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Original Research Paper

Oncology

TREATMENT OUTCOME OF EXTERNAL BEAM RADIOTHERAPY (EBRT) WITH INTRACAVITARY RADIOTHERAPY (ICRT) IN CA CERVIX : AN INSTITUTIONAL EXPERIENCE

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ABSTRACT

Introduction : Ca Cervix is the second most common malignancy in Indian women. Most of the cases present in advanced stage. Radiotherapy is an important modality of treatment. Combination of EBRT and ICRT is an effective strategy which is based on the principle that we are able to give high radiation dose to tumor while sparing surrounding normal tissue.**Aim and Objectives :** The aim was to evaluate the 3 year overall survival (OS) and disease-free survival (DFS) of patients treated by EBRT and ICRT. The objectives were to evaluate radiation toxicities and to evaluate rate of residual disease, recurrence and distant metastases.**Materials and Methods :** It is a Retrospective analytical study. We analyzed 468 newly diagnosed cases of Ca Cervix registered in department between January2009 to December2013. Out of which 382 completed radical radiotherapy (EBRT+ICRT).
Results : At the end of 3 years 58(15.18%) patients lost to follow-up, 48(12.56%) residual disease, 60(15.70%) local recurrence and 26(6.80%) had distant metastases. The DFS was 73.91% in Stage-I and 62.8% in Stage-II while 51.38% in Stage-III and 29.82% in Stage-IV. The OS was 82.6% in Stage-I, 71.9% in Stage-II, 65.19% in Stage-III and 42.1% in Stage-IV. The difference between early and advanced disease is statistically significant with p-value of 0.016.Conclusions : EBRT and ICRT is effective treatment in terms of overall survival and disease-free survival. Associated radiation induced rectal and bladder toxicities are acceptable & manageable. Early stage and overall treatment time are favorable prognostic factors for 3 year DFS & OS.

KEYWORDS : Ca Cervix, External Beam Radiotherapy, Intracavitary Radiotherapy, Overall Survival

INTRODUCTION

Ca Cervix is the second most common malignancy in Indian women. Its annual incidence is 122844 and causes 67477 deaths annually. It is the second most leading cause of cancer deaths in Indian women.[1]

In developing countries like India about 80% of women with cervical cancer are diagnosed at advanced stage, which is significantly associated with poor prognosis.[2]

Radiotherapy is an important modality of treatment. Combination of EBRT and ICRT is an effective strategy which is based on the principle that we are able to give high radiation dose to tumor while sparing surrounding normal tissue.[3]

The dose to the Point-A should be low-dose-rate (LDR) equivalent of 80-85 Gy for early stage disease and 85-90 Gy for advanced stage. The pelvic sidewall dose recommendations are 50-55 Gy for early lesions and 55-65 Gy for advanced ones. In order to minimize the toxicities, bladder and rectal doses should be kept below 80 Gy and 75 Gy LDR equivalent doses, respectively.[4]

Concurrent chemotherapy improves progression-free and overall survival for high-risk, early-stage patients who undergo radical hysterectomy with pelvic lymphadenectomy as well as causes significant improvement in pelvic control and overall survival in advanced cases.[5]

AIM AND OBJECTIVES

The aim of this study was to evaluate the 3-year overall survival (OS) and disease-free survival (DFS) of patients treated by EBRT and ICRT. The objectives were to evaluate radiation induced toxicities during and after completion of treatment and to evaluate rate of residual, recurrence and distant metastases in the follow-up period.

MATERIALS AND METHODS

It is a Retrospective analytical study. We analyzed 468 newly diagnosed cases of Ca Cervix registered in department between January2009 to December2013. All cases were staged according to FIGO staging.[6] Out of the 468 patients, 382 completed radical radiotherapy (EBRT+ICRT). The remaining 86 patients either did not receive ICRT due to gross residual disease (22) & co-morbidities (14) or they were excluded from study due to incomplete/irregular treatment (39) or their records could not be traced (11).

