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Research Article

A Randomized Study to Compare the Outcome and Tolerability of Hypofractionated Chemoradiotherapy Versus Conventional Chemoradiotherapy in Advance Carcinoma of Cervix

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Abstract

Aims: Aim of this study was to evaluate the toxicity profile and locoregional response rate comparing hypofractionated chemoradiation with conventional chemoradiation.

Materials and Methodology: We conducted a prospective study done in 59 untreated patients of squamous cell carcinoma of cervix (FIGO stage II –IVA) with histologically confirmed diagnosis and no evidence of distant metastasis. They were randomized to Arm A (HRT) and Arm B (CRT), 29 patients in arm A and 30 patients in arm B. Arm A received EBRT 39Gy in 13#, while Arm B received 46Gy in 23# with standard pelvic field box technique. Both arm received concurrent cisplatin 100mg/m2 three weekly. EBRT was followed by 3 sessions of Intracavitory Brachytherepy (ICBT) at a week interval to a dose of 7Gy per session to point A by HDR. End point of the study were tumor response, acute (3 months) and late toxicities (1 year).

Results: 29 patients in Arm A and 30 patients in Arm B were recruited over 18 months. All patients completed minimum follow up of 1 year. 26 patients completed treatment in Arm A and 26 patients completed treatment in Arm B. Maximum acute toxicity in Arm A in term of skin reaction was grade I (57.6%) and proctitis is grade I (64.3%) with median time for completion of treatment 7-8 weeks. Maximum acute toxicity in Arm B in skin reaction was grade I (73%) and proctitis grade I (53.4%) with median time for completion of treatment 7-8 weeks. Complete response at 3 months is 100% in arm A and 92.3% in arm B. Overall Survival at 6 months was 80.7% equivalent in both arms. Progression free survival at 6 months was 65.3% and 76.9% in arm A and arm B respectively.

Conclusion: Tumor response in patients treated with hypofractionated radiotherapy appears comparable to that of standard fractionation with manageable toxicity profile.

Keywords: Cancer; Tumour Control Probability (TCP); Toxicity

Introduction

Cancer of cervix uteri is the 4th most common cancer among women worldwide, with an estimated 6,04,127 (3.1%) new cases and 3,41,831 deaths (7.5%) per year (GLOBOCAN 2022) [1]. Cervical cancer is the second most common cancer in India in women accounting for 18.3% of all cancer in women. 1,23,907 women are diagnosed with cervical cancer and 4,13,381 die from the disease (GLOBOCAN 2020) [1]. Concomitant chemo-radiation (CRT) with weekly cisplatin has become the "standard of care" for treatment of advanced cases of carcinoma cervix [2]. Cisplatin has been the most active agent identified. After the NCI alert in 1999 [3] cisplatin-based concurrent chemoradiotherapy has become widely used in the treatment of locally advanced carcinoma cervix. Long radiotherapy course is a major factor for defaulting radiotherapy

patients in developing countries. Treatment break or discontinuance leads to treatment failure. Higher dose and shorter treatment duration were associated with higher tumour control probability (TCP). According to his study the best TCP fit was achieved with an onset time (Tk) of acceleration of 19 days and a number of tumor clonogens (K) of 139 [4]. This suggests that hypofractionation could be a potential choice of treatment for carcinoma of the cervix. Conventional fractionation in radiotherapy delivers 1.8-2Gy per fraction 5 days a week. There is a long waiting period when these patients are treated with conventional fraction and there is also a long waiting period for intracavitary brachytherapy post EBRT completion in high burden of patients with resource limited setting. All these factor resulting in longer treatment time. With the majority of the carcinoma of the cervix being squamous cell carcinoma, one disadvantage of a long waiting period is that squamous carcinoma is a rapidly multiplying tumor with a potential doubling time (T-POT) of approximately 5 days [5]. Hence, from initial assessment to the time of simulation and treatment, most patients are upstaged, with a consequent poorer prognosis. Hypofractionation involves giving a smaller number of larger doses per fraction. Treatment regimens involving fewer fractions, is clearly more convenient for patients and is of benefit in resource constraint health systems. Overall treatment time is important for fast growing tumors and as for carcinoma of the cervix, local tumor control is decreased by 0.5% each day the overall treatment time is prolonged past 49 days [6].

