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"Role of Twice Weekly HDR- Brachytherapy in Management of Carcinoma Of Uterine Cervix-Experience of Rural Centre in India"

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Materials and Methods : Hundred patients with locally advanced (stages IIB to IVA according to FIGO classification) carcinoma of uterine cervix were enrolled, radiotherapy was conventionally administered: 50.4 Gy/28 fractions by external beam (whole pelvis) followed by HDR-ICBT, 4 fractions of 7 Gy each. Paclitaxel was administered on weekly basis at dose of 40 mg/m^2 during entire course of external beam radiotherapy as a radio sensitizer. Overall treatment time 50 days.

Keywords : *twice weekly HDR brachytherapy, paclitaxel, cervical carcinoma.*

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Results : Treatment response was evaluated three months after the end of radiotherapy by means of clinical examination and ultrasonography. Complete Regression (CR) in 83%, partial response (PR) 14% and progressive disease 3%. At 26 months of median follow up 73 patients alive, 58 patients are disease free.

Conclusion : The twice weekly HDRICBT regimen may improve the local control rate with low complications as well as reduced overall treatment time.

Keywords : twice weekly HDR brachytherapy, paclitaxel, cervical carcinoma.

I. Introduction

Invasive cervical cancer is the second most common malignancy in the women worldwide, after breast cancer, this accounts nearly 5,00,000 new cases and 250000 death per year [1] Of these, 80% occur in developing countries and 20% in developed countries[2]. The incidence rate in India among various cancer registries shows 17.2 to 30.7 per 100,000 women with highest incidence in Chennai, Brashi and lowest Incidence in Mumbai (NCRP 2001). The number of cervical cancer deaths in India is projected to increase 79000 by the Year 2010. In our department cancer cervix constitutes 25% of total cases seen.

Whereas, either radiotherapy (RT) (external RT+ Brachytherapy) or surgery represents the mainstay of treatment for patients with early stage cancer, while multimodality treatment strategies, including RT combine with cisplatin based chemotherapy (CT) or neoadjuvant chemotherapy or CT followed by radical surgery have been reported to improve disease free as well as overall survival. Concurrent chemoradiation (CCRT) is established treatment modality in locally advanced cervical cancer. Brachytherapy has important role in management of cervical carcinoma, either alone in early cases or in combination with external RT. LDR brachytherapy is gold standard but due to potential disadvantage of LDR like radiation exposure to staff, long treatment time hence possibility of applicator displacement etc. so LDR is replaced by HDR, but HDR treatment is always fractionated, if brachytherapy started after completion of EBRT, due to large bulky tumour and, if once weekly application was done than possibility of treatment prolongation and tumour repopulation so there is need of twice weekly HDR brachytherapy.

In locally advanced cervical cancer, many phase I and II studied, paclitaxel alone or in combination with cisplatin, carboplatin in patients undergoing pelvic radiation therapy. This acts as radiosensitizer and synergistic action along with radiotherapy. [3][4]

Traditional prognostic factors in cervical cancer have been studied. Patients related prognostic factors include age, anaemia and smoking.[5][6][7]and[8] Tumour related factors includes stage, tumour size, nodal involvement, and hypoxia [9]. Radiation related factors include overall treatment time, dose, use of brachytherapy and concurrent chemotherapy. Shorter treatment times, higher doses, use of brachytherapy, and use of chemotherapy are all associated with better outcomes.[10],[11].[12],[13]

CCRT is the established treatment modality in locally advanced carcinoma of uterine cervix. Many drugs like cisplstin, 5-fluorouracil and more recently paclitaxel are used as radiosensitizer. In addition to direct cytotoxic effect shows the theoretical advantage to sensitize malignant tissue to the effect of radiation. CT in facts may act synergisticacally with RT and inhibiting

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the repair of sub lethal damage along with promoting the synchronization of cells into a radiation sensitive phase of the cycle, and reducing the fraction of hypoxic cells resistant to radiation. Furthermore CT may independently increase the rate of death of tumor cells.
In rural centre cervical cancer is leading malignancy and majority of patients presented with locally advanced staged. This prospective non randomized study with 100 patients of locally advanced cervical carcinoma was conducted to evaluate the adverse effect of treatment prolongation treated with radical radiotherapy. This is the preliminary reports of our experience at a median follow up of 26 months.

