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Research Paper

A Prospective Cohort Study Comparing Three Dimensional Image Guided Intracavitary Brachytherapy and Conventional Brachytherapy for Dosimetry in Carcinoma Cervix

Medical Science

KEYWORDS : Image guided brachytherapy,High Risk Clinical Target Volume,Carcinoma cervix

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ABSTRACT

PURPOSE:A dosimetric comparison between the standard point A intracavitary brachytherapy technique and Image Guided Brachytherapy (IGBT) technique, to assess the feasibility of IGBT in the Indian scenario

METHODS: Between August 2013 and June 2015, 30 patients of carcinoma cervix were enrolled in the study. Two plans were created for each patient, the conventional plan prescribing dose to point A and CT scan based IGBT plan, prescribing dose to High Risk Clinical Target Volume(HRCTV)

RESULTS:On analysis, there was a significant difference in terms of mean dose to the Bladder (p = 0.0045) and Rectum (p = 0.0316). IGBT planning provided better coverage to the HRCTV (p = 0.04) and reduced doses to the Bladder (p = 0.0003) and Rectum (p = 0.0007) when total EQD2 doses were compared. In terms of dose received by 0.1cc, 1cc and 2cc of OARs, there was significant reduction by IGBT planning as compared to conventional planning. All patients received treatment according to IGBT planning. None of the patients reported acute grade 3 or 4 bladder or rectal toxicity at 2 months or 5 months post treatment

CONCLUSIONS:Image-based brachytherapy techniques allow us to precisely identify HR CTV and OARs. Dose optimization results in adequate target coverage and reduces delivery of unacceptable high doses to Organs At Risk

INTRODUCTION

Cancer of the cervix is preventable, yet approximately 493,100 new cases and more than 273,000 deaths occur each year among women worldwide[1]. India, which accounts for one sixth of the world's population, also bears one fifth of the world's burden of cervical cancer[2]. There are approximately 130,000 new cases of cervical cancer in India per year and the disease is reported to be responsible for almost 20 percent of all female deaths[1].

Radiotherapy (RT) occupies an important role in the treatment of most gynaecologic malignancies, in particular, cervical cancer. All patients receive combined modality of treatment i.e. whole pelvic radiation therapy (WPRT) with Intracavitary Radiotherapy (ICRT). Though there have been rapid advancement in delivery techniques of external beam radiation, there is not much evolution in the technique of delivering intracavitary brachytherapy. Traditionally, the Manchester system characterized doses to four points: point A, point B, Bladder point and Rectum point. The duration of the irradiation was based on the dose rate at point A, which was located 2 cm superior to the cervical orifice (os) and 2 cm lateral to the cervical canal. Point B was defined 3 cm laterally to point A when the central canal was not displaced[3]. Subsequently, the gyneacological dosimetry system recommended by the ICRU (Report 38) related the dose distribution to the target volume rather than to a specific point[4]. The report identified a dose level of 60 Gy as the appropriate reference dose level for LDR treatments. This resulted in a requirement to specify the dimensions of the pear-shaped 60 Gy isodose reference volume.

However, in the last few years, concepts for three-Dimensional image based treatment planning in cervix cancer Brachytherapy have been developed. In 2005, recommendations for three-Dimensional image based Brachytherapy were published by the Groupe Europeen de Curietherapie of the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO)[5,6] and have now become the standard. This technique allows better assessment of dose distributions in different volumes, such as gross tumor volume (GTV), clinical target volume (CTV) and OARs (rectum, bladder and intestines). During the complex chain of this procedure, image assistance is provided for disease assessment, provisional treatment planning (pre-planning), applicator placement and reconstruction, as well as for contouring, definitive treatment planning, and for quality control of dose delivery. With IGBT, changes of topography adjacent to the applicator, caused by tumor regression, oedema, organ changes and dilation are identified. Thus the CTV for IGBT (High risk CTV) is primarily based on the tumor volume at the time of Brachytherapy and takes into account both time and spatial domains.

