

Original Research Article

# A comparative study of Conventional and CT based planning of Target volumes and organs at risk in Intra cavitory brachytherapy for Carcinoma of cervix

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## Abstract

**Introduction:** Cervical cancer is the third most common malignancy in women worldwide, and it remains the leading cause of cancer related deaths in women in developing countries. In the management of cervical cancer, both intracavitary brachytherapy (ICBT) and external radiotherapy (ERT) are essential as they deliver a high dose to the primary tumor and low doses to adjacent organ. The dose can be delivered either by conventional orthogonal radiograph mapping or by the 3-dimensional computed tomography mapping. In the present study, we have compared both the techniques.

**Aim and objectives:** To compare intracavitary brachytherapy (ICBT) planning methods for cervical cancer based on orthogonal radiographs (conventional plan) and computed tomography sections (CT plan).

**Materials and methods:** This was a prospective study, conducted in the department of Radiotherapy, MNJ Institute of Oncology and Regional Cancer Centre, over a period of two years from November 2012 to November 2014. The study consisted of total 25 registered patients having confirmed diagnosis of Squamous cell carcinoma of cervix. All the patients underwent conventional and CT planning for brachytherapy. One arm received the conventional plan of radiotherapy while the other arm received computed tomography (CT) based plan.

**Results:** The patient age ranged from 35 to 65 years. The mean age was 47 years. The results of the study demonstrates that CT-guided brachytherapy planning is superior in terms of both conformity of target coverage and evaluation of OARs .Although this superiority was clear for small GTVs, for large GTVs both the conventional and CT-Plans had the drawbacks of inadequate target coverage and /or excessive radiation doses to normal organs.

**Conclusions:** The conventional plan with the point A calculation relies on reference points on orthogonal films ,not tumor volumes defined on CT, which may cause underestimation of tumor doses. Likewise, the calculation of rectum and bladder doses made with ICRU reference points, not with bladder and rectal volumes may not reflect the actual organ doses. To overcome such problems, 3D CT-guided brachytherapy treatment planning is recommended.

## Key words

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Cervical cancer, Brachytherapy, Conventional, 3D CT guided.

## Introduction

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Cervical cancer is the third most common malignancy in women worldwide, and it remains the leading cause of cancer related deaths in women in developing countries. About 7.5% of the women in general population are estimated to harbor cervical HPV infection at a given time, and 82.5% of invasive cervical cancers are attributed to HPV 16 or 18 [1]. At our institute (MNJ Institute of Oncology and Regional Cancer Centre) about 30% - 55% of female out-patients constitute carcinoma cervix.

Margaret Cleaves was the first person to use intrauterine radium to treat malignancy after the discovery of radium by Madame Curie [2]. Since then advances in radiotherapy have resulted in better loco regional control and increase in disease free survival.

Over the recent past, high dose rate intracavitary (HDR) brachytherapy as compared to low dose rate brachytherapy (LDR) has increased considerably as it has a short treatment time, lesser cost and hospital time, and increased patient comfort [3].

In the management of cervical cancer, both intracavitary brachytherapy (ICBT) and external radiotherapy (ERT) are essential as they deliver a high dose to the primary tumor and low doses to adjacent organs. This helps in better local control

and patient survival without increase in toxicity [4].

Quantification of doses received by bladder and rectum is very important as they are the dose-limiting structures in ICA and at the same time it is very difficult to quantify them. Conventionally, orthogonal radiographs are used to map the doses for the ICA with the help of ICRU (International Commission On Radiation Units and Measurement) reference points which underestimate doses received by the rectum and bladder. Three-dimensional image-based brachytherapy planning helps in the accurate quantification of doses received by various volumes of surrounding critical structures. In order to document, validate and compare volume-based doses to rectum and bladder with the conventional standard ICRU 38 rectal and bladder points, this dosimetric study was undertaken.

## Aim and objectives

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To compare intracavitary brachytherapy (ICBT) planning methods for cervical cancer based on orthogonal radiographs (conventional plan) and CT sections (CT plan). The comparison was focused on target volume coverage and dose volume analysis of organs at risk (OAR), by representing point doses defined by the International Commission on Radiation Units and Measurement (ICRU) and dose volume histograms (DVH) from 3D planning.

## **Materials and methods**

This was a prospective study, conducted in the department of Radiotherapy, MNJ Institute of Oncology and Regional Cancer Centre, over a period of two years from November 2012 to November 2014.