Materials and Methodology

Patients with non-metastatic locally advanced Carcinoma Cervix with histopathologically proven diagnosis suitable for radiotherapy were randomly divided into two groups: Arm A EBRT/39Gy/13# while Arm B EBRT/46Gy/23# with standard pelvic technique. Both arms received concurrent cisplatin (100mg/m^2) three weekly. EBRT was followed by 3 sessions of ICRT at a week interval to a dose of 7Gy per session to point A by HDR.

Assessment during treatment

From the commencement of treatment, all the patients included in the study were assessed weekly during treatment and prior to every brachytherapy insertion for response and acute toxicity.

Assessment after the completion of treatment

All the patients were assessed 6 weeks after the completion of treatment to detect acute complications like skin reaction, mucositis. Acute treatment related toxicities were graded using Radiation Therapy Oncology Group (RTOG) criteria. The assessment of tumor response was assessed by using the RECIST (1.1) response criteria. Late side effects were defined as sequelae reported six months from completion of radiotherapy and were recorded for the sites bladder; bowel, vagina, skin and others. All toxicities were graded as Radiation Therapy Oncology Group (RTOG) criteria. Radiological assessment for tumor was done when indicated. All the patients were followed up regularly on OPD basis for a period of atleast 6 months, weekly for four weeks in first month and then monthly. At every visit, each patient was clinically evaluated for local control of disease and treatment related complications. To evaluate the local disease control, local vaginal examination using inspection, palpation will be done at each follow up and response will be assessed. On the suspicion of any local reoccurrence, biopsy will be taken for histopathology and correlated clinically. Late toxicity will be assessed after 6 months of completion of radiotherapy. The patients will be assessed for any evidence of distant metastasis during each follow up. In case of any suspicion, relevant investigations will be done to rule out the presence of distant metastasis. Radiological assessment for response by CT Scan at 2 months and 6 months after completion of radiotherapy.

Result

The predominantly affected age group of Arm A 51.4 years and of arm B was 48.65 years. All patients had (KPS) Karnofsky Performance Status 70 or above in both arms. Brachytherapy was successfully performed in 88.23% patients in study group and 83.33% in control group, respectively. Median follow up period for Arm-A was 6.5 months. Median follow-up for Arm-B was 6 months. 7 patients lost to follow up in each arm. Out of 26 patients who completed follow up of 1 year total of 20 patients were disease free is 80% in study group and 70% in control group whereas 5 patients had residual disease 30%. In study group and 20% in control group. One patient expired in control group after developing lung metastasis 2 month after treatment completion. Hematotoxicity was noted in 10% patients in study group and 7.6% patients in control group. Skin toxicity was noted in a total of 53.92% patients. Gastro Intestinal (GI) toxicity was noted in a total of 78.43% patient.

Discussion

Cervical cancer is more common in rural population and lower socioeconomic group in India. Low education and poor socioeconomic status is potential barrier between patient and medical sys-