India has a huge burden of cervical cancers with majority of patients presenting at advanced stages (IIB, IIIB, IVA). We conducted a dosimetric comparison between standard point A delivery technique and IGBT technique to assess the feasibility of IGBT in the Indian scenario. The primary objective was to compare doses to the High Risk CTV (HRCTV) and organs at risk (OARs) by dose volume histograms of patients treated by Three Dimensional Image Guided Intracavitary Brachytherapy and Conventional Brachytherapy technique in Carcinoma Cervix. The secondary objective was to analyse the acute toxicity profile in these patients.

MATERIALS AND METHODS

A. Data collection:

This study was conducted from August 2013 to June 2015. The age group of the patient population between 20 – 85 yrs was included in the study. All patients with a proven histopathology (HPE) for malignancy of either Squamous cell carcinoma, or Adenocarcinoma, and/or Adeno-Squmaous cell carcinoma and confirmed by a pathologist, and confirmed staging by clinical examination and intact cervical cancer with International Federation of Gynaecology and Obstetrics Stage IB_2, IIA_2, IIB, IIIA, and IIIB were included in the study. Patients with stage IVA or IVB, cases that had received prior pelvic irradiation and post operative cases were excluded from the analysis. An ethics committee approval was taken prior to the study. All patients included in the analysis gave informed consent for being enrolled in the study.

B. Work up:

All Patients got a basic work up that included HIV testing, Complete blood picture, Blood Urea and Serum Creatinine, Serum

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bilirubin, Ultrasound abdomen and pelvis , Chest X-ray. Cystoscopy was done if indicated.

C. Treatment technique
After 30-40 Gy of EBRT, patients suitable for intracavitary Brachytherapy were enrolled in the study. HDR Brachytherapy using Ir 192 was prescribed. Each patient was assessed for the feasibility of intracavitary Brachytherapy and CT compatible applicators were applied for each patient. Fletcher suit applicator with different tandem lengths and ovoid diameters was employed depending upon the patient's anatomy. Tandem length varied between 4-6 cm and ovoid diameter between 2-3 cm. Packing was done to push away bladder and rectum from highest dose regions. Gauze soaked in povidone iodine preparation (Betadine, Purdue pharmaceuticals L.P Wilson, NC, USA) was used as packing material. For each patient a CT scan was taken using our departmental scanner (Philips Brilliance CT, Da Best, Netherlands). The scan parameters consisted of a large field-of-view pelvic protocol with a 3-mm-slice thickness/table index. The CT scans were obtained from the L3-L4 vertebral body to mid thigh region.

After imaging, the patient was shifted to HDR Brachytherapy (Varisource Ix, Palo Alto, CA, USA) room for treatment. Digital images were sent via Dicom to Brachyvision Treatment Planning System (TPS) version 7.3 (Varian, Palo Alto, CA, USA) through Varian ARIA (Varian, Palo Alto, CA, USA) network. The High Risk Clinical target volume (HR CTV) and Point A were defined on the reconstructed CT images. The high risk clinical target volume consisted of the cervical tumor and any extra cervical tumoral extention.. Normal tissues (OARs) included bladder and rectum. Two plans were created – one prescribing the dose to point A (conventional plan) and another prescribing the dose to the target volume / HRCTV (three dimensional volume plan). GEC-ESTRO working group guidelines were followed for contouring volumes and planning using CT-scan.

A fractional 100% dose was prescribed to point A in the conventional plan and to the HRCTV in the Three Dimensional CT plan. For both plans , the DVHs was computed for target volumes, the bladder and the rectum. The mean dose and the dose received by 90% of the target volume (D90) was compared for both the plans. For the organs at risk, the mean dose and the dose received by 0.1cc, 1cc and 2cc volume (D0.1cc, D1cc and D2cc respectively) was compared.

All patients received treatment according to the Three Dimensional Based CT planning.

