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Single external beam radiotherapy boost in cervical cancer where brachytherapy is not available.

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Abstract

Introduction: A combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is well established as the standard radical radiotherapy (RT) for cervical cancer. But in our center there is brachytherapy machine but no source is available. Around 80% patients attending in our Department are poor and come from rural area. These patients can not able to go to our capital city Dhaka for brachytherapy due to their poverty which is 220km in distance. For these patients, we initiated EBRT alone with 3-dimensional conformal radiotherapy (3DCRT). The purpose of this study is to evaluate the radiation toxicity and tumor response with EBRT alone without ICBT for patients with cervical cancer. **Methods:** Between June 2015 to December 2015, 8 patients with cervical cancer were treated with a high dose 3-dimensional conformal boost (3DCB). There were four in stage IIA, three in stage IIB and one in stage IIIB. Total dose of EBRT was 65-70 Gy in conventional fractionation (CF). They received whole pelvis RT with a median dose of 50 Gy (range 45-50 Gy) and midline shielding done at 40 Gy. Then a boost of 20-25 Gy to central tumor was given after a gap of two weeks. **Results:** 7 patients achieved complete response (CP) 87.5% and one patient had a partial response (PR) 12.5%. Therefore the response rate (CP + PR) was 100%. All patients tolerated the dose well without any severe adverse effects. However, acute toxicity of mild dysuria was seen in two patients and one patient suffered from mild diarrhoea. Conclusions: The use of the high dose 3DCB in the treatment of the cervical cancer is safe and feasible where ICRT is unable to perform. Escalation of 3DCB dose and assessment of late effect is currently under evaluation.

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 traditionally, it is known that a cure is rarely achieved without a high dose of radiation delivered by ICBT. However, in the actual clinical setting it is sometimes necessary to perform EBRT alone for patients where ICBT is not feasible due to a failure to insert a tandem, a narrow vagina, relapse at the cervical stump, or the refusal of the patient. For these medical condition some Radiotherapy Center practice EBRT alone for the treatment of cervical cancer where brachytherapy can not perform [4]. Study carried out by Kanji Matsuura et al. [5]. For these patients, from 2002 initiated EBRT alone with 3-dimensional conformal radiotherapy (3DCRT) in order to improve LC. Their radiotherapy treatment modality was EBRT alone with the concomitant boost (CCB). The observation was that the 3-year overall survival (OAS) and local control (LC) rates were 43.8% and 75.0%, respectively. No severe acute and late adverse effects were encountered for any of the patients. These results suggested that 3DCRT with the CCB program is a feasible treatment modality.

Our Radiotherapy Department is at Shaheed Ziaur Rahman Medical Collage Hospital, in Bogra town, which is 220Km away at north side from the capital city Dhaka. We have brachytherapy machine but unfortunately source is not available from the begining. More than 80% cancer patients attending in our Department are from rural area and their economic status are poor. These patients can not go to our capital city Dhaka for brachytherapy due to their lower financial condition. For these patients, we have initiated EBRT alone with three-dimensional conformal radiotherapy (3DCRT) in order to improve local control (LC).

Materials and Methods

Between June 2015 to December 2015 8 patients with cervical cancer were treated with a high dose 3DCB without ICBT. Before starting the 3DCB we explained to the patients that the standard definitive radiotherapy (RT) method was a combination of EBRT and ICRT, but use of a high dose 3DCB could be an option in patients unable to undergo ICRT. 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. Threshold value for identifying metastasic LNs was 10 mm short axis diameter. For staging purposes, a radiation oncologist and a gynecologist performed a physical examination. Staging was performed according to the International Federation of gynecology and Obstetrics (FIGO) classification. Four patients with newly diagnosed uterine cervical cancer, two patients with a stump carcinoma and two patients with a vault recurrence were included in the analysis. Patient with recurrence received a radical hysterectomy due to stage I cervical cancer. One patient with a stump carcinoma received a hysterectomy due to myoma. The median age of the patients was 50 years (range 40- 62 years). The patients and the tumor characteristics are summarized in table 1.

