

Comparative Evaluation of Concurrent Chemotherapy & Hyperfractionated radiotherapy Versus Conventional Radiotherapy alone in the Treatment of Locally Advanced Carcinoma Cervix—A Prospective Randomised Study

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Abstract

The aim of this study was to determine whether the addition of concurrent cisplatin and hyperfractionation in external pelvic radiotherapy improves local control and survival in patients with locally advanced carcinoma cervix as compared to treatment with conventional radiotherapy alone. The morbidity of two treatment protocols was also compared. Sixty patients of newly diagnosed squamous cell carcinoma cervix, FIGO stage IIB and III were randomised into the following two treatment protocols : **Group A (study group)** : Cisplatin 30 mg/m² weekly x 5 courses and external beam pelvic radiotherapy 50 Gy/33#4.5 weeks with hyperfractionation in first and fourth weeks. **Group B (control group)** : External beam pelvic radiotherapy 46 Gy/23#4.5 weeks. Patients in both the groups were then treated with intracavitary brachytherapy by LDR/MDR Selectron and a dose of 28 Gy was delivered to point A. The patients who were not suitable for intracavitary treatment were treated by supplementary external beam pelvic radiotherapy 20 Gy/10#2 weeks. The actuarial local control at 4 years was 60% in group A and 42% in Group B ($p < 0.05$). The actuarial disease free survival at 4 years was 52% in Group A and 35% in Group B ($p < 0.05$). Only grade I acute and delayed haematological toxicity and grade I nausea and vomiting as acute toxicity were significantly higher for Group A patients as compared to Group B. Concomitant chemotherapy with hyperfractionated radiotherapy is well tolerated and seems to offer potential benefit for improving the locoregional control in locally advanced carcinoma of cervix.

Key Words

Carcinoma Cervix; Hyperfractionated Radiotherapy plus Concurrent Chemotherapy; Conventional Radiotherapy.

Introduction

Carcinoma cervix constitutes about 40% of all female malignancies and 85% of all gynaecological malignancies (1). The most common histological type is the squamous cell carcinoma which comprises about 95%

of all cases (2). The local spread of the disease is the most common and important, although para-aortic and distant metastases are not unknown. At our centre, more than 70% of cases present in FIGO stage IIB, III. The

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treatment of these cases is radiotherapy administered to tissue tolerance level. Despite all advances in the management of cervical carcinoma, results of treatment of advanced stages remain sub-optimal. With radical radiation therapy alone, 5 year survival rates for locally advanced carcinoma cervix vary in range of 50 to 76% (3,4). The sites of failure in these patients are pelvis only in 12-18%, pelvis and distant metastases in 11-27% and distant metastases in 15-20% (5). Various alternate therapeutic modalities evolved to improve local control are hyperbaric oxygen, neutron beam teletherapy brachytherapy and post-radiation surgical extirpation. Although these methods may improve local control, they are either impractical in a typical clinical setting or have a high rate of morbidity (6-7).

Cisplatin is one of the most active drugs in carcinoma cervix and is a documented radiation potentiator (8). Furthermore, if cisplatin could be administered in therapeutic doses, it is hypothesised that micrometastases and circulating tumour cells could also be eliminated thus potentially controlling distant disease as well.

Recently, concomitant chemotherapy and radiotherapy has become the focus of interest in locally advanced carcinoma cervix. Concurrent chemotherapy inhibits the repair of sublethal damage from radiation, synchronises cells to a particularly radiosensitive phase of the cell cycle and is cytotoxic in vitro (9). Concurrent therapy produces no delay in the start of definitive irradiation. The entire treatment course is not prolonged and the effects of tumour proliferation are therefore minimised. The potential interaction of concurrent chemotherapy with radiation treatment may lead to increased tumour cell kill.

The conventional fractionation for radiation therapy because of empiricism and convenience, has evolved into five fractions per week. However, with the aim of increasing the therapeutic differential between the tumour and the late responding normal tissues, a number of other fractionation schedules have been proposed.