II. Materials and Methods

During a period from July 2007 to June 2010, 100 patients of cervical carcinoma attending the department of Radiotherapy were included in prospective non randomized trials of CCRT.

a) Eligibility Criteria Were

- No previous oncology treatment except biopsy.
- Histological/cytological diagnosis of malignant disease.
- Age between 28-65years.
- HB >l0gm.
- Blood urea &creatinine not higher than twice normal value.
- ECOG performance scale score of 0-2.
- Informed consent oral and written from patients.
- ANC >2000, platelets >100000, bilirubin <1.5, serum creatnine, 1.5mg%.
- SGOT or SGPT <2 upper normal, creatinine clearance 50ml/min.
- No clinically significant medical problem like heart disease.
- No prior radiation therapy. Patients characteristic are shows in [Table no.1]

b) Pretreatment Evaluation

- Detailed history and complete physical examination including bimanual pelvic examinations.
- Radiographic studies like X- ray pelvis, X-rays chest, USG abdomen and pelvis, if possible CT scan and MRI of pelvis also done.
- Laboratory studies including routine investigation like Hemoglobin estimation, total leukocyte count; differential count and platelet count; blood sugar and liver functions test, biochemical analysis.
- Clinical staging based on FIGO staging.

c) Treatment Designed

The treatment protocol schedule consisted of a course of RT combined with concomitant paclitaxel administered weekly during entire course of external RT.

d) Chemotherapy

Paclitaxel a dose of 40mg/m^2 was diluted in 100 ml of normal saline and administered by 30 minute infusion. Dexona 8 mg, Ranitidine 50 mg and Ondensetron 8 mg IV bolus, given 30 min before paclitaxel.

III. Radiotherapy

All patients received RT to whole pelvis 50.4Gy/ 28 fractions, one fraction per day, five days per week, with two opposed pelvic field A-P and P-A and four fields. Two fields technique were planned when inter portal distance (IPD) less than 20 cm. and four fields, when IPD was more than 20 cm. Last three fractions delivered using midline shielding, followed by HDRICBT 4 fractions of 7 Gy each (total 28Gy) to reference point A (2 cm superior and 2 cm lateral to the cervical Os) on twice weekly basis. Total dose to point A was 8360 cGy. Overall treatment time (OTT) was 50 days (range 49 to 52 days).

IV. Evaluation of Follow-up

Before each course of CT patients were evaluated and during RT they were seen weekly by Radiation oncologist for normal tissue reaction and tumor response. Routine investigations were performed and if required supportive management was given. As per RTOG criteria adverse reaction was documented. During CT all patients were admitted in ward. All patients were examined after completion RT than 6 weeks followed by 3 monthly intervals. Blood count, x-ray chest, USG abdomen. Patients belong to rural area were also motivated to come for regular follow-up.

V. Response

After completion of treatment, all patients were evaluated for response and acute toxicity. Response was evaluated three months after the end of radiotherapy by means of clinical examination and USG. Complete regression (CR) was defined as disappearance of the disease according to both clinical and radiological examination. Partial regression (PR) was defined as tumor size regression more than 50%. A regression of less than 50% or stable disease (SD) was defined as no change (NC). Acute hematological toxicity was monitored weekly during treatment through serum examination and blood cell counts. Patient symptoms like diarrhoea, vomiting, dysuria were reported. Toxicity was scored according to WHO criteria.

VI. Results

All patients completed planned course of RT. Complete Regression in 83 patients (83%), partial response in 14 patients (14%), while three patients had progressive disease (3%) stage wise response shown in[Table no.2]. Severe adverse effects during treatment-

are mention in [Table No.3]. Late radiation reactions mention in [Table No. 4]. While response of treatment with OTT less than 50 days verses more than 50 days mention in [Table no. 5] After two years from last patents treated analysis done, only 73 patients on regular follow up, overall survival and disease free survival mention in [Table no.6], eight patients have locoreginal recurrences, three patients have liver metastasis, one patient have liver and lung metastasis, two patients have bone metastasis. One patient has supraclavicular lymphadenopathy. Eight patients died during follow up and rest patients missed for follow up. Vaginal fibrosis developed in almost every patent, one patients developed rectovaginal fistula, two patients developed gross haematuria and eight patients developed rectal bleeding. Rectal bleeding cases were managed with steroid enema. Heamaturea cases were managed with symptomatically. Other recurrence cases were managed with either palliative radiotherapy or chemotherapy (cisplatinum& paclitaxel based)

Our study is in preliminary stage only 26 months follow-up done, long term follow-up is needed to derive response of treatment, recurrences and late complications. No cases of cardiac toxicity and alopecia were recorded.

