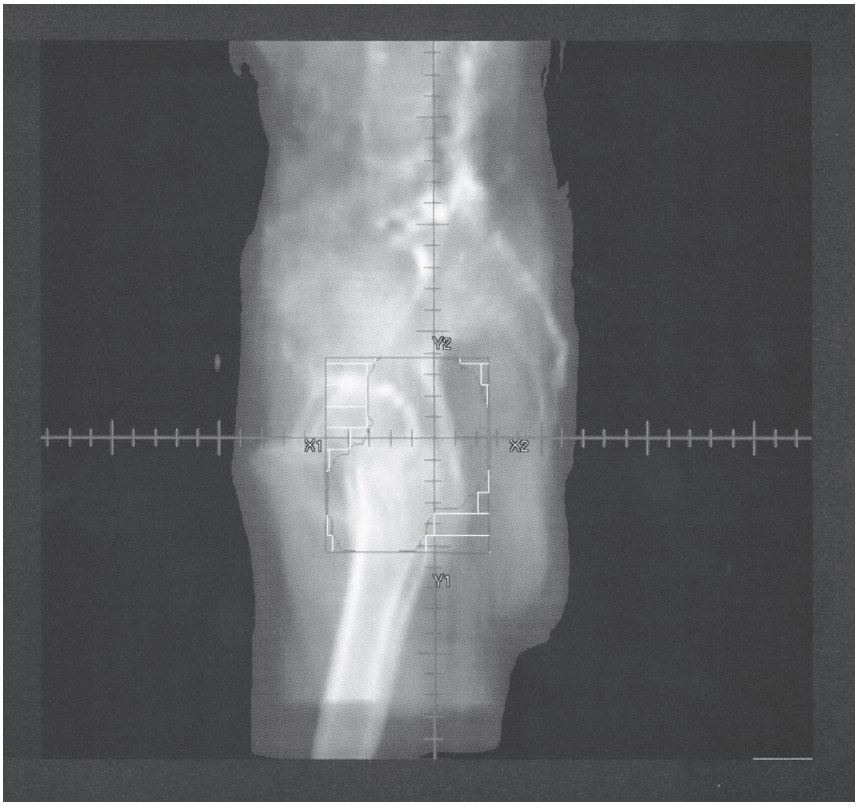

Fig. 2. Digitally reconstructed radiographic image of the tumor and parametrium as the irradiation field in small field.

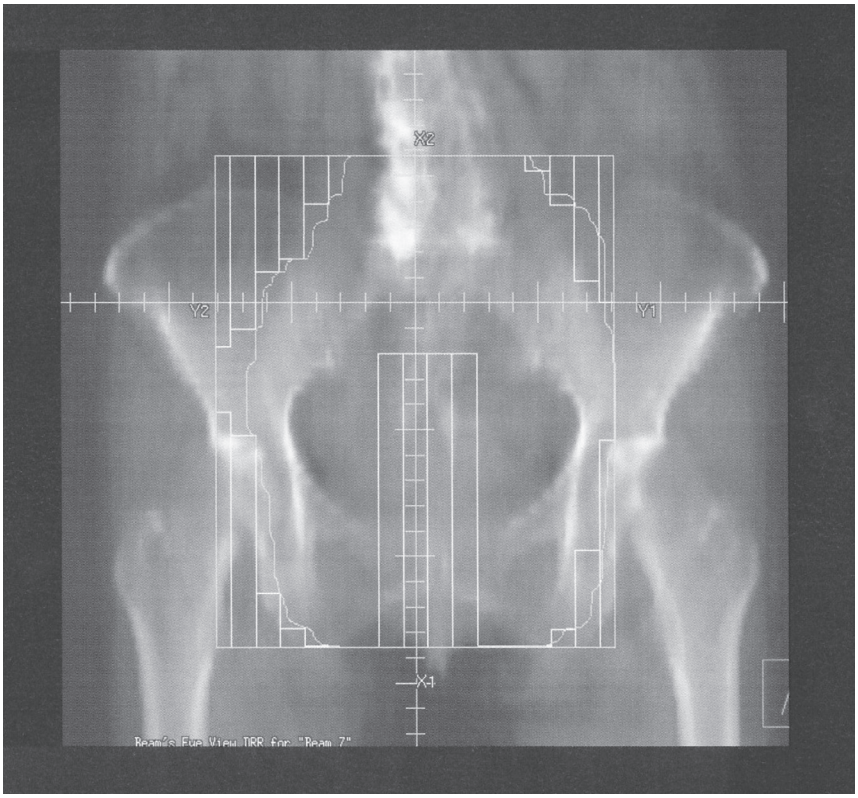

Fig. 3. Digitally reconstructed radiographic image of the center shield field.

Table 3. Initial assessment and acute adverse events

	Case 1	Case 2	Case 3
overall treatment time	37days	38days	40days
initial assessment	CR	CR	CR
follow-up duration	9.8 months	11.9 months	12.4 month
recurrence	not detected	not detected	not detected
acute adverse events			
hematological toxicity			
anemia	2	1	2
leucopenia	3	3	1
neutropenia	2	3	1
thrombocytopenia	1	2	0
AST increased	0	0	0
ALT increased	0	0	0
total-bilirubin increased	0	0	0
creatinin increased	0	0	(-)*
non-hematological toxicity			
raditaion dermatitis	0	0	0
gastrointestinal disorder	1	2	1
renal and urinary disorder	0	0	0

CR ; complete response, AST ; Asparatate aminotransferase, ALT ; Alanine aminotransferase, * ; chemotherapy was not received,