With hyperfractionated external radiotherapy, it is possible to increase the total tumour dose and thus improve the locoregional control but with reduced acute toxicity and similar late complications.

Our clinical trial is an attempt to exploit the potential benefit of both concomitant chemotherapy with cisplatin and intermittent hyperfractionation in patients with locally advanced carcinoma cervix.

Materials and Methods

1. Pretreatment Evaluation

Between September 1996 and February 1998, 60 patients of newly diagnosed carcinoma cervix were enrolled in this study. Eligibility criteria included biopsy proven squamous cell carcinoma of cervix, FIGO stage IIB or III, age less than 70 years, Karnofsky performance score is more than 70, no history of uncontrolled chronic disease e.g. ischaemic heart disease, hypertension, diabetes mellitus. A complete blood count, liver and renal chemistries, blood sugar test, a chest X-ray, intravenous pyelogram and cystoscopy were mandatory for all patients whereas ultrasonography and computed tomography were optional investigations.

These patients were randomised into two groups A and B.

2. Methodology

Study Group A

Chemotherapy : The patients in study group were planned for treatment with concurrent chemoradiation. Cisplatin was administered weekly before radiotherapy in a dose of 30 mg/m², starting on first day of treatment and total of 5 courses were planned. All patients had repeat complete blood counts, blood urea and serum creatinine before every course of chemotherapy.

Radiation : External radiation therapy in study group included intermittent hyperfractionation in first and fourth weeks :

Total dose	50 Gy	Duration	4.5 weeks
Fractionation	1st & 4th	120 cGy/fraction, 2 fractions/day (5 days/week) with 6 hours gap between 2 fractions	
	2nd, 3rd & 5th weeks	200 cGy/fraction, 1 fraction/day (5 days/week)	

Control Group B

These patients received conventional external radiation therapy :

Total dose	36 Gy	Duration	4.5 weeks
Fractionation	200 cGy/fraction,	1 fraction/day	(5 days/week)

Radiotherapy technique

All patients received external radiation to whole pelvis on a Cobalt-60 teletherapy unit or a 6-MV linear accelerator using anterior and posterior opposing fields with superior border at LS-S1 vertebral junction and inferior border at lower margin of obturator foramina. This was followed by a single intracavitary treatment on the LDR/MDR Selectron machine to a dose of 28 Gy to point A at dose rate of 180 ± 10 cGy/hour. The patients who were unsuitable for intracavitary application were treated by supplementary external radiation to whole pelvis to a dose of 20 Gy/10#/2 weeks.

Evaluation of toxicity

Treatment induced toxicity if any was documented throughout treatment and follow up using WHO grading system for haematological, renal toxicities and nausea/vomiting. Franco-Italian complication reporting glossary was used for rectal, urologic and vaginal complications (10).

Follow-up and Assessment

After the completion of treatment, the patients were examined every six to eight weeks for one year and every three months thereafter. Follow up period ranged from 10-42 months. At each follow up, patients were clinically evaluated for locoregional control of disease. The tumour control or complete response was defined as the complete disappearance of visible and palpable disease. Local

failure was recorded in the event of a recurrent tumour or if the primary tumour never completely disappeared. On the suspicion of any local recurrence, cervical smear was taken for cytology and correlated clinically. Patients were also evaluated for distant failure which included para-aortic node failures. To evaluate the distant metastasis, relevant investigation were done as indicated.

Calculation of Biological Effective Dose (BED)

Since intracavitary part of treatment was similar for both groups with respect to dose rate as well as total dose to point A, BED for only the external radiotherapy parts of the treatment in both the groups was calculated using incomplete repair L.Q. model (11) :

Where,

$$BED = md \left[1 + \left(\frac{\beta}{\alpha} \right) d \{ 1 + H(\theta) \} \right]$$

$$H(\theta) = \left(\frac{2}{m} \right) \left[\frac{\theta}{1-\theta} \left\{ m - \frac{(1-\theta^n)}{1-\theta} \right\} \right]$$

$$\theta = e^{-\mu x}$$

x = time interval between closely spaced fractions

μ = repair constant of sublethal damage (1.4 h⁻¹ for acute effects 0.46 h⁻¹ for late effects)

m = number of fractions per day

d = dose per fraction

α/β = tissue specific parameter (a/b values for various tissues were chosen as commonly used in the literature: for acute effects and cervix tumour, α/β - 10 Gy and for late effects, α/β = 3 Gy).