D. Dose prescription:
Primary treatment incuded 45-50 Gy EBRT plus HDR Brachytherapy every week using Ir 192 isotope (7 Gy in 3 fractions to total of 21 Gy) along with concurrent weekly cisplation (40 mg/m2). Our goal was to achieve a total biologically equivalent dose (EBRT + IGBT) of around 80-90 Gy. Target coverage (D90) should equal 100% of prescription. OAR constraints included dose to the bladder ($D98_{EBRT}$ + $D2cc_{IGBT}$) less than 90Gy and rectum dose ($D98_{EBRT}$ + $D2cc_{IGBT}$) less than 75Gy.

E. Follow Up
Patients were advised to come for first follow up visit after 2 months of completing radiation therapy (RT), then every 3 months for one year, followed by every six months for one year and then a yearly follow up. In each follow up visit, a clinical examination was done to evaluate for response to treatment and to look for post RT residual disease. Pap smear (if residual disease present), renal function tests (Blood Urea and Serum Creatinine) for renal failure and finally Ultrasound (USG) abdomen and pelvis were advised if there was suspicion of urinary obstruction, pedal edema, lymphadenopathy or recurrence. X-ray chest, CT/MRI abdomen and pelvis, MRI of Brain and Bone Scan were done in symptomatic patients.

Radiation induced acute bladder and rectal morbidity were scored using RTOG Acute morbidity scoring criteria.

F. Statistical analysis:
For comparison of doses to the target and organs at risk, statistical analysis was performed using paired t test (windowstat version 9.2). A p value of less than 0.05 was considered as significant.

RESULTS:
A total of 30 patients were enrolled in the study and two plans were created for each patient (conventional point A plan and image guided brachytherapy plan). Mean age in the study was 50 years with range 36-81 years, and the commonest histology in the study was Squamous cell carcinoma. All patients in the study received weekly *cis*-diamminedichloroplatinum (CDDP) 40mg/m^2, with a minimum of 3 and a maximum 5 cycles, and with an average of 4 chemotherapies. Characteristics of the patients enrolled in the study are described in **Table 1.**

Dosimetric comparison of IGBT and Conventional plans
The HR CTV doses were calculated from the cumulative DVH in terms of mean and dose received by 90 percent of the target volume (D90). The doses to OARs were calculated from the cumulative DVH in terms of mean dose to the Bladder and Rectum and dose received by 0.1cc, 1cc and 2cc of the organ at risk volume. The equivalent dose at 2 Gy per fraction (EQD2) was calculated for HR CTV D90 and added to EBRT dose to obtain total dose to the HR CTV. The equivalent dose at 2 Gy per fraction was also calculated for Bladder and Rectum 2cc volumes and added to the EBRT Bladder and Rectum doses respectively. Image Guided Brachytherapy isodose distribution in axial view is showed in **Fig 1.**

Comparison of mean doses:
In terms of mean dose to the HR CTV, no statistically significant difference was found between the two techniques. However, there was a significant difference in terms of mean dose to the Bladder ($p = 0.004$) and Rectum ($p = 0.03$), the dose being lesser with Image Guided Brachytherapy planning as compared to Conventional Point A planning. The mean doses delivered to HR CTV, Bladder and Rectum are compared in **Table 2**.

Comparison of EQD2 doses:
In terms of total dose (EBRT + Brachytherapy EQD2 doses), there was a statistically significant difference between the two techniques. IGBT planning provided better coverage to the PTV ($p = 0.04$) and reduced doses to the Bladder ($p = 0.0003$) and Rectum ($p = 0.0007$). The comparison of EQD2 doses is described in **Table3**.

Comparison of 0.1cc, 1cc and 2cc OAR doses:
In terms of dose received by 0.1cc, 1cc and 2cc of the OARs, there was a significant reduction of doses by IGBT planning as compared to conventional planning **Table 4.**

Follow up :
At first follow-up (2 months after completion of treatment), clinical examination was done and only on clinical suspicion other diagnostics and blood tests were done. All 30 patients who completed the planned treatment had no loco-regional disease and were free of presenting clinical symptoms. Two patients had Grade I cystitis and 1 patient had Grade II cystitis.