The study consisted of total 25 registered patients having confirmed diagnosis of Squamous cell carcinoma of cervix. All the patients underwent conventional and CT planning for brachytherapy. One arm received the conventional plan of radiotherapy while the other arm received computed tomography (CT) based plan.

### **Patient selection**

**Inclusion criteria:** Age less than 70 years, Histological confirmation by biopsy: Squamous Cell carcinoma, ECOG performance status < 2, Stage IB to IIIB, No extra para-aortic lymphadenopathy, Hemoglobin >8 gm%., Complete blood picture, renal function tests, liver function tests, within normal limits.

All the patients having less than 8 gm% of Hemoglobin were given transfusion to raise the hemoglobin to more than 8 gm% prior to radiation treatment.

**Exclusion criteria:** Age more than 70 years, other histological variants of cervical cancer, ECOG performance status > 2, Stage IV, previously treated cases and other co-morbid conditions

All patients were given a course of antibiotics before starting therapy.

Pre-treatment evaluation included detailed history, complete general, local and systemic examination. Investigations included complete Blood picture, renal function tests, liver function tests, screening for HIV/HBS Ag, biopsy from the primary tumor (edge of gross tumor or 4 quadrants), X-ray Chest (PA view), and ultrasound abdomen and pelvis.

CT perfusion scan of abdomen and pelvis and MRI/PET CT were optional. All investigations

within the normal limits were a prerequisite. Informed written consent was taken from all the subjects.

### **Protocol design**

Stage IB to IIIB, Squamous Cell Carcinoma of cervix

Arm A: A total of 25 conventional plans of 25 patients

EBRT dose of 50 Gy in 200cGy/Fr. 5 # / week over 5 weeks and HDR-ICA on 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> week (depending on local assessment) 3Fr. 700cGy per fraction to point A.

Chemotherapy: Cisplatin weekly (40 mg/m<sup>2</sup>/week)

The HDR plan was done by conventional plan. (Chemotherapy and EBRT were not given on the day of ICA)

Arm B: A total of 25 CT plans of same 25 patients

Radiation: Pelvic RT 50-50.4 Gy 1.8- 2 Gy/Fr. 5 # / week over 5 weeks

Followed by HDR- ICR 3Fr. 700 cGy/Fr. The HDR plan was done by CT simulation.

Chemotherapy: Cisplatin weekly (40 mg/m<sup>2</sup>/week) on Day 1, 8, 15 and 22.

### **EBRT Delivery**

Linac unit external beam radiation was used to deliver 100cm SAD. Parallel opposed anterior and posterior portal (or) Box tech were used.

### **Radiotherapy Technique**

Simulation

Position: Supine (comfortable and easily reproducible) or prone (reduces bowel toxicity) or with belly board

Bladder was full so as to reduce dose to the small intestine.

CTV (Clinical target volume): Gross disease(if present), utero-sacral ligament, uterus, cervix, vagina with sufficient margin, parametrial tissue, pelvic lymph nodes including internal, external and common iliac lymph nodes, para aortic lymph nodes ( selected cases), pre-sacral nodes, tumor bed ( post op)

Beam energy- 15 MV photon

### **Conventional Method**

Vaginal tube or barium to delineate extent of tumor

Portals: Two portals AP / PA or four fields box technique by AP, PA and 2 laterals

Superior: L4 - L5 interspace

Inferior: Inferior border of obturator foramen or if there was a vaginal extension, 3cm clear margin below lower extent of the lesion (if lower vagina is involved, inguinal nodes should be treated.

Lateral: 1.5 cm lateral to the bony pelvis

Anterior: Pubic symphysis

Posterior: Designed to cover at least 50% of the rectum in stage IB or extend up to sacral hollow in patients with advanced tumors.

All portals were treated at each session and dose was calculated at mid plane.

