



A Prospective randomized study to compare the outcome and tolerability of Hypofractionated chemoradiotherapy versus conventional chemoradiotherapy in Advance Carcinoma of Cervix

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Abstract

Background: Cervical cancer is the second most common cancer in India in women accounting for 22.86% of all cancer cases in women. Aim of this study is to investigate tumor response and toxicities in Advance Carcinoma of Cervix treated by hypofractionated radiotherapy compared with conventional fractionation radiotherapy.

Materials and Methods: We conducted a Prospective study done between September 2017 to September 2019. 40 untreated patients of squamous cell carcinoma of cervix (FIGO stage II –IVA) with histologically confirmed diagnosis and no evidence of distant metastasis & chronic medical condition were randomised to Arm A (CRT) and Arm B (HRT), 20 patients in each arm. Arm A received EBRT 46 Gy in 23 #, 5# per week for 4.5 week while Arm B received 39 Gy in 13 # at 5 # per week with standard pelvic AP/PA or four field box technique. Both arm received concurrent cisplatin 40mg/m² weekly. EBRT was followed by 2 session of Intracavitary brachytherapy at a week interval to a dose of 9Gy per session to point A by HDR. 3 patients in HRT arm and 2 patients in CRT arm defaulted treatment and hence excluded from study. End point of the study were tumor response, acute and late toxicities.

Results: Complete response was achieved by 64.70 % in HRT arm as compared to 66.67% in CRT arm. Partial response was achieved by 35.30% as compared to 33.33 but the differences was statistically not significant at two month. (p value= 0.2589) Grade 3/4 skin toxicity was significantly higher in the HRT (17.3 %) arm as compared to conventional. Acute toxicities (Grade I, II) are statistically non-significant & managed conservatively.

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

Keywords: Hypofractionation, carcinoma cervix, concurrent chemoradiation.

Introduction

Cervical cancer is the second most common cancer in India among women accounting for 16.5% of all cancer in women. 96,922 women were diagnosed with cervical cancer and 60,078 died due to the disease in a year. (GLOBOCAN 2018)^[1]. Most of the cases present in advanced and late stage, and 63%-89% have regional disease at the time of presentation. The ASR is highest 23.07/100,000 in Mizoram (Aizawl city) state and the lowest is 4.91/100,000 in Dibrugarh district.^[2] Concomitant chemo-radiation (CRT) with weekly cisplatin has become the “standard of care” for treatment of advanced cases of carcinoma cervix.^[3] Cisplatin has been the most active agent identified. After the NCI alert in 1999.^[4] 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 effective 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^[5]. 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 intra cavitory 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 tumour with a potential doubling time (T-POT) of approximately 5 days^[8]. 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 that the overall treatment time is prolonged past 49 days^[6]

Aim & Objectives

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

Materials and Methods

Our study was a two arm prospective study included a total of 40 patients (20 for Arm A-conventional chemoradiation and 20 for Arm B-hypofractionated chemoradiation) of histologically proven squamous cell carcinoma of cervix fulfilling the inclusion and exclusion criteria.

Inclusion Criteria

- 1) Histologically proven squamous cell carcinoma of uterine cervix.
- 2) Patients previously not treated for cervical cancer.
- 3) Patients' age less than 70 years.
- 4) Karnofsky performance scale > 70
- 5) Complete hemogram with Hb>10gm/dl; TLC>4000/cmm, platelet count >1,00,000/cmm

Exclusion Criteria

- 1) Distant metastasis.
- 2) Prior history of radiation, surgery or chemotherapy for the disease.
- 3) Poor general condition with karnofsky performance scale of < 70 .
- 4) Associated medical condition such as renal disease, liver disease or heart disease

5) Histology other than squamous cell carcinoma.