EBRT was given with Cobalt-60 unit by AP-PA or four-field box technique, 50Gy in 25 fractions, with 5 fractions per week, over 5-6 weeks duration, with midline block at 45Gy. Concurrent chemotherapy was given with Inj. Cisplatin 35mg/m2 weekly.

ICRT was given within 2-8 weeks due to the large number of patients. Iridium-192 source was used for HDR-ICRT. Doses delivered were 21 Gy in 3 fractions at weekly interval (7Gy/#). The dose was prescribed to point-A. The 3-channel Fletcher-Suit applicator was used based on the Manchester System.

Standard follow-up protocol - monthly for 6 months, then 3 monthly for 2 years and 6 monthly up to 3-4 years and then annually. Patients were examined clinically & with USG; PAP smears were taken when required. All complications were graded as per RTOG criteria particularly for radiation induced cystitis, proctitis and intestinal toxicities.[7]

The follow-up duration was between 9-76 months. Patients were considered lost to follow-up if they did not complete our standard follow-up protocol.

For multivariate analysis, the Cox proportional hazards regression analysis was used to assess the strengths of various factors with 3-year DFS and OS. The statistical analyses and Kaplan-Meier survival curve were calculated by using STATA software version 14.

RESULTS

Total 382 patients were found to be eligible for the study. The age range was 31 years to 74 years with the median of 52 years. There were 23 (6.02%) patients in the Stage-IB, 121(31.67%) patients in Stage-II, 181(47.38%) patients in Stage-III, and 57 (14.92%) patients in Stage-IVA. There were 73 (19.10%) patients operated. These patients were mostly in the early stage disease while the other patients were in the advanced stage disease. Most of the patients 335 (87.69) received concurrent chemotherapy with inj Cisplatin

35mg/m2 wkly The median overall treatment time was 84 days with range of 61-106 days. None of the patients after EBRT received ICRT within a weeks interval. This is because of large number of patients and inadequate treatment facilities. Most of the patients were able to receive ICRT after 4 weeks interval. The maximum gap between EBRT and ICRT was of 8 weeks. We have devided the patients into two groups. The first group patients received ICRT in 1-4 weeks interval and the other group received ICRT after 5-8 weeks interval between EBRT and ICRT. There were 153 (40.05%) patients in the 1-4 weeks interval group while 229 (59.91%) patients were in the 5-8 weeks interval group.

The follow up duration was between 9-76 months with a median of 43 months.Table-1 shows patients characteristics.

Table 1. Patients characteristics

Factors			n = 382	%
Age (in years)		Range	31-74	–
		Median	52	–
Stage (FIGO)	Early	I	23	06.02
		II	121	31.67
	Late	III	181	47.38
		IV	57	14.92
Post-operated	Yes	73	19.10	
	No	309	80.89	
Concurrent chemotherapy with EBRT	Yes	335	87.69	
	No	47	12.30	
Gap between EBRT and ICRT	1-4 wks	153	40.05	
	5-8 wks	229	59.94	
Overall treatment time (in days)	Range	61-106	--	
	Median	84	--	
Follow up (in months)	Range	9-76	--	
	Median	43	--	

All the patients were evaluated for radiation induced toxicities. The most common toxicity was found to be proctitis and cystitis. There were 74(19.36%) patients who suffered radiation proctitis and 47(12.30%) patients who had radiation cystitis. The other toxicities that were observed during follow-up are intestinal toxicities8(2.9%) and vaginal stenosis24(6.28%). Most of the patients had Grade-II and Grade-I toxicities while few had Grade-III toxicities. None of the patients suffered Grade-IV toxicity. Table 2. shows different radiation induced toxicities observed and their severity in grades.

The toxicities observed were not severe and were treated only symptomatically. For radiation cystitis patients were advised to take plenty of oral fluids and were given analgesics. Few patients required to be treated with intravainous fluids. Vaginal stenosis and intestinal toxicities were not significant enough to be actively treated. Radiation proctitis was treated with stool softener, antiinflammatory agents and steroid enemas.

