OUTCOME OF CERVIX CANCER PATIENTS TREATED WITH HIGH DOSE RATE BRACHYTHERAPY AT KING ABDUL AZIZ UNIVERSITY HOSPITAL

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Abstract:

Purpose: To review the treatment results of cervix cancer patients treated with high dose rate brachytherapy at King Abdul Aziz University Hospital.

Methods: All cervix cancer patients treated with high dose rate brachytherapy at King Abdul Aziz university hospital between January 2004 and December 2006 have been reviewed. The patient's demographic data, treatment parameters and follow up have been reported and histopathological grade and stage has been correlated with initial response to treatment and disease Free survival has been calculated.

Results: Twenty four patients with mean age of 51.6 years. All patients had squamous cell carcinoma; 12.5% G1, 54.2% G II and 33.3% G III. Stage IA 12.5%, IB 4.2%, IIA 16.7%, IIB 25%, IIIA 8.3%, IIIB 20.8% and IVA 12.5%, treatment toxicity was diarrhea GII in 12.5% and G II cystitis in 21%.
Initial treatment response was 50% CR, 25% PR, 8.3% SD, and 16.7% DP.
After a mean follow up period of 39 months, the mean DFS was 27.3 months 95% confidence interval (CI) 23.52 – 31.07. The median DFS was 29 months (95% CI , 23 – 35 months). Two year DFS was 60% and the 3 year DFS was 27%.
There was no correlation between DFS and histopathological grade ($p = 0.53$) or FIGO stage ($p = 0.66$), and no correlation was found between DFS and response to treatment ($p = 0.88$). On multivariate analysis, histopathological grade, FIGO stage, initial response all had no influence on DFS.

Conclusion: The use of external beam radiation therapy concomitant with weekly cisplatin followed by high dose rate brachytherapy is an acceptable treatment modality for carcinoma of the cervix with mild treatment related toxicity.

Keywords: Cervix cancer, HDR brachytherapy .

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Introduction:

The median survival of patients with carcinoma of cervix treated with radiation therapy alone is relatively low particularly those with advanced stages of disease where survival is not more than 20%. [1]

Concomitant cisplatinum chemotherapy and radiotherapy had improved the local control, disease free and overall survival in the treatment of cervix cancer. [2-6]

High dose rate (HDR) brachytherapy some advantages over low dse rate (LDR) brachytherapy. The treatment time of HDR brachytherapy is much shorter than LDR so it is more convenient to the patients as an out patient procedure without the need for longer hospitalization with prolonged radiation protection precautions. Many studies showed similar local control and survival when using HDR as compared with LDR. [7-9]

The aim of this study is to review all cervix cancer patients treated with HDR brachytherapy at king abdul aziz university hospital.

Patients and methods:

All patients with carcinoma of the cervix who were treated at the radiotherapy unit of king Abdul Aziz university hospital for radical radiotherapy during the period of January 2004 till December 2006 were reviewed. All Patients had a confirmed diagnosis of cancer and signed an informed consent.

Initial staging work up included history, physical examination, examination under anathesia (EUA), MRI of the pelvis and computerized tomography of chest abdomen.

Patients were treated with external beam radiotherapy (EBRT) with concurrent weekly cisplatin followed by HDR brachytherpy. Patients had CT simulation in supine position with 3 mm thick CT slices. Eclipse (VARIAN) planning system was used for dosimetry. Four fields (box) technique was used. Upper boarder at L5/L4, lower boarder at 4 cm below vaginal extend of the tumour, lateral boarders at 2 cm lateral to true pelvis rim, anterior boarder at tip of symphysis pubis and posterior boarder was behind anterior wall of sacrum. 3D planning with customized blocks were used ***(Figures 1)***. A dose of 4500 cGy was prescribed a 25 fractions over 5 weeks (180 cGy per fraction) using 18 mv photon energy.

Brachytherpy started within one week of completing external beam radiotherapy. We have a CT scan inside the brachytherapy room and all patients had Flitcher suit device (FSD) inserted in the standard fashion and a CT scan for planning and dosimetry. A Varisource HDR machine of Varian was used for the treatment and a BrachyVision planning system was used for dosimetry following the ICRU recommendations. A dose of 7 Gy had been prescribed to point A and the planning CT was used to ensure that the target volume is covered. All patients had three insertions, once every week (7 GY times 3).

Initial response to treatment was evaluated after 6 weeks from the end of the last brachytherapy treatment using clinical examination and pelvic MRI. Response rate was defined according to disease response criteria [12] as complete response (CR) is a complete disappearance of all disease, partial response (PR) is reduction of 50% or more of the maximum bi-directional diameter of the lesion, stable disease (SD) is no change of the dimensions of the lesion or reduction of less than 50% of the maximum bi-directional diameter of the lesion, and disease progression (DP) is increase in the maximum bi-directional diameter of the lesion or appearance of new lesions. Disease free survival was calculated from the date of initial diagnosis till disease progression.

Statistical analysis of the data was done using SPSS software, and Kaplan -Meier method was used for disease free survival. Correlation of different variables with disease response was done using Chi- square test for categorical variables and for multivariate using logistic regression analysis.

Correlation between DFS and different prognostic variables was done using Cox Regression method.

Results:

Twenty-four patients were reviewed. The mean age was 58.6 (±15.5 years; SD), and the range was 33-85 years. All patients were squamous cell carcinoma, ***(table 1)*** shows the characteristics of the patients in the study.

During radiation therapy 70.8% had G1 bowel toxicity, 20.8% had GII, and 10.4% had GI cystitis. The initial response to radiotherapy showed CR in 50%, PR in 28%, SD in 10 % and DP in 16.7%.

