



Optimum Radiation Fractionation Schedule in Advanced Cancer Cervix; A Study from Low Resource North Indian Cancer Center

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Introduction: Cervical cancer is the fourth most commonly occurring lethal cancer among women worldwide. The primary curative treatment option for women suffering from locally advanced cervical cancer includes external beam radiotherapy (EBRT) with concurrent weekly platinum-based radiosensitizing chemotherapy and brachytherapy (BT) to obtain finest treatment outcomes.

Aim: The purpose of this study is to assess tumor response following HDRBT preceded by EBRT and to identify optimum radiation fractionation schedule for better response with tolerable radiation toxicity.

Material and methods: 91 patients diagnosed with carcinoma of uterine cervix were screened for inclusion in the study. Patients were categorized according to FIGO Staging system. The patient was put in lithotomy position and given anesthesia and Fletcher suit applicator was applied to the patient, pushed the bladder and rectum and finally shifted to the HDR treatment unit. All the associations were tested by using chi square test.

Results: In our study it was found that majority (44%) of the cases were aged 51-60 years. Vaginal bleeding and squamous cell carcinoma was found in most of the cases. The acute radiation toxicities were more in elderly age group and the association was found to be statistically significant ($p < 0.05$) except Genitourinary - cystitis. Age group 51-60 years was significantly associated with response ($p = 0.034$) with lower risk of partial response (OR=0.31 (0.10-0.95)), while the symptom Backache/Pain in abdomen had significantly higher risk of partial response ($p = 0.002$, OR=16.24 (1.7-154.8)).

Conclusion: When compared to traditional techniques, HDR can achieve very high rates of local control while lowering morbidity.

Introduction

Cervical cancer is the fourth most commonly occurring lethal cancer among women worldwide [1]. Statistical data fetched from Indian reports suggests that India itself accounts for one-fourth of the global burden of cervical cancer [2]. It has been observed that in India it accounts for 17% of cancer deaths among women during their reproductive age group [1].

Patients presenting with small volume stage IB1 and IIA disease according to International Federation of Gynecologists and Obstetricians (FIGO) can be provided treatment either by radical hysterectomy and lymphadenectomy or radical radiotherapy as prime procedures. The two methods have equivalent survival rates (Level 1b) [3, 4]. The combination of surgery and radiotherapy escalates morbidity and should be avoided if possible [5]. Local control and survival are improved by the inclusion of concomitant chemotherapy in all stages, though the benefit may be lesser when only one node is positive or when the tumour size is < 2 centimetres (cm) (Level 1b) [5, 6]. Overall

treatment time should not exceed 56 days, including intracavitary brachytherapy (ICBT), for squamous carcinoma (Level 1b) [7, 8]. Hemoglobin levels during treatment aid in prognosis, with the best results in those subjects with hemoglobin greater than 12 grams per deciliter (g/dl) throughout treatment (Level 2b) [9].

The primary curative treatment option for women suffering from locally advanced cervical cancer includes external beam radiotherapy (EBRT) with concurrent weekly platinum-based radiosensitizing chemotherapy and brachytherapy (BT) to obtain finest treatment outcomes [10]. BT enables for dose escalation of the tumour and acts as cornerstone thereby minimizing the toxicity of nearby organs at-risk (OARs). Through multiple past clinical reports it was concluded that BT plays an essential role in the curative treatment paradigm, as it confers both local control and survival advantage when compared to cohorts who were treated through EBRT alone as a radiation treatment modality [11, 12].

BT, being a highly conformal form of radiation technique, allows delivery of high doses to the tumour, and is the cornerstone for optimal clinical outcomes and toxicities.

