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CONCURRENT CHEMORADIATION WITH SEQUENTIAL VERSUS INTERDIGITATED BRACHYTHERAPY FOR LOCALLY ADVANCED CARCINOMA CERVIX – AN OPEN LABEL RANDOMISED CLINICAL TRIAL

Oncology

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ABSTRACT

Background: This is a prospective study to evaluate the effects of treatment duration shortening by means of Interdigitated brachytherapy comparing with conventional external beam radiotherapy followed by brachytherapy.

Material & Methods: In study arm, The high dose rate intracavitary brachytherapy using Ir192 was interdigitated from the 3rd week of EBRT, was given in 3fractions. In control arm, brachy started after 1week of EBRT.

During treatment patients were reviewed weekly. After treatment completion, patients were reviewed at six weeks, then three-monthly thereafter.

Results: This study has achieved good response (96 % CR post Brachytherapy at 3 month) and local control rate (95% v/s 68% at end of follow up),which was better than sequential arm , with slightly better DFS but No OS difference.

Conclusion: Interdigitated Brachytherapy can be delivered as a standard mode of treatment in cancer cervix. Continuing this study for prolonged period and recruiting more patients will help in arriving at conclusive results

KEYWORDS

Interdigitated Brachytherapy, Cervix , Chemoradiation , Medical College Kolkata

Introduction

Carcinoma of the uterine cervix is the one of the leading sites of primary cancer among Indian women.Several studies have described lower pelvic control and survival rates with prolongation of treatment duration.

This is a prospective study to evaluate the effects of treatment duration shortening by means of Interdigitated brachytherapy comparing with conventional external beam radiotherapy followed by brachythrapy .

In a country like ours , where carcinoma cervix mainly affects women of lower socio-economic condition, reduced treatment duration means, the women, if capable of household activities/earnings ,can begin those early. Compliance is expected to be better with shorter treatment duration and maximum number of treatment completion is expected.

Aim & Objective

Primary Objective - Assessment of Clinical response , disease free interval, time to progression of disease.

Secondary Objective - Assessment of Acute & Late toxicity of bladder, rectum, skin, vaginal mucous membrane, GI & Hematological system.

Material & Method

- **Study Population :** All biopsy proven cases of locally advanced Carcinoma cervix(HPE- squamous, adeno, adeno-squamous variety) attending radiotherapy OPD of Medical College Kolkata.
- **Study Period :** January 2016 –June 2017 and was divided into preparatory phase, data collection phase ,data compilation phase, data analysis phase and preparation phase.
- **Sample Size :** 31 Patients in each arm, total no of patients was 62.
- **Study Design :** Open label randomised clinical trial.

- **Exclusion Criteria :**
- Age <25yrs,or$\geq$70yrs
- Pregnancy or lactation
- History of hysterectomy
- Stage IVB disease
- Patients not willing to have anaesthesia
- Patient with any benign rectal or bladder disorder
- Patient with genital prolapse or with deformities of the knee or Hip

Technique of Study :

Arm A (Study arm n=31)

In this arm, patients were treated with EBRT by Tele-cobalt machine to a dose of 50 Gy in 25 fractions over 5 weeks. The high dose rate intracavitary brachytherapy using Ir192 was interdigitated from the 3rd week of EBRT, was given in 3fractions(single fraction of 7Gy per week) . EBRT was omitted on the day of brachytherapy and the missed fraction was administered on Saturday. During the whole study period Inj. Cisplatin was given 40mg/m2 weekly.(Treatment completion within 5weeks).

Arm B (Control arm n = 31)

In this arm, patients were treated with external beam radiotherapy (EBRT) by Tele-cobalt machine to a dose of 50 Gy in 25 fractions over 5 weeks, followed by high dose rate intracavitary brachytherapy using Ir192 started within 1 week of completion of EBRT and was given in 3 fractions (single fraction of 7Gy per week). During the period of EBRT, Inj. Cisplatin was given 40mg/m2 weekly.(Treatment completion within 8weeks).