### **Brachytherapy**

ICA Procedure:

- Bowel preparation
- General anesthesia /sedation.
- Perineum was cleaned
- Foleys catheterization was done with 7ml of 1:2 diluted urografin inflated in balloon.
- Cervical canal was found by gentle probing and dilated, gold seed marker was placed into healthy tissue in cervix or upper vagina, for checking radiographically on subsequent treatment
- Uterine canal length was measured with sound and intrauterine tube was inserted.
- Ovoids were inserted
- Anterior and posterior packing was done
- Rectal tube was inserted
- Patients were treated with HDR brachytherapy
- Dose fractionation: 700 cGy / Fr

### **Conventional Plan:**

All patients had traditional radiography based treatment plans. The radiation source position, point A (left and right), point B (left and right), and ICRU reference bladder and rectal points were inserted in the planning system using

orthogonal radiographic films obtained with metallic dummy markers inserted inside the applicator. The ICRU bladder reference point was identified using a Foley catheter, with the balloon filled with the 7.0 ml of contrast material. The rectal point was defined as 5mm behind the posterior vaginal wall (ICRU reference point). The 7 Gy dose was optimized to point A, during conventional planning the doses to point A, bladder and rectum were calculated. The radiography-based planning provides dimensions and doses only at selected points.

### **3D CT Planning**

A CT scan with 2.5 -mm slice thickness through the pelvis was performed for each patient with the CT compatible applicator in place. All CT slices were transferred, via a hospital network, to the treatment planning system before a physician contoured the target volume and OARS on each slice of the CT scan. Dwell positions inside of the uterine tandem and ovoids were identified automatically from CT images using the planning system. The dose was optimized to target the Gross tumor volume (GTV) and was prescribed 7 Gy. Delineation of the GTV was performed based on the CT information at the time of the brachytherapy and supported by clinical and radiographic findings, as recommended by 'Image -guided Brachytherapy Working Group.' The Working group proposes that the primary GTV be defined through imaging plus any clinically visualized or palpable tumor extensions. A safety margin for the students's t test was performed for comparison of GTV, rectum, bladder, doses between groups. A comparison of the conventional plan and CT-plan was performed using the Wilcoxon signed -ranks test for all doses. p values less than 0.05 were considered statistically significant.

### **Plan Evaluation**

Point A: 100% dose

Bladder Dose: Bladder dose to 90% of point A.

Total bladder dose below 80 Gy

(LDR equivalent at 50 cGy/hr) 65-75% of point A for HDR

Rectal dose: Total rectal dose below 75 Gy 55-65% of point A for HDR.

## Results

In this prospective comparative study of total 25 conventional plans on arm A and 25 CT-based ICBT plans on arm B of same 25 patients with squamous cell carcinoma of cervix, the following observations were made.

Arm A -25 conventional plans

Arm B -25 CT-plans

All the patients were prescribed for 700 cGy HDR per fraction. Gamma med applicator was applied for all patients.

For Conventional plans ICRU point A dose, mean dose of bladder, mean dose of rectum were calculated.

For CT- plans, target volume coverage, mean dose of bladder, D2cc (dose to 2cc volume of tissue) of bladder, mean dose of rectum, and D2cc of rectum were calculated.

Target volume coverage--

There was not much difference in target volume receiving doses in comparison of CT- plans and conventional plans.

The mean ICRU dose of bladder in conventional plans was compared with D2cc of bladder of the CT plan, and mean ICRU dose of rectum in conventional plans was compared with D2cc of rectum in the CT plan.

The patient age ranged from 35 to 65 years. The mean age was 47 years. Tumor stage was evaluated according to the (FIGO) classification. 13 patients (52 %) had stage II B, 12 (48 %) had stage III B. The plans were categorized into group I (GTV<50cc) and group II (GTV>50cc). When the dose was prescribed to point A, the mean percentage of 7Gy to point A was 100% in conventional plans relying on the reference point and not on the tumor volume. In CT Plans for group I and II the coverage was 90-95 %, and 85-90 % respectively. That means, the target volume coverage was inversely related to the volume of the target and the extension of the tumor. In patients with larger tumors or tumors

extending to the vagina or parametrium, the 7Gy isodose line was more likely to not fully cover the GTV obtained from CT.

The mean bladder dose of conventional 25 plans was 276.64cGy and the mean D2cc of 25 CT-plans was 304.16cGy. The mean difference was 27.52cGy and the p value was 0.007 which was statistically significant.

The mean rectal dose of conventional 25 plans was 255.80cGy. The mean D2cc rectal dose of 25 CT plans was 295.36cGy. The difference 2 means was 39.560cGy. The p value was 0.018 which was significant.

When the study compared in 2 groups according to GTV volume the difference in the bladder doses in Group I were more significant. (p value 0.005)

When the study compared the mean doses of bladder and rectum, the mean dose of bladder was 276.640cGy and the mean dose of rectum was 255.800cGy in conventional plan which were more than mean dose of bladder 252.800cGy and the mean dose of rectum was 202.200cGy in CT – plans (**Table – 1, 2, 3**).