Various guidelines have been established for the treatment of cervical cancer which also includes brachytherapy [13, 14]. However; these guidelines are chiefly designed and applicable for the western world and are of limited value in low and middle-income countries (LMICs) including India. Furthermore, LMICs have an exclusive ethnic and cultural background, disease patterns, health care systems and access to treatment facilities [15]. The treatment practices are commonly influenced by regional variances in cultural and socioeconomic factors, resources availability and expertise, knowledge and technology improvements etc., resulting in extremely heterogeneous patterns of care [16, 17]. The majority of the centers in India, currently, practice high-dose-rate (HDR) brachytherapy for cervical cancers [18].

The dose distribution will be manually calculated by changing relative dwell time values before an appropriate solution is reached, computer being used only to measure the dose distribution after the dosimetrist has agreed on the method. This method, or its combination with traditional optimization algorithms like geometrical or dose point optimization, necessitates time and expertise. It's necessary to distinguish between a planning method that optimizes doses based on anatomic structures and optimized planning systems that optimize doses based on the position of active dwells or a few other dose points. The final step toward fully anatomy-based conformal dose preparation is to use an anatomy-based optimization. The purpose of this study is to assess tumor response following HDRBT preceded by EBRT and to identify optimum radiation fractionation schedule for better response with tolerable radiation toxicity.

Materials and Methods

This study was conducted in patients attending outpatient department of radiotherapy at North Indian hospital. 91 patients diagnosed with carcinoma of uterine cervix were screened for inclusion in the study. All patients underwent complete evaluation by history taking, gynaecological examination and systemic examination. Certain symptoms such as vaginal bleeding and discharge, pain in lower abdomen, backache difficulty in micturition and defecation etc. were also noted. All patients underwent complete evaluation by history taking, gynaecological examination and systemic examination. Malignancy was histologically proven through biopsy in all patients. Complete blood count, liver function tests, renal function tests, chest radiograph and, ultrasound abdomen and pelvis were some of the examinations carried out for all patients. CECT abdomen and pelvis or MRI pelvis was also done. Patients were categorized according to the stages on the basis of FIGO Staging system [5]. Ethical clearance was obtained from institutional ethical committee prior to the study. Written informed consent was taken from the patients before start of treatment (Table 1).

Inclusion criteria	Exclusion criteria
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Histo-pathologically confirmed carcinoma of uterine cervix cases.	Patients with any kind of pelvic infection, fibroid, ascites and other concurrent systemic illness.
FIGO stage IIA, IIB (bulky), IIIB	Pregnant women or lactating mothers
Karnofsky score >0	
Patients who has given approved informed consent	

Table 1: Inclusion and Exclusion Criteria.

Treatment Allocation

All enrolled patients in this study after histopathological confirmation carcinoma; surface marking was done on the pelvis of the patients for teletherapy usually 15 X 15 field size and treated by APPA fields by the Telecobalt unit. Those patients who had separation of more than 20 cm were treated by four-field box technique. Two orthogonal X-rays pelvis and/ or CT assisted scanogram and slices and plato treatment planning system was utilized. After the completion of the external beam RT, the patients were evaluated for regression of tumor and given symptomatic treatment if required. Procedure was done under strict aseptic conditions under conscious sedation. The patient was put in lithotomy position and examined without anaesthesia for reassessment. The part was prepared followed by short anaesthesia ketamine). An assessment of fornices was done to decide upon the size of ovoids to be used whether half, small, medium and large.

The length of the uterus was assessed with uterine sound. The treatment was done for uterine length from 4 cm to 6 cm. Then the fletcher suit applicator was applied to the patient and adequate packing was done with gauge or placement of tungsten retractor to push the bladder and rectum. The patient was shifted to the HDR treatment unit where the catheters were connected and individualized treatment was received by the microselection afterloading system.

Treatment protocol

Combined external beam therapy and high dose brachy therapy in stages IIA,IIB and IIIB, IB>3 cm.

