

Original Research Article

A prospective comparative study between two high-dose-rate brachytherapy schedules following external-beam radiotherapy for locally advanced carcinoma cervix at a tertiary cancer centre

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Abstract

Background: High-dose-rate intracavitary brachytherapy is an essential component of curative radiotherapy for cervical cancer. The optimal timing and fractionation schedule should balance local tumour response, treatment duration and toxicity to adjacent organs. **Objective:** To compare treatment response, local control, acute toxicity and overall treatment time between twice-weekly and once-weekly high-dose-rate intracavitary brachytherapy after external-beam radiotherapy in patients with locally advanced cervical cancer. **Methods:** This prospective comparative study was conducted at the Department of Radiation Oncology, MNJ Institute of Oncology and Regional Cancer Centre, Hyderabad, from September 2019 to July 2021. Forty eligible patients were allocated by simple randomisation to two groups of 20. The study group received pelvic external-beam radiotherapy (45 Gy in 25 fractions) followed by HDR brachytherapy of 7 Gy per fraction twice weekly for four fractions. The control group received external-beam radiotherapy (50 Gy in 25 fractions) followed by HDR brachytherapy of 7 Gy once weekly for three fractions. Clinical response, acute bladder, rectal, vaginal and skin toxicity, and overall treatment time were assessed. **Results:** The mean age was 47.95 years in the study group and 53.95 years in the control group. Complete response was recorded in 18/20 (90%) versus 14/20 (70%) patients at the first-month assessment, and in 18/20 (90%) versus 16/20 (80%) at six months, respectively. Vaginal stenosis was reported in 6/20 (30%) study-group patients and 13/20 (65%) control-group patients (reported $p=0.05$). All study-group patients completed treatment in fewer than 50 days, compared with control group. Differences in reported bladder and rectal toxicity were not statistically significant. **Conclusion:** In this single-centre study, the twice-weekly schedule was associated with a shorter overall treatment time, a higher observed complete-response proportion at follow-up and less vaginal stenosis. Interpretation is limited by the small sample, and shorter follow-up.

Keywords: Cervical cancer, Pap smear, Liquid-based cytology, Screening, Histopathology, CIN

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Introduction

Globally, cervical cancer continues to be one of the most common cancers among females, being the fourth most common after breast, colorectal, and lung cancer. Over 569,847 women reported in 2018, 311,365 died of the disease. Adjusting for population growth and aging, the global incidence rate for cervical cancer declined by 1.2% from 2005–2015. The majority of cases are in Africa, because of the paucity of screening measures and the prevalence of immunodeficiency because of human immunodeficiency virus (HIV). In low- and middle-income countries (LMICs), it is more common, being the second most common cancer in incidence among women and the third most common in terms of mortality. The majority of new cases and deaths (approximately 85% and 90%, respectively) occur in low-resource regions or among people from socioeconomically weaker sections of society. According to GLOBOCAN 2018 statistics among women in India, cervical cancer is the 2nd most common cancer after carcinoma breast. Every year in India 96,922 women are diagnosed with cervical cancer and 60,078 die from disease. Moreover, due to difficulties of access and affordability, compliance to, and follow up of, treatment is much worse for women of low socioeconomic section, leading to further morbidity and mortality from the disease. The mainstay of treatment for such cases has traditionally been concurrent chemoradiation: Combination of EBRT and chemotherapy followed by ICRT. NCI has recommended that concurrent cisplatin-based chemotherapy with

radiation therapy should be incorporated in the management of women who require radiation therapy for treatment of carcinoma cervix. Radical radiotherapy plays an important role in treatment of carcinoma cervix and combination a combination of external beam radiotherapy (EBRT) and Brachytherapy (BT) is an effective treatment modality in advanced stages of Cancer Cervix with an intention to cure. Traditionally the treatment of carcinoma cervix has been by AP-PA field and X-ray simulation. However, success achieved with this treatment carries a risk of inadvertent normal tissue irradiation of the small bowel, bladder and rectum. This was then followed by CT based plan Fractionation and dose adjustments of the total dose are very important factors in lowering the frequency of complications without compromising on the treatment results. High Dose Rate Intracavitary Brachytherapy (HDR-ICBT) is an integral part of treatment in cervical cancer with curative intent. HDR-ICBT is always fractionated, if brachytherapy started after EBRT and once in a week application was done then there is prolongation of overall treatment time (OTT) which leads to tumour repopulation and poor tumour control. To reduce repopulation, OTT should be shortened either by increasing dose per fractionation or administering more fractions per week, first approach has more complications. So to decrease OTT twice weekly regimen should be preferred. In our study OTT was 49-52 days (median 50 days). In our study to decrease OTT, brachytherapy started after completion of EBRT and two implants per week were done. Result shows that twice weekly HDR brachytherapy seems to be safer and better therapeutic outcome with improve local control rate. As per our knowledge this is the only study where 7Gy per fractions on twice weekly basis with acceptable complications [1-3]

Aim of the study:

To evaluate the effectiveness and safety of HDR-ICBT delivered at 7 Gy per fraction to Point A, twice weekly for two weeks in case of Carcinoma Cervix after pelvic EBRT.

