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High Dose Three-Dimensional Conformal Boost Using the Real-Time Tumor Tracking Radiotherapy System in Cervical Cancer Patients Unable to Receive Intracavitary Brachytherapy

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Purpose: The purpose of this study is to evaluate the clinical results of treatment with a high dose of 3-dimensional conformal boost (3DCB) using a real-time tracking radiation therapy (RTRT) system in cervical cancer patients. **Materials and Methods:** Between January 2001 and December 2004, 10 patients with cervical cancer were treated with a high dose 3DCB using RTRT system. Nine patients received whole pelvis radiation therapy (RT) with a median dose of 50 Gy (range, 40-50 Gy) before the 3DCB. The median dose of the 3DCB was 30 Gy (range, 25-30 Gy). Eight patients received the 3DCB twice a week with a daily fraction of 5 Gy. The determined endpoints were tumor response, overall survival, local failure free survival, and distant metastasis free survival. The duration of survival was calculated from the time of the start of radiotherapy. **Results:** All patients were alive at the time of analysis and the median follow-up was 17.6 months (range, 4.9-27.3 months). Complete response was achieved in nine patients and one patient had a partial response. The 1- and 2-year local failure free survival was 78.8% and 54%, respectively. The 1- and 2-year distant metastasis free survival was 90% and 72%, respectively. Late toxicity of a grade 2 rectal hemorrhage was seen in one patient. A subcutaneous abscess was encountered in one patient. **Conclusion:** The use of the high dose 3DCB in the treatment of cervical cancer is safe and feasible where intracavitary brachytherapy (ICBT) is unable to be performed. The escalation of the 3DCB dose is currently under evaluation.

Key Words: Uterine cervical neoplasms, radiotherapy, brachytherapy

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INTRODUCTION

Intracavitary brachytherapy (ICBT) in combination with external-beam radiotherapy (EBRT) has long been accepted as the standard treatment for uterine cervical cancer.[1] ICBT is used to deliver high radiation doses to the clinical target volume (CTV) by replacing radioactive sources that are in direct contact with the gross tumor. Traditionally, it is known that a cure is rarely achieved without a high dose of radiation delivered by ICBT. However, the clinical reality is that the treatment with EBRT alone is needed in patients where ICBT is not feasible due to a failure to insert a tandem, a narrow vagina, relapses at the cervical stump, or the refusal of the patient. Interstitial brachytherapy is often helpful in these cases, but it involves invasive procedures and its success is highly dependent on the ability of the operator.[2]

Replacing the use of ICBT with an EBRT boost should be applicable with the advances of the conformal radiation delivery technique. Some innovative researchers have challenged the use of ICBT by using EBRT instead with modest results obtained.[3-8] However, in these studies, severe complications were observed in some patients. While the use of ICBT can keep a fixed geometry between the CTV and the applicator, minimizing the error in delivering the planned dose distribution to the target, EBRT has shortcomings with regards to setup errors and possible internal organ motion. To overcome these shortcomings, a fluoroscopic real-time tumor tracking radiotherapy (RTRT) system was developed and applied for the treatment of pelvic malignancies.[9-11] We have previously reported the feasibility and accuracy of the use of a high dose three-dimensional conformal boost (3DCB) with the RTRT system in patients with gynecologic malignancies.[12] The RTRT system was useful to reduce the uncertainty due to external and internal error, confirming that a planning target volume (PTV) margin of 7-8 mm should be applied in the protocol setting.

To maintain similar therapy conditions to the tumor as with ICBT, the daily dose and the overall treatment time with the use of a high dose 3DCB are needed to be kept similar as with ICBT. The usual fractionation scheme for ICBT in our institution was 25 Gy/5 fractions or 35 Gy/7 fractions, with a daily fraction of 5 Gy and two fractions per week.[13] Using the RTRT technology, we applied a hypofractionated 3DCB mimicking ICBT in patients with uterine cervical cancer that were unable to undergo ICBT after EBRT.

In this report, early clinical results of cervical cancer patients treated with high dose 3DCB using the RTRT system were evaluated. The possibility of high precision conformal therapy using the RTRT technology as an alternative to ICBT is discussed.