EBRT-ICRT

External beam therapy was followed for intracavitary high dose rate HDR micro-selection application at a gap of 2-3 weeks after completion of external beam radiotherapy Cases of cancer uterine cervix randomly received 4600cG in 23fractions, 45000cG in 20 fractions and 5000cG in 25 fractions preceded by ICRT. HDR dose- 800 cGy at point a repeated after 1 week ie; 2 fractions of HDR application with dose at point A being 800 cGy in each. None of the patients were given chemotherapy and all the cases were untreated prior to the study period. External beam therapy was delivered by theratron 780 C cobalt teletherapy unit and ICRT by HDR microselector after loading system using Ir 192 as the radioactive source.

Follow up

The patients were studied according to age, presenting complaints, clinical manifestation, histology, haemoglobin and treatment response acute radiation reactions. The patients were followed first after 2 weeks; 4 weeks and then 8 week till the completion of study period.

Statistical analysis

The results were analyzed using descriptive statistics and making comparisons among various groups. Categorical data were summarized as proportions and percentages (%) while discrete (quantitative) as mean (SD). All the associations were tested by using chi square test. Logistic regression analysis was performed for making model of treatment response outcome with general & clinical Profile of Patients. Statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Majority (44%) of the cases were aged 51-60 years, most common symptoms was P/v bleeding (60.4%) followed by white discharge (29.7%). Other symptoms were Backache/Pain in abdomen (5.5%), burning micturition (2.2%) while in 2.2% cases it was non-specific. According to histopathology squamous cell carcinoma was found in majority 84.6% cases while in remaining 15.4% cases adenocarcinoma was observed. IIIb was the most common stage as found in 70.3% cases, while stage IIa and IIb was found in 2.2% and 27.5% cases respectively (Table 2) (Figure 1).

	Variable	Total	
		No.	%
Age	20 - 30 yr	5	5.5
	31 - 40 yr	8	8.8
	41 - 50 yr	25	27.5
	51 - 60 yr	40	44
	61 - 70 yr	10	11
	71 - 80 yr	3	3.3
Symptoms	P/v Bleeding	55	60.4
	White Discharge	27	29.7
	Backache/Pain in abdomen	5	5.5
	Burning micturition	2	2.2
	No specific	2	2.2
Histopathology	squamous cell	77	84.6
	Adenocarcinoma	14	15.4
stage	IIa	2	2.2
	IIb	25	27.5
	IIIb	64	70.3

Table 2: General & Clinical Profile of Patients (n=91).

Figure 1. General & Clinical Profile of Patients.

The analysis to find any association of treatment response with General & Clinical Profile of Patients (Table 3) revealed that the age group 51-60 years was significantly associated with response ($p=0.034$) with lower risk of partial response (OR=0.31 (0.10-0.95), while the symptom Backache/Pain in abdomen had significantly higher risk of partial response ($p=0.002$, OR=16.24 (1.7-154.8)).

Variable		CR (N=70)		PR (N=21)		chi sq	p-value	OR (95% CI)
		No.	%	No.	%			
Age	20 - 30 yr	4	5.7	1	4.8	0.03	0.867	0.82 (0.09-7.81)

	31 - 40 yr	4	5.7	4	19	3.58	0.058	3.88 (0.88-17.14)
	41 - 50 yr	19	27.1	6	28.6	0.02	0.898	1.07 (0.36-3.17)
	51 - 60 yr	35	50	5	23.8	4.5	0.034	0.31 (0.10-0.95)
	61 - 70 yr	6	8.6	4	19	1.81	0.178	2.51 (0.64-9.91)
	71 - 80 yr	2	2.9	1	4.8	0.18	0.668	1.70 (0.15-19.73)
Symptoms	P/v Bleeding	42	60	13	61.9	0.03	0.876	1.08 (0.40-2.95)
	White Discharge	23	32.9	4	19	1.48	0.224	0.48 (0.15-1.59)
	Backache/Pain in abdomen	1	1.4	4	19	9.66	0.002	16.24 (1.70-154.76)
	Burning micturition	2	2.9	0	0	0.61	0.433	NA
	No specific	2	2.9	0	0	0.61	0.433	NA
Histo-pathology	squamous cell	63	90	14	66.7	6.76	0.009	0.22 (0.07-0.74)
	Adenocarcinoma	7	10	7	33.3	6.76	0.009	4.50 (1.36-14.90)
stage	IIa	2	2.9	0	0	0.61	0.433	NA
	IIb	24	34.3	1	4.8	7.07	0.008	0.10 (0.01-0.76)
	IIIb	44	62.9	20	95.2	8.12	0.004	11.82 (1.50-93.29)