Pre Treatment Evaluation

The pre treatment evaluation in all patients had included

- Complete history, general physical examination complete systemic examination
- BSA
- The assessment of general condition were be done by using karnofsky performance status
- Hematological assessment was done by complete hemogram including Hb TLC, DLC.
- Biochemical assessment to assess the kidney and liver function was done by blood urea, serum creatinine, creatinin clearance, SGOT, SGPT.
- Radiological assessment include CXP – PA view were done in all patients
- Whenever clinically indicated USG abdomen and pelvis and CT/MRI pelvis done.
- The patients were staged according to FIGO staging system.

Methodology

- Histologically proven squamous cell carcinoma patients were investigated and the eligible patient were randomized into two arms with the help of randomisation.
- ARM-A(CRT) Received EBRT/46Gy/ 23 #/ 2 GY per 5 days a week followed by intracavitary brachytherapy(9 GY per# weekly x2 weeks) with concurrent Inj. Cisplatin 40 mg/m² weekly .
- ARM B(HRT) Recieved EBRT 39 Gy in 13 fraction , 3 GY per fraction , 5 days a week followed by intracavitary brachytherapy (9 GY per# weekly x 2 weeks) with concurrent Inj. Cisplatin 40 mg/m² weekly
- All the patients received pelvic external beam radiotherapy in supine position by using megavoltage beam on telecobalt / Linear Accelerator by two parallel opposed AP / PA portals with Source Axis Distance (SAD) technique at 80 &

100 cm respectively. The 4 field box technique was adopted in obese patients with separation more than 20 cm. Minimum margins were the upper margin of L4-5 (superiorly), the lower margin of the obturator foramen or the lowest extension of the disease (inferiorly), and 1.5-2.0 cm beyond lateral margins of true bony pelvis. For the lateral fields, the anterior margin was the anterior edge of pubic symphysis. The posterior margins at the S2-S3 interspace were used.

- Two fractions of HDR intracavitary brachytherapy was delivered, One to two week following completion of external beam radiotherapy, using micro Selectron HDR unit (Nucletron BV, The Netherlands) at weekly interval. Individual computer treatment planning was done using Oncentra treatment planning system. A radiation dose of 9 Gy was prescribed to the Manchester point- A by HDR technique. The patients with suboptimal regression and deformed anatomy and geometry were treated with boost external radiotherapy dose of 20Gy in 10 fractions over 2-week period.

Assessment

From the commencement of treatment, all the patients included in the study were assessed weekly during treatment for response and acute toxicity. Acute treatment related toxicities were graded using Radiation Therapy Oncology Group (RTOG) criteria. All the patient were assessed two months after the completion of treatment,

- To detect tumor response by using clinical examination.
- To detect acute complications like skin reaction, mucositis

The assessment of tumor response was assessed by using the RECIST (1.1) response criteri. 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.

Statistical Analysis

The data thus obtained was assessed, analysed and compared to find out difference in both groups in terms of tumor response, acute & chronic toxicity. Continuous variables (age, hemoglobin) were presented as Mean ± SD (standard deviation). Follow-up in months was presented as median and range. Categorical variables were expressed in actual numbers and percentages. Categorical variables were compared by using chi-square test. All the tests were two sided. P value reports are two tailed and P-value <0.05 was considered statistically significant.

Result

Table 1 Patients characteristics (age wise distribution)

Age (Years)	CRT ARM (n=18)		HRT ARM (n=17)	
	No.	%	No.	%
21-30	0	0	1	5.88
31-40	1	5.55	2	11.76
41-50	9	50	6	35.29
51-60	5	27.78	7	41.17
61-70	3	16.66	1	5.88
Total	18	100	17	100

Table 2 Patients characteristics (FIGO stage wise distribution)

STAGES	CRT ARM (n=18)		HRT ARM (n=17)	
	No.	%	No.	%
IIA	6	33.33	7	41.10
IIB	8	44.44	6	35.29
IIIA	0	0	2	11.76
IIIB	4	22.22	2	11.76
TOTAL	18	100	17	100
P = 0.9028 (non significant)				