MATERIALS AND METHODS

Patients

Between January 2001 and December 2004, 10 patients with cervical cancer were treated with a high dose 3DCB using the RTRT system without ICBT. Before starting the 3DCB, we explained to the patients that the standard definitive radiotherapy (RT) method was a combination of EBRT and ICBT, but the use of a high dose 3DCB with the RTRT system could be an option in patients unable to undergo ICBT. All patients decided to receive a high dose 3DCB. Pre-treatment evaluation included a complete history and physical examination, biopsy, abdominal and pelvic computed tomography (CT), and chest X-ray. Lymph node sampling was not performed routinely. Threshold value for identifying metastatic LNs was 10 mm short axis diameter. Patients with an outside pathology diagnosis had their pathology slides reviewed at our institution. For staging purposes, a radiation oncologist and a gynecologic oncologist performed a physical examination. Staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) classification.[14]

Five patients with newly diagnosed uterine cervical cancer, two patients with a stump carcinoma, and three patients with a vault recurrence were included in the analysis. Three patients with a vault recurrence received a radical hysterectomy due to FIGO stage I cervical cancer. Postoperative radiotherapy was added in 1 patient (patient 2). Two patients with a stump carcinoma received a hysterectomy due to myoma. The median age of the patients was 64 years (range, 32-78 years). The patient and tumor characteristics are summarized in Table 1.

Table 1. Characteristics of 10 LN (-) Patients

Patient number	Age (yrs)	KPS	Site	Histology	FIGO stage	Tumor size (cc)
1	32	90	Cervix	Small	IIB	80
2	65	90	Vault	Squamous	IIB	30
3	35	90	Cervix	Adenosarcoma	IIIB	192
4	70	80	Cervix	Squamous	IIIB	240
5	63	90	Vault	Squamous	IIB	24
6	69	80	Cervix	Squamous	IIIB	80
7	57	90	Vault	Squamous	IIIB	40
8	67	80	Cervix	Squamous	IIIB	64
9	60	90	Stump	Squamous	IIA	18
10	78	70	Stump	Squamous	IIA	20

LN, lymph node; KPS, Karnofsky performance score; FIGO, International Federation of Gynecology and Obstetrics; Small, small cell carcinoma; Squamous, squamous cell carcinoma.

Treatment planning and treatment

The general principles of treatment planning and delivery were reported in previous studies.[9-12] If ICBT and interstitial RT were abandoned and the patients agreed to enter this study, three radiopaque gold markers were implanted in or near the tumor by a trans-vaginal approach using specially made equipment (Medikit, Tokyo, Japan). After the gold markers were implanted, a planning CT scan was performed using a 1 mm slice thickness for the level involving the tumor mass and three gold markers (Fig. 1). The treatment planning was performed using the Focus® system (CMS, St. Louis, MO USA). The CTV encompassed the gross tumor volume with a safety margin. Usually, a safety margin of up to 5 mm was taken. In lateral directions, a safety margin of 8 mm was used. For the PTV, a 7-8 mm margin from the CTV was applied. After finishing the treatment planning, the coordinates of the target volume, isocenter, and three markers were registered and sent to the RTRT system. After adjusting the patient set-up using the RTRT system, the treatment was delivered. We checked the intrafractional movement of the marker several times during each treatment while the gantry was moving to the next position. The details of set-up and the radiation delivery procedure in our protocol setting were reported previously.[12]

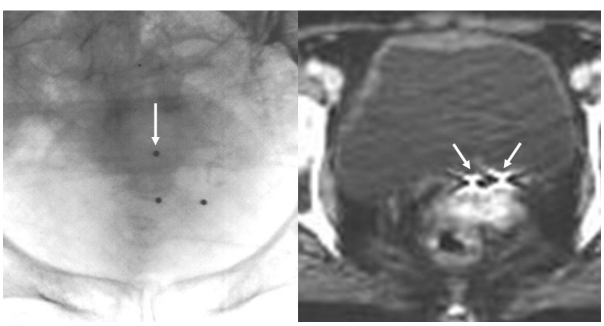

Fig. 1. Fluoroscopy and planning CT image of three gold markers placed in a patient.

The treatment characteristics of the patients are summarized in Table 2. Nine patients received a whole pelvis RT with a median dose of 50 Gy (range, 40-50 Gy). Midline shielding was performed in six patients after a dose of 40 Gy. The median dose of the 3DCB was 30 Gy (range, 25-30 Gy). The 3DCB was delivered by a 3D-conformal technique (7 patients) and forward planning intensity-modulated radiation therapy (IMRT) technique (3 patients). Eight patients received the 3DCB twice a week with a daily fraction of 5 Gy, as with the ICBT fractionation scheme of our institution.[12] Two patients received 2.5 Gy daily fractions 3-4 times a week. The treatment volume typically covered the gross tumor and the area of parametrium invasion. Concurrent chemotherapy with weekly cisplatin was administered to three patients.