Table 3. Association of Treatment Response with General & Clinical Profile of Patients (n=91).

By histopathology squamous cell carcinoma had significantly lower risk of partial response (p=0.009, OR=0.22 (0.07-0.74)) compared to adenocarcinoma (p=0.009, OR=4.50 (1.36-14.90)).

Among stages, IIb had significantly lower risk of partial response (p=0.008, OR=0.10 (0.01-0.76)) while IIIb had significantly higher risk of partial response (p=0.004, OR=11.82 (1.50-93.29)).

The Logistic Regression Analysis to find relationship of treatment response outcome with general & clinical Profile of Patients (Table 4) revealed minimum risk of partial response or maximum chances of complete response are those which have minimum beta coefficient in the category of the study variable which in this case was corresponding to age group 51-60 yr, complaints of burning micturition, squamous cell type and lower stage (IIa).

Variable	B	S.E.	Sig.	Exp(B)
Age			0.386	
20 - 30 yr	-18.05	22248.8	0.999	1.45E-08
31 - 40 yr	-16.09	22248.8	0.999	1.03E-07
41 - 50 yr	-17.49	22248.8	0.999	2.52E-08
51 - 60 yr	-18.51	22248.8	0.999	9.12E-09
61 - 70 yr	-17.66	22248.8	0.999	2.14E-08
71 - 80 yr	0			
Complaints			0.673	
P/v Bleeding	33.51	32311.98	0.999	3.56E+14
White Discharge	33.27	32311.98	0.999	2.80E+14

Backache/	36.27	32311.98	0.999	5.62E+15
Pain in abdomen				
Burning micturation	15.47	44518.77	1	5.25E+06
No specific	0			
Squamous cell	-1.32	0.84	0.117	0.266
Adenocarcinoma	0			
Stage			0.149	
IIa	-19.83	36276.52	1	2.44E-09
IIb	-2.65	1.18	0.024	0.07
IIIb	0			
Constant	-15.26	23431.92	0.999	0

Table 4. Logistic Regression Analysis to Find Relationship of Treatment Response Outcome with General & Clinical Profile of Patients (n=91).

Association of Toxicities with Age

The acute radiation toxicities were more in elderly age group and the association was found to be statistically significant ($p < 0.05$) except Genitourinary - cystitis. However complaint, Histopath and stage did not show significant association with acute radiation toxicities except moist desquamation with complaint which was seen more in Backache/Pain in abdomen and No specific ($p < 0.001$). (Table 5A, 5B, 5C, 5D) Confluent mucositis was seen more in proportion among partial response cases compared to complete response (2.9% vs 14.3%, $p = 0.044$) (Table 6).

Toxicities	Total		20 - 30 yr (N=5)		31 - 40 yr (N=8)		41 - 50 yr (N=25)		51 - 60 yr (N=40)		61 - 70 yr (N=10)		71 - 80 yr (N=3)		chi sq	p-value
	N	%	N	%	N	%	N	%	N	%	N	%	N	%		
Skin - Moist desquamation	3	3.3	0	0	0	0	0	0	0	0	3	30	0	0	25.1	<0.001
Ulceration	5	5.5	0	0	0	0	0	0	2	5	3	30	0	0	14	0.016
Confluent mucositis	5	5.5	0	0	0	0	5	20	0	0	0	0	0	0	14	0.016
Diarrhoea	47	51.6	2	40	2	25	3	12	29	72.5	8	80	3	100	31.3	<0.001
Enteritis/ Proctitis	28	30.8	0	0	1	12.5	1	4	18	45	6	60	2	66.7	21.5	0.001
Genitourinary - cystitis	3	3.3	0	0	0	0	0	0	1	2.5	2	20	0	0	10.2	0.069

Table 5A. Association of Toxicities with Age.