Patient characteristics			
Age group (years)	ARM A	ARM B	
21-30	1 (3.6%)	0	P value = 0.185 Chi square value = 6.2
31-40	4 (14.3%)	5 (19.2%)	
41-50	12 (42.9%)	5 (19.2%)	
51-60	8 (28.6%)	8 (30.8%)	
61-70	3 (10.7%)	8 (30.8%)	
Staging (FIGO)			
IB1	4 (14.3%)	4 (15.4%)	P value = 0.058 Chi Square Value = 12.205
IB2	4 (14.3%)	2 (7.7%)	
IIA1	7 (25%)	1 (3.8%)	
IIA2	3 (10.7%)	9 (34.6%)	
IIB	4 (14.3%)	3 (11.5%)	
IIIA	5 (17.9%)	2 (7.7%)	
IIIB	1 (3.6%)	5 (19.2%)	
Parity distribution	4.07 ± 1.33	4.15 ± 2.31	P value = 0.874 CI = -1.13 to 0.965
Hb level distribution	10.39 ± 2.02	10.23 ± 2.05	P value = 0.771 CI = -0.951 to 1.275
Overall treatment time			
<6 weeks	5 (17.9%)	0 (0)	P value = <0.001 Chi Square value = 19.28
6-8 weeks	10 (35.7%)	0 (0)	
>8 weeks	13 (46.4%)	26 (100%)	
Reactions			
Acute skin reaction	ARM A	ARM B	
I	15 (53.6%)	21 (80.8%)	P value = 0.104 Chi Square Value = 4.52
II	11 (39.3%)	4 (15.4%)	
III	2 (7.1%)	1 (3.8%)	
Acute mucosal reaction			
I	21 (75%)	19 (73.1%)	P value =).798 Chi Square Value = 0.451
II	5 (17.9%)	6 (23.1%)	
III	2 (7.1%)	1 (3.8%)	
Acute bladder reaction			
I	15 (53.6%)	16 (61.5%)	P value = 0.826 Chi Square value = 0.383
II	7 (25%)	5 (19.2%)	
III	6 (21.4%)	5 (19.2%)	
Acute gi reactions			
I	15 (53.6%)	17 (65.4%)	P value = 0.438 Chi Square value = 1.65
II	6 (21.4%)	6 (23.1%)	
III	7 (25%)	3 (11.5%)	

Acute rectal toxicity			
I	18 (64.3%)	14 (53.8%)	P value = 0.661
II	6 (21.4%)	6 (23.1%)	Chi Square value = 0.827
III	4 (14.3%)	6 (23.1%)	

Table 1

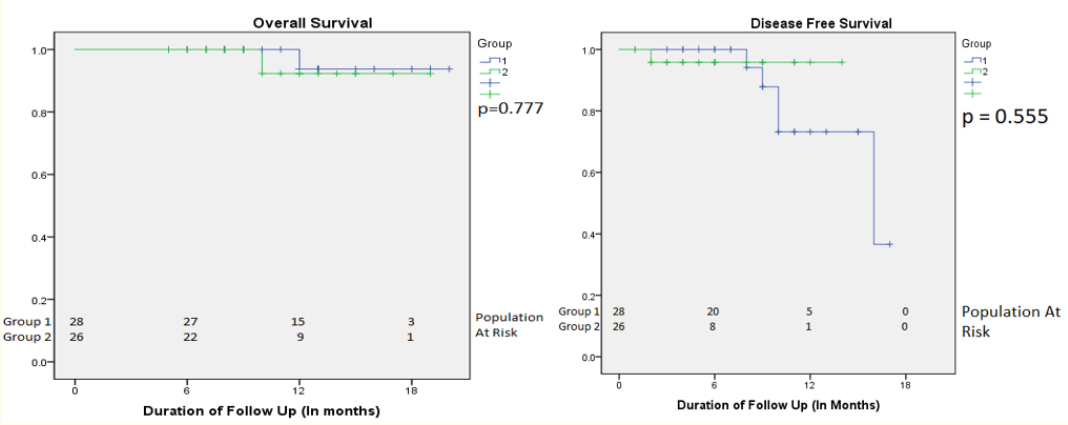

Figure 1: Overall Survival (OS). **Figure 2:** Disease Free Survival (DFS).

