ORIGINAL RESEARCH PAPER

Oncology

KEY WORDS: Carcinoma Cervix, external beam radiotherapy, interdigitated brachytherapy, toxicity.

A COMPARATIVE STUDY EVALUATING THE TOXICITY OF SEQUENTIAL VERSUS INTERDIGITATED BRACHYTHERAPY WITH EBRT IN CANCER CERVIX

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ABSTRACT

cervical cancer in India is a predominant carcinoma after breast cancer particularly in rural areas where it ranks on top of the other carcinoma in females, the treatment of carcinoma cervix is EBRT followed by intracavitary brachytherapy which generally requires 8 weeks of treatment, studies suggest that shortening the treatment time leads to better tumour shrinkage by interdigitating the brachytherapy along with EBRT. The aim of this study to evaluate the toxicity,response to treatment and overall survival of shortening of treatment duration by means of interdigitated brachytherapy in comparison to sequential brachytherapy with conventional EBRT.

INTRODUCTION-

As per GLOBOCAN 2018, cervical cancer is the fourth most common cancer in women with an estimated 569,847 new Cases and 311,365 deaths in 2018.[1]In India, cervical cancer is the second most common Cancer in women after breast cancer accounting for almost 16.5% of all female cancer age standardised incidence rate is 14.7 per100,000 female population and age standardised mortality Rate per 10,000 population is reported to be 9.2. The higher death rate are often attributed for the most part to the shortage of applicable healthcare infrastructure in India. Cervical cancer in its advanced stage has a poorer outcome in terms of both prognosis and quality of life, causing approximately 60,078 deaths in India according to GLOBOCON 2018 [2,3]

Brachytherapy is an important element in the management of carcinoma cervix, and it is found to considerably improved survival.[4,5] High dose rate (HDR) as well as low dose rate (LDR) brachytherapy appears to be comparable treatments in terms of patient outcomes in term of survival as supported on the basis of existing many randomized controlled trials [6,7]. The Advantages of High-dose-rate brachytherapy, amongst others, include opportunities for treatment on outpatient basis, less risk of staff exposure to radiation and consistent applicator positioning [8,9]. There is also an improvement in dose attained with variable dwell-time source. It is essential that treatment with brachytherapy and EBRT be completed within a period of 8 weeks' time. A short treatment is reported to be associated with a comparatively better tumour control resulting into better survival rates {10, 11}.

EBRT and HDR brachytherapy can be interdigitated so as to be able to reduce the duration of treatment. EBRT usually is given in fractions of 1.8 Gy to 45 Gy. It's a good policy to administer higher dose of EBRT initially to decrease the extent of residual disease. The treatment strategy must ensure that pelvic lymph nodes be given at least 5 days of EBRT every week as long as possible without producing serious side effects. Concurrent use of chemotherapy for at least 5 weeks consecutively. These strategies are crucial for improvement in brachytherapy consequently causing shrinkage of tumour thereby effectively increasing the distance between organs at risk and the tumour mass [12]. The other strategy may include early administration of 1st brachytherapy in the course of EBRT and giving one fraction every weekly. In these cases, brachytherapy is not given on the same day on which EBRT is given. The purpose of both of these strategies is to reduce the duration of treatment and improvement in the outcome of patients [13].

Lee et al declared that the median dose to attain a 50% reduction in tumour size is approximately 30.8 Gy. Similarly, the median number of passed days for a complete response was 42 days. On the basis of this it could be inferred that it takes around 3 weeks to achieve a 50 percent clinical response for individuals undergoing concurrent cisplatin-based chemo-radiotherapy and High dose rate brachyt herapy[14,15]

A study done by Santosh et al concluded that cervical regression occurs at the end of 3rd week, which corresponds to 30 Gy of EBRT, and it is optimal to introduce brachytherapy at end of 3rdweek. Reduction in overall treatment time doesn't cause increased acute toxicities and also resulted in better locoregional control [16]

These facts prove that interdigitating brachytherapy with EBRT is feasible and also studies suggest greater than 7 Gy per dose of HDR brachytherapy is associated with greater toxicities. This led to interest in assessment of local toxicities in cervical cancer patients treated concurrently with EBRT and HDR brachytherapy of dose 7Gy in three fractions, expecting less toxicities compared with higher dose per fractionations.

