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RESEARCH ARTICLE

IMAGE BASED HDR BRACHYTHERAPY USING ULTRASOUND IN CARCINOMA OF THE CERVIX

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ABSTRACT

Introduction: This prospective study was done to determine the use and effectiveness of transabdominal ultrasound (TAUS) for intracavitary brachytherapy in carcinoma cervix.

Materials and Methods: 20 patients of carcinoma cervix of stage II and III, treated with chemoradiation and intracavitary brachytherapy were assessed. Patients received external beam radiotherapy (EBRT) on Linear Accelerator to a total dose of 50 Gy in 25 fractions along with weekly Cisplatin. HDR Brachytherapy three fractions 7Gy per fraction, 3 fractions. TAUS was done to ensure the tandem position and to obtain tandem to uterine surface measurements in the sagittal and transverse planes. Based on these, applicator geometry was reconstructed in PLATO. Two treatment plans were generated for each patient one based on the dose prescribed to point A and an ultrasound based target and graphical optimization was done to conform dose to uterine dimensions. Plans were optimized. Dosimetric parameters with regard to the dose received by the margin of the tumor volume, posterior wall of the urinary bladder and anterior rectal wall were compared for the two plans.

Results: 4(20%) patients required TAUS guided repositioning of applicators. There was a statistically significant difference between the two plans in point A dose (P=<0.001), ICRU 38 bladder point dose (P=0.001), and rectal points dose (P=<0.001). Local control was 95% at six months follow up.

Conclusions: Transabdominal ultrasound is a reasonably accurate, quick, accessible, and cost-effective method for conformal brachytherapy planning.

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INTRODUCTION

Carcinoma Cervix is the second most common malignancy in women worldwide, and it remains a leading cause of cancer related death in women in developing countries. The comprehensive global cancer statistics from International Agency for Research on Cancer indicated that gynaecological cancers accounted for 19% of the 5.1 million estimated new cancer cases, 2.9 million cancer deaths and 13 million 5-year prevalent cancer cases among women in the world in 2002, of which carcinoma Cervix accounted for 4,93,000 new cases and 2,73,000 deaths. More than 80% of cervical cancer was found to occur in developing countries (Sankarnarayanan, 2006). The carcinoma Cervix risk is 1% during the life of a woman living in a developed country, whereas the corresponding value for a woman living in a country without preventive programs is 5%. At our institute about 1/3rd of female out-patients constitute carcinoma cervix.

Brachytherapy: In the management of carcinoma cervix radiation plays an important role.

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Brachytherapy and chemoradiotherapy are essential in curing patients who have advanced cervix cancer (Tod and Meredith, 1938; Wilkinson and Ramachandran, 1989). The curative potential of radiation therapy in the management of Carcinoma Cervix is greatly dependent on the use of Intracavitary Brachytherapy (Gonçalves, 2010). Brachytherapy delivers an increased dose of radiation to the cervical tumor while sparing the surrounding normal tissues. This is achieved because of the steep dose fall-off associated with the radioactive sources used. Such organ-specific dose delivery is not possible with external-beam radiotherapy, including intensity-modulated radiotherapy or any of its variants, as organ motion limits their precision. Brachytherapy for cervix cancer has been used since the beginning of the 20th Century. Brachytherapy in cervical cancer is still widely based on 2D X-ray imaging with prescription of dose according to point 'A' and with limited individualization. The source loading and dose prescription to conventional point-A is not consistent with the individual tumor extent. Point A was originally described to represent the dose received is the area of paracervical triangle as the work of T.F.Todd showed that initial lesion of radiation necrosis of rectum was due to high dose effects in the paracervical region and not due to direct effects on rectum (Vistad *et al.,* 2006). So dose prescription to point A does not represent actual dose to