Follow-up

Patients were scheduled for follow-up visits every 3 months. We determined the dates of local and distant failure using imaging studies, primarily abdomen and pelvic CT scans, which were performed at approximately three-month intervals during the initial two years of follow-up.

End points and statistical analysis

The major endpoints of this study were tumor response, overall survival (OS), local failure free survival (local failure, defined as any recurrence within the RT volume), and distant metastasis free survival. Nodal recurrences were also evaluated. Late toxicity was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation

Table 2. Treatment Characteristics of the Patients

Patient number	Pelvis dose (Gy)	Midline shielding at (Gy)	3DCB dose (Gy)	3DCB fraction size (Gy)	3DCB fractionation (number/weekly)	3DCB technique	Concurrent CTX
1	50	40	30	5	2	3DCRT	Yes
2	0	-	30	2.5	3	3DCRT	-
3	50	40	25	2.5	4	3DCRT	Yes
4	50	40	30	5	2	FIMRT	-
5	50	40	30	5	2	3DCRT	-
6	50	-	30	5	2	3DCRT	-
7	50	40	30	5	2	FIMRT	-
8	50	-	30	5	2	FIMRT	Yes
9	50	-	30	5	2	3DCRT	-
10	40	-	30	5	2	3DCRT	-

3DCB, 3-dimensional conformal boost; 3DCRT, 3-dimentional conformal radiation therapy; FIMRT, forward planning intensity-modulated radiation therapy; CTX, chemotherapy.

morbidity scoring scheme.[15]

The duration of the follow-up period was calculated from the date of the first visit to our clinic. The duration of survival was calculated from the day of commencing RT. The survival time was censored at the time of the last follow-up on record if death was not observed. Dates of local and distant failure were determined using imaging studies. Survival probabilities were estimated non-parametrically using the Kaplan-Meier's product limit method.[16]

RESULTS

Clinical response

The endpoints are summarized in Table 3. Of 10 patients, complete response (CR) of the tumor was achieved in nine patients (90%), and one patient had a partial response (PR). Therefore, the response rate (CR + PR) was 100%. Fig. 2 shows the tumor response in case 5.

Disease control and survival

All patients were still alive at the time of analysis and the median follow-up was 17.6 months (range 4.9-27.3 months) (Fig. 3). Four patients were alive without disease, and six patients were alive with disease. Four patients had local failure and the crude rate of local control was 60%. Two patients had distant metastases and the crude rate of distant disease control was 80%. One patient had a liver and bone metastasis and the other patient had a metastasis to the para-aortic lymph node and the adrenal gland. The actuarial 1 year and 2 year local failure free survival was 78.8% and 54%, respectively. The actuarial 1 year and 2 year distant metastasis free survival was 90% and 72%, respectively.

Treatment toxicities

All patients tolerated the 3DCB very well and no severe adverse effects were encountered. However, acute toxicity of grade 1 diarrhea was seen in five patients. Late toxicity of grade 2 rectal hemorrhage was seen in one patient. A subcutaneous abscess was encountered in one patient 6 months after the completion of RT.

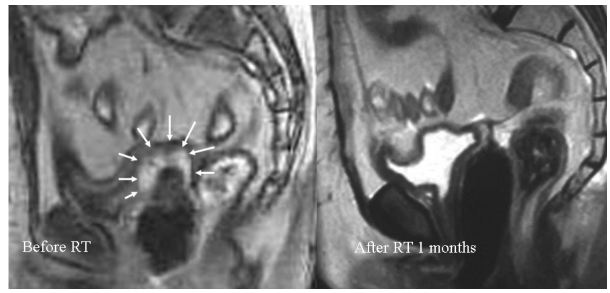

Fig. 2. Clinical response of the tumor in case 5.