Follow up

During treatment patients were reviewed weekly. After treatment completion, patients were reviewed at six weeks, then three-monthly thereafter.

- Statistical Analysis by IBM SPSS software version 23.

Results

Comparison of age distribution between the two groups was done by the unpaired t test. The test was not statistically significant. Parity and KPS comparisons were done using the Mann Whitney U test which showed that they were both comparable. Most common stage was Stage III B & IIIA in study and control group respectively. Other demographic parameters were also comparable between two groups.

The overall treatment time was shorter in Interdigitated arm with a mean value of 36.2 days compared to 57.3 days in Sequential arm. (P = 0.034).

Dosimetry of Brachytherapy was also comparable in both arms.

Tumor Response & Toxicities were compared using Chi Square test & unpaired t test. Disease free survival & overall survival were compared by Kaplan Meir survival analysis.

Minimum follow up period was 9 month and maximum was 18 month, with a mean follow up duration of 12.6 months. At 6 month 5 patients in control arm developed progression & 5 patient showed partial response. While in study arm only one patient showed partial response and rest showed complete remission of disease. Long term tumour control was also significantly better in study arm with improved DFS. (P = 0.04). one patient in study arm & three patients in control arm died due to disease. However 1yr overall survival was not statistically different in both arms. (P = 0.315).

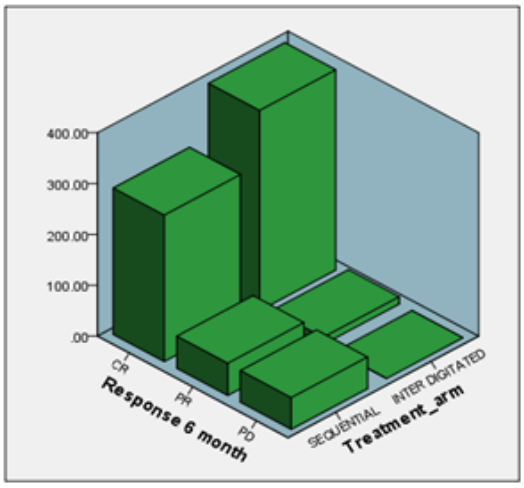
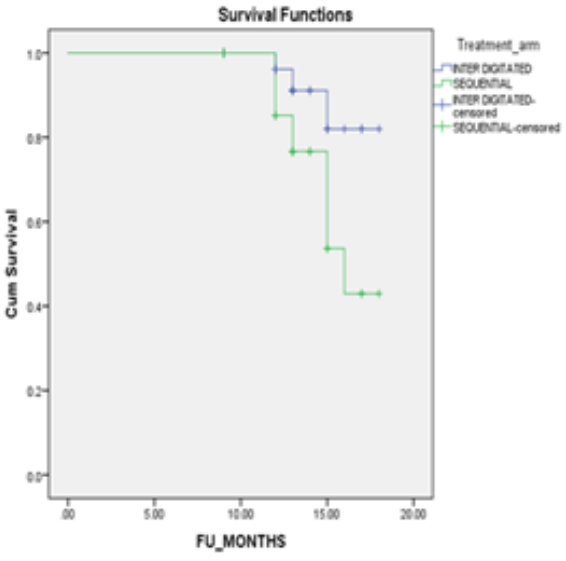


Fig 1 – Bar Diagram showing Tumor response at 6 month



Log Rank (Mantle Cox) P = 0.047

Fig 2 – Kaplan Meir Survival curve showing DFS in two groups.

Hematological toxicity mainly anemia & lecopenia was more in the study arm at 6week, (P=0.006) though at 12 month results were comparable. Patients in the study arm developed more nausea, vomiting, diarrhoea (GI Toxicity) but the result was not significant. (P=0.105). No patients developed grade 3 & 4 toxicities (Both acute & late).