Table 6 -Overall Treatment Time (OTT) Comparison

OTT (Wk)	CRT ARM(n=18)		RESPONSE AFTER 2 MONTH		HRT ARM(n=17)		RESPONSE AFTER 2 MONTH	
	No.	%	CR	PR	No.	%	CR	PR
<6 WK	0	0	0	0	7	41.2	6	1
6-8 WK	8	44.4	6	2	5	29.4	3	2
>8 WK	10	55.6	6	4	5	29.4	2	3
TOTAL	18	100	12	6	17	100	11	6
P = 0.006 (significant)								

Table 3 Patients characteristics (Parity wise distribution)

PARITY	CRT ARM (n=18)		HRT ARM (n=17)	
	No.	%	No.	%
0-3	3	16.66	9	52.94
4-6	13	72.22	6	35.29
>6	2	11.11	2	11.76
TOTAL	18	100	17	100
P = 0.0622 (non significant)				

Table 4 Patients characteristics (Hb level range wise distribution)

Hb (gm)%	CRT ARM (n=18)		HRT ARM (n=17)	
	No.	%	No.	%
>12	3	16.67	3	17.64
10-12	11	61.11	10	58.82
<10	4	22.22	4	23.52
Total	18	100	17	100

Table 5 Clinical response 2 months after treatment completion

TUMOR RESPONSE	CRT ARM (n=18)		HRT ARM (n=17)	
	No.	%	No.	%
CR	12	66.67	11	64.70
PR	5	33.33	06	35.30
DEATH	1	5.56	0	0
TOTAL	18	100	17	100
P = 0.9028 (non significant)				

The mean age of arm A 51.4 years & of arm B were 48.65 years. All patients had (KPS) Karnofsky performance status 70 or above in both arms. Brachytherapy was successfully performed in 15(88.23%) patients in study group and 15(83.33%) in control group, respectively.

Follow up for Arm-A was in range of 2-20 months. Mean follow up for Arm-A was 8.72 months with standard deviation (SD) of 5.69 months. Median follow up period for Arm-A was 6.5 months. Follow-up for Arm-B was in range of 2-15 months. Mean follow-up for Arm-B was 7.11 months with standard deviation (SD) of 3.78 months. Median follow-up for Arm-B was 6 month. 7 patients lost to follow up in each arm. 4 patients in each arm lost to follow up before completing 6 month of follow up. So Out of 26 patients who completed follow up of 6 months a total of 20 patients were disease free i.e. 10 (80%) in study group and 10(70%) in control group whereas 5 patients had residual disease; 3(30%) in study group and 2(20%) in control group. One patient expired in control group after developing lung metastasis 2 month after treatment completion. Hematotoxicity was noted in 7 (10%) patients in study group and 8(7.6%) patients in control group. Grade I, II and III toxicity in study group were 1 (8%), 4 (48%) and 2 (4%), respectively in study group & 2(8%), 4 (48%) and 2 (4%), respectively in control group.

Skin toxicity was noted in a total of 55 (53.92%) patients (30 in study group and 25 in control group). Grade I, II and III toxicity in study group were 1 (8%), 4 (48%) and 2 (4%), respectively in study group & 2(8%), 4 (48%) and 2 (4%), respectively in control group. There was no grade IV skin toxicity in study arm. Whereas grade I and II toxicity noted in control group were 8 (15.38%) and 16 (30.77%) patients, respectively. There was one grade III toxicity (1.92%). No grade IV skin toxicity was noted in control arm,

Gastro Intestinal (GI) toxicity [Table 9] was noted in a total of 80(78.43%) patients (41 in study group and 39 in control group). Grade I, II and III toxicity in study group were 27(54%), 12(24%)

and 2(4%), respectively. There was no grade IV GIT toxicity. Grade I and II toxicity noted in control group were 20(38.4%) and 8(15.4%), respectively. There was only one patient who had grade III toxicity (1.9%) in control group. No grade IV toxicity was reported.

