VOLUME - 12, ISSUE - 05, MAY - 2023 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Oncology/Radiotherapy

A PROSPECTIVE STUDY TO ASSESS RESPONSE AND TOXICITY OF HYPERFRACTIONATED CONCURRENT CHEMO-RADIOTHERAPY AS COMPARE TO CONVENTIONAL REGIMEN IN LOCALLY ADVANCED CASE OF CARCINOMA CERVIX

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ABSTRACT

Objective: To study the response and toxicity in hyperfractionation radiotherapy [HFRT] schedule in locally advanced carcinoma of cervix and to compare with conventional schedule. **Materials and Methods:** Total number of 60 patients FIGO stage IIB to IVA were selected for the study. Thirty patients were treated with HFRT while 30 patients with conventional schedule. In HFRT all the patients were given RT dose of 60 gray (Gy) in 50 fractions (#) @ 1.2 Gy/# and 2#/day at 6 hours interval while in conventional schedule all the patients were given 50Gy/25# @ 2Gy/#, 1#/day.Injection cisplatin intravenous was administered thrice weekly in both the treatment schedules. After one week of completion of external beam radiotherapy (EBRT), the Intracavitary radiation therapy (ICRT) was given. All the patients were given 3 fractions each of 7 Gy at the interval of 1 week between each two fractions. **Result:** Complete response was shown by 23 [76.6%] and 21 [70%] patients while partial response was shown by 2 [6.6%] and 5 [16.6%] patients in HFRT and conventional schedule respectively. Mucosal reaction and haematological toxicity occur during and after treatment but all toxicities were manageable by growth factor and hydration on outpatient or in patient department. **Conclusion:** HFRT along with concurrent chemotherapy have produced clinically slightly better tumour control without enhancing normal tissue damage. However, HFRT may lead to increased late bowel complications and must be used judiciously in the treatment of cervical cancer.

KEYWORDS : Cervical cancer; Conventional radiotherapy; hyperfractionation radiotherapy

INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 604,000 new cases and 342,000 deaths worldwide in 2020. Cervical cancer is the most commonly diagnosed cancer in 23 countries and is the leading cause of cancer death in 36 countries. Iimportant cofactors include some sexually transmittable infections (HIV and Chlamydia trachomatis), smoking, a higher number of childbirths, and long-term use of oral contraceptives.[1]

Incidence and mortality rates have declined in most areas of the world for the past few decades. The declines are ascribed to factors linked to either increasing average socioeconomic levels or a diminishing risk of persistent infection with high-risk HPV, resulting from improvements in genital hygiene, reduced parity, and a diminishing prevalence of sexually transmitted disease. [2]

The main treatment modalities for cervical cancer are surgery, radiotherapy concurrent with chemotherapy, brachytherapy and chemotherapy. In early stage of uterine cervix cancer,surgery or brachytherapy is the modality of treatment and in the locally advanced uterine cervix cancer external beam radiotherapy (EBRT) with or without concurrent chemotherapy and brachytherapy is one of the best modalities of treatment. In palliative setting, chemotherapy or radiotherapy are the treatment of choice.Conventional radiotherapy [RT] schedule mostly used in treatment of cervical cancer but hyperfractionation radiotherapy [HFRT] schedule was suggested in some studies where smaller-than-standard doses per fraction were used. It can be achieved without extending the overall treatment duration by treating once a day for 6 or 7 days per week but is usually given as two fractions per day, five days per week. It aims to increase the therapeutic differential between late-responding normal tissues and acute-responding tumors by exploiting differences in response to dose fractionation.

Hyperfractionation has improved tumor control rates but also increased acute toxicity. A meta-analysis of randomized trials treating mostly cancer of the oropharynx, larynx and gynaecologic cancer and comparing conventional RT with HFRT with or without total dose reduction showed increased survival benefit of 8% at 5 years.[3]

Hyperfractionation employs small-dose fractions to allow higher total doses to be delivered within the tolerance of late-responding normal tissues, thus enabling a higher biologically effective dose to the tumor. For this rationale to hold, the α/β ratio for both tumor cells and acute responding tissues must be greater than that for the dose-limiting normal

tissue and HFRT include radio-sensitization through cell cycle redistribution and lesser dependence on oxygen effect.[4]

Hyperfractionation shows improved tumor control by increasing total dose delivery. Delivering a smaller dose per fraction allows a normal cell to regenerate fully as sufficient time is given in between fractions and simultaneously decreasing tumor repopulation and increasing reoxygenation. So, this study has been carried out to analyse the results in terms of locoregional control, tumor regression and acute toxicity in HFRT to conventional regimen in locally advanced case of carcinoma of cervix.