METHODS–

A prospective single blinded randomised control study carried out in a total 60 patients,30 patient in each arm (Arm A & ArmB) histologically proven squamous cell carcinoma cervix patients from stage IIB to IIIB, presented to the dept of radiation oncology GMCH Nagpur from a period Jan 2017 to June 2018

ARM A-

In this arm, patients were treated with 50 Gy/25#s of external beam radiotherapy (EBRT) over 5 weeks, followed by HDR 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.

ARM B-

In this arm During first 2 weeks patients received 5 fractions of EBRT (2Gy per day) per week i.e. Monday to Friday with 2days rest, which was followed by 3 more fractions of EBRT in the 3rd week i.e. from Monday to Wednesday. At the end of 13 fractions of EBRT i.e. on Thursday of 3rd week, patients were assessed for HDR brachytherapy insertion. If found fit or brachytherapy, were included in the study, patient received 1st HDR brachytherapy on the 14th working day i.e. Thursday of the 3rd week.EBRT was continued on Friday and Saturday on same week. This treatment schedule was continued till the end of 5thweek. Midline block given after 44 Gy, Cisplatin was given for all patients of a dose 40mg/m2 on beginning of

every week i.e. on every Monday. Care taken not to give cisplatin on the day of brachytherapy.

Inclusion criteria

- Those who have given informed consent to be part of study.
- Histologically proven squamous cell carcinoma cervix patients,
- FIGO stage IIB to IIIB
- Age < 60 years.
- ECOG (0-2).
- Hb > 9 gm/dl, normal kidney function and liver function.
- No evidence of distant metastasis.

Exclusion criteria

- FIGO stage IV
- Those not fit for HDR brachytherapy after receiving 28 Gy of external beam radiation therapy (i.e. 14 fractions).
- ECOG (3 to 4)
- Pregnant women
- Those who refused consent

Follow Up-

After the completion of treatment, follow up examination was done every two months for 1 year at every visit, each patient was clinically evaluated for local control of disease and examined for any evidence of distant metastasis. Per vaginal (P/V) and per rectal (P/R) examination were done at each follow up and signs & symptoms of acute toxicity were assessed according to RTOG criteria Statistical Analysis - Statistical analysis done using SPSS software, Version 19. The toxicities were presented as frequencies and percen tag es.Person's analysis was done to see any correlation between point A,Point B ICRU bladder and rectal point doses.P value less than 0.05 was taken as statistically significant.

RESULTS-

Mean age at the time of diagnosis in Arm A was 48.06 years ranging from 45 years to 50 years (SD=7.13) and in Arm B it was 51.26 years ranging from 47 yrs. to 54 yrs. (SD= 9.38). Mean age of the patients in both the groups were found to be comparable and there was no statistically significant difference in between the mean age of both the groups. More than 50% of the patients were presented in stage IIIB in both arms, followed by stage IIB and Stage IIA patients. The dosimetry parameters of brachytherapy were comparable in both arms

Table 1: Age Groups In the studied cases.

	Mean Age	Std Deviation
Group A	48.06	7.13
Group B	51.26	9.38
P= 0.1423 (Not Significant)		

Skin Toxicity:-

In arm A out of 30 studied cases 27 (90%) patients were found to be affected by Grade 1 skin toxicity and remaining 3 (10%) patients were found to have grade 2 skin toxicity. In Arm B grade 1 and grade 2 skin toxicity were found in 18 (60%) and 12 (40%) patients respectively. Grade 1 skin toxicity was comparable in both arms but Grade 2 skin Toxicity was higher in Arm B than in Arm A(p=0.007).

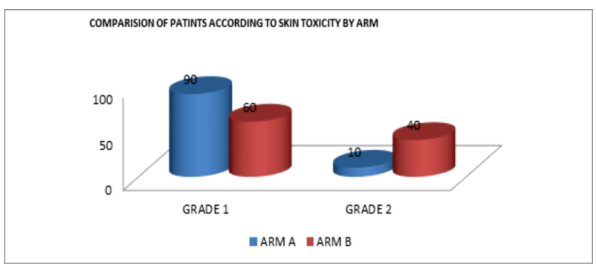


Figure 1: Incidence of skin toxicity in studied cases.

