COMPARATIVE ANALYSIS OF HYPERFRACTIONATED RADIOTHERAPY VERSUS CONVENTIONAL RADIOTHERAPY IN CARCINOMA CERVIX

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ABSTRACT

BACKGROUND

Cervical cancer is the most common gynaecological malignancy in women for which Concurrent chemoradiation followed by brachytherapy showed established benefits in both organ preservation and survival. The rationale behind hyper-fractionation is that the therapeutic ratio can be improved by increasing the number of fractions and total dose without exceeding the tolerance of late-reacting normal tissues.

Aims- 1. To assess the feasibility of hyperfractionated schedule in squamous cell carcinoma of uterine cervix. 2. To assess the response and acute toxicity of hyperfractionated schedule and compare with conventional fractionation.

MATERIALS AND METHODS

50 patients in the age group of 30 to 60 years with biopsy-proven squamous cell carcinoma of the uterine cervix of stage IIB and IIIB who visited the Department of radiotherapy, MMC & RGGGH from 2002 to 2004 were included - 25 patients in control arm: conventional EBRT 50 Gy (200 cGy/# in 25 fractions) + LDR and 25 in trial arm: hyperfractionated EBRT 57.6 Gy (1.2 Gy/# in 48 fractions - 2#/day separated by 6 hours over 24 days) + LDR. LDR dose delivered was 26 Gy (<0.4 Gy/hr over 1-3 days) in both arms. Response was assessed both clinically and radiologically, 6 weeks after the completion of treatment. Response was assessed using RECIST criteria version 1.1. Toxicity was assessed using Common Toxicity Criteria version 3.0 and RTOG Morbidity scoring criteria version.

RESULTS

Complete response was observed in 68% and 84% of control and trial arms respectively and was more in patients with <40 years of age, haemoglobin less than 11 gm% and bilateral parametrial involvement. Acute toxicity was more common in the hyper-fractionated arm which subsided within 2 weeks of completion of treatment. No grade III or IV acute reactions were observed. The median follow-up duration was 5 years. 16 patients- 9 of hyperfractionated arm and 7 of conventional arm were seen at the end of 5 years and were locoregionally free. At 5 years, DFS was 43.75% for conventional and 56.25% for hyperfractionation. Late toxicity observed during follow-up included telangiectasia (3 patients), subcutaneous fibrosis (2 patients), proctitis (1 patient) and stenosis (3 patients) was observed.

CONCLUSION

Hyperfractionated radiotherapy is thus feasible in locally advanced carcinoma cervix with better loco-regional control. Acute morbidity observed with this fractionation schedule is manageable and within acceptable limits.

KEYWORDS

Radiotherapy, Hyperfractionated Radiotherapy, Carcinoma Cervix, Oncology.

HOW TO CITE THIS ARTICLE: Kalaiyarasi NV, Giridharan R. Comparative analysis of hyperfractionated radiotherapy versus conventional radiotherapy in carcinoma cervix. J. Evolution Med. Dent. Sci. 2017;6(3):171-175, DOI: 10.14260/Jemds/2017/42

BACKGROUND

Cervical cancer is the most common gynaecological malignancy in women. The main treatment for locally advanced cervical cancers is Concurrent chemoradiation followed by brachytherapy with established benefits in both organ preservation and survival.^{1,2,3,4,5} Radiotherapy is aimed at controlling the primary tumour, while chemotherapy can also be used to eradicate distant metastases.⁴

Several randomized studies showed that Platinum based chemotherapy along with radiation results in 12% benefit in overall survival and progression-free survival and improved tumour control and 30-50% reduction in deaths when compared to radiation therapy alone.^{6,7,8,9,10,11} Altered fractionation schedules have shown significant benefit in head and neck cancers.¹² The following study is a comparative study to establish the benefits and feasibility of hyperfractionation in carcinoma cervix. The rationale behind hyper-fractionation is that the therapeutic ratio can be improved by increasing the total dose without exceeding the tolerance of late reacting normal tissues.^{12,13} Fraction size is the most important factor in determining late reactions. Since the fraction size is reduced in hyper-fractionation, the late reactions can be significantly reduced in this protocol.¹² The rationale of intracavitary brachytherapy forms a major part of concurrent chemoradiation for locally advanced cervical cancers. The total dose to point A depends on the stage, at least 85 Gy for IIIB.⁷

Financial or Other, Competing Interest: None.