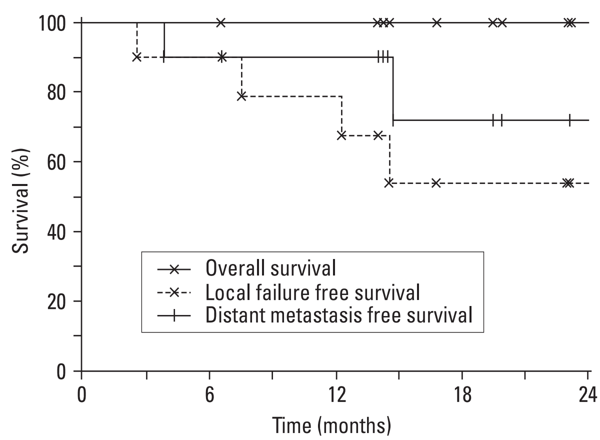

Fig. 3. Survival plotting.

Table 3. Summary of the Treatment Results

Patient number	Tumor response	Local recurrence	Distant metastasis	Complications	FU periods (months)	Current status
1	CR	-	Liver, bone	G2 rectal	16.9	AWD
2	CR	-	-	-	23.7	NED
3	PR	Y	-	-	21.0	AWD
4	CR	Y	-	-	18.2	AWD
5	CR	-	-	-	27.3	NED
6	CR	-	-	Subcutaneous abscess	12.5	NED
7	CR	Y	-	-	14.9	AWD
8	CR	-	PA node, adrenal gland	-	21.7	AWD
9	CR	Y	-	-	12.5	AWD
10	CR	-	-	-	5.0	NED

FU, follow-up; CR, complete response; PR, partial response; Y, yes; PA, para-aortic; G, grade; AWD, alive with disease; NED, no evidence of disease.

DISCUSSION

It is well known that ICBT is an essential component of RT for uterine cervical cancer.[1] With a direct contact to the tumor, ICBT effectively delivers the tumoricidal dose while sparing the surrounding normal tissue. However, a small but definite proportion of patients are not suitable to undergo ICBT for several clinical reasons. Thus, we intended to treat those patients with a high dose 3DCB replacing the ICBT portion of the entire treatment. The RTRT technology provides the effective tools to realize individual-based, precise adaptive irradiation for moving, shrinking, and deforming targets, such as gynecologic malignancies. In an effort to mimic the ICBT portion of the treatment, we applied RTRT technology in the current protocol settings.

The treatment results of the use of the high dose 3DCB in the present study were not satisfying. The local failure free survival was relatively low at 2 years. Though there were six patients with disease recurrence, the OS was still 100% because of the short-term follow-up. It is thought that a further follow-up with more patients could confirm the treatment results and the effectiveness of our study protocol. In our study, the adaptive set-up of patients using the RTRT system was proved as a safe adjunct showing a minimal level of late complications. It seems that further escalation of the 3DCB dose could be pursued safely. Among patients with local failure, three patients had FIGO IIIB disease and two patients had a large tumor size (patient 3 and 4). The escalation of the 3DCB dose is being evaluated to improve local control for these patients with locally advanced diseases.

Some investigators have performed definitive external radiation therapy without ICBT for uterine cervical cancer.[3,4,6] Table 4 shows the treatment results of these studies. Matsuura, et al.[3] used concomitant boost with accelerated hyperfractionation to shorten the overall treatment time as compared to ICBT. However, due to a small study population and short term follow-up, the level of local control (85.7%) and survival comparable to the results of standard treatment has not yet been confirmed. The particle radiation therapy series has shown better long-term local control and survival.[4,6] However, these studies showed a significant level of late morbidity. Detrimental set-up errors and internal organ motion contributed to late morbidity resulting from a high dose to the surrounding normal tissues. The use of a better adaptive set-up strategy is needed for the successful execution of definitive EBRT for gynecologic malignancies.

Except in the clinical situation in which proper ICBT cannot be performed, the use of ICBT is being challenged in many studies. Several researchers have performed a dosimetric comparison between the use of IMRT and ICBT in terms of dose homogeneity and target coverage.[17-20] Chan, et al.[21] compared different EBRT techniques as an alternative to ICBT. These investigators showed that the use of IMRT could improve target coverage and reduce the dose to critical structures. Moreover, when used in conjunction with a suitable immobilization system, IMRT may provide an alternative to ICBT. The average minimum tumor dose was significantly greater and the mean percent tumor volume receiving more than the prescription dose was higher with IMRT. The mean volume at the tolerance limit decreased for the bladder. These advantages of IMRT