Upper Gastrointestinal Toxicity- Upper gastrointestinal toxicity i.e. nausea, vomiting and abdominal pain was more in interdigitated arm and the results were statistically significant (p=0.00) but none of the studied patients developed Grade 3 or Grade 4 toxicity.

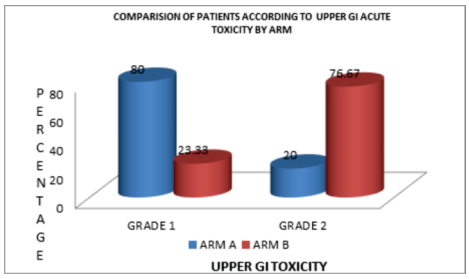


Figure 2: Upper Gastrointestinal Toxicity In Studied Cases.

Lower Gastrointestinal Toxicity- The grade 2 diarrhoea was higher in interdigitated arm (Arm B) than in sequential arm (Arm A) (p=0.00)Arm B was having more Grade 1 and Grade 2 rectal discomfort toxicity than in Arm A (P=0.426). So overall Grade 2 Diarrhea and rectal discomfort was more in interdigitated arm than in sequential arm (p=0.108).

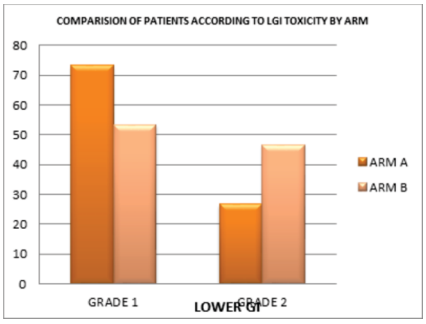


Figure 3: Lower Gastrointestinal Toxicity in Studied Cases.

Genitourinary Toxicity-

Overall Genitourinary Toxicity, Grade 2 toxicity was more in Arm B than in Arm A but Arm A also having more Grade 1 Toxicity than Arm B patients. (p=0.00).

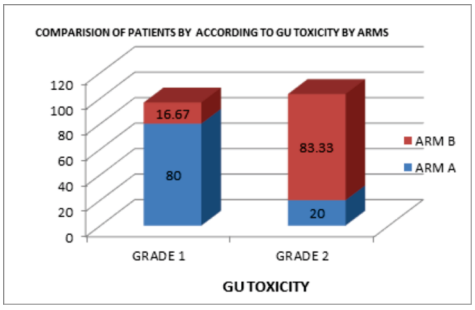


Figure 4: Genitourinary Toxicity in studied cases.

Hematological Toxicity -

patients with grade 2 Anaemia and Neutropenia was more in interdigitated arm than in sequential arm and Grade 1 haematological toxicity was comparable in both the arms (p=0.00)

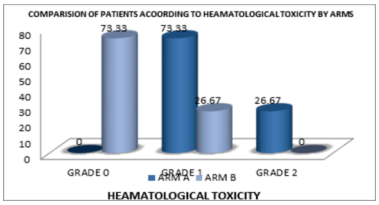
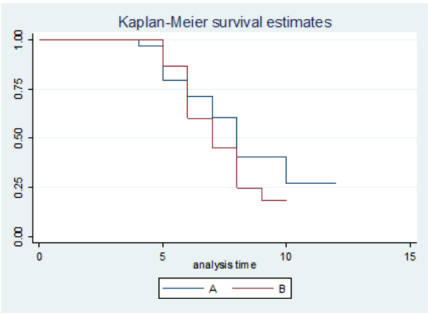


Figure 5: Haematological Toxicity in studied cases.

The Mean follow up was 6.7 months for Arm A and Arm B was 6.93 months.The median follow up in Arm A was 6 months (range 5-12 months) and in Arm B 7 months (range 5-10 months). In sequential arm 12 patients had CR and 18 were PR while in interdigitated arm 19 patients have CR and 11 Patients have PR. The tumour control was better in interdigitate arm and the 1-year overall survival was not statistically significant (p=0.088).