the tumor and it may result in either undercoverage of tumor extent or unnecessary dosage to surrounding normal tissues. Moreover this method provides information for several specified point doses defined by International Commission on Radiation Units and Measurements Report 38 (ICRU-38), such as at point A, the bladder point, the rectum point, but not the dose-volume information of targets or organs of interest (Vistad *et al.,* 2006). Another disadvantage is that point based brachytherapy could not exploit the advantage of 'optimization' which is a process of titration of doses between target and organs at risk in order to achieve optimal doses to tumor and organs at risk(because optimization could not be done if there is no target at all). Historically, applications have largely relied on standard insertion techniques, but less than ideal placements and difficult insertions have led many practitioners to use various imaging methods for confirmation of tandem placement. These include transabdominal ultrasound (TAUS), transvaginal ultrasound (US), transrectal ultrasound (TRUS), computed tomography(CT), magnetic resonance image(MRI) and surgical interventions such as laparotomy and laparoscopy. The emphasis has largely been on detecting uterine perforations and myometrial penetrations to avoid unnecessary acute physical side-effects of treatment such as bleeding, infection or abscess formation, pain and pelvic discomfort. Detection of perforation also minimizes the chances of radiation-induced complications to surrounding tissues such as enteritis, fistulas and necrosis. Among the imaging modalities ultrasound is easily accessible, cost effective, not time consuming and patient will not have an additional exposure to radiation. The ability to establish, in real time, the correlation of the tandem within the target organ and to successfully determine the size and shape of the uterus, in conjunction with the use of a high dose rate (HDR) stepping source treatment system, has influenced significantly the practice of BT.

Aims and Objectives

- To study ultrasound image based intra cavitary HDR brachytherapy planning in carcinoma cervix patients and to compare it with orthogonal radiographs based planning.
- To evaluate treatment related toxicity.

MATERIALS AND METHODS

This was a prospective study of 20 patients with carcinoma cervix stage IB-III, who were treated with external beam radiotherapy, intracavitary brachytherapy and chemotherapy with weekly Cisplatin. Following institutional ethics committee approval patients who fulfill the inclusion criteria were enrolled in the study. Patients were treated by external beam radiotherapy and intracavitary brachytherapy along with concurrent weekly cisplatin 40mg/m^2. Patient's demographic data, clinical history and social history were taken. After a through physical examination and pelvic examination, tissue for histopathological examination, chest radiograph PA view, ultrasound abdomen, complete blood picture, renal function tests and liver function tests were also done.

Data analysis

Demographic characteristics were described using frequency and percentages. Mean, SD were used to describe the results of level of quality in the sample by using SPSS 20.

Treatment

Patients received external beam radiotherapy on Linear Accelerator to a total dose of 50 Gy in 25 fractions 2Gy per fraction with mega voltage (6MV/15MV) energy photons and treatment position verification was done by taking portal image weekly during the treatment period. Concurrent chemotherapy with Inj. Cisplatin 40mg per m^2 was given weekly (Fig.1). After completion of 15 fractions of external beam radiotherapy, patient was assessed by pelvic examination for feasibility of intracavitary brachytherapy (BT). The BT protocol was three fractions of High Dose Rate brachytherapy 7Gy per fraction, 3 fractions to a total dose of 21 Gy.

Brachytherapy application procedure

Procedure was done in brachytherapy operation theatre. Patients were sedated using intra venous Promethazine and Pentazocine. Patient was positioned in lithotomy position for applicator insertion. Pelvic examination was done to assess the response and to determine the size of vaginal ovoid. A Foley's catheter inserted, the balloon was filled with 7 ml diluted contrast and positioned against the bladder neck. The uterus was sounded to ascertain the required length of the tandem and the cervical canal is dilated if necessary. The selected tandem and the ovoids were inserted. Vaginal packing was done using gauze soaked radio opaque solution diluted with normal saline and radio opaque rectal marker was placed.

Imaging: X-ray and ULTRASOUND

Following applicator placement and vaginal packing, orthogonal radiographs in both Antero Posterior and Right Lateral view were taken in the supine position. These radiographs were transferred to treatment planning system (PLATO) and used for reconstruction of the applicator position and geometry (Fig 2). Around 400ml normal saline infused into bladder and transabdominal ultrasound was done to ensure that the tandem is centered within the uterus and to obtain tandem to uterine surface measurements in the sagittal and transverse planes(fig 7 & 8). These were plotted on representative graph (appendix III). Based on these target volume anatomy of the uterus and the applicator geometry reconstructed in the PLATO planning system. Treatment plans were generated for the orthoradiograph and ultrasound based target and graphical optimization was done in the US – based plan to conform the dose to uterine dimensions. The following parameters were noted for comparison between the orthoradiograph and US based plans.

