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A PROSPECTIVE STUDY TO SEE THE FEASIBILITY, TOXICITY AND EFFICACY OF TWICE WEEKLY INTERDIGITATED, INTRACAVITARY HIGH DOSE RATE BRACHYTHERAPY IN PATIENTS OF LOCALLY ADVANCED CARCINOMA CERVIX UNDERGOING CONCURRENT CHEMORADIATION

Oncology

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ABSTRACT

INTRODUCTION: Due to accelerated repopulation, the treatment of inoperable locally advanced Cervical carcinoma(LACC) should be completed within 8 weeks. In this study, we aim to further reduce the treatment time by interdigitating brachytherapy with CCRT.

AIMS AND OBJECTIVES: To assess the response according to RECIST criteria, version 1.1 and acute toxicities according to the Radiation Therapy Oncology Group [RTOG] criteria.

MATERIALS AND METHODS: After undergoing metastatic work up, patients with histologically proved LACC were treated with CCRT. After 17 fractions eligible patients received HDR brachytherapy twice weekly with a dose of 7Gy/fraction in 4 fractions.No radiation or chemotherapy were given on brachytherapy days.During treatment, patients were reviewed weekly clinically and with blood reports and thereafter 6 weekly for 3 months and 3 monthly till the end of the study.

RESULTS: Most common toxicity encountered during study was GI toxicty (81.1%) followed by haematological toxicity(48.6%) and skin toxicity(21.6%).Most grave toxicity was proctitis which was seen in 6 patients(16.2%).In this study overall response rate at 6 weeks after treatment completion(complete response and partial response) was 100% with complete response(86.5%) and partial response(13.5%).The median duration of follow-up after initial 6 weeks post-treatment assessment was 6 months.

KEYWORDS

Interdigitate brachytherapy ,toxicity, locally advanced cervical cancer,CCRT.

INTRODUCTION:

Cancer of the cervix is the third most common cancer with estimated 1.04 lakh new cases during 2020[1].Unfortunately, it often affects young women resulting in loss of the ability to bear future children.Mortality due to cervical cancer is also an indicator of health inequities as 86% of all deaths due to cervical cancer are in developing, low-and middle-income countries.Due to lack of education and knowledge most of the cervical cancer patients present in late stages.For the past 10 years cisplatin based chemo-radiation (CRT) has been the treatment of choice for all patients with locally advanced cervical cancer. Radiation therapy consists of EBRT (used to treat whole pelvis and the parametria including pelvic lymph nodes) and brachytherapy (used to treat central disease- cervix, vagina and medial parametria with intra-cavitary sources). In patients treated with radiation therapy, overall treatment time should be within 8 weeks, and any planned or unplanned interruptions or delays should be avoided. To prevent accelerated repopulation of cancer cells, treatment time is further reduced by timely integration of external beam and intracavitary irradiation in patients with carcinoma of cervix . When overall treatment time exceeded 56 days , 10 year local recurrence-free survival rate decreased.

MATERIALS AND METHODS :

This was a single institutional, prospective, longitudinal, interventional study.After undergoing pretreatment assessment with history, clinical examination, baseline laboratory investigation and imaging ,37 histologically proved and newly diagnosed ,non metastatic locally advanced (FIGO stage IB2 to IVA) squamous cell carcinoma of cervix attending department of Radiotherapy, Institute of Postgraduate Medical Education and Research and SSKM Hospital, Kolkata from January 2018 to August 2019 aged 18 to 65 years having good performance status(ECOG 0-2) ,creatinine clearance more than or equal to 60 ml/min and no prior history of malignancy, chemotherapy and radiotherapy or serious co-morbidities ,were included in this study.

Treatment were started with CCRT. This involved External Beam Radiation Therapy (EBRT) in a dose of 50 Gy in conventional fractionation of 2 Gy per day (five fractions per week, once daily) with concurrent weekly Injection Cisplatin 40mg/m2, given one hour before EBRT.With this, intracavitary HDR brachytherapy twice weekly in a dose of 7 Gy in 4 fractions each,(2 fractions per week)were given after 17 fractions of EBRT .No EBRT or chemotherapy would be given on brachytherapy days.

Table 1:Treatment protocol

	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Week1		★	●	●	●	●	
Week2		★	●	●	●	●	
Week3		★	●	●	●	●	
Week4		★	●	●	⬟	●	
Week5		⬟	★	●	⬟	●	
Week6		⬟	★	●	●		

★ CCRT DAYS

● RT ONLY DAYS

⬟ BT DAYS ONLY

EBRT PLANNING:

EBRT was given through BHABATRON II which is a cobalt 60 machine.For IFD less than 20 cm , patient was treated with AP-PA field.For IFD more than 20 cm, patients were treated with four field technique,i.e AP-PA and two lateral fields.In both the cases, treatment was in 2- dimensional technique.On each Monday patients were assessed by physical examination, history, and blood for CBC and S.Ur, Cr. On the basis of these, patients received chemotherapy on that day and were advised to continue radiotherapy.