tem resulting in seeking medical help in advanced stage of their disease. Advanced disease is best managed by concurrent chemo radiotherapy. Goal of treatment is maximizing tumor control while maintaining functional and quality of life. In our present study most patients belong to age group 41-60 (77.14%) with a mean age of 50.08 years which is in accordance with literature as peak age is between 55-59 years (Sreedevi A., *et al*.) [7] Disease is less common below 20 years; this may be because of lesser incidence of sexual exposure. In our study most of the patients belongs to FIGO stage IIB (40%) followed by IIA (37.14%) There was no significant difference in distribution among the two arms. As has been reported in literature, in most of the patients were multiparous (65.71%) having parity more than 3 (MUNOZ., *et al*.) [8] Hypofractionated radiotherapy delivers high dose per fraction (>2-2.5Gy), daily for 5 days with a gap of 24 hours. Reduction in the total dose is needed taking into consideration high dose per fraction so as to reduce the normal tissue effects The dose fractionations used in our being 39Gy in 13# over 17 days. The biological equivalence in term of BED was 50.4Gy. Patients were subsequently treated with HDR brachytherapy of 9Gy weekly, to a total of 18Gy with concurrent chemotherapy. The combined BED of external RT and intracavitary brachytherapy being 84.9Gy. Treatment regimen involving fewer fractions, is clearly more convenient for patients and is of benefit in resource constraint health systems. A study by Huang., *et al*. (2012), verifies the fact that accelerated repopulation does exist in cervical cancer and has a relatively short onset time. Higher dose and shorter treatment duration were associated with higher tumor control probability (TCP). According to him the best TCP fit was achieved with an onset time (Tk) of acceleration of 19 days and a number of tumour clonogens (K) of 139 [10]. Which has been put to test in this study. There is a statistically significant (p = 0.006) benefit of reduction in overall treatment time (<6 weeks) in terms of tumor response in HRT arm. It may later translate in to better overall survival but longer duration of follow up is required to comment on overall survival benefit.

Our study has also shown that both the treatment modalities give comparable response rate and local tumor control in patients .The complete response rate was seen in 70% of cases in arm A and in 80% of cases of arm B at 6 months after the completion of treatment. Similar result was observed in study by Muckaden., *et al*. [11]. The haematological, dermatological and GI toxicities were the major toxicities found in our study. Among the haematological toxicities ≥Grade 2 anemia was seen in 32.33% cases of arm A and

in 35.28% of cases of arm B This difference between conventional arm and hypofractionated arm was statistically not significant (p = 0.9944) and managed effectively using packed red blood cells transfusion whenever indicated to keep the average hemoglobin well above 10 gm/dl during the entire duration of radiation therapy. Arm B showed similar lower GI toxicities (Rectal) compared to arm A. Grade 3 skin and mucosal toxicity was seen more in arm B (17.64%). Though the genitourinary toxicities (Bladder) are seen more in arm B as compared to arm A and were of grade I and II only and the difference is not statistically significant. In my study, there was no patient with acute grade 3 or 4skin and/or GU complications. Though the acute radiation sequelae seem to be higher in test arm but they are of mainly grade I/II reactions and statistically not significant and manageable conservatively. In this study, due to lack of long term follow-up period, the late toxicities cannot be compared. Grade 1 proctitis was seen more in Arm A (30%) compared to Arm B (20%). Grade II proctitis was seen more in Arm B (30%) compared to Arm A (20%). A study by Bosset., *et al*. reported the rate of late rectal morbidity was between 2-25 in radiotherapy patients [13]. From a study by Swaroop., *et al*. it appeared that the time of development of bleeding per rectum is between 6 months to one year after completion of radiation therapy and is caused by friable mucosal angiogenesis [12]. According to studies reported in the literature, late urinary tract complications are seen frequently 3-5 years after treatment [13].

Conclusion

In conclusion, this study demonstrates that, within study limitations and despite increased but clinically manageable toxicity, the hypofractionated radiotherapy has comparable outcomes for patients with advanced cervical carcinoma compared with current standard of care. Reduced overall treatment time can be helpful for patients in better compliance, shorter hospital stay and for hospital in more number of patient coverage in a fixed time period. Further studies are required to define optimal patient selection for this combination and to delineate the specific contributions of hypofractionated radiotherapy to survival outcomes. However, it may be used in old aged patient in which long course of treatment is not feasible.

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