- Dose to point A.
- Coverage of target volume.
- Dose to bladder and rectum.

In a similar way all the 3 fractions were planned based on the US-derived dimensions of the uterus and cervix. Plan was optimized to deliver 100% dose to the target volume and to prescribe 100% dose to tumor volume simultaneously to achieve acceptable doses to the urinary bladder and rectum according to ICRU 38 recommendations. Treatment was delivered to the volume derived from ultrasound image based plan, and the dosimetric parameters with regard to the dose received by the margin of the tumor volume, posterior wall of the urinary bladder and anterior rectal wall are compared for the two plans.

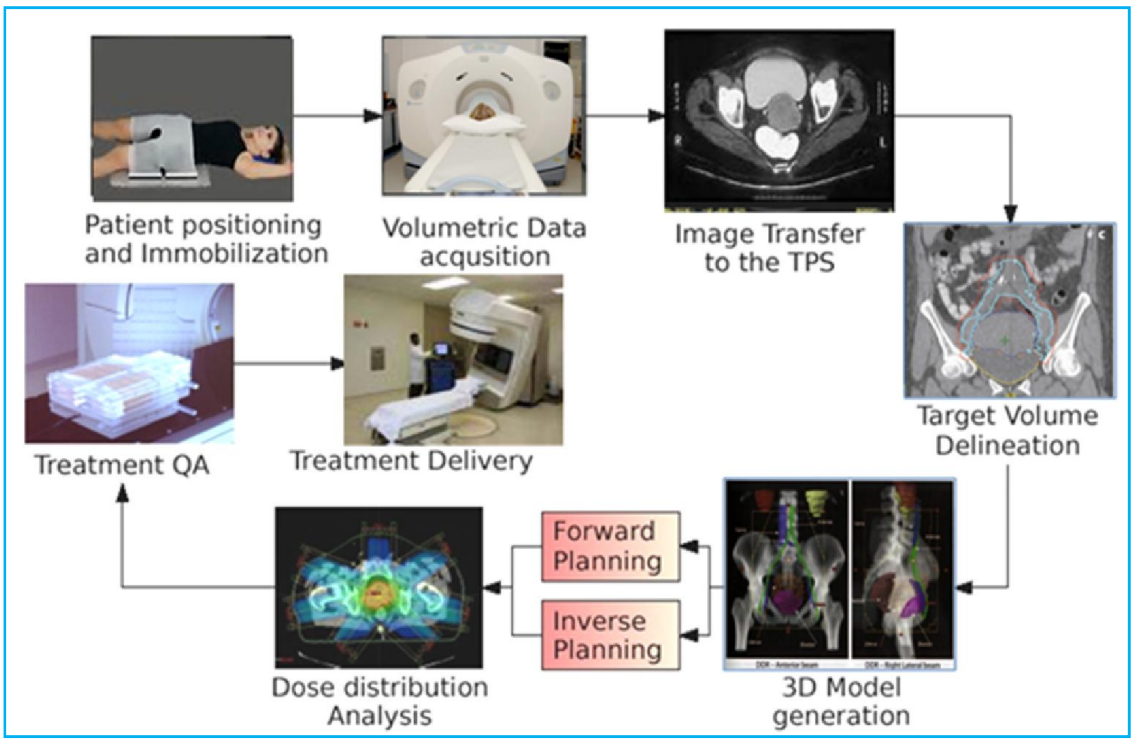

Figure 1. EBRT workflow

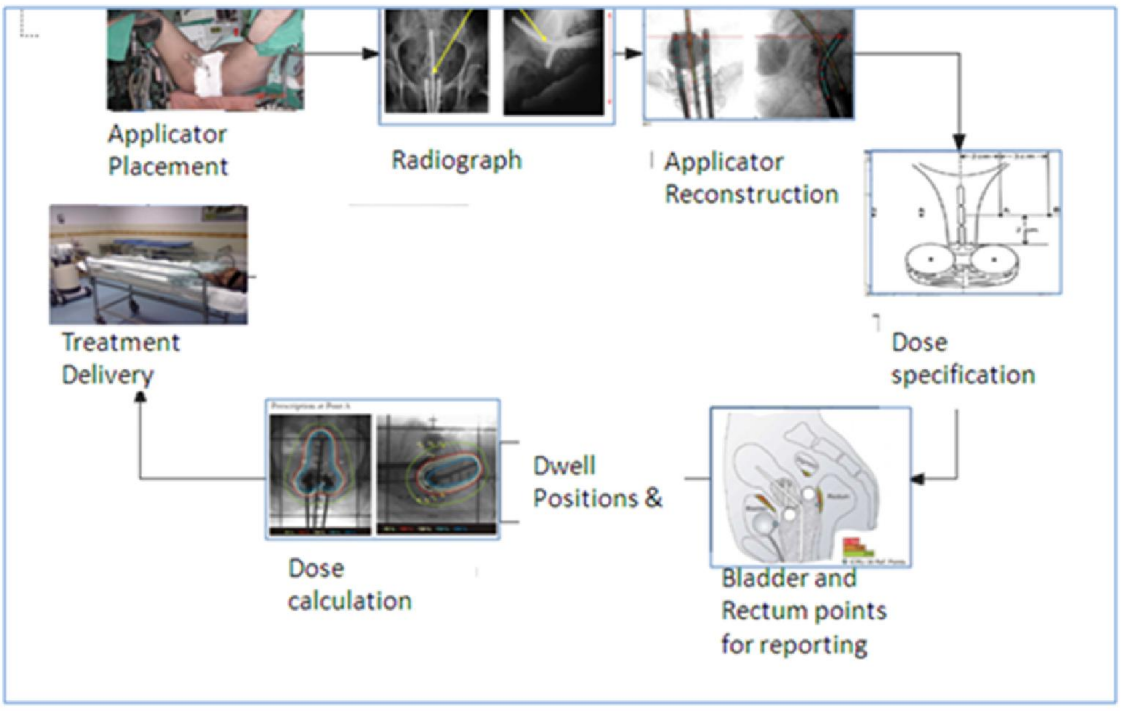

Figure 2. Brachy therapy work flow

Observations and results

Twenty patients were included in this study. Among 20 them 10 were stage III, eight were stage II and two patients were stage IB. All patients received EBRT with 50Gy, in 25 fractions, five days in a week. Standard four-field box technique was used in all patients. All patients received chemotherapy with weekly Cisplatin 40mg/m^2 and 18 of them received at least 4 cycles. Table-1 shows the patient and tumor characteristics and treatment received by the twenty patients included in this study. In standard 2D plan, point 'A' was normalized to receive 7 Gy with standard loading pattern at our institute.

Treatment plans were generated for the orthoradiograph and ultrasound based volumes, graphical optimization was done to conform the dose to uterine dimensions. The following parameters were noted for comparison using the ultrasound based measurements for reference.

- Dose to point A.
- Coverage of target volume.
- Dose to bladder and rectum.

Doses for three fractions were averaged and compared. In 4(20%) of cases central tandem was not in uterine cavity, and

required transabdominal ultrasound guidance to keep the applicator in uterine canal. Doses to Point A, ICRU 38 bladder and rectal points were compared between point A plan and US plan. There was a statistically significant difference between both the plans in Point A dose (P=<0.001), ICRU 38 bladder point dose (P=0.001), and rectal points (P=<0.001). Local control was 95% at six months follow up. Acute bowel and urinary bladder toxicity (G3, G4) was <2%.