After a mean follow up period of 39 months (range 20-56 months), the mean DFS was 27.3 months (standard error SE 1.93) and (95% confidence interval [CI]: 23.52 – 31.07) . The median DFS was 29 months (SE 3.06), (95% CI, 23– 35 months). The 2 year DFS was 60% and the 3 year DFS was 27%.

Correlation of different prognostic variables in univariate, analysis showed that, there was a border line correlation between the histopathological grade and the FIGO stage ($p = 0.043$) with more incidence of advanced stages at presentation in higher grade lesions (in patients with GIII 25% had stages IIB-IVA, while only 4.2% had stage IA). On the other hand all patients with GI (12.5%) had stage I A, and IB.

Histopathological grade had no correlation with response rate ($p = 0.05$). However, there was a trend to better response, CR rate of 45.8% in grade I and II lesions as compared to 4.1% in grade III lesions.

Although patients who had initial CR or SD had better DFS (40%, and 42% DFS rate at 36 months) as compared to 22% for those who had DP, the difference was not sta-

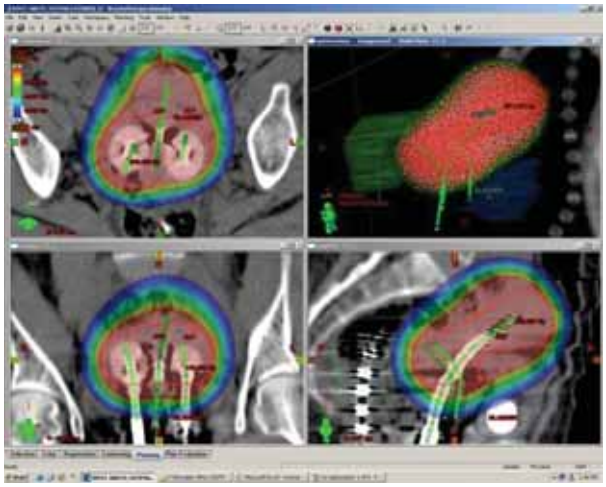

Figure 1: Three dimensional configuration of the target volume (in red)

Table 1. Patient's characteristics on presentation in the study

Feature	Number	Percentage
Symptoms: Bleeding	22	91.7
Discharge	16	66.7
Pain	11	45.8
Tumor grade Grade I	3	12.5
Grade II	13	54.2
Grade III	8	33.3
FIGO stage * Stage I A	3	12.5
Stage IB	1	4.2
Stage IIA	4	16.7
Stage IIB	6	25
Stage IIIA	2	8.3
Stage IIIB	5	20.8
Stage IVA	3	12.5

* FIGO : Fédération Internationale de Gynécologie et d'Obstétrique

Appendix 1. RTOG (Radiation Therapy Oncology Group) toxicity criteria (diarrhea, cystitis)

RTOG Grade	Diarrhea	Cystitis
Grade 0	Non	Non
Grade I	Increase of 2-3 stools per day	Microscopic hematuria
Grade II	Increase of 4-6 stools per day, or nocturnal stools , or moderate cramping	Gross hematuria , no clots
Grade III	Increase of 7-9 stools per day, or incontinence or severe cramping	Gross hematuria , presence of clots
Grade IV	Increase of > or = 10stools per day, or grossly bloody diarrhoea , or need for parental support	Requires transfusion

tistically significant (p = 0.88).
On multivariate analysis using logistic regression analysis it was found that the DFS was not influenced by histopathological grade (p = 0.35), stage (p = 0.68), or response rate (p= 0.15) .

Discussion:

Approximately 10,370 women had been diagnosed with cervical cancer in 2005. This represents 0.13% of all cancer deaths in women and the Saudi tumor registry (2004) showed that cancer cervix represent 4.6% of all cancer diagnosed in women [12].
Radical radiotherapy has been used to treat cervix cancer with results similar to surgery for early stage cancer. [13-16]
Five controled trails showed that concurrent use of cisplatin based chemotherapy with radiotherapy is superior to radiotherapy alone in the treatment of cervix cancer. [17-20]
Although, LDR brachytherapy has been traditionally used in the treatment of cervix cancer, HDR is now widely used because of shorter treatment time and less radiation exposure to medical staff. Three randomized trials had shown a similar outcome and complication with LDR and HDR in the treatment of cervix cancer. [21-23]
In this study the initial response to radiation therapy showed that CR was 50%, PR 28 %, SD 10 % and DP was 16.7%. And during treatment 70.8% had G1 bowel toxicity and 20.8% had GII. While 10.4% had GI cystitis. The 2 year DFS was 60% and the 3 year DFS was 27%.
Distefano et al (24) reported 54 patients with cervix carcinoma treated with concurrent chemoradiation therapy and CR rate was 45.1% while in this study it was 50%. However the 3 years DFS rate was higher in Distefano study, 72.2% as compared to 27% in this study, this may be because 87% of patients in this study with pathological grade II, III and the majority of our patients were advanced stage at presentation (67% were staged IIB-IVA).
Chen et al in a similar study showed a 3 years DFS rate of 55% and the toxicity profile was higher compared to the current study GIII diarrhea 10%, and GIII-IV bladder toxicity 4%. [25].
Ferringo et al in a larger study of 138 patients with carcinoma of cervix treated with HDR, the incidence of G1 bowel toxocity was 14% as compared to 20.8% in this study and bladder GII toxicity was seen in 11% of patients as compared with no G11 bladder toxicity in this study. [26]
In conclusion, this study showed that the current protocol of concomitant weekly cisplatin and external beam radiotherapy followed by HDR brachytherapy is an effective regimen for treating carcinoma of the cervix resulting in a good initial response and acceptable toxicity profile.

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