



IMPACT OF OVERALL SHORT TREATMENT TIME (BY 2 DIFFERENT ICRT SCHEDULE ALONG WITH CTRT) IN CANCER CERVIX

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ABSTRACT

Cervical cancer has been the most important cancer in women in India over the past two decades. Although cancer of the cervix can develop in women of all ages, it usually develops in women aged 35-55 years.^[1] World Health Organization estimates that nearly 530,000 women are diagnosed with cervical cancer annually across the world and India contributes around 134,000 of all those cases.^[2] The data published by International Agency for Research on Cancer shows that every fourth death due to cervical cancer occurs in India, and by 2025 the death rate could increase by 70%.

KEYWORDS: Intracavitary brachytherapy (ICBT) for cervical cancer is best conformal.

INTRODUCTION

Cervical cancer has been the most important cancer in women in India over the past two decades. Although cancer of the cervix can develop in women of all ages, it usually develops in women aged 35-55 years.^[1] World Health Organization estimates that nearly 530,000 women are diagnosed with cervical cancer annually across the world and India contributes around 134,000 of all those cases.^[2] The data published by International Agency for Research on Cancer shows that every fourth death due to cervical cancer occurs in India, and by 2025 the death rate could increase by 70%.

Intracavitary brachytherapy (ICBT) for cervical cancer is best conformal treatment that can deliver high dosage to the primary tumor without delivering excessive dosage to the surrounding normal tissue. Brachytherapy is a standard of care for cervical cancer along with external beam radiotherapy. American and European guidelines recommend brachytherapy as a key component of radiotherapy for cervical cancer.^[3] High Dose Rate brachytherapy can be used either as an alternative to EBRT or in combination with EBRT and/or chemotherapy. After 1999, concurrent chemo radiotherapy (CCRT) became the standard after the national cancer institute (NCI) recommendation.^[4] However, the benefits of concurrent chemotherapy on definitive radiotherapy might not be applicable to concomitant EBRT plus HDR-ICBT and are not clear yet in Asian countries.^[5]

Despite high cure rate relapse is inevitable especially in higher stage (stage IIB and above); chemotherapy with weekly Gemcitabine and Cisplatin / Carboplatin concurrently with radiation favours better outcome at the cost of toxicity.

The present study is conducted to compare sequential HDR (standard of care) versus concurrent HDR Brachytherapy in carcinoma of uterine cervix in terms of safety and efficacy. Keeping in mind that total treatment time should not more than 52 days as the rate of failure (Loss of local control & overall survival) increase by 1% per day; we try to finish the treatment within 6W to silence the repopulation tumor cells. The primary endpoint considered was 3-year overall survival, and the secondary endpoints were tumor response, 3-year progression-free survival, adverse events, treatment compliance and late adverse events.

MATERIAL AND METHODS

Patients

Patients with International Federation of Gynecology and Obstetrics (FIGO) stage Ib to IIIb pathologically confirmed carcinoma of the cervix were enrolled in this study from October 2012 to December 2013. Patients were included if they were between the ages of 30 to 70 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and no prior treatment for cervical cancer. Other eligibility criteria included the following: hemoglobin ≥ 10 gm %; white blood corpuscle $> 4000/\text{mm}^3$; TPC $1.5 \text{ L}/\text{mm}^3$; Blood urea < 40 mg %; Serum Creatinine < 1.4 mg%.

Bilirubin <1.2 mg%; SGOT & PT <40 IU/L. Patient were excluded if they were given prior radiation to pelvis, had any other malignancy or any existing serious medical/surgical illness.

Study Design

Our study was an open-label; randomized, comparative study conducted in compliance with Good Clinical Practice, Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Written informed consent was obtained from each patient before enrollment.

296 eligible patients were randomized by a computer-generated series of random numbers into two groups to receive Intracavitary HDR Brachytherapy (ICRT)

[Group 1 CCRT 50 Gy / 25 # / 5 W ---> after 1 ICBT 7Gy x 3 one week apart] or in combination with concurrent chemotherapy and external beam radiotherapy (CCRT) [Group 2 CCRT 50 Gy/ 25# / 6 W along with ICBT 5 Gy x 5 one week apart from 2nd week of CCRT].

Table 2: Histopathology & Stage.

		Gr.1CCRT->ICBT (154)	Gr.2 CCRT+ ICBT (142)
1) HPE	Squamous Cell Ca	138	131
	Adeno Squamous	07	04
	Adenocarcinoma	09	07
2) STAGE	II A	19	10
	II B	24	27
	III A	43	41
	III B	68	64

Chemotherapy

Cisplatin (CDDP) was administered in a dose of 40 mg/m², weekly for 5 weeks given concurrently with the external-beam RT in 2 hours or less before the external-beam treatment for that day. Appropriate medication was given before and after the CDDP administration.

Follow-up

All patients were evaluated weekly for toxicity during radiotherapy through physical examinations and blood tests, Hb must be 10gm% or above. After completion of treatment, patients were seen every month for the first 6 months, once in every 3 months for next 6 months, once in every 6 months for next 2 years and yearly thereafter.

RESULTS

Patients were treated as per the protocol. Overall treatment time was 8 W in group 1 and 6 W in group 2. Vaginal stenosis was observed in older age group patients. There was no serious complication to rectum and bladder.