DISCUSSION:-

Shortening of treatment time and interdigitated brachyth erapy is expected to increase the acute toxicities but majority of toxicities that occurred in the study were of Grade 1 or Grade 2. There was no Grade 3 or more toxicities in both the Arms in our study whereas Keys (3.8%,Grade 3),Pearcy (2.4%,Grade 3) and Rose(0.6%,Grade 3) observed Grade 3 skin toxicities in few patients also Basu et al observed 19.23% grade 2 toxicity in interdigitate arm than 11.53% in sequential arm[17,18,19].

Basu et al suggesting Nausea (p=0.056) and vomiting (p=0.032) was more in interdigitated arm, the results were comparable in our study more Grade 2 toxicity 53.33% in Arm B (interdigitate) than 40% Grade 2 toxicity in arm A (sequential),otherwise only 6.67% developed grade 3 toxicity which was in interdigitate arm. Grade 1 toxicity were more in sequential arm 60% than 40% in interdigitate arm [20]

Prakash bhagat et al said that grade 1 and grade 2 anorexia was observed in a significant number of patients treated with either modality their results were comparable with overall 60% Grade 2 Anorexia and 40% Grade 1 Anorexia in both Arms (P=0.114) in our study. Also, there was a significant difference in both Arms A & B for abdominal pain. In interdigitate patients Grade 2 abdominal pain was 66.67% which was more than 16.67% in Arm A (P=0.00), overall there is a significant difference in Upper Gastrointestinal Toxicity in both the Arms (p=0.00).

Lower Gastrointestinal side effects such as diarrhoea (p=0.105) and proctitis (p=0.046) was higher in interdigitate arm in a study done by Basu et al, bhagat et al also suggested having Diarrhoea (p=0.049) and Proctitis (p=0.92) were higher in interdigitated arm.In our study the frequency of Diarrhoea was more in Interdigitate Arm with 72.33% Grade 2 toxicity than 53.33% Grade 2 toxicity in sequential arm.Grade 1 toxicities were more in sequential Arm than in interdigitate arm. Dysuria and Urinary Frequency/Urgency was the most common bladder related toxicity encountered in a study by bhagat et al (for Dysuria p=0.87 and for frequency/urgency p=0.12) there was significant Grade 2 urinary frequency and dysuria in interdigitate arm in our study (p=0.00),there was no Grade 3 and 4 urinary toxicity in our study, Keys(Grade 2-23.3%,3-7.7%,4-1.1%) and Rose(Grade 1-6.3%,2-3.4%,3-1.7%,4-1.1%) observed higher toxicity for all grades which were comparable with our study for Grade 1 and Grade 2 toxicity.

The haematological toxicities were as such low in our study, bhagat et al noted a drop in haemoglobin and leukopenia observed frequently (p=0.51).Rose et al reported grade 2 14.8% and 11.9% of grade 3 neutropenia, in our study anaemia and leukopenia was comparable to bhagat et al results with p= 0.273 and p=0.551 respectively [21].

Overall the incidence of grade 3 toxicity in present study was very low, most toxicities that observed are Grade 1 and Grade 2 which was managed conservatively, nograde 3 haematological toxicities was observed. No undue treatment interruptions were encountered.

Limitations:-

- Single Institutional Study.
- Mean follow up period was for 6 months, inappropriate to comment on chronic toxicity as it requires longer follow up
- Patients with severe co morbidities were excluded
- Small Sample Size due to time constraints.
- Needs expertise in Brachytherapy due to difficult tandem insertion in study arm.

CONCLUSION:-

- Optimizing the brachytherapy schedule concurrently external beam radiation for early and locally advanced cervical cancer is challenging but possible without compromising the quality care.
- Interdigitating Brachytherapy with external beam radiation by 3 weeks reduces the overall treatment time which is the corner stone for complete cure rate.The comparison sequential versus interdigitated brachytherapy with external radiation produced satisfac tory pelvic control with manageable rectal and bladder toxicities. The acute toxicities in both arms were not life threatening and managed conservatively.
- Interdigitated Brachytherapy can be delivered as a standard mode of treatment in cancer cervix patients. Continuing this study for prolonged period and recruiting more patients will help in arriving at conclusive results.

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