At 5 months follow up, all 30 patients were available for analysis and had clinical examination and found to have no loco-regional disease. One patient complained of burning micturition (Grade I

cystitis) and was managed conservatively. One patient reported occasional bleeding P/R (Grade II proctitis) and was advised conservative management with change in diet and use of laxatives.

DISCUSSION :

Brachytherapy allows a high dose deposition to the primary tumor while minimizing the dose to adjacent normal organs. Thus, brachytherapy plays an important role in the treatment of cervical cancer. A key development for initiation of modern conformal planning techniques for brachytherapy represented the GEC-ESTRO release of guidelines for image-based brachytherapy in 2005/2006 which proposed three dimensional volume concepts based on modern imaging and dose volume histograms of target volume and organs at risks.[5,6] Since this advent the use of image-guided brachytherapy was tested and introduced in specialized centers. With 3D conformal planning, benefits in terms of reducing the dose to OARs and improving dose to the target could be demonstrated, [7] which was in concordance to the findings of the present study.

IGBT relies on solid scientific concepts allowing optimization of brachytherapy planning based on the tumor extent and the individual patient anatomy. Preliminary results suggest that compared to historic controls, IGBT may indeed improve local control and decrease late complications. Among 141 cervical cancer patients stage IB–IVA who had MRI-based IGRT according to GEC-ESTRO guidelines, local control was achieved in 134 patients (95%) at a median follow-up of 51 months [8] . Local recurrences occurred in 35% of patients with a large tumor at diagnosis (>5 cm) and at the time of the implant (>5 cm). Regression of the tumor was a good prognostic factor as patients with large tumor at diagnosis and significant regression (< 5 cm) during pelvic radiotherapy had a recurrence rate of 10.9%. There was a correlation between local control and the tumor dose for patients with large tumors. Local recurrence rate was 4 and 20% for HR-CTV D90 more than 87 and < 87 Gy respectively. An update of the study demonstrated a relationship between the dose to the rectum and late toxicities. Grade 2–4 rectal side effects occurred in 5, 10, and 20% of patients for rectal D2cc of 67, 78, and 90 Gy, respectively [9] . There was no significant correlation between bladder dose and late toxicities.

In the current study, we assessed the conventional brachytherapy plan based on dose prescribed to point A and the CT-based brachytherapy plan based on dose prescribed to target volume in patients with cervical cancer. CT-based treatment planning provided detailed anatomical data for both tumor and normal tissue volumes, and allowed for true 3D plan optimization. Dosimetric analysis showed statistically significant differences in favour of CT-based 3D optimized plans versus conventional planning, and indicated that dose levels to the bladder and rectum were substantially reduced.

The clinical impact of CT-based brachytherapy was reported by Tan et al. [10] with twenty-eight patients. All patients received EBRT followed by HDR brachytherapy (7*3) with CT-guided BT. Cervix, uterus and OARs were contoured according to GEC-ESTRO recommendations. For target, D90 and V100 were evaluated and for OARs, D2 cc were evaluated by EQD2. The 3-year cancer-specific survival was 81%, with a pelvic control rate of 96%. In 24 pts, the D90 equal to 74 Gy or more (alpha/beta = 10). The patients who had local recurrence had D90 of 63.8 Gy. Serious late morbidity was 14%. Seventeen patients had satisfactory OAR doses by standard loading pattern and 7 patients had to optimize to reduce risk of toxicity.

Our study demonstrated a clear advantage of CT based image-guided brachytherapy versus conventional planned brachytherapy showing significantly reduced doses for bladder ($p < 0.0003$; D2cc 82.11 versus 100.17 Gy EQD2 $\alpha/\beta 3$) and rectum ($p < 0.0007$; D2cc 73.41 versus 84.13 Gy EQD2 $\alpha/\beta 3$), and improved coverage of HR-CTV ($p = 0.04$; D90; 76.48 versus 74.13 Gy EQD2 $\alpha/\beta 10$). The present study showed no grade 3 or 4 acute side effects. Only grade 1 and 2 acute morbidity was registered.