METHOD AND MATERIAL

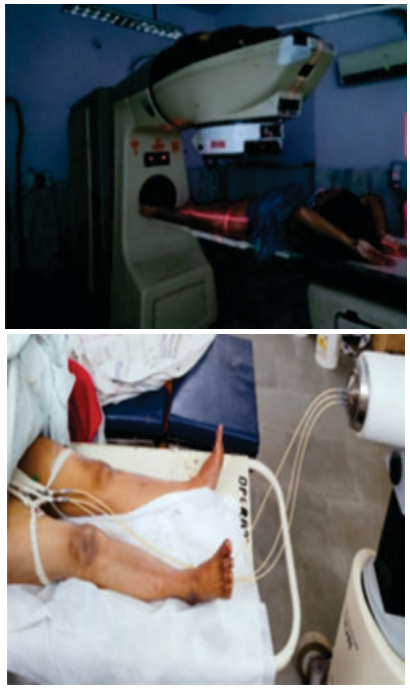
A prospective comparative study was conducted, 60 patients were enrolled in the study after obtaining written and informed consent and explaining them about the treatment type, outcome and possible toxicities. Female patients of age 18-70 years with karnofsky performance status of >70, biopsy-proven, FIGO Stage (2018) IIB to IVA, no evidence of metastatic disease and have not received chemoradiotherapy previously were included in this study. Pregnant and lactating women, any active sexually transmitted diseases, pelvic inflammatory disease and urinary tract infection and patient with associated medical condition like uncontrolled hypertension, ischemic heart disease, uncontrolled diabetes mellitus, pulmonary tuberculosis were excluded from the study.

A complete history was taken including age, occupation, religion, addiction and presenting complaint and duration of symptoms. General physical examination (especially gynaecological examination) including supraclavicular and inguinal lymph node and general condition, weight, height of the patient, pallor, icterus, cyanosis, edema were recorded as these are indirect indicators of the patient's nutritional status and used for cisplatin dose calculation. Local and systemic examinations were conducted. Investigations including haematological (complete blood count, biochemical examinations as liver function test, renal function test and serum electrolytes), chest x-ray posterio- anterior view, ultrasonography abdomen and pelvis, contrast-enhanced computed tomography abdomen and pelvis or magnetic resonance imaging can was done. Histopathological confirmation of diagnosis was done with cervical biopsy

Patients were randomized into two arms : HFRT and conventional schedule. In HFRT all the patients were given total radiotherapy dose of 60 gray (Gy) in 50 fractions (#) @ 1.2 Gy/# and 2#/day at 6 hours interval with 5 days treatment per week hyper-fractionated schedule. In conventional schedule all the patients were treated by conventional fractionation dose schedule of 50Gy/25# @ 2Gy/#, 1#/day and 5 day treatment/week for 5 weeks. In both the treatment schedules all the patients were administered injection cisplatin 100 mg/m^2 on three weekly basis. Before initiation of chemotherapy, premedication and intravenous hydration was given to each patient.

Radiotherapy to all the patients in both the arms was delivered by Teletherapy machine cobalt-60 theratron-780C (Theratronix, Canada) after surface marking of treatment fields and verification by marker x-rays. Portals for pelvic field, Superior border; At the L4-5 space to include external and internal iliac Lymph node, extended to the L3-4 space if common iliac nodal coverage. Extended to the T11-12 space if paraaortic coverage is indicated. Inferior border; at inferior border of the obturator foramen, For vaginal involvement: 2 cm below the lower most extent of disease. Lateral borders; 1.5-2cm margin on the widest portion of pelvic brim.

After a period of 7-10 days, patients were assessed for Brachytherapy. ICRT was delivered 7 Gy/# 3 # using microSelectron high dose radiotherapy (HDR) unit.



(a)

(b)

Figure 1: Treatment setup of one of the patient on (a) Co-60 Teletherapy machine Theratron 780-C and (b) Ir-192 HDR Brachytherapy machine microSelectron V2.

Ultrasonography whole abdomen and pelvis were performed as a response assessment tool once before beginning of radiation therapy and repeated again at the time of conclusion of the therapy. Patients were monitored for skin, vaginal mucosa, gastrointestinal, genitourinary, and hematological toxicities on weekly basis. Assessment of toxicities in terms of acute & late, was done by using Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).

Biologically effective dose (BED) calculated using linear quadratic (LQ)-based formula with an overall time factor included,

Where *n* fractions of *d* Gy are given in an overall time of *T* days and tumor repopulation doesn't start until day *Tk* (using k for kick-off, or onset, of the delayed repopulation during fractionated irradiation).