Submission 25-11-2016, Peer Review 28-12-2016,

Acceptance 04-01-2017, Published 09-01-2017.

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DOI: 10.14260/Jemds/2017/42

Aim of the Study

1. To assess the feasibility of hyperfractionated schedule in squamous cell carcinoma of uterine cervix.
2. To assess the locoregional control without increasing the late complications.
3. To assess the response and acute toxicity of hyperfractionated schedule.
4. To compare the response with conventional radiotherapy.

MATERIALS AND METHODS

The present study was carried out in Department of Radiation Oncology, Madras Medical College. In this study 50 patients in the age group of 30 to 60 years who visited outpatient department from 2002 to 2004 were assigned to arm A and arm B by computer generated random permuted blocks values.

Control Arm A- 25 patients- to receive conventional external beam radiation therapy followed by ICCA LDR brachytherapy.

Trial Arm B- 25 patients- to receive hyperfractionated external beam radiation therapy followed by ICCA LDR brachytherapy.

Inclusion Criteria

1. Age less than 60 years.
2. Multiparous.
3. Performance status KPS > 70.
4. Hb > 10 gm%.
5. Stage IIB, IIIA, IIIB.
6. Histology- keratinizing or non-keratinizing squamous cell carcinoma.
7. Renal parameters normal. Creatinine clearance >80 ml/min.

Exclusion Criteria

1. Hb <10 gm%.
2. Age >60 years.
3. Hypertension, Diabetes, Tuberculosis.
4. Previous surgery, Previous RT.
5. Renal parameters abnormal.
6. Pregnancy, other malignancy.
7. Lack of informed consent.

Pre- Treatment Evaluation

1. Thorough history including menstrual, marital and socioeconomic status.
2. Careful per vaginal and per rectal examination was done to assess extent of tumour.
3. Laboratory investigations including.
 - a. Complete Haemogram.
 - b. Blood chemistry with blood urea, sugar and serum creatinine was done.
 - c. Urine Routine- albumin, sugar, microscopy.
 - d. Biopsy and Histopathological examination.
4. Radiological Investigations- Chest x-ray, USG Abdomen, IVU.
5. Cystoscopy and Proctoscopy.
6. ELISA to rule out HIV.
7. MRI abdomen- contrast enhanced preferable.

ARMS	A: Control- Conventional	B: Trial- Hyperfractionation
Total Dose	50 Gy	57.6 Gy
Daily Dose	200 cGy	240 cGy
Dose per Fraction	200 cGy	120 cGy
Total No. Fractions	25	48
Total Duration	5 Weeks	4.4 Weeks
Treatment protocol		

Simulation was done using orthogonal x-rays for both external beam radiation and brachytherapy. In trial arm, a total dose of 57.6 Gy was delivered in 1.2 Gy/#, twice daily with a gap of atleast 6 hours in between, five days a week for 5 weeks. External Beam Radiation Therapy was given using Cobalt 60 teletherapy machine (Theatron phoenix). A pair of opposing AP / PA portals was used for EBRT. Four Field box technique was used in patients with field separation more than 20 cms. LDR Brachytherapy was delivered using CESIUM 137 under epidural anaesthesia with 2% lignocaine. By intracavitary application, another 26 Gy was delivered to Point A at a dose rate <0.4 cGy/hr over a maximum of 65 hours (2.7 days).

Total dose to Point A - 76 Gy.

Point B - 60 Gy.

Bladder - Less than 75 Gy.

Rectum - Less than 67.5 Gy.

Chemotherapy - Weekly Cisplatin 40 mg/m² for 5 weeks during EBRT in arm A only.

All 50 patients were available for the final analysis. Average total treatment time was 54 days. Gaps during treatment were mainly observed due to low WBC and/or platelet count or ant grade 3 or 4 reactions.

BED value Gy10 - conventional - 56.5 Gy.

BED value Gy3 - conventional - Bladder - 76 Gy, Rectum - 76 Gy.

BED value Gy10 - hyperfractionation - 64.5 Gy.

BED value Gy3 - hyperfractionation - Bladder - 74.8 Gy, Rectum - 75.5 Gy.

EQD2- Tumour - conventional - 45.8 Gy.

EQD2- Tumour - hyperfractionation - 53.8 Gy.