Toxicities				Complaints						chi sq	p-value
	P/v Bleeding		White Discharge	Backache/Pain in abdomen		Burning micturation		No specific			

	n		n		n		n		n			
	N	%	N	%	N	%	N	%	N	%		
Skin - moist desquamation	0	0	0	0	2	40	0	0	1	50	37.68	<0.001
Ulceration	1	1.8	3	11.1	1	20	0	0	0	0	5.33	0.255
Confluent mucositis	5	9.1	0	0	0	0	0	0	0	0	3.46	0.484
Diarrhoea	23	41.8	16	59.3	4	80	2	100	2	100	8.11	0.088
Enteritis/Proctitis	12	21.8	10	37	4	80	1	50	1	50	8.95	0.062
Genitourinary - cystitis	1	1.8	1	3.7	1	20	0	0	0	0	4.9	0.297

Table 5B: Association of Toxicities with Complaints.

Toxicities	Histopathology				chi sq	p-value
	Squamous cell		Adenocarcinoma			
	N	%	N	%		
Skin - moist desquamation	2	2.6	1	7.1	0.77	0.381
Ulceration	4	5.2	1	7.1	0.09	0.769
Confluent mucositis	5	6.5	0	0	0.96	0.327
Diarrhoea	39	50.6	8	57.1	0.2	0.655
Enteritis/Proctitis	23	29.9	5	35.7	0.19	0.663
Genitourinary - cystitis	2	2.6	1	7.1	0.77	0.381

Table 5C: Association of Toxicities with Histopathology.

Toxicities	Stage						chi sq	p-value
	IIa		IIb		IIIb			
	N	%	N	%	N	%		
Skin - moist desquamation	0	0.00	0	0.00	3	4.70	1.31	0.52
Ulceration	0	0.00	0	0.00	5	7.80	2.23	0.328
Confluent mucositis	0	0.00	1	4.00	4	6.30	0.29	0.863
Diarrhoea	1	50.00	9	36.00	37	57.80	3.43	0.18
Enteritis/Proctitis	0	0.00	8	32.00	20	31.30	0.91	0.633
Genitourinary - cystitis	0	0.00	0	0.00	3	4.70	1.31	0.52

Table 5D: Association of Toxicities with Stage.

Toxicities	Response				chi sq	p-value
	CR		PR			
	N	%	N	%		
Skin - moist desquamation	1	1.40	2	9.50	3.32	0.068

n								
Ulceration	3		4.30	2		9.50	0.85	0.356
Confluent mucositis	2		2.90	3		14.30	4.06	0.044
Diarrhoea	35		50.00	12		57.10	0.33	0.566
Enteritis/Proctitis	21		30.00	7		33.30	0.08	0.772
Genitourinary - cystitis	2		2.90	1		4.80	0.18	0.668

Table 6: Association of Toxicities with Response.

Discussion

By virtue of HDR brachytherapy, high dose of radiation can be given in a shorter period of time (outpatient department) which reduces patient discomfort and inconvenience. Regardless of its practical benefits, HDR brachytherapy has experienced significant resistance because of worries regarding its possible toxicity and theoretical radiobiologic disadvantage as HDR involves a greater probability of late effects for a given level of tumor control. Certain crucial factors that aid in lowering the frequency of complications without compromising the treatment results are fractionation and dose adjustment of total dose.