DISCUSSION

In the management of carcinoma cervix radiation plays a dominant role. Brachytherapy and chemo-radiotherapy are essential in curing patients who have advanced Carcinoma cervix. The curative potential of radiation therapy in the management of Carcinoma Cervix is greatly dependent on the use of Intracavitary Brachytherapy which delivers an increased dose of radiation to the cervical tumor while sparing the surrounding normal tissues. Brachytherapy in cervical cancer is still widely based on 2D X-ray imaging with prescription of dose according to point A and with limited individualization. The source loading and dose prescription to conventional point-A is not consistent with the individual tumor extent. Point A was originally described to represent the dose received in the area of paracervical triangle as the work of T.F.Todd showed that initial lesion of radiation necrosis of rectum was due to high dose effects in the paracervical region and not due to direct effects on rectum. So dose prescription to point A does not represent actual dose to the tumor and it may result in either undercoverage of tumor extent or unnecessary dosage to surrounding normal tissues. Unlike External Beam Radiotherapy, volume based prescription was recommended in ICRU Report 38 in 1985. It was described to prescribe to 60Gy isodose surface volume, which is a cumulative dose received by External Radiation and intracavity treatment. This was also calculated using orthogonal films. As the tumour cannot be seen on radiographs, the actual tumour volume could not be correlated to the treatment volume. So, these were not followed at most of the centres. It was also recommended in ICRU 38 dose to Organs at risk bladder and rectum point doses. These point doses were also calculated on orthogonal pelvic radiograph images and did not correlate to actual OAR doses. Deshpande et al compared CT-based dosimetry with International Commission on Radiation Units and Measurements (ICRU 38) bladder and rectum reference points in patients of carcinoma of uterine cervix treated with intracavitary brachytherapy. In that study mean $2cm^3$ doses of rectum and bladder were found to be 1.11 (+/-0.2) and 1.56 (+/-0.6) times the mean ICRU reference points respectively. This dosimteric study suggested that ICRU rectal point dose correlates well with maximum rectal dose, while ICRU bladder point underestimates the maximum bladder dose. Also now we know that sigmoid colon is an important OAR in intracavitary treatment but it was not considered as an OAR.

Another disadvantage is that point based brachytherapy could not exploit the advantage of 'optimization' which is a process of iteration of doses between target and organs at risk in order to achieve optimal doses to tumor and organs at risk (because optimization could not be done if there is no target seen). With the development of computed tomography (CT) and MRI-compatible HDR applicators, image-guided 3D brachytherapy became possible. With MRI it became possible to visualize the extent of tumor. The Image-Guided Brachytherapy Working Group (IGBWG) from the USA was the first to publish proposed guidelines. This was followed by the Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) Working Group publications. Essentially, the two groups had similar recommendations with only a few disparities, mainly in the nomenclature used. It has been subsequently agreed upon by the two groups that further clinical and research work will be based on the GEC-ESTRO recommendations. The GEC-ESTRO recommendations aimed to define different treatment volumes and parameters mainly based on MRI findings at diagnosis and at each brachytherapy treatment. With the introduction of MR based target concepts it is possible to move from prescription at point A to prescription of dose to a 3D target volume in terms of dose volume histogram (DVH) parameters. Furthermore dose optimization can be performed based on MR image guidance, whereby standard loading patterns are modified to individualized dose prescriptions which is tailored to target and organs at risk at the time of brachytherapy. Based on the clinical experience collected so far, the MRI-based ICBT approach is expected to have a major impact on the clinical outcome with a concomitant decrease in the rates of both local failure and morbidity. Traditionally dose has been prescribed to point 'A' which was designated to treat the tumor before the CT era. Now Image based ICBT has emerged as a new modality of delivering brachytherapy for the treatment of uterine cervical cancer. MRI provides superior soft tissue resolution and is the best imaging modality for depicting cervical tumor size and extent compared with the ultrasonography and CT. Nag et al., introduced image based ICBT. The American Brachytherapy Society and GEC – ESTRO published guidelines (7, 8 & 9) emphasizing the importance of CTV based dose prescription rather than dose prescription to point A. Potter et al reported their single institute's result that showed that MR image-based ICBT with or without Interstitial brachytherapy showed better results and fewer complications than previous treatment methods. They compared their treatment results between two treatment periods. In the period 1998-2000 they treated patients without the help of an MRI and between 2001- 2003 they used MRI treatment planning. The local control rate for tumors larger than 5cm improved from 71% (1998-2000) to 90% (2001-2003).