DISCUSSION

All patients achieved CR in the present study, demonstrating that the disease is curable, even though the evaluation has limitations such as the small number of cases and no long-term follow-ups. Because early detection of tumor recurrence greatly influences long-term prognosis, cytodiagnosis, internal examination, cytology and ultrasonography are necessary to follow-up closely. [25-27] Although this was the first study to use HF radiotherapy for the treatment of CC, we were able to obtain good treatment outcomes. The treatment efficacy of CCRT on cervical cancer has been demonstrated in Japan. The Japan Radiation Oncology Study Group (JROSG) has reported that a 50-month overall survival rate in patients with stage IB/II CC and those with stage III/IV was 82 and 66%, respectively, after CCRT with weekly cisplatin 30-40 mg/m2. [28] In a multi-institutional phase II clinical study of 120 patients (60 stage IIB patients with bulky tumor and 60 stage IIIB ones) in eight Asian countries, Kato *et al*. reported that 83% of the patients could complete four or five cycles of weekly cisplatin chemotherapy. [29] In the study, EBRT with whole pelvic irradiation at 30-40 Gy was followed by irradiation with a center shield and high dose rate ICBT. As a result, the 2-year overall survival rate and 2-year local control rate were 80% and 87% in stage IIB and 77 and 80% in stage IIIB. In a study of stage III (24 cases) and IVa (4 cases) CC, Parker *et al*. obtained the 5-year overall survival and local control rates of 60 and 66%, respectively. [30] And, a trial with carbon beam therapy [31] and the application of surgical procedure in cases of unsatisfactory treatment outcome have been reported. [32]

Although we anticipated in observing severe acute adverse events in this study, they stayed in an ac-

ceptable range. Theoretically, acute adverse events will increase in AHF radiotherapy. Even though two patients using chemotherapy concurrently developed grade 3 leucopenia, they were able to complete chemotherapy as planned, without interruption or termination. This might have been because we used the field-in-field method to narrow the field irradiated at 2.8 Gy/day. We also did not observe chemotherapy-related severe organ dysfunction, such as liver and kidney. Further study will be needed to assess late adverse events due to radiotherapy, such as intestinal bleeding and stenosis, bleeding and atrophy of bladder, and lymphedema. [33] However, because one of the advantages of selecting HF radiotherapy over CF radiotherapy is the low occurrence of late adverse event, it would be unlikely to observe more adverse events than conventional radiotherapy. For these reasons, we believe this radiotherapy is feasible even though it is at its initial stage.

The most commonly used chemotherapy today is weekly cisplatin at a dose of 40 mg/m2. [2, 34, 35] Kato *et al*. reported that acute grade 3 leukopenia and grade 3 gastrointestinal toxicity developed in 21 and 6% of patients, with weekly cisplatin 40 mg/m2. [29] However, none of the patients had to terminate radiotherapy due to acute adverse events, which is consistent with the finding in this study. In addition, the 2-year major late rectal and bladder complication rate was 2.5% and 0%, respectively, with two cases of rectovaginal fistulas and one case of rectal ulcer. Different types of chemotherapy have been performed in recent years. Einstein *et al*. improved a 3-year progression free survival rate by administering cisplatin every 5 days instead of weekly. [36] The Gynecologic Oncology Group in the US have shown the potential and safety of concurrent paclitaxel and cisplatin chemotherapy in a phase I/II trial [37] as well as its safety in paraaortic lymph node metastasis cases. [38] More recently, there was a report of better treatment efficacy with concurrent cisplatin and gemcitabine chemotherapy than with cisplatin monotherapy. [39] Despite its severe hematological toxicity, cisplatin and gemcitabine combination chemotherapy achieved a 3-year progression free survival rate of 74.4% compared with 65.0% in the cisplatin monotherapy (p=0.029), with a significantly improved overall survival rate (HR=0.68, p=0.0224). The concomitant use of molecular-targeting drugs has also been investigated in recent years. Moreover intraarterial chemotherapy is used with radiotherapy to enhance the effect of local treatments, and the example is relatively fair outcomes obtained in the intraarterial cisplatin/nedaplatin and intravenous 5-fluorouracil with concurrent radiation therapy. [40] However, despite its ability to improve local control, the therapy has not yet gathered enough evidence on the survival rates, and it is an important problem to prevent distant metastases. With regard to EBRT with whole pelvic irradiation, two-field irradiation has been widely used, but four-field irradiation is reportedly reduce the radiation dose to the gastrointestinal tract and thus reduce adverse events. [41]

Furthermore, OTT was 37-40 days in this study, and this was significantly shorter than the median OTT of 63 days in the RCT conducted by Rose *et al*. [2] When we pay attention to OTTs in other studies, such as 49 days in the JROSG study [28], it appears likely that a shorter OTT is a major contributor to better treatment efficacy. Using AHF, we could shorten OTT, much shorter than those in the above studies, and we believe this was one of the major factors that contributed to the antitumor effects. In addition, we can reduce hospital stay through the introduction of AHF. And it reduces the medical care cost and alleviates the mental burden or stress of patients' hospitalization.

The limitations of this study are the small sample size and short observation period. This is because the aim of this study was to assess the acceptability of acute adverse events and the feasibility of the treatment strategy and to obtain the initial assessment. Further study is needed to carefully assess the occurrence of late adverse events and tumor recurrence while increasing the number of cases and improving overall survival and disease free survival rates. We will continue this research in the Shimane University Hospital as well as in the DMUH.

ACKNOWLEDGEMENTS

All authors declare no financial support from any organization for the submitted work.

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