Then, the expected difference between the two groups was calculated using simple Chi-square method:

Statistical Analysis

The primary end points were pelvic disease control, distant failure, disease free survival and treatment related morbidity. Survival was calculated from the date of entry into the study to the date of death or the last follow up. The actuarial values of local control and disease free survival were evaluated using the life table method. The p value estimated are those of a two-tailed test and the significance level was chosen to be 5%.

Observations and Results

Characteristics of patients : The majority of patients were in the fourth and fifth decades. The stage wise distribution in both the groups was also comparable. In group A, 6 patients were in stage II-B and 24 patients in stage IIIB. In group B, 4 patients were in stage IIB and 26 patients in stage IIIB.

Treatment delays/misses : Four patients in study group had delay in completing external radiotherapy because of acute toxicities in form of diarrhoea (1 patient), grade III vomiting (2 patients) and skin reactions (1 patient). However, the delay was never more than 10% of the overall scheduled duration. In the study group 33% (10/30) patients could not receive all the five courses of chemotherapy as planned because of haematological toxicity. (Table 1).

Table 1
Treatment Delays and/or Misses

	Study group (n=30)	Control group (n=30)
• Delay in completing external radiation	4 (13.3%)	1
• *ICA not possible	0	3 (10%)
• Number of chemotherapy courses received:	5/5 courses 20 (67%) 4/5 courses 7 } (33%) 3/5 courses 3 }	**NA

* ICA - Intracavitary application
** NA - Not applicable

Tumour Control : In the study group 70% (21/30) of patients and 47% (14/30) in control group were clinically disease free at last follow-up. (Table 2).

Table 2
Disease Control and Patterns of Failure

Disease status	Study	Control (n=30)
• Pelvic Control	23(76%)	18(60%)
• Pelvic failure alone	5	9
• Pelvic + distant failure	2	3
• Distant failure alone	2	4
• Overall control	21(70%)	14(47%)

Survival : Most of the failures took place in first two years in both the groups. The four years actuarial local control rate was 60% for the study group compared to 42% for the control group with p-value <0.05 (Fig. 1). The actuarial four years disease free survival was 52% for the study group compared to 35% for the control group with p-value <0.05 (Fig. 2).

Fig. 1: Actuarial pelvic disease control rate

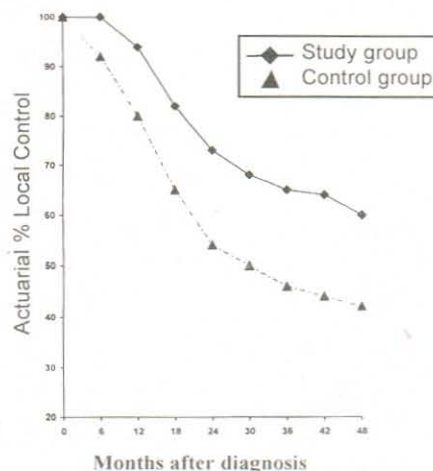
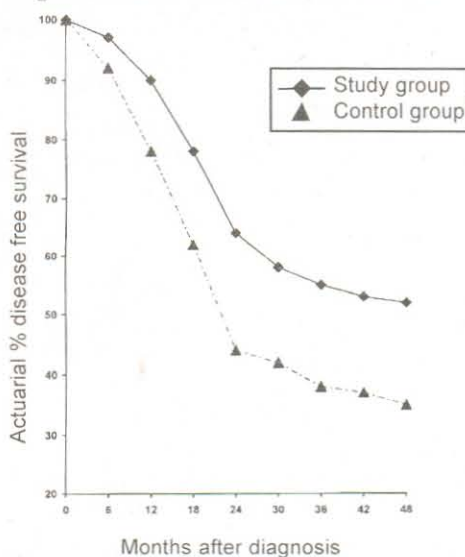


Fig. 2: Actuarial disease-free survival rate



Adverse Effects : There were no treatment related deaths in the study group. The types and frequencies of adverse effects are shown in Table 3.