VII. Discussion

Definitive RT represents the standard treatment for locally advanced (FIGO stage IIB-IVA) cervical carcinoma. RT is usually performed applying whole pelvic fields with a dose up to 50 Gy followed by boost with ICBT. Despite large tumor doses conventionally administered (65 Gy or more), failures are not uncommon. According to Perez [14] the actuarial highest probability of loco regional control after RT alone is 60% for stage III. On the other hand, achieving local CR after RT represent an important predictive factor of survival, being a 5 years survival rate of 76% when local CR is obtained, versus 41% when CR is not achieved.[15]The improvement of pelvic control cannot be reached by increasing radiation dose beyond the current levels without prohibitive morbidity. The consequences, in recent years, have been the development of chemo-radiotherapy regimens with which favorable results have been reported.

In locally advanced cervical carcinoma CCRT with cisplatin or cisplatin in combination with fluorouracil to external and ICBT improved the survival rate [16], [17] and[18]Paclitxel was also used along with RT either alone or in combination with cisplatin or carboplatin by many workers[19],[20]and[21] shows that paclitaxel either alone or in combination with other agent act as radiosensitizer with good pelvic control. In our study shows that concurrent administration of paclitaxel at the weekly dose of 40 mg/m^2 and RT with conventional fractionation is feasible. The acute toxicity is not increased in respect to what is commonly observed during a conventional course of exclusive radiation treatment. A complete response of 83% considered as satisfactory results.

Over all treatment time (OTT) is one of most important prognostic factor, [11]. reported that there is loss of pelvic failure rate approximately 1% loss of tumor control per day of prolongation of treatment time beyond 30 days in 830 patients with cervical carcinoma treated with irradiation alone.Petereit et al[12] reported that the five year survival and pelvic control rate differed significantly with treatment time <55 days vs. >55 days: 65 and 54% (p= 0.03), 87 and 72% (p= 0.006), respectively. In addition, survival was decreased by 0.6% per day and pelvic control by 0.7% per days for all stages.

Delaloyeet.al. [22] and Lanciano et.al. [10] Suggested that shorter treatment duration is a factor associated with longer survival and pelvic control in carcinoma cervix, OTT less than or equal to 55 days. In order to shorten OTT, brachytherapy could perform at or near the end of EBRT.

MandalAbhijit et al. (2007):[23]Study found that stage II patients showed comparable local control rate (75% vs. 79%) and 5-year disease free survival rate (73.3% vs.76.3%) with OTT <50 days and OTT >50 days respectively, but stage III patients showed a statically significant (P<0.001) higher local control rate (100% vs. 76.5%) and 5-year disease free survival rate (100% vs. 68.6%) with OTT <50 days and OTT >50 days respectively.

In our study it was found that there was a strong correlation between OTT and local control, stage IIB patients showed local control rate (100% vs. 83.3%), stage IIIB patients showed comparable local control rate (82.6% vs. 88.2%) and stage IVA patients local control rate (72.7% vs. 0. %). with OTT≤50 days and OTT >50 days respectively. Patients who completed treatment ≤50 days as compare to >50 days shows statistically significant local control (p<0.05), in different stages.

Yukihiro Hama et al. [24]have been studied effectiveness and safety of twice-weekly HDRICBT in cervical carcinoma, showed that twice-weekly regimen substantially improve local control (p<.01) and reduced moderate and severe complications (p <.01). However, despite improvements in local control and severe complications, overall survival was not significantly improved, because 93% of patients who developed local-regional recurrences had also distant metastasis, and most of death occurs due to metastasis and multiorgan failure.

ABS recommendation for HDRICBT[25]: The overall treatment time would be unduly prolonged if the HDR was started after completion of EBRT as a weekly session. If disease is advanced due to large tumor volume, brachytherapy implant was not possible during EBRT. So it is advisable to perform two implants per

week after the EBRT has been completed.To reduce repopulation, OTT should be shortened either by increasing dose per fraction or administering more fractions per week. If the number of fractions increased from one to two a week, the dose per fraction to point A reduced. In our study number of fractions increased but dose per fraction was not reduced, because we started brachytherapy after completion of EBRT. 7 Gy per fraction twice weekly regimen was well tolerated with fewer complications and good local control.

In our study OTT was 49-52 days (median 50days). In our study to decreases OTT, brachytherapy started after completion of EBRT and two implants per week were done. Result shows that twice weekly HDR brachytherapy seems to be safer and better therapeutic outcome