Table1. Charesteristics of 8 LN (-) Patients

Patient number	Age (yrs)	KPS	Site	Histology	FIGO stage	Tumor size (cm)
1	55	90	Vault	Sq.cell.ca.	IIIB	8x6x5
2	40	70	Cervix	Sq.cell.ca.	IIIB	6x5x7.3
3	52	90	Cervix	Sq.cell.ca.	IIA	5x4x5
4	62	90	Stump	Sq.cell.ca.	IIA	3x4x4.2
5	45	80	Stump	Sq.cell.ca.	IIA	5.5x4x3.6
6	42	90	Cervix	Sq.cell.ca.	IIB	5.5x4x3.4
7	60	80	Vault	Sq.cell.ca.	IIIB	6x4.9x8
8	55	80	Cervix	Sq.cell.ca.	IIB	5x7x4.5

LN. lymph node; KPS. Karnofsky performance score; FIGO. International Federation of Gynecology and Obstetrics; Sq.cell ca. Squamous cell carcinoma.

Treatment planning

External radiotherapy (EBRT)

The patients were treated with EBRT alone administered by a combination of whole pelvic irradiation (WPI) and local irradiation (LI). All patients underwent CT simulation, and EBRT was administered with 3DCRT. EBRT was delivered using a linear accelerator with an X-ray energy of ≥6-MV photons. The patients were instructed to void their bladder and rectum as a countermeasure to avoid uterus motion which is influenced by

rectal filling and bladder filling just before both CT simulation and daily treatment. The clinical target volume (CTV) of WPI included the gross tumor volume of the primary tumor, uterine cervix, uterus corpus, vagina, parametrial tissue and regional nodes (common iliac, internal iliac, external iliac, hypogastric, obturator and presacral nodes). 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 were used to reduce the total dose to the surrounding tissue, especially to the rectum and bladder.

The patients were treated with conventional fractional (CF) schedule. The treatment characteristics of the patients are summarized in the table 2. These 8 patients received WPI with a median dose of 50 Gray (range 45-50Gy). Midline shielding was performed in 5 patients after a dose of 40 Gy. The median dose of 3DCB was 20 Gray (range 20-25 Gy). Concurrent chemotherapy with weekly cisplatin was administered to three patients.

Table 2. Treatment Characteristics of the Patients

Patients number	Pelvis dose (Gy)	Midline shielding at (Gy)	3DCB dose (Gy)	RT Technique	Concurrent CTX
1	50	-	20	3DCRT	YES
2	50	-	20	3DCRT	YES
3	50	40	20	3DCRT	
4	50	40	20	3DCRT	
5	50	40	20	3DCRT	
6	45	40	25	3DCRT	
7	45	-	25	3DCRT	
8	45	40	25	3DCRT	YES

3DCB, 3-dimentional conformal boost; 3DCRT, 3-dimentional conformal radiotherapy; CTX, chemotherapy.

Follow-up

Patients were reviewed at weekly intervals during radiotherapy treatment. Clinical Assessment of the symptoms of acute toxicity was done following modified RTOG/EORTC scoring system. Local control of the disease was checked throw pelvic CT scan and thorough gynaenecological examination at 6 weeks interval after completion of the radiotherapy treatment.

Results

The clinical response rate was evaluated at 6 weeks after the completion of treatment, according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [5]. All patients

were still alive at the time of analysis. Of 8

patients 7 patients (87.5%) achieved complete response (CR) and 1 patient (12.5%) achieved partial response (PR). Therefore the response rate (CP + PR) was 100%.

Treatment toxicities

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 one patient and acute toxicity of mild dysuria were seen in two patients. Symptomatic treatment was provided to relief them from their complication. Treatment

results are summarized in table 3.

Table 3. Summery of the Treatment Rersults

Patients number	Post RT Tumor Size (cm)	Tumor response	Complications	Current status
1	0	CR	Mild dysuria	NED
2	0	CR	Mild diarrhoea	NED
3	0	CR		NED
4	0	CR		NED
5	0	CR		NED
6	0	CR		NED
7	1x1.5x0.8	PR		AWD
8	0	CR	Mild dysuria	NED

CR, complete response; PR, partial response; AWD, alive with disease; NED, no evidence of disease.

Discussion

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 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 [6]. In addition, the interfractional variations in the cervix position are large [7], 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.

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.

Conclusion

The intended application of this technique is not to replace brachytherapy as a modality, but rather as a tool for situations where brachytherapy is not available.

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