In our study it was found that majority (44%) of the cases were aged 51-60 years. According to Globocan reports In India the peak age for cervical cancer incidence is 55-59 years [19]. The major symptoms that were discovered included P/v bleeding (60.4%) followed by white discharge (29.7%). Other symptoms were Backache/ Pain in abdomen (5.5%), burning micturition (2.2%) while in 2.2% cases it was non-specific. P/v bleeding and white discharge have been the common symptoms of cervical carcinoma according to Shah et al and Nganwai et al however the percentage is contradictory to our results 86.9 and 77.7 % menstrual abnormality and 94.2% and 92.4% abnormal vaginal discharge respectively [20, 21].

According to histopathology squamous cell carcinoma was found in majority 84.6% cases while in remaining 15.4% cases adenocarcinoma was observed. IIb was the most common stage as found in 70.3% cases, while stage IIa and IIb was found in 2.2% and 27.5% cases respectively. Histopathological analysis done by Bhandari et al revealed that 92.5 % were Squamous cell carcinoma (SCC), and 7.5 % were Adenocarcinoma which were again not concomitant with our results. However our results were consistent with his study in terms of stages as he also found that the common stage was 67 % IIb followed by 11.1 % in stage IVa, 9.8 % in stage IIb, 8.5 % in IIa, and 3.5 % in stage Ib [22].

Our results revealed that revealed that the age group 51-60 years was significantly associated with response ($p=0.034$) with lower risk of partial response ($OR=0.31$ (0.10-0.95)), while the symptom Backache/ Pain in abdomen had significantly higher risk of partial response ($p=0.002$, $OR=16.24$ (1.7-154.8)). However the results were consistent with the outcomes attained by Saibishkumar et al. revealed that age > 50 y was linked with higher rates of no residual tumor [15] while Rahakbauw et al found no statistical relationship [23]. By histopathology squamous cell carcinoma had significantly lower risk of partial response ($p=0.009$, $OR=0.22$ (0.07-0.74)) compared to adenocarcinoma ($p=0.009$, $OR=4.50$ (1.36-14.90)). Similar study done by Fletcher et al. revealed that the squamous cell carcinoma group responded similarly to those with non-squamous cell carcinoma. Among stages, IIb had significantly lower risk of partial response ($p=0.008$, $OR=0.10$ (0.01-0.76)) while IIb had significantly higher risk of partial response ($p=0.004$, $OR=11.82$ (1.50-93.29)) [24].

The Logistic Regression Analysis to find relationship of treatment response outcome with general & clinical profile of patients revealed minimum risk of partial response or maximum chances of

complete response are those which have minimum beta coefficient in the category of the study variable which in this case was corresponding to age group 51-60 year, complaints of Burning micturition, squamous cell type, lower stage (IIa) and Hb level more than 10 mg/dl. Similar results were found by Rahakbauw et al which revealed that 26-50-year-olds tended to exhibit decreased response, by 0.87 times, compared to those older than age 50 [23].

The acute radiation toxicities were more in elderly age group and the association was found to be statistically significant ($p < 0.05$) except Genitourinary – cystitis. However complaint, Histopath and stage did not show significant association with acute radiation toxicities except moist desquamation with complaint which was seen more in Backache/Pain in abdomen. No specific ($p < 0.001$) Confluent mucositis was seen more in proportion among partial response cases compared to complete response (2.9% vs 14.3%, $p = 0.044$). Consistently, Kunos [25] and Laurentius et al [26], also found higher haematological toxicity in elderly patients.

In conclusion, recent advances have been incorporated in brachytherapy for cervical cancer which allow for better demarcation and coverage of the tumor, as well as improved avoidance of OARs. As a result, when compared to traditional techniques, HDR can achieve very high rates of local control while lowering morbidity. This article gives a summary of a small effort in defining an optimum radiation schedule in Indian patients who present advanced stages and when there is heavy patient load. Taking into account of increased hospital burden of locally advanced cancer cervix patients in Indian context, increase in sample size and extending the follow-up duration may produce more reliable results.

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