Krishnatry et al. published 17 previously untreated patients with cervical cancer. [11] Brachytherapy using a MRI-compatible applicator followed by both CT and MRI were applied and compared. The HR-CTV and organs at risk (bladder, rectum, sigmoid and intestines) were contoured on CT using only clinical findings and on MRI using GEC-ESTRO guidelines. The volume and doses for tumor and organs at risk were evaluated using two-sided t-test. There is significant underestimation of tumor height and overestimation of the width ($p < 0.05$). However, there was no significant difference in V (100), D (90) and D (100) for high- and intermediate-risk clinical target volume in computed tomography versus magnetic resonance imaging. The volumes and doses to 0.1, 1 and 2 cc for organs at risk were also similar. They concluded that MRI is the gold standard for tumor delineation, but CT-based contouring can be used comfortably for delineation of organs at risk.

CONCLUSIONS :

Though our study had certain limitations of small sample size and short follow up, it yielded important conclusions. Image-based brachytherapy techniques allow us to precisely identify HR-CTV and OARs. Dose optimization results in adequate target coverage and reduces delivery of unacceptable high doses to OARs . DVHs of volume-based planning provide us with additional important information (D90, D0.1cc, D1 cc and D2cc) and help us to optimize the dose distribution in all target volumes and OARs. The preliminary findings in terms of acute toxicity were very promising as well. No tumor relapse was registered at 5 months follow-up.

FIG 1: Image Guided Brachytherapy Isodose Distribution Axial View

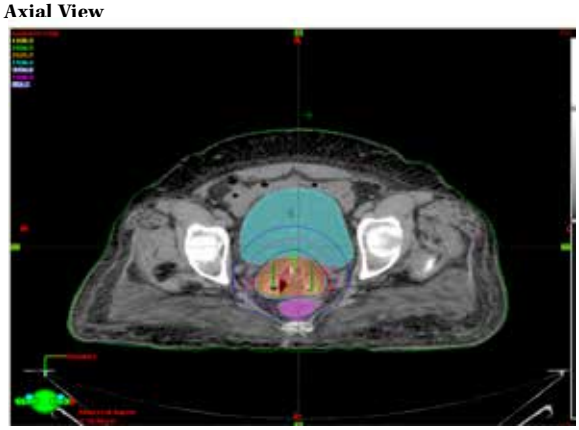

Table 1: Patient and treatment characteristics

AGE	
RANGE	36 – 81
MEDIAN	50
FIGO STAGE	
I B2	2
II A	2
II B	19
III B	7
PATHOLOGICAL GRADE	
WELL DIFFERENTIATED	3
MODERATELY DIFFERENTIATED	25
POORLY DIFFERENTIATED	2

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EBRT TECHNIQUE	
CONVENTIONAL	20
3DCRT	2
IMRT	8

Table 2. Comparision of mean doses (cGy)

	IGBT	CONVENTIONAL	P VALUE
PTV MEAN	4924.67	4560.03	0.086
BLADDER MEAN	891.37	1036.60	0.0045
RECTUM MEAN	830.77	909.63	0.0316

Table 3. Comparision of EQD2 doses (Gy)

	IGBT	CONVENTIONAL	P VALUE
PTV EQD_2 (EBRT D98 + BRACHY D90)	76.48	73.19	0.04
BLADDER EQD_2 (EBRT D2CC + BRACHY D2CC)	82.11	100.17	0.0003
RECTUM EQD_2 (EBRT D2CC + BRACHY D2CC)	73.41	84.13	0.0007

Table 4. Comparison of 0.1cc, 1cc and 2cc OAR doses

	IGBT	CONVENTIONAL
BLADDER		
D 0.1CC	2467.70	3174.67
D 1CC	2013.44	2505.60
D 2CC	1779.20	2275.03
RECTUM		
D 0.1CC	2248.44	2620.67
D 1CC	1799.17	2034.10
D 2CC	1453.94	1810.17

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