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Objectives :

To analyze and compare response rate, local tumour control between twice weekly versus once weekly HDR-ICBT.

To analyze and compare the acute toxicities of bladder, rectum, vagina and skin.

To compare overall Treatment time [4,5]

Material and Methods

The prospective randomised study was conducted at department of RadioTherapy at MNJ institute of oncology/RCC, Hyderabad. The study period was from September 2019 to July 2021.

A total of 40 patients were taken for the study from OPD after taking informed consent.

Pre-treatment evaluation:

Complete history and physical examination including punch biopsy from the cervical lesion.

Complete blood picture, renal function tests and liver function tests.

Chest x-ray PA view

Ultrasound of the abdomen and pelvis.

INCLUSION CRITERIA:

Positive biopsy for squamous cell carcinoma, Adenocarcinoma, Adenosquamous carcinoma

Stage IB-IIIB Carcinoma cervix patient according to FIGO Guidelines.

Age 30-70 yrs.

Informed consent.

Eastern Cooperative Oncology Group (ECOG) Performance status 0-2.

Non Metastatic disease.

EXCLUSION CRITERIA:

Distant metastatic patients will be excluded .

Patients with poor performance status .

Prior surgery and /or Radiation to pelvis.

The existence of synchronous multiple malignancies .

Age <30 or >70 years

Clinical Examination General Examination

Basic parameters including weight, height and body surface area
Complete systemic examination

Local Examination (Per speculum, P/V and per rectal examination) and biopsy from growth for histopathological confirmation.

Assessment of cervical lymph nodal status and palpation of bilateral supraclavicular fossa for presence of lymph nodes

Baseline Investigations Complete hemogram (Hemoglobin, Total count, Differential count, Platelet count) and biochemical values (RBS, LFT, RFT, Serum Electrolytes).

HIV / HBsAg.

Chest x-ray Ultrasound abdomen and pelvis.

Virtual simulation CT scan for radiotherapy planning

Randomization to Groups:

After patients signed the consent form, they were randomized into either Group A or Group B by Simple Randomization.

Control group– Concurrent chemo-radiation 50 Gy at 2 Gy per fraction over 25 fractions, followed by once weekly Brachytherapy, dose of 7GY to point A for three weeks.

Study group– Concurrent chemo-radiation 45 Gy at 1.8 Gy per fraction over 25 fractions followed by twice weekly Brachytherapy, dose of 7GY to point A for two weeks.

Check patient eligibility- informed consent from patient- simple randomisation- ARM A/ ARM B BRACHYTHERAPY ASSESSMENT OF ACUTE TOXICITIES BY RTOG/CTCAE GRADING

Treatment plan:

This study was a single-blinded study where the investigators were aware of the intervention planned.

Dose Prescription: Three dimensional conformal plans were generated with the ECLIPSE Treatment planning system and consisted of four coplanar beams anteroposterior – posteroanterior and two lateral beams.

The goal was to encompass the planning target volume by 95% of the prescription dose.

Treatment is delivered once daily, 5 fractions per week, over 5 weeks.

The dose prescription and reported to target volumes was done as per ICRU-83

Target and nodal volume delineation was done as per institutional protocols as per internationally accepted guideline.

Table 1: Treatment schedules

Group	External-beam radiotherapy	HDR intracavitary brachytherapy
Study group (n=20)	45 Gy in 25 fractions of 1.8 Gy	7 Gy per fraction, twice weekly, four fractions (Wednesdays and Fridays)
Control group (n=20)	50 Gy in 25 fractions of 2 Gy	7 Gy per fraction, once weekly, three fractions (Wednesdays)

Chemotherapy: Patients in both study and control group received concurrent weekly cisplatin at a dose of 40mg/m².

Brachytherapy : Patients after completing the schedule of radiotherapy irrespective of the delay were evaluated for response and assessed for intracavitary brachytherapy (ICBT) feasibility.

Patients were admitted a day ahead of HDR fractionation and ICRT was delivered using Varian Gamma Med high dose rate (HDR) unit with remote after loading technique.

TOXICITY ASSESSMENT AND MANAGEMENT

Patients were evaluated weekly or as required during EBRT for following toxicities using Radiation Therapy Oncology Group (RTOG) grading and Common Terminology Criteria for Adverse Events (CTCAE) grading Version 4.03

Hematological Toxicity

GI Toxicity

Genito-Urinary Toxicity

Skin Toxicity

Post - treatment assessment:

On completion of therapy, assessment of toxicity and response was done after 4 weeks by detailed history and physical examinations, and whenever needed by abdominal ultrasonography/ CT scan, chest x-

ray, cystoscopy, and proctosigmoidoscopy. Biochemical tests like complete blood count, renal function test and liver function test were also done as required. Patients were asked to follow up at 1 month followed by every three months for the study period. [6,7]

Statistical Analysis

All statistical analysis, wherever applicable, were done by using IBM SPSS software Version 25. The p-value was calculated by Fischer's exact test at 95% confidence interval. The p-values were considered significant when $p \leq 0.05$

Results**Participant characteristics**

Forty patients were evaluated, with no reported loss during treatment or follow-up. The mean age was 47.95 years (SD 10.13) in the study group and 53.95 years (SD 8.02) in the control group; the reported between-group p value was 0.336. Most patients had tumours measuring 5 cm or less (85% in the study group and 90% in the control group). Ulceroproliferative growth was the most common clinical pattern, reported in 70% and 80%, respectively. The most frequent histological category was large-cell non-keratinising squamous cell carcinoma.