Table 3
ADVERSE AFFECTS

	Concomitant Chemotherapy and Hyperfractionated Radiotherapy (n=30)					Conventional Radiotherapy alone (n=30)				
	Grade I	Grade II	Grade III	Grade IV	Total	Grade I	Grade II	Grade III	Grade IV	Total
ACUTE TOXICITY										
Hematological	10	4	3	0	17(56.6%)	-	-	-	-	-
Renal	2	0	0	0	2(6.6%)	-	-	-	-	-
Nausea/Vomiting	8	6	2	0	16(53%)	-	4	2	0	6(20%)
Bowel	5	2	0	0	7(23%)	0	6	0	0	6(20%)
Skin	0	3	1	0	4(13%)	0	2	1	0	3(10%)
Total events					46					15 p<0.05
DELAYED TOXICITY										
Hematological	7	3	1	1	12(42%)	2	-	-	-	2(6.6%)
Renal	2	0	0	0	2(6.6%)	-	-	-	-	-
Rectal	2	2	1	0	5(16.6%)	3	2	1	0	6(20%)
Urinary Bladder	0	0	1	0	1(3.3%)	-	-	-	-	-
Vaginal complications	2	0	0	0	2(6.6%)	5	3	0	0	8(26.6%)
Total events					22					16 p>0.05

BED Comparison : In Table 4, we have compared the effect of hyperfractionation schedule versus conventional external radiotherapy schedule.

Table 4
Biological Effective Dose (Bed)-Comparison with Observed Results

Tissue	a / b (Gy)	BED (External R.T.)		Expected difference in results	Observed difference in results
		Study (Gy)	Study (Gy)		
Tumour (Cervix)	10	58.08	55.20	5.22%	16%
Late Effects Rectum (R)					-3.4* (R)
Bladder (B)	3	77.54	76.67	1.13%	3.3% (B)
Vagina (V)					-20%* (V)

(-) *Minus sign denotes lesser incidence of the particular effect in the study group compared to the control group.

Discussion

Historically, locally advanced carcinoma of cervix has been treated with radiotherapy alone. Despite improvements in radiation equipment and techniques, in approximately two thirds of the cases, relapse and progression occurs within the area that was irradiated (3, 4). So, it is logical to combine radiotherapy with another antineoplastic modality i.e. chemotherapy in an

attempt to increase tumour control. This would enhance the effect of radiotherapy by additive cell kill, radiosensitisation or both. Cisplatin is believed to augment the effects of radiation by inhibiting the repair of radiation-induced sublethal damage and by sensitising the hypoxic cells to radiation and because of its cytotoxic effects, the drug reduces the bulk of tumours, which leads to the reoxygenation of the tumour and entry of the cells into a radiation sensitive phase of the cell cycle. Britten et al found that radiotherapy and concomitant cisplatin chemotherapy increased the rates of death of these tumour cells (12).

Hyperfractionated external radiotherapy offers potential benefit of improving locoregional control while keeping same late morbidity. There are two main concepts regarding the repopulation of the tumour cells while on radiotherapy. According to Withers et al, the tumour cells proliferation accelerates around the fourth weeks after beginning radiotherapy (13). Other including Fowler assume that proliferation speeds up as soon as tumour shrinks which can be as soon as two to three fractions have been delivered (14). Taking into account both the above said concepts, an intermittent hyperfractionation external radiotherapy schedule for the

study group was designed. This intended to increase the total tumour dose while expecting same late effects as with conventional radiotherapy. No compromise was made on the dose of intracavitary part of treatment.