Table 2. Radiation toxicities

Toxicity	Patients		Grades of severity			
	n	%	1	2	3	4
Radiation Cystitis	47	12.30	09 (19.14)	33 (70.21)	05 (10.67)	00
Vaginal stenosis	24	6.28	04 (16.66)	18 (75)	02 (8.33)	00
Intestinal toxicities	08	2.09	4 (50)	03 (37.5)	01 (12.5)	00
Radiation Proctitis	74	19.36	23 (38.23)	35 (41.17)	16 (20.58)	00
Total	153	40.05	--	--	--	--

At the end of 3 years it was observed that 58(15.18%) patients lost to follow-up. 48(12.56%) patients had residual disease. Local recurrence was seen in 60(15.70%) patients. 26(6.80%) patients were found to have distant metastases. Both, local recurrence and distant metastases at once was observed in 13(3.4%) patients. The stage wise outcome at the end of 3 years is shown in Table 3.

Table 3. Stage wise outcome at the end of 3 years

Stage	No. of Patients	Residual disease	Local recurrence	Distant metastasis	Both LR&DM	Lost to follow-up
I	23	00	03 (13.04)	00	00	03 (13.04)
II	121	13 (10.74)	14 (11.57)	05 (4.13)	01 (0.82)	17 (14.04)
III	181	24 (13.25)	28 (15.46)	13 (7.18)	07 (3.86)	28 (15.46)
IV	57	11 (19.29)	15 (26.31)	08 (14.03)	05 (08.77)	10 (17.54)
Total	382	48 (12.56)	60 (15.70)	26 (6.80)	13 (3.40)	58 (15.18)

The disease free survival was better in patients with early stage compared to the advanced stage patients. It was 73.91% in Stage-I patients and 62.8% in Stage-II patients while 51.38% in Stage-III and 29.82% in Stage-IV (p-value 0.106).

The 3 year DFS rate was better in Post-operated patients. In Post-operated patients the DFS was 69.86% and in non-operated patients it was 49.19%. This difference was statistically significant with p-value being 0.044.

The patients who received concurrent chemotherapy, DFS rate was 54.32% and 44.68% in patients who did not receive. Though the DFS rate is better in patients receiving concurrent chemotherapy the difference is not statistically significant (p-value 0.274)

The patients who received ICRT within 1-4 weeks after EBRT, shown better DFS of 70.58% than the patients who received ICRT at 5-8 weeks, 41.48%. This difference is also statistically significant with p-value of <0.001.

The details of DFS at the end of 3 years are shown in Table 4.

Table 4. Disease free survival at the end of 3 years

Factors			No. of Patients	3 yr DFS	%	Hazard Ratio	95% CI	PValue
Stage	Early	I	23	17	73.91	1.36	0.93-1.98	0.106
		II	121	76	62.80			
	Late	III	181	93	51.38			
		IV	57	17	29.82			
Post-operated		Yes	73	51	69.86	1.77	1.01-3.11	0.044
		No	309	152	49.19			
Concurrent chemotherapy		Yes	335	182	54.32	1.47	0.79-2.72	0.274
		No	47	21	44.68			
Gap between EBRT and ICRT		1-4 wks	153	108	70.58	2.91	2.05-4.15	<0.001
		5-8 wks	229	95	41.48			

Similarly, the overall survival for early stage disease was found to be better than for advanced stage disease. The OS was 82.6% in Stage-I patients and 71.9% in Stage-II patients. In advanced stage patients, the OS was 65.19% in Stage-III and 42.1% in Stage-IV patients. The difference between early stage and advanced stage disease is found to be statistically significant with p-value of 0.016.

The OS for Post-operated patients was 80.82% and for non-operated patients it was 61.16%. This difference is statistically significant with p-value being 0.012.

The patients receiving concurrent chemotherapy shown to have better OS of 65.97% compared to those who did not receive concurrent chemotherapy (57.44%). But the difference is not statistically significant and the p-value is 0.325.