Discussion

Cervical cancer is one of the most common gynecological malignancies in India. It is more common in rural population and lower socioeconomic group. Low education and poor socioeconomic status is potential barrier between patient and medical system. Such patients seek medical help in advanced stage of their disease. Advance carcinoma cervix 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**)^[2] The mean age of the patients at the time of presentation was (51.44±9.34) years in arm A with a range (35 -70 years) while it was (48.65±9.73) years in arm B with a range of (22-61years). 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 our study most of the patients were multiparous (65.71%) having parity more than 3 (**MUNOZ et al.**)^[7]

Impact of Overall treatment time

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 treatment time and number of fractions is hence reduced. The dose fractionations used in our

study being 39 Gy in 13 fractions over 17 days. The biological equivalence in term of BED was 50.4 Gy. 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 84.9 Gy. Treatment regimens involving fewer fractions, is clearly more convenient for patients and is of benefit in resource constraint health systems. **Girinsky et al** in 386 patients with stage 2b or 3 carcinoma of the cervix, observed that the 10 year local recurrence free survival rate decreased when overall treatment time exceeded 52 days. A 1.1% loss of pelvic tumour control per day was also observed in their regression analysis^[9]. 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 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 tumour clonogens (K) of 139^[10]. **Chatani et al.** in 216 patients with stage IIB to III cervical carcinoma treated with combination of EBRT and HDR brachytherapy noted that the OTT was the most significant factor for local tumor control in multivariate analysis (p=0.0005) for relapse free survival stage (p=0.0001), OTT (p=0.0035) and Hb level (p=0.0174) were the three most important prognostic factors^[11]. This suggests that hypofractionation could be a potential choice of treatment for carcinoma of the cervix. 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.

Locoregional response: Our study has shown that both the treatment modalities give comparable response rate and local tumor control in patients

with Ca cervix. 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.**^[12]

Acute toxicities: The haematological, dermatological and gastrointestinal toxicities were the major toxicities found in our study.

Among the haematological toxicities \geq Grade 2 Anaemia 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 haemoglobin well above 10 gm/dl during the entire duration of radiation therapy. Upper GI toxicities of Grade 1 and 2 were similar in both the arms. 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 4 skin 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. Arm B cases showed more Grade 3 toxicities compared to arm A. Grade III acute toxicity were found in 3 pt. in test arm leading to 1-2 week of treatment break, But that did not translated in to loss of tumor control in 2 patients & 1 pt. lost to follow up after treatment completion

Late Toxicities

In this study, due to lack of long term follow-up period, the late toxicities cannot be compared. However only the toxicities noted after 6months of completion of treatment is taken. There was no patient with late bladder complications up to a maximum follow-up of 20 months. 40% patients

showed Grade 1 & Grade -2 late vaginal toxicities in each arm. Grade 1 proctitis was seen more in Arm A 3 out of 10 patients (30 %) compared to Arm B 2 out of 10 patients (20%). Grade II proctitis was seen more in Arm B 3 out of 10 patients (30 %) compared to Arm A 2 out of 10 patients (20%). Chronic lower abdominal pain was also more in arm B 6 out of 10 (60%) as compared to Arm A 4 out of 10 (40%). 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^[14]. However, **Yegappan et al.** have reported a mean duration of 19.9 months for toxicity after radiotherapy for development of bleeding per rectum^[16]. According to studies reported in the literature, late urinary tract complications are seen frequently 3-5 years after treatment.^{[15], [16], [17]}

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.

Limitation

Follow-up of the present study was relatively short and prevents us from commenting on the long term disease free survival, overall survival, and a more comprehensive evaluation of the late toxicities too. Another limitation of our study was

the relatively smaller sample size and consequently, subgroup analyses could not be materialized.

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