Despite the criticism of initial chemoradiation studies in carcinoma cervix with hydroxyurea (15), the results of these studies and those of trials assessing concurrent chemoradiation for other tumours stimulated further studies in locally advanced cervical cancer with various drugs such as fluorouracil, cisplatin, mitomycin, carboplatin and paclitaxel (16-19). Out of all these drugs, cisplatin is the most active as a single agent with response rate as high as 50% (20). The effect of radiotherapy with concomitant treatment with cisplatin alone has been studied in several phase 2 trials (21,22). In a small study of 45 patients with cervical cancer by Choo *et. al.* radiotherapy and chemotherapy with cisplatin (25 mg/m² per week) increased the rate of local control by 35 percent ($p < 0.025$) for comparison with radiotherapy alone) but there was no long term improvement in survival (21).

The results in the present study show that concomitant cisplatin chemotherapy with hyperfractionation in the external radiotherapy was more effective for locally advanced cervical cancer than conventional radical radiotherapy alone and reduced both local and distant recurrences leading to significantly higher actuarial local control and disease free survival rates (Figs. 1 and 2). Although chemotherapy increased the hematologic toxicity, this effect was reversible and the incidence of rectal/urologic late side effects was similar in the two treatment groups.

The toxicity of various chemoradiation studies has also been reported in detail and the most common adverse effect encountered is grade I-II haematological toxicity or nausea/vomiting (20). In a series by Fields *et. al.* median of four cisplatin cycles (out of planned five courses) were administered with a range of two to five courses (22). In our series, 67% (20/30) patients received all the five courses, with a range of three to five courses. Also, there was a minimal delay in completing external

radiation schedule in four patients because of the acute toxicities in the combined modality group. Grade I-II haematological toxicity was the main toxicity in our chemoradiation group but overall the toxicity as acceptable and well tolerated by the patients.

This study differed from previous chemoradiation studies in that the external radiotherapy schedule was also modified with an intermittent hyperfractionation. The experience with hyperfractionated external radiotherapy in carcinoma cervix is limited. Cherian Varghese *et. al.* used a continuous hyperfractionation programme delivering a total dose of 60 Gy/50 fractions/5 weeks to the whole pelvis, followed by single intracavitary treatment and reported enhanced acute normal tissue reactions whereas no significant difference was noted in tumour control (23). In another study by Sergio *et. al.* where only external pelvic radiotherapy 72 Gy/60 fractions/6 weeks was used, a statistically higher incidence of acute bowel toxicity was noticed without any advantage in tumour control (24). The only previous chemoradiation study with hyperfractionation in external radiotherapy is by Heaton *et al* who used cisplatin, 5-FU and hyperfractionated week-on/week-off external radiotherapy in 29 patients and in this study, pelvic control rate was 58% and five years disease free survival was 34% with an acceptable complication rate (25).

Various randomised trials of chemoradiation in cervical cancer have been reported which strengthen the body of evidence supporting the use of combined therapy in women with advanced cervical cancer. Rose *et al* performed a randomised trial in patients with locally advanced cervical cancer with chemoradiation using three different concurrent chemotherapy regimens - (1) cisplatin alone, (2) cisplatin, fluorouracil and hydroxyurea, (3) hydroxyurea alone. The relative risks of progression of disease or death were 0.57 in group 1 and 0.55 in group 2 as compared with group 3 ($p < 0.001$ for both comparisons) (26).

In a phase 3 study by Morris *et. al.* among patients with stage IB to IVA, the cumulative rates of survival at five years were 73% among patients treated with

combination of chemotherapy and pelvic radiation versus 58% among patients treated with pelvic and paraaortic radiation ($p=0.004$). The cumulative rates of disease free survival at five years were 67% in the combined therapy group compared to 40% among patients in the radiotherapy alone groups ($p<0.001$). The seriousness of side effects was similar in the two groups, with a higher rate of reversible hematologic effects in the chemoradiation group (27).

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