Table 4. Outcomes for Various Studies Evaluating the Role of EBRT to Replace ICBT

Author (yr)	Patients (No.)	FIGO Stage	Treatment	Local control	Survival	Complication
Kagei, et al.[6]	25	IIB - IVA	Photon + Proton beam therapy Pelvis with X-ray 50.4 Gy / 28 Fx Tumor boost 37 - 101 Gy	75% (5 yr)	59% (10 yr)	24% grade 2 - 4 GI complication 8% grade 2 - 4 complication
Kato, et al.[4]	44	IIIB - IVA	Carbon ion radiotherapy Pelvis 35.2 - 44.8 GyE Tumor Boost 24 - 28 GyE	45 - 79% (5 yr)	37 - 43% (5 yr)	25% Grade 2 - 4 GI complication 9.1% Grade 2 GU complication
Matsuura, et al.[3]	7	IB - IVA	Concomittant boost AHF Pelvis 45 Gy / 25 Fx Tumor boost 21 - 28 Gy / 15 Fx	85.7% (2 yr)	85.7% (2 yr)	28.6% Grade 2 rectal complication
Present study	10	IIA - IIIB	High dose 3DCB using RTRT Pelvis 40 - 50 Gy / 20 - 25 Fx Tumor boost 30 Gy / 6 Fx	54% (2 yr)	72% (2 yr)	10% Grade 2 rectal complication 10% Subcutaneous abscess

EBRT, external beam radiation therapy; ICBT, intracavitary brachytherapy; FIGO, International Federation of Gynecology and Obstetrics; Fx, fractions; Gy, gray; GyE, gray equivalent; AHF, accelerated hyperfractionation; 3DCB, 3-dimensional conformal boost; RTRT, real-time tracking radiotherapy; GI, gastrointestinal; GU, genitourinary.

over ICBT are accentuated, especially in large volume tumors.

A weakness of ICBT is that tumors may have a particular size or geometry that places much of the tumor volume in peripheral under-dosed regions. Furthermore, critical structures may be over-dosed because of their proximity to the radioactive sources. To optimize the ICBT planning at best, some recommendations have been published on the use of 3-dimensional image-based treatment planning in ICBT.[22-24] However, even with the best optimization, it seems that the weakness of ICBT could not be removed completely due to the interplay between the tumor shape and the limited degree of freedom of the applicator geometry. Chao, et al.[25] investigated the consequences of uterosacral space involvement in patients with stage IIIB cervical cancer. These investigators concluded that the combination of ICBT and EBRT did not deliver an adequate dose to the tumor in the uterosacral space, and an improved dose delivery regimen should be investigated.

Non-uniform doses are unavoidable in ICBT resulting in a hot spot and cold spot that develop in the tumor. This inhomogeneity in the dose delivered by the ICBT is both advantageous and disadvantageous for tumor control. Since a dose deficit to a 1% sub-volume of the target larger than 20% of the prescription dose may lead to serious loss of tumor control probability (TCP), even if 80% of the target receives a 10% boost, particular attention is required for small-volume cold regions in the target.[26] Once the target is covered adequately, the use of deliberate non-uniform doses may increase the TCP. Tome, et al.[26,27] reported that up to 30% of a sub-volume boost to the 60-80% of the target volume appeared worthwhile or necessary to maximize the TCP. IMRT gives the best scenario of inhomogeneous irradiation with adequate target coverage. The simultaneous integrated boost (SIB) technique of IMRT was successfully applied in the treatment of head and neck cancer.[28] Thus, IMRT using RTRT technology can be the best modality for EBRT to replace ICBT in the treatment of cervical cancer. We have reported the feasibility of the use of synchronized IMRT using the RTRT system. Unlike the thoracic and upper gastrointestinal malignancies in which a narrow gating window is needed, it is thought that this technique could be applied successfully in the treatment of pelvic malignancies without an excess fluoroscopy dose to the skin surface.[29]

In conclusion, although more patients with longer follow-up periods are needed to evaluate the usefulness of high dose 3DCB, especially to determine the long-term toxicity level, our results suggest that a high dose of 3DCB replacing ICBT in the treatment of gynecologic malignancies is safe and feasible where ICBT is unable to be performed. To improve local control, the escalation of the radiation dose should be pursued. The use of synchronized IMRT with the RTRT system is a promising therapy and needs to be investigated further.

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