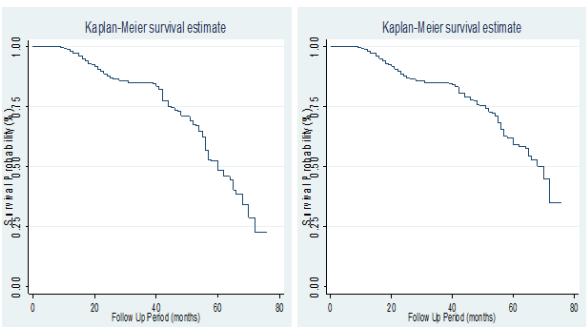
The patients who received ICRT after 1-4 weeks of EBRT better OS (87.58%) than those who received ICRT after 5-8 weeks interval (49.78%). This difference is statistically significant and the p-value is <0.001. The Table 5. shows the details of overall survival at the end of 3 years.

Table 5. Overall survival at the end of 3 years

Factors			No. of Patients	3 yr DFS	%	Hazard Ratio	95% CI	PValue
Stage	Early	I	23	19	82.60	1.34	0.88-2.03	0.016
		II	121	87	71.90			
	Late	III	181	118	65.19			
		IV	57	24	42.10			
Post-operated		Yes	73	59	80.82	2.47	1.21-5.03	0.012
		No	309	189	61.16			
Concurrent chemotherapy		Yes	335	221	65.97	1.43	0.77-2.67	0.325
		No	47	27	57. 44			
Gap between EBRT and ICRT		1-4 wks	153	134	87.58	4.83	2.81-8.28	<0.001
		5-8 wks	229	114	49.78			

Figure 1. elaborates the comparison between 3 year survival estimate of DFS and OS. There is no significant difference in the two curves as this estimate was done at short period of only 3 years.

Figure 1. Kaplan-Meier survival estimate at the end of 3 years



DISCUSSION

Concurrent chemoradiotherapy followed by ICRT is the standard treatment for all stages of Ca Cervix.[8]

Even Post-operated cases may also require adjuvant radiotherapy with EBRT and ICRT if there is close or positive margins, pelvic lymph node involvement and parametrial invasion on postoperative histopathology.[9]

In our study we found that 18.36% patients did not receive complete treatment and 15.18% patients lost to follow-up. This is because of poverty, illiteracy and negligence among the patients being treated at our institute.

Ideally, Overall treatment time should be less than 50 days, as prolonged duration of treatment has adverse effects on local control and disease-free survival rate.[10,11]

But it was 61-106 days with a median of 84 days in our study, because of inadequate treatment facilities and excessive number of patients leading to long waiting period for ICRT treatment. Even some of those patients who got their treatment started early, could not continue it because of longer duration of the treatment.

The OTT required to be less than 8 weeks duration, after which the local tumor control and overall survival of the patients shown to be decreased by around 1% per day.[12] But almost all of our patients had OTT of more than 8 weeks.

Our findings were comparable with the most studies that showed similar DFS and OS. Rate of residual disease, local recurrence and distant metastases were also comparable.

Rakhsha et. al. showed three year DFS as 75% in early stage and 39.62% in advanced stage disease. In our study DFS was observed to be 68.35% in early stage and 40.06% in advanced stage disease. The OS was 80.95% in early stage and 41.5% in advanced stage disease which was 77.25% in early stage and 53.64% in advanced stage disease. The bladder and rectal radiation induced toxicities 10.4% and 23.3% whereas in our study it was 12.3% and 19.36% respectively. [13]

Azad et. al. showed three year DFS rate of 72% in early stage disease and 26.92% in advanced stage disease, which was 68.35% in early stage and 40.06% in advanced stage disease. The 3 year OS was 76.25% for early stage and 38% for advanced stage disease. In our study OS was 77.25% in early stage and 53.64% in advanced stage disease. The bladder and rectal radiation induced toxicities were 6.14% and 9.35% which in our study was 12.3% and 19.36% respectively.[14]

CONCLUSIONS

We conclude that EBRT and ICRT is an effective treatment in terms of overall survival and disease-free survival. The associated radiation induced rectal and bladder toxicities are acceptable & manageable. Early stage, post-operated status and minimum overall treatment time are favorable prognostic factors for 3 year DFS & OS.

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