Table 1 Demographic profile of patient

Parameter	HFRT (n=30),n(%)	Conventional Schedule (n=30), n(%)
Age		
18-29	02(6.6%)	01 (3.3%)
30-39	09 (30%)	10 (33.3%)
40-49	10 (33.3%)	12 (40%)
50-59	06 (20%)	05 (16.6%)
60-69	03 (10%)	02 (6.6%)
Habitat		
Rural	18 (60%)	22 (73.3%)
Urban	12 (40%)	08 (26.6%)
Staging		
IVA	05 (16.6%)	03 (10%)
IIIC	03 (10%)	04 (13.4%)
IIIB	06 (20%)	04 (13.4%)
IIIA	04 (13.3%)	05 (16.6%)
IIB	12 (40%)	14 (46.6%)

Growth		
Ulcerative	05 (16.6%)	05 (16.6%)
Infiltrative	08 (26.6%)	10 (33.3%)
Ulcero-proliferative	17 (56.6%)	15 (50%)
Histopathology		
Squamous cell Carcinoma	22 (73.3%)	19 (63.3%)
Adenocarcinoma	07 (23.3%)	09 (30%)
Adeno-squamous carcinoma	01 (3.3%)	02 (6.6%)
Histopathological grading		
Well differentiated	22 (73.3%)	21 (70%)
Moderately differentiated	06 (20%)	06 (20%)
Poorly differentiated	02 (6.6%)	03 (10%)
Parity		
1	0 (00%)	01 (3.3%)
2-3	06 (20%)	05 (16.6%)
4-5	18 (60%)	19 (63.3%)
>6	06 (20%)	05 (16.6%)
Symptoms		
Discharge per vagina	01 (3.3%)	06 (20%)
Contact bleeding	03 (10%)	02 (6.6%)
Blood mixed discharge/bleeding	26 (86.6%)	19 (63.3%)
Pelvic pain	01 (3.3%)	03 (10%)

RESULT

At the study centre, the newly diagnosed patients of carcinoma are approximately 4000-4100 every year. Total 60 patients have been taken in our study, we compare the conventional radiotherapy and HFRT along with chemotherapy in carcinoma of uterine cervix FIGO stage IIB to IVA.

Evaluating all the patients in this study found that in Arm A, complete response from treatment was shown by 23 patients, 2 patients showed partial response and 5 were either lost to follow up or died during the study course. In Arm B, 21 patients showed complete response, 5 patients showed partial response and 4 patients were either lost to follow up or died. Response difference was not significant in both the arm as shown in table 2.

Table 2 Response of two different treatment schedules

Parameter	Arm A (n=30), n(%)	Arm B (n=30), n(%)
Complete response	23 (76.6%)	21 (70%)
Partial response	02 (6.6%)	05 (16.6%)
Stable disease	0 (00%)	0 (00%)
Progressive disease	0 (00%)	0 (00%)
Lost to follow up/death	05 (16.6%)	04 (13.3%)

Major toxicity was evaluated in terms of skin reaction, vaginal mucosa reaction, gastrointestinal reaction, genitourinary reaction and haematological toxicity during EBRT along with chemotherapy and HDR brachytherapy related toxicity in all patients as tabulated below (table 3 and 4 respectively).

Table 3 Toxicity during EBRT along with inj. Cisplatin at 5th week

Parameter	Arm A (n=30)	Arm B (n=30)
Skin reaction		
Grade 1	13	10
Grade 2	15	18
Grade 3	02	02
Vaginal mucosa reaction		
Grade 1	13	10
Grade 2	14	17
Grade 3	03	03
Gastrointestinal reaction		
Grade 1	15	10
Grade 2	12	16
Grade 3	03	04
Genitourinary reaction		
Grade 1	06	06
Grade 2	23	23
Grade 3	01	01
Anaemia		
Grade 1	14	18
Grade 2	15	12
Grade 3	0	0
Thrombocytopenia		
Grade 1	0	02
Grade 2	0	0
Grade 3	0	0

Table 4 Different toxicities related to brachytherapy

Parameter	Arm A (n=30),	Arm B (n=30),
Uterine perforation	0	02
Vaginal Laceration	0	01
Fever/ infection	03	04
Gastro-intestinal		
Diarrhea	07	05
Abdominal cramping	17	19
Genitourinary		
Dysuria	11	12
Increase urinary frequency	04	02
Nocturia	02	0
Haematuria	0	0
Erythema	06	07
Moist desquamation	02	01
Acute Radiation Vaginitis	05	08