CONCURRENT CHEMOTHERAPY:

Any complaints were documented and necessary managements done.In this study injection cisplatin (40mg/m2) weekly was the chemotherapy. Cisplatin is a non cell cycle specific chemotherapeutic drug which acts by DNA adduct formation mechanism.

BRACHYTHERAPY PLANNING:

After 17 fractions of radiotherapy patients were assessed by p/v, p/r, p/s.If there was adequate space for insertion of Fletcher Suite Delclos applicator , those patients were treated with interdigitated brachytherapy. Brachytherapy was given on Monday and Thursday. On those days patients did not receive chemotherapy and radiotherapy. On those weeks ,patients received chemotherapy on tuesday. Patients were advised to take tab Lorazepam(1mg) -1 tab, tab Bisacodyl

(10mg)-1 tab at night before the day of brachytherapy and on the morning of brachytherapy.Patients were also advised not to take food since morning on the BT date.During brachytherapy procedure patients were in lithotomy position.Deep sedation was used with injection diazepam i.v and injection pentazocin i.m. Dressing and drapping and catheterisation was done then.Next P/V,P/R,P/ S examination was done to know the disease status. Uterine length was measured by uterine sound, angulation was also assessed. According to measurement, the os guard was fixed on central tandem and then inserted.After this ovoid or semi-ovoid applicators were inserted.First right side then left side.The direction of the ovoid or semi-ovoid was postero-laterally. After insertion packing was done.

As soon as completion of the procedure patients were taken to CT simulator room for imaging.If imaging was found satisfactory ,the simulation films were sent to ONCENTRA SOFTWARE(OTP).Then planning was done and treatment was delivered by Nucleatron machine which used Iridium^{192} as radioactive isotope through a remote after loading, intra cavitatory technique.

For EBRT EQD2 was 50 Gy, for Brachytherapy EQD2 was 39.7 Gy, So total EQD2 = 89.7 Gy.

DATA COLLECTION AND FOLLOW UP:

Initial data was collected before treatment. The remaining data was collected on Monday during the treatment procedure then every 6 weeks for the 1st 3 months ,then 3 monthly. Data was analysed on Microsoft Excel 2016 and SPSS version 23 with appropriate statistical tests as applicable. The period of potential follow-up is defined as the difference between the time of initial diagnosis and the closeout date. If the patient was lost to follow-up, her last date of visit was considered.

RESULTS:

37 patients were included in the study.Patients with mean age at diagnosis(51.2±9.5 years). 75.4% patients were post-menopausal at diagnosis and 24.6% were pre-menopausal.Most common histopathology in this study was moderately-differentiated squamous cell carcinoma(77.3%) followed by well-differentiated squamous cell carcinoma(14.3%).Average age of menarche of the patients was 11.9±0.9 years.Most of the patients in this study had a history of early age of marriage(16±1.8 years),early age of first child birth(16.9±1.6 years) and multigravida (4.1±1.1).Most of the patients belonged to BPL category(64.9%) with 56.8% literates and 43.2% illiterates.Mean overall treatment time was 44 ±5 days.Most common toxicity encountered during study was GI toxicity (81.1%) of grade 1(30%) and grade 2(56.7%). Followed by haematological toxicity(48.6%) of grade 1 and 2(24.3% each) and skin toxicity(21.6%).Most grave toxicity was proctitis which was seen in 6 patients(16.2%).Average weight loss was 4.5 kg (range 2.5 kg to 10 kg).Mean radiation dose per fraction to bladder was 436.1±84.3 (D2cc EQD2 521 cGy).Mean radiation dose per fraction to rectum was 305.2±76.8 (D2cc EQD2 331.6 cGy).In this study overall response rate at 6 weeks after treatment completion(complete response and partial response) was 100% with complete response(86.5%) and partial response(13.5%).The median duration of follow-up after initial 6 weeks post-treatment assessment is 6 months with minimum follow-up duration being 3 months-maximum 15 months.7 patients were lost to follow-up.Out of 32 complete responders, 2 patients developed recurrence(6.3%) after 7.5 months and 11 months after completion of treatment. Among 5 partial responders 1 died due to non malignant cause,1 patient progressed to metastatic disease and ultimately received palliative chemotherapy and the rest remained as stable disease.