Table 2: Clinical response

Assessment time	Study group: complete response	Control group: complete response
1 month	18/20 (90%)	14/20 (70%)
3 months	20/20 (100%)	17/20 (85%)
6 months	18/20 (90%)	16/20 (80%)

The observed proportion with complete response was higher in the twice-weekly group at each reported assessment. The $p=0.23$ for the first- and second-follow-up comparisons and $p=0.19$ for the third-follow-up comparison; these differences were not statistically significant. At six months, one study-group patient was recorded as having local recurrence and one control-group patient as having lung metastasis. These small event counts preclude firm conclusions about comparative disease control.

Table 3: Toxicity

Reported toxicity	Study group (n=20)	Control group (n=20)	Reported p value
Bladder toxicity: none	16 (80%)	13 (65%)	0.56
Rectal toxicity: none	17 (85%)	14 (70%)	0.60
Vaginal stenosis	6 (30%)	13 (65%)	0.05
Skin toxicity: grade 1	13 (65%)	8 (40%)	0.17
Skin toxicity: grade 2	3 (15%)	8 (40%)	0.17

Bladder and rectal toxicity were numerically less frequent in the study group, but the reported comparisons were not statistically significant. Vaginal stenosis was less frequent in the study group, with a p value of 0.05. Skin toxicity distributions differed numerically between groups, but the reported comparison was not statistically significant.

Overall treatment time

All 20 patients in the twice-weekly group completed treatment in fewer than 50 days, compared with none of the 20 patients in the once-weekly group; this difference was statistically significant ($p=0.001$). This finding is consistent with the shorter planned brachytherapy schedule in the study group.

Discussion

Data from cancer registries in developing countries suggest that about 80 to 90 percent of confirmed cervical cancer cases occur among women age 35 years or older because cervical cancer progresses slowly from precancerous condition to advanced cancer.

The main objective of our study is to achieve a suitable HDR brachytherapy fractionation protocol for safety regarding both complication and efficiency in respect of tumor control. At the end of study (July 2021), it was seen that 18 patients (90%) out of 20 in study Group and 16 patients (80%) out of 20 in control Group had complete response. The patterns of failure were studied for all the patients in all the groups. Out of 20 patients in study Group, 1 patient (5%) developed local failure in the pelvis only and 1 patient (5%) in para-aortic. Out of 20 patients in the Control Group, 3 patients (15%) had residual disease at the end of 3 months. 1 patient (5%) developed distant metastases to the lung.

When the final result tabulation was done, 1 patient in the control group has died due to distant metastases to the lung.

The strongest statistically significant differences reported were in overall treatment time and vaginal stenosis. [8-10]

The importance of limiting overall treatment time is biologically plausible and consistent with prior cervical cancer radiotherapy literature, which has associated treatment prolongation with poorer pelvic control. The lower frequency of vaginal stenosis in the twice-weekly group is noteworthy, but should be interpreted cautiously given the small sample and limited follow-up. [11-13]

Limitations Of The Study

There is small sample size in this study due to COVID-19 pandemic. Large sample size is needed for better outcomes. The follow-up period in this study is short. Long follow-up is needed to see the complications and overall survival. Patients counselling needed as there is twice weekly schedule, more chances of treatment interruptions by patient. [14,15]

Conclusion

Carcinoma cervix is the most common cause of female malignancy in India with one of the most common causes of morbidity and mortality in perimenopausal and postmenopausal women. HDR brachytherapy has proved to be a standard treatment modality in carcinoma cervix. In this study, the main objective is to observe the results using two

groups (7 Gy/3 fraction of weekly brachytherapy and 7 Gy/4 fraction of twice weekly HDR brachytherapy in locally advanced carcinoma of uterine cervix). It is observed that fractionation schedule and dose in Study Group (7 Gy/4 fraction twice weekly) has produced satisfactory results in terms of response rate, local control (90%) and less acute toxicity of bladder and rectum compared to Control Group. Hence, this study can be concluded with the assumption that EBRT (45 Gy/25#) followed by HDR intracavitary brachytherapy using 7 Gy/fraction twice in a week for 4 fractions in locally advanced carcinoma cervix may be a good option as it has similar local control and less toxicity. Continuing this study for prolonged period and recruiting more patients will help in arriving at more conclusive results.

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