Ultrasound based intracavitary brachytherapy

Historically, applications have largely relied on standard insertion techniques, but less than ideal placements and difficult insertions have led many practitioners to use various imaging methods for confirmation of tandem placement. These include transabdominal ultrasound (TAUS), transvaginal ultrasound (US), transrectal ultrasound(TRUS), computed tomography(CT), magnetic resonance image(MRI) and surgical interventions such as laparotomy and laparoscopy. The emphasis has largely been on detecting uterine perforations and myometrial penetrations to avoid unnecessary acute physical side-effects of treatment such as bleeding, infection or abscess formation, pain and pelvic discomfort. Detection of perforation also minimizes the chances of radiation-induced complications to surrounding tissues such as enteritis, fistulas and necrosis. Among the imaging modalities ultrasound is easily accessible, cost effective, not time consuming and patient will not have an additional exposure to radiation. The ability to establish, in real time, the correlation of the tandem within the target organ and to successfully determine the size and shape of the uterus, in conjunction with

the use of a high dose rate (HDR) stepping source treatment system, has influenced significantly the practice of BT. In the process of moving from 2D (radiograph and standard loading) to USG based target definition and target optimization it is essential to relate classic dose prescription and standard loading patterns to new routes of 3D dose prescription and dose optimization. A major advantage to be expected from Image based ICBT seems to be that, through more precise 3D assessment of organ related dose volume relationships, adverse side effects and local failure may become better predictable and therefore avoidable. As shown in this study and other studies, classical point dose 'A' assessment is associated with considerable uncertainties. This may be part of the explanation that has been difficult to assess dose-effect relationships by using point doses- in particular regarding point 'A' and correlation with local control. The limitations of the present study are that it is a non randomized prospective study that includes small number of patients. However this study was a learning curve for Image based Brachytherapy and future studies can be done by increasing the tumor dose as it is now possible to keep the doses to the OAR within the constraints.

Summary

This was a prospective study of Ultrasound Image based brachytherapy in carcinoma cervix comparing various parameters including Dose to point A, Coverage of target volume and dose to bladder and rectum in standard point 'A' based plan versus ultrasound image based optimized plan. Twenty patients diagnosed cases Squamous Cell Carcinoma of Cervix suitable for radical Radiation treatment were enrolled after written consent. After routine workup protocol of the Department, a diagrammatic depiction of the clinical topography of the tumour was done on a prescribed format. All patients received External beam radiotherapy to a dose of 50Gy in 25 fractions, in 5 weeks with concurrent Chemotherapy with 4-5 cycles of Inj. Cisplatin 40mg/m^2 and three sessions of Intracavitary HDR Brachytherapy application under short anesthesia. Before intracavitary application all patients were examined locally for the tumor extent under anesthesia and topographical representation of the same was done again on the standard diagram. Application was done with suitable applicators then orthogonal radiographs were taken. Ultra sound guidance required in few cases for the placement of applicator. Transabdominal ultrasonography image based treatment volume defined. Conventional radiograph based plan developed. Plan was optimized to deliver 100% dose to the target volume and to prescribe 100% dose to tumor volume simultaneously to achieve acceptable doses to the urinary bladder and rectum according to ICRU 38 recommendations. Treatment was delivered to the volume derived from ultrasound image based plan, and the dosimetric parameters with regard to the dose received by the margin of the tumor volume, posterior wall of the urinary bladder and anterior rectal wall are compared for the two plans. It was seen that

- There was a statistically significant difference between both the plans in Point A dose (P=<0.001),
- ICRU 38 bladder point dose (P=0.001),
- ICRU 38 rectal points (P=<0.001).

Conclusions

- This study showed that discrepancies between point doses and DVH parameters support the use of 3D image based dose planning and use of DVH parameters for better assessment of both target and OAR dose in BT of cervical cancer. Furthermore, TAUS based ICBT significantly improves the therapeutic ratio, by decreasing OAR dose in small tumors and improving target dose in large tumors.
- Advantages of TAUS image based ICBT planning are low cost imaging, an accurate applicator placement, no additional radiation dose exposure, less overall planning time and treatment delivery time and as it was having good correlation with MRI based measurements seen in previous studies, therefore should be recommended.

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