The results of the study demonstrate that CT-guided brachytherapy planning is superior in terms of both conformity of target coverage and evaluation of OARs. Although this superiority was clear for small GTVs, for large GTVs both the conventional and CT-Plans had the drawbacks of inadequate target coverage and/or excessive radiation doses to normal organs.

## Discussion

In India, carcinoma of uterine cervix is the most common malignancy among women and it is the leading cause of cancer related deaths accounting for 26% of all cancer deaths in India [1].

At MNJ Institute of Oncology and Regional Cancer Centre, around 30 – 40% of newly registered cases are of cervical cancer. This study

was mainly done with an intention to compare intracavitary brachytherapy (ICBT) planning methods for cervical cancer, based on orthogonal radiographs (conventional plan ) and CT sections (CT plan); the comparison focused on target volume coverage and dose volume analysis of organs at risk (OARs).

**Table – 1:** Comparison of conventional and CT planned D2cc doses of bladder and rectum.

Plan CT/Conventional	cGy	Paired t test	Probability	Wilcoxon matched pair rank test	Probability
CT- D2cc bladder dose	304.16				
Conventional	276.64				
Difference	27.52	2.928	0.007	24	0
CT- D2cc rectal dose	295.36				
Conventional	255.80				
Difference	39.560	2.551	0.018	22.00	0

**Table – 2:** Conventional and CT planned D2cc bladder and rectal doses based on gross tumor volume groups.

Group I (n=13)	cGy	Paired t test	Probability	Wilcoxon matched pair rank test	Probability
CT- D2cc bladder dose	350.923				
Conventional	310.077				
Difference	40.846	3.474	0.005	0	0
CT- D2cc rectal dose	295.385				
Conventional	257.692				
Difference	37.692	2.036	0.064	0	0
Group II (n=12)					
CT- D2cc bladder dose	253.5				
Conventional	240.417				
Difference	13.083	0.921	0.377	12	0.017
CT- D2cc rectal dose	295.333				
Conventional	253.75				
Difference	41.583	1.587	0.141	10	0.01

CT compatible Gamma med applicators were used during ICBT application. All patients underwent both conventional and 3D planning. Every attempt was made to keep the applicator in position even during the conventional and CT planning procedures.

The point A ICRU dose, mean rectum and bladder doses were calculated from the

conventional plans. For the comparison of target volume coverage, the point A dose from the conventional plan, GTV volume in CT plan and % of target volume coverage with prescribed dose from the CT plan were calculated. When the dose 7Gy prescribed to point A in conventional plan, the mean % of dose at point A was 100% as conventional plans relies on reference point not on the tumor volume.

**Table – 3:** Comparison of mean doses of bladder and rectum on conventional and CT plans.

Plan/ Tissue	cGy	Paired t test	Probability	Wilcoxon matched pair rank test	Probability
Conventional mean bladder dose	276.6				
CT planned mean bladder dose	252.8				
Difference	23.84	3.813	0.001	34.5	0
Conventional mean rectal dose	255.8				
CT planned mean rectal dose	202.2				
Difference	53.6	5.688	0	14	0

Whereas, in CT plan –when the dose 7Gy prescribed to GTV, with in the 7 Gy isodose level, the target volume coverage was 85-95%.The target volume coverage was inversely related to the volume of the target and extension of the tumor. For evaluating the maximum doses to OARs, the dose to a clinically significant volume is used: that clinically significant volume can be defined as the volume exposed to a minimum dose in the part of the OAR that receives the highest dose .Several investigators have compared the dose volume based on either the exterior organ contour or only the organ wall, for the bladder and rectum. To evaluate organ wall dose correctly, the volume 2cc is considered, because the D2 computed for the external contour are almost the same as the D2 to

the organ wall. Also, this 2.0cc volume of tissue in the highest dose region is probably more clinically relevant. From the CT plan the D2cc of bladder and rectum and mean doses of bladder and rectum were calculated. The D 2cc rectum and bladder doses of the CT plan were found to be greater than the corresponding ICRU reference doses. The mean doses of bladder and rectum of CT-plans were less than conventional plans.

Kapp, et al. [5] analyzed 331 patients with gynecologic tumors to evaluate the dose to normal tissues. They found that CT-based dosimetry showed higher doses to bladder and rectum as compared to the orthogonal films and their findings are in contrast to our findings.