Statistical Analysis

The distribution of the cases to the study and control arm with respect to factors and variables studies were presented using descriptive statistics. The difference in proportion of cases between study and control groups of factors measured on a nominal scale was tested for statistical significance using chi-square test. Yates correction was employed. Odds ratio was employed to study the extent of complete response achieved in the study group compared to control group. Fischer's exact probability test was used whenever zero frequencies are encountered. Student t test is used whenever the factors studied are measured on interval scale.

$$\chi^2_c = \sum \frac{(O_i - E_i)^2}{E_i}$$

The subscript "c" is the degree of freedom. "O" is your observed value and E is your expected value. P value was calculated. If less than 0.05, then it is significant. Statistical analysis was done using Window 10 Excel.

Response Evaluation

Tumour response was evaluated 6 weeks after completion of radiation clinically and CT scan/MRI- Abdomen and pelvis using RECIST criteria version 1.1.

Complete Response- No clinically detectable lesion.

Partial Response- 50% regression of measurable tumour. No tumour area shows any progression. No new area of lesion made out.

Static Response- No change in tumour size. No tumour area shows any progression. No new area of lesion made out.

Progression- Increase in tumour size with treatment by 25% or appearance of new lesions or tumour induced death.

Toxicity

Complete blood count and biochemistry was performed on a weekly basis. Radiation induced toxicity was graded using Common Toxicity Criteria version 3.0 and RTOG acute radiation morbidity scoring criteria. In the case of WBC less than 1000/ μ l or platelets less than 50,000/ μ l for a period longer than 5 days, or in the case of any severe grade 3 or 4, radiation therapy was interrupted until recovery.

Follow Up Procedure

Patients were assessed for disease status 1 month after the end of treatment and every month for 3 months and then once in 3 months for a period of one year. During follow up, a thorough history, physical examination and a complete pelvic examination was done. Patients with residual disease were taken up for salvage surgery. Late toxicities like subcutaneous fibrosis and telangiectasia was observed and recorded during follow up of patients in our OPD.

RESULTS

		Arm A	Arm B
Age	31-40	12	8
	41-50	8	11
	51-60	5	6
	61-70	5	5
KPS	90	8	5
	80	13	18
	70	4	2
	60	5	5
Parity	>5	8	7
	3 to 4	12	13
	1 to 2	5	5
	1	5	5
Hb Status	10 to 11	10	20
	11.1 - 12	14	3
	12.1 - 13	14	3
	>13	1	2
Tumour Stage	IIB	14	18
	IIIA	-	-
	IIIB	11	7
	IIIC	11	7
Parametrial Involvement	IIB	14	18
	IIIA	-	-
	IIIB	11	7
	IIIC	11	7

Patient characteristics

The patient characteristics were thus and was comparable.

At the end of 50 Gy and 57.6 Gy in control and trial arms respectively, all patients were clinically examined for response. The overall response was 100%. None of the patient showed evidence of progression or static disease. However, the number of complete responders and partial responders varied in the 2 arms shown in following tables:

Stage	No. of PTS	CR Number	CR %	PR Number	PR %
II B	14	6	42	8	57
IIIB	11	4	36	7	63
Total	25	10	40	15	60

Results of control ARM

Stage	No. of PTS	CR Number	CR %	PR Number	PR %
II B	18	13	72	6	33
III B	7	5	71	1	14
Total	25	18	72	7	28

Results of trial ARM

P Value >0.01

Analysis after Brachytherapy

Analysis of immediate response was done after the end of planned treatment in the respective arms. This was done by clinical and radiological examination.

Stage	No. of Patients	CR Number	CR %	PR Number	PR %
II B	14	10	71	4	28
IIIB	11	7	63	4	36
Total	25	17	68	8	32

Results of control ARM

Stage	No of Patients	CR Number	CR %	PR Number	PR %
II B	18	16	88	2	11
III B	7	5	71	2	28
Total	25	21	84	4	16

Results of trial ARM

Stage	ARM A		ARM B	
	CR%	PR%	CR%	PR%
IIB	71	28	88	11
IIIB	63	36	71	28
Total	68	32	84	16

Comparative analysis

P Value 0.01- Statistically Significant

Immediate response rates at the end of treatment

Complete response vs age of patient

P value- 0.002- Statistically Significant

Complete response vs performance status

P value- 0.26- Not Statistically Significant

Complete response vs hemoglobin status

P value- 1.25- Not Statistically Significant

Complete response vs parametrial involvement

P value- 0.11- not statistically significant

Complete response vs tumour stage

P value- 0.11- not statistically significant

Analysis of Partial Responders in Control ARM

Higher rates of partial response was seen in

1. Age <60 Yrs. (PR 40%).
2. Performance status 70 (PR 75%).
3. Hb status 10-11 g% (PR 40%).
4. HPE keratinizing type (PR 36%).
5. Parametrial disease bilateral (PR 35%).