Twenty one patients developed grade 1 & five patients developed grade 2 acute skin toxicity in Interdigitated arm, while twenty two patients developed grade 1 & three patients developed grade 2 skin toxicity in the sequential arm. There were no grade 3 & 4 toxicities in either arm. This result was not statistically significant. Late skin toxicities were also comparable & insignificant.

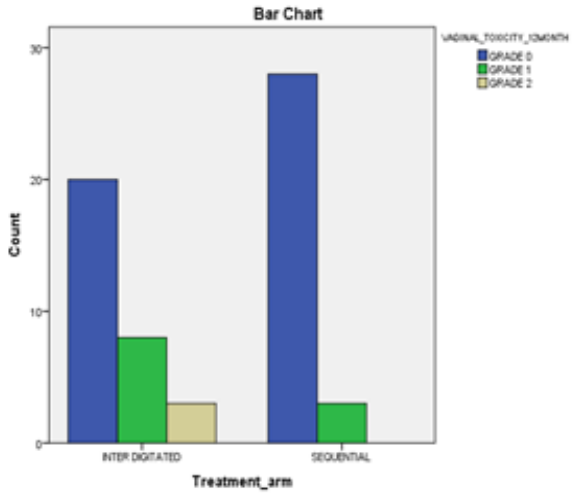


Fig 3 – Bar Diagram showing late vaginal toxicity in both arms.

Both acute (mucositis) & late (dyspareunia) vaginal toxicity were significantly greater in the study arm. However there were no Grade 3 & Grade 4 vaginal toxicity in any arm at any stage of follow up.

Discussion

In this study, youngest included patients were in their 4th decade of life and elderly patients were in their 6th decade of life .Though present in inclusion criteria ,No patient came in her 3 rd decade of life reflecting age distribution of cervical malignancy.

Several studies have described lower pelvic control and survival rates with prolongation of treatment duration.(8,9,10,11).

In a multi centred retrospective study in China ,Shan-Wen chan, Ji-An Liang, Shih-Neng yang,Hui-Ling ko,Fang-jenLin has described how critical treatment time prolongation has effect on outcome.

From September 1992 to December 1997 , 257 patients diagnosed with Uterine cervical cancer(of stages between 35 IB,26 IIA,122 IIB,10 IIIA,57 IIIB,7 IVA)who underwent external radiotherapy combined with between two and four courses of High dose rate intracavitary Brachytherapy and a minimum 3 year follow up (median 57 months) were analysed.

Result shows treatment time prolongation >63 days negatively influence the cause specific survival and pelvic control rate.

Most of the workers tried interdigitated Brachytherapy as the method to achieve reduction in treatment duration , as well as given in American Brachytherapy society guideline , because accelerated fractionation is not standerdised intreatment of cervical cancer.

Between 1971 to 1995 in a study, T Ota, N Takeshima, T Tabata, K Hasumi and K Takizawa in Department of Gynecology, Cancer Institute Hospital, , Koutou-ku, Tokyo , Japan among study population of 1495 patients of cervical cancer,treated with weekly 2-3 fractions of interdigitated Brachytherapy (4 Gy fraction size) has shown that the cumulative 5-year survival rates for stagesIb, II, and III/IVa disease were 93.5, 77.0, and 60.3%, respectively, ten-year survival rates for stages Ib, II, and III/IVa disease were 90.9, 74.5, and 56.1%, respectively

Limitation

- Single Institutional Study.
- Small Sample Size due to time constraints.
- Short follow up (mean 12.6 month , range 9 to18 months) .
- Needs expertise in Brachytherapy due to difficult tandem insertion in study arm.

Conclusion

- In the present study our aim was to observe the results by interdigitating HDR ICRT with external radiation. The comparison of two different sequences of external radiation and high dose rate brachytherapy has produced satisfactory pelvic

control with manageable rectal and bladder toxicities.
- The acute effects were not life threatening and managed conservatively.
- Interdigitated Brachytherapy can be delivered as a standard mode of treatment in cancer cervix. Continuing this study for prolonged period and recruiting more patients will help in arriving at conclusive results.

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