DISCUSSION

India has a population of 436.76 million women aged 15 years and older who are at risk of developing cervical cancer. Every year 122844 women are diagnosed with cervical cancer and 67477 die from the disease. In India cervical cancer is the second most common cancer among women between 15 and 44 years of age. Based on Indian studies some epidemiological risk factors are early age of marriage, multiple pregnancies, poor genital hygiene, malnutrition, use of oral contraceptive pills and lack of awareness.[8]

In our study ,although the patients had a history of early age of marriage (16±1.8 years),multi- parity(4.1±1.1), low socioeconomic status(64.9%) but in contrast they are literate 56.8%.

That the most common histology of cervical cancer is squamous cell carcinoma[2] is absolutely true in our study, where we found that most of the cervical cancer cases were moderately- differentiated squamous cell carcinoma(77.3%) followed by well-differentiated squamous cell carcinoma(14.3%).

In a paper by Lodha M et al presented at the International Gynecologic Cancer Society Regional Meeting on Gynecologic Cancers, IGCS 2011 New Delhi India to assess the effect of shortening of overall treatment time on local control, disease free survival & toxicity by interdigitating HDR intracavitary brachytherapy with concurrent chemoradiation in carcinoma cervix, conducted at BMCHRC from May 2007 to Nov. 2008 showed that the study concluded that HDRBT interdigitated with EBRT appears to be as effective as the conventional schedule with comparable toxicities.[3] A study by Nawed Alam et al ,of Aligarh Muslim University, on interdigitated versus sequential high-dose-rate intracavitary brachytherapy with external beam radiotherapy in locally advanced carcinoma cervix to decrease OTT and to compare clinical outcomes in locally advanced carcinoma cervix showed 72 out of 82 patients completed treatment and Mean OTT in study group and control group was 40 and 60 days, respectively. The median follow-up duration was 10 months (3-18).Most of the acute and late toxities were of grade 1 and 2 type and comparable in both study and control groups.Treatment interruption due to treatment-related toxicity was slightly higher in the study group than in the control group, but statistically insignificant. OS negotiability was not found to be a limiting factor for interdigitated ICBT. Study concluded that there was equivalent response in both arms, and advantage of significant reduction in OTT by interdigitated brachytherapy.[4]

In our study mean overall treatment time was 44 ±5 days.The median duration of follow-up after initial 6 weeks post-treatment assessment is 6 months with minimum follow-up duration being 3 months-maximum 15 months.Most common toxicity encountered during study was GI toxicity (81.1%) of grade 1(30%) and grade 2(56.7%). Followed by haematological toxicity(48.6%) of grade 1 and 2(24.3% each) and skin toxicity(21.6%).Most grave toxicity was proctitis which was seen in 6 patients(16.2%).So the results are corroborative with above study.

We tried to find out the correlation between OTT and proctitis which showed a negative correlation (variables are related with inversely proportional to each other) but was not found to be statistically significant.

An open label randomised clinical trial by Abhishek Basu et al on concurrent chemoradiation with sequential versus interdigitated brachytherapy for locally advanced carcinoma cervix to evaluate the effects of treatment duration shortening by means of interdigitated brachytherapy comparing with conventional external beam radiotherapy followed by brachytherapy.During treatment patients were reviewed weekly. After treatment completion, patients were reviewed at six weeks, then three- monthly thereafter.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.The study concluded that interdigitated Brachytherapy can be delivered as a standard mode of treatment in cancer cervix[5]. Continuing this study for prolonged period and recruiting more patients will help in arriving at conclusive results ,which is quite relatable to our study where overall response rate at 6 weeks after treatment completion(complete response and partial response) was 100% with complete response(86.5%) and partial response(13.5%).

Recommended EQD2 in order to maximize local control is 85-90 Gy and the EQD2 limit for the rectum and sigmoid is 70–75 Gy and for the bladder is 90 Gy.[6]

In our study the total EQD2 was as follows:
For EBRT 50 Gy in 25 fractions, 2 Gy /fractions:EQD2 = 50 Gy

For Brachytherapy 7Gy / fractions for 4 fractions:EQD2= 39.7Gy(applying EQD2=n*d*((d+alpha/beta)/(2+alpha/beta))

Total EQD2 = 89.7 Gy.

In our study the total dose was within the recommended dose limit. Similarly Mean radiation dose to bladder (2cc) was EQD2 71.8 Gy. Mean radiation dose to rectum (2cc) was EQD2 65.2cGy .Both were

within recommended limit of respective OARs.

LIMITATIONS:

1. Parametrial boost and interstitial implant were not done. The problems of persistent parametrial disease and enlarged lymph nodes were solved by contouring the lymph nodes and modifying the brachytherapy fraction sizes that may cover the adjacent parametria. Total dose was always kept under recommended dose.
2. Sample size was small and study period was too short.chronic toxicity was not analysed.
3. For further conclusion randomised trial should be done.

CONCLUSION:

To conclude, this study is feasible as the toxicities were limited and manageable. Most of the patients responded well without significant recurrence. For further conclusion, large number of patients should be included and compared to a control arm.

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