During first three months of follow-up, it was observed that in group 1, two patients developed central failure

Radiotherapy

External-beam megavoltage RT was administered to the whole pelvis. This was achieved by the 'four field box technique' by 3 DCRT.

High dose rate (HDR) brachytherapy followed CCRT in group 1 patients and a dose of 7 Gy weekly for 3 weeks was given after 1 week of completion of EBRT. In group 2 patients, ICRT was given at a dose of 5 Gy weekly for 5 weeks starting from second week of external radiation. The dose to critical structure was within 75% of point A dose. Most of Japanese study favouring 5 fraction of ICBT of 5 Gy weekly.

Table 1: Dose of HDR brachytherapy.

	Group 1 (n=154) CCRT →ICRT	Group 2 (n=142) CCRT + ICRT
HDR brachytherapy	7 Gy weekly X 3 weeks	5 Gy weekly X 5 weeks
Initiation period	1 week after completion of EBRT	2 nd week of EBRT

with para-aortic lymphadenopathy. One patient developed ascitis and on investigation it was seen to be due to liver cirrhosis. In group 2, 1 patient developed ascitis, pleural and pericardial effusion with growth in cervix, ovarian mass. Ca-125 was seen to be 1653 U/L and leveled as ovarian malignancy because ascetic fluid was positive for malignant cell (ADCA). This patient was put on chemotherapy. 1 more patients develop hepatic metastasis in Gr 2.

At the 6th month of post-treatment follow-up, 3 patients in group 1 developed hepatic metastasis while two patients in group 2 developed bone metastasis and 1 developed lung metastasis.

At 1 year follow-up, 1 patient in group 1 developed hematuria whereas 2 patients in group 2 developed hematuria along with rectal bleeding, both were managed conservatively.

Total of 11 patients presented with metastasis in Gr. 1 however only 5 patients in Gr.2 developed metastasis.

At 3rd yrs. follow up 52 patients developed systemic failure in Gr.1 while 32 patients of Gr 2 had systemic failure.

Acute adverse effects were more in group 2 especially hematological; otherwise both arm had similar

dermatological adverse effects, urinary and rectal symptoms. Group 2 had good application and dose to critical structures was much lower when compared to group 1. Local control seemed to be better in group 2 even in higher stages.

Table 3: Failure after treatment.

	Gr. 1 CCRT → ICBT	Gr. 2 CCRT + ICBT
3rd Month	Sq CC -1/138, AdCa 1/9 = Total 2	Sq CC - 1/131 = Total 1
6 th Month	Sq CC - 3 / 138 = Total 3	Sq CC - 2/130 ,AdCa -1/7 =Total 3
1 Yr.	SqCC -9/138, AdCa 2/9 =Total 11	SqCC - 5/130 = Total 5
3 Yr.	SqCC - 47/138,AdCa 3/9,AdSq 2/7 Total = 52	SqCC- 28/130, AdCa-3/7,AdSq 1/4 Total = 32

Total Failure Gr. 1 = 68 /154, Gr. 2 = 41/142

Table 4: Failure pattern.

Site of Failure	Gr. 1 CCRT → ICBT	Gr. 2 CCRT + ICBT
Lung	21	08
Liver	27	23
Bone	13	06
Brain	07	04
	Total = 68	Total = 41

DISCUSSIONS

Brachytherapy plays a very important role in obtaining high cure rates with minimum complications. A good intracavitary insertion delivers a very high radiation dose to the cervix, upper vagina and medial parametria without exceeding the tolerance doses for rectum and bladder. The randomized trials comparing low dose rate (LDR) with high dose rate (HDR) brachytherapy in carcinoma cervix have shown that the two modalities are comparable in terms of local control and survival.^[6-9]

Five randomized phase III trials of radical RT alone versus concurrent cisplatin-based chemotherapy and RT, and their meta-analysis have shown an absolute benefit in overall survival and Progression free survival with chemo-radiotherapy in patients with stage IB2 to IVA disease as well as high risk patients after hysterectomy.^[10-17]

After External beam radiotherapy, during ICBT we face certain technical difficulties as stenosed OS is difficult to localise; inability to find out the OS results in only 2 ovoid insertion without central tendem and Pear & banana shape cannot be achieve; stenosed OS need dilatation and sometimes leads to perforation of uterus. Many a time patients have not reported on time, especially outstation patients call after 1 W of CCRT.

Concurrent ICBT provides good view of disease and opportunity to assess the treatment response weekly along with good application.

In our experience, weekly HDR brachytherapy concurrent with EBRT along with chemotherapy have

been found to be better but long term follow up on this treatment is required to provide concrete evidence. Concurrent EBRT, chemotherapy and ICRT provide better out come with manageable side effects. This shortens overall treatment time enabling more intense treatment without increasing morbidity.

CONCLUSIONS

In conclusion, though mono-institutional this study revealed that concurrent radiotherapy, chemotherapy and HDR brachytherapy provides better outcome with manageable side effects in women with FIGO Ib to IIIb cervical cancer. A larger randomized trial with long term follow up is needed to establish the effect of concurrent weekly HDR brachytherapy along with chemo-radio therapy for women with advanced cervical cancer.

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