DISCUSSION

The dose in grey at which the linear and quadratic components of cell death are equal is represented by the alpha/beta ratio. The alpha/beta ratio of late responding tissues is low (actually, alpha/beta = 3 Gy); a higher alpha/beta ratio (assuming 10 Gy for the ratio). Squamous cell carcinoma of the uterine cervix is one of the tumor with a high alpha/beta ratio, whereas the most normal pelvic tissues, which typically prevent the pelvis from becoming more dose-sensitive, have a low alpha/beta ratio. These traits have been theoretically proven by hyperfractionated radiotherapy in squamous cell carcinoma patient.[5]

Majority of the patient having carcinoma of uterine cervix were in the age group of 40-49 year of age and least in 18-29 year age group. In study arm 10 patients were falling in 40-49 year of age whereas in control arm 12 patient were in this age group. Similar results have also been reported by Yang M, Du J, Lu H, *et al.*[7] age group of 15-49 years, the increasing trends of incidence. According to *Gupta, et al.*[6] mean age was 47 years in both the study arm, maximum patients are below 50 years of age. (Table 1)

In the developing country like India, the disease is usually in advanced stage at the time of diagnosis, which is evident by the stage distribution of the cases in the present study. In Arm A and Arm B , maximum percentage of patients are in Stage IIB carcinoma i.e. 40% and 46.6% respectively, similar observation was found in *Gupta, et al.*[6] The majority of the patients presented with Stage IIB. According to *N. Tubiana-Mathieu et al.*[8] study Twenty-five patients presented with advanced Figo stage carcinoma. 4 were stage IIB, 10 stage III and 11 in stage IV. All patients with stage IV disease had bladder involvement and one had rectum involvement also. In Arm A, 56.6% patients have ulcero-proliferative growth while 16.6% have ulcerative growth whereas in Arm B, 50% patients showing ulceroproliferative growth. Hence, in both the arms, ulceroproliferative lesions were commonly seen and In Arm A, 73.3% patients suffered from squamous cell carcinoma and 3.3% suffered from adeno-squamous carcinoma. In Arm B, 63.3% patients suffering from squamous cell carcinoma. Squamous cell carcinoma is the most common type of carcinoma of uterine cervix on histopathological basis. Major

contribution is of well differentiated type, in study Arm its 73.3% while in control Arm its 70%. Similar observation was present in *Gupta, et al.*[6] Ulceroproliferative growth was a common pattern. well-differentiated squamous cell carcinoma was dominant histology in both the groups and *N. Tubiana-Mathieu et al.* [8] study, all patients presented were having squamous cell carcinomas. (Table 1)

Gupta, et al. [6] The study group consisted of 11 patients, treated by hyperfractionated schedule of 60 Gy/50 fractions/5 days/week over 5 weeks. Two fractions of 120 cGy per fraction per day were given at interval of 6 h. Injection cisplatin (50 mg/m2) I/V was administered on day 1, followed by injection 5-fluorouracil (750 mg/m2) I/V for 5 days, and the same regimen was repeated in the last week of external radiotherapy. After observing encouraging results, compared study with standard protocol in a retrospective manner which included 11 patients as a control group, who were treated by conventional fractionation of 50 Gy/25 fractions, 2 Gy/fraction/5 days/week for 5 weeks with injection cisplatin 50 mg I/V weekly. Study group, 81.8% of the patients showed complete response as compared to 72.72% in the control group as a biologically effective dose in hyperfractionated schedule was 67.2 Gy as compared to 60 Gy in conventional schedule. The partial response in the study and control groups was 18.18% and 27.27%, respectively. *Shahi K.S. et al.*[9] included 22 patients in the study (12 in the study group and 10 in the control group). The control group was treated by conventional fractionation 60 Gy/30 fractions (f), 2 Gy/f, 5 days/week for 6 weeks. The study group was treated in hyperfractionation schedule 72 Gy/60f, 5 days/week over 6 weeks. Two fractions of 120 cGy/day were given at interval of 6 h. The complete response was 80% and 91.7% in the control and study groups, respectively. In our study, a total number of 60 patients FIGO stage IIB to IVA were treated, arm A patients were given total radiotherapy dose of 60 Gy in 50 fractions (#) @ 1.2 Gy/# and 2#/day at 6 hours interval with 5 day treatment per week hyper-fractionated schedule. Injection cisplatin (100 mg/m^2) I/V was administered on three weekly basis. Chemotherapy with Injection cisplatin was given on day 1 of the 1st week of pelvic external radiation at a dose of 100 mg/m^2 before radiotherapy, and the next injection cisplatin was given every 3 weeks until the radiation therapy concluded and in arm B, patients were treated by conventional fractionation dose schedule of 50Gy/25# @ 2Gy/#, 1#/Day and 5 Day treatment/week for 5 weeks with injection cisplatin 100 mg/m^2 on three weekly bases. Radiotherapy to all the patients in both arms has been delivered by cobalt-60 theratron-780C teletherapy machine after surface marking of treatment fields and verification by marker x-rays. Intracavitary radiation therapy (ICRT) were given 1 week after completion of external beam radiation therapy (EBRT). All the patients were given 3 fractions each of 7 Gy at the interval of 1 week between each two fractions. In our study in arm A, complete response from treatment was shown by 23 patients, 2 patients showed partial response and 5 were either lost to follow up or died during the study course. In arm B, 21 patients showed complete response, 5 patients showed partial response and 4 patients were either lost to follow up or died.