Potter, et al. [6] reported results in 189 patients treated with HDR brachytherapy and EBRT. They concluded that HDR brachytherapy combined with EBRT is an excellent method if sufficient radiation doses and volumes are applied to the target tissue. They further recommended the using MRI guided plan for the same.

CT-based clinical outcomes were reported by the Adenbrooks Hospital. According to Tan, et al. [7], CT based tandem-ring HDR brachytherapy technique tailored to individual patient, improved the local control of the disease very well. They also observed that there was no significant increase in the related toxicity.

Fellner, et al. [8] compared treatment planning for cervical carcinoma based on CT sections and 3D dose Computations, and when these techniques were not available, dose evaluations based on orthogonal radiographs. They concluded that these different methods addressing the transfer from point doses to volumes for planning the treatment are feasible and practical for the treatment of cervical carcinoma in brachytherapy.

Wanderas, et al. [9] reviewed data from 19 patients (72 fractions) retrospectively. In their study, Standard library plans were compared to individually optimized plans using a Fletcher HDR applicator. For standard treatment planning, the tolerance dose limits were exceeded in the bladder, rectum and sigmoid in 26%, 4% and 15% of the plans, respectively. This was observed most often for the smallest target volumes.

Eich, et al. [10] in 11 applications of HDR brachytherapy for cervical carcinoma, calculated doses to ICRU points on orthogonal radiographs, and the doses at rectum reference points were compared with in vivo measurements. The in vivo measurements were 1.5 Gy below the doses determined for the ICRU rectum reference point. The advantage of in vivo dosimetry is the possibility to determine rectal dose during

radiation. The advantages of computer –aided planning at ICRU reference points are that calculations are available before radiation and they can be taken into account for treatment planning.

Patil, et al. [11] found significant correlation between ICRU point doses to the bladder and rectum; and volumetric doses. Their study concludes that whenever volumetric doses are to be given, it is important to have prior information about volumetric imaging.

Pelloski, et al. [12] compared CT -based volumetric calculations and ICRU reference point radiation doses in 60 patients with cervical cancer treated with LDR brachytherapy. Of 118 insertions performed, 93 were evaluated, and the minimal doses delivered to the 2 or 3 cm of bladder or rectum (DBV2 and DRV2, respectively) were determined on a dose - volume histogram (DVH). They concluded that the ICRU dose was a reasonable surrogate for the DRV2 but not for the DBV2. Furthermore, these calculations may not be applicable to other treatment guidelines or intracavitary applicators.

Brachytherapy treatment based on three-dimensional imaging gives better tumor definition and helps delivery of radiation to the precise location. This reduces the dose to the normal tissues and also the associated toxicity. In the present day practice, HDR is being used more frequently. This requires correct placement of the applicator and also the precise location of the normal tissue. The point-based radiographic dosimetry has limited utility in the presence of 3 D imaging techniques [13, 14].

Kim, et al. [15] have recommended formal contouring education programs to reduce the variability of inter observer contours.

Vahrson, et al. [16] reported a significantly greater survival rate for stage-III patients using HDR brachytherapy.

In the series of Ferrigno, et al. [17] stage-III patients treated with HDR brachytherapy had a poorer outcome when compared with those treated with LDR brachytherapy. This could be due to other factors, like tumor volume, parametrial invasion, lymph node metastasis, and vaginal involvement. At the time of brachytherapy when the tumor is still large, the point-A prescription by orthogonal radiographs is not sufficient to cover the entire tumor volume. To target such large volume tumors, three dimensional (3D) image-based treatment planning is better and preferable.

Onal, et al. [4] also have observed that the CT-plan is superior to the conventional plan as the latter overestimates tumor doses and underestimates OAR doses.

Advantages of 3D imaging include safeguarding the OAR by avoiding excessive exposure. Once the implant is in place, 3D imaging with either CT or MRI can be used for clear target definition and localization and to assess the OARs.

Disadvantages include an increased amount of physician and physicist time for treatment planning, and also the need to undergo training to understand the methodology [18].

## Conclusion

The conventional plan with the point A calculation relies on reference points on orthogonal films, not tumor volumes defined on CT, which may cause underestimation of tumor doses. Likewise, the calculation of rectum and bladder doses made with ICRU reference points, not with bladder and rectal volumes may not reflect the actual organ doses. To overcome such problems, 3DCT-guided brachytherapy treatment planning is recommended.

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