Analysis of Partial Responders in Trial ARM

Higher rates of partial response was seen in,

1. Age <40 yrs. (PR 25%).
2. Performance status 70 (PR 50%).
3. Hb status <11 g% (PR 25%).
4. Parametrial disease bilateral (PR 20%).
5. Stage IIIB (PR 29%).

These partial responders were subjected to either adjuvant chemotherapy or surgery depending on the extent of residue present.

BED Value	Conventional ARM A	Hyperfractionation ARM B
Gy10	56.5 Gy	64.5 Gy
Gy3	Bladder 76 Gy	74.8 Gy
	Rectum 76 Gy	75.5 Gy
EQD2	45.8 Gy	53.8 Gy

Acute Effects	RTOG Grade	Control ARM	Trial ARM	P Value
Skin	Gr-1	5 (20%)	10 (40%)	0.0003
	Gr-2	2 (8%)	6 (24%)	
Rectum	Gr-1	4 (16%)	10 (40%)	0.0009
	Gr-2	2 (8%)	4 (16%)	
Bladder	Gr-1	4 (16%)	8 (32%)	-

Toxicities / morbidities observed

The above showed higher toxicities in the hyperfractionation arm and this was statistically significant. There were no treatment dropouts or treatment related deaths during this study.

The median follow up duration was 5 years. 16 patients – 9 of the hyperfractionated arm and 7 of the conventional arm were seen at last follow up and were locoregionally free of disease. The rest of the patients were lost to follow up.

	No. of Patients on follow up at End of 5 Years	Complete Response	Partial Response	Progressive Disease
Conventional-Arm A	7- 6 (IIB) 1 (IIIB)	7 (100%)	-	-
Hyper-fractionation-Arm B	9- 8 (IIB) 1 (IIIB)	9 (100%)	-	-

Late toxicity	Conventional (7 Patients)	Hyperfractionation (9 Patients)
Telangiectasia	1	2
Subcutaneous Fibrosis	2	-
Proctitis	1	-
Stenosis	2	1
<i>Late toxicity observed during follow up</i>		

Late toxicity observed in the hyperfractionation arm was less as expected. P value obtained was 0.21 which is not statistically significant. Survival analysis showed that at 5 years, disease free survival 43.75% in the conventional arm and 56.25% in the hyperfractionation arm.

DISCUSSION

Carcinoma cervix is the commonest malignancy affecting females of developing countries. Locoregional failure is the primary cause of decreased survival due to parametrial involvement. The 5 yr survival rates for stage IIB and IIIB with bilateral parametrial involvement is 58% and 28% respectively. ABS recommends 60 Gy dose to the parametrium for optimum response. By giving hyperfractionated radiotherapy dose to the parametrium is increased to 57.6 Gy and the tumour volume is reduced further making brachytherapy feasible.

In this trial after 57.6 Gy of EBRT in hyperfractionation, out of 25 patients, 18 patients attained complete response. The complete responders in trial arm included 4 (100%) with unilateral disease and 7 (50%) with bilateral parametrial involvement.

In our trial, after hyperfractionated external beam radiotherapy, brachytherapy was given using LDR. LDR brachytherapy was selected because acute toxicities due to hyperfractionated EBRT compared to conventional RT was high and is HDR was selected that will also add to the toxicity so LDR was chosen.

The toxicities and morbidities observed were minimal. There were no treatment dropouts or treatment related deaths during this study.

In this trial, acute reactions were more with hyperfractionated RT. No grade III or IV complications were observed. All acute reactions subsided within 2 weeks of completion of treatment. No rest period was required in between. Good loco-regional control was achieved.

CONCLUSION

1. Hyper-fractionated radiotherapy is feasible in locally advanced carcinoma uterine cervix.
2. Acute morbidity is within acceptable limits.

3. Late toxicity was observed in both conventional and hyperfractionation arm and was less in altered fractionation arm.

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