Skin reaction seen due to EBRT, mostly appear after one week of radiation. In arm A, after 1st week of treatment 21 patients showed grade 1 skin reaction and after 5th week , 13 patients had grade 1 while 15 had grade 2 skin reaction. In arm B, after 1st week 19 patients had grade 1 skin reaction and after 5th week , 10 patients had grade 1 while 18 had grade 2 skin reaction. Skin reaction is managed by emollient, oil and moisturizer application over skin. In case of severe skin reaction, patients were admitted in the ward, adequate hydration was done and were treated as per symptoms. *Gupta, et al.* [6] study grade 1 skin reaction were present in 8 patients and Grade 2 skin reaction in 3 patients in study arm and control arm both. Vaginal mucosa reaction in arm A, Grade 1 reaction were seen in 27 patients and grade 2 reactions in 3 patients after 1st week of treatment. More of grade 2 reaction is seen in arm B patients (8 patients). After 5th week of treatment, in arm A; 13, 14,3 patients were showing grade 1,2,3 reactions respectively whereas in arm B ; 10, 17, 3 patients were showing grade 1,2,3 reactions respectively, *Gupta, et al.* [6] grade 1 vaginal mucosa reaction present in all patient of study participant.

Though hematological toxicity is seen after radiotherapy or chemotherapy but concomitant chemotherapy in general can be used with organ preserving intent, resulting in improved cosmesis and function. Second , chemotherapy is radiosensitizer, improving the probability of local tumor control and in some case survival, by aiding the destruction of radioresistant clones. Third, chemotherapy given as a part of concurrent chemoradiation may act systemically and potentially eradicate distant micro-metastasis. In our study, anaemia after 1st week of treatment, in arm A; 20, 8 patients are having grade 1, 2 respectively while in arm B; 22, 8 patients are having grade 1, 2 respectively. After 5th week of treatment, in arm A; 14, 15 patients are having grade 1,2 toxicity respectively while in arm B; 18, 12 patients are having grade 1,2 hematological toxicity respectively. *Gupta, et al.* [6] Grade 1 and 2 seen in 4, 6 patients and 7, 5 patients in study arm and control arm respectively.

Brachytherapy related toxicities in arm A, out of 23 patients, 3 patients have fever/infection contributing to 13% of total patients whereas in arm B; 19% have fever/infection, 9.5% have uterine perforation, 4.7% have vaginal lacerations, so out of 21 patients from arm B;7 were affected. In arm A, 73.9% suffered from abdominal cramp while 30.4% are having diarrhoea. In arm B, same trend was observed, 90.4% have abdominal cramps and 23.8% have diarrhoea. In arm A, most common complication is dysuria (47.8%) and least common is nocturia and moist desquamation (8.6%) each. In arm B most common genitourinary complication is dysuria (57%) and least is moist desquamation (4.7%).

CONCLUSIONS

A comparative study was carried out to analyse the response and toxicities in HFRT and conventional regimen in Ca. uterine cervix cases. Number of patients who showed complete response was 23 [76.6%] and partial response was 2 [6.6%] in HFRT, while complete response 21 [70%] and partial response 5 [16.6%] in conventional treatment.

HFRT along with concurrent chemotherapy is quite feasible, well tolerated and have less acute toxicities when compared with the conventional radiotherapy. HFRT along with concurrent chemotherapy had produced clinically better tumour control without enhancing normal tissue damage. Response of the HFRT was quite better than patients treated with conventional schedule. However, HFRT could lead to increased late bowel complications and must be used judiciously in the treatment of cervical cancer.

This study shown, with the admonition of relatively smaller sample size in each arm of 30 patients each, limits the extrapolation of the result to the general population. Longer follow up is required to assess the delayed toxicity, overall survival and disease free survival. Due to hyperfractionation schedule, late sequalae of radiation were seen which requires longer follow up. In this study, limited follow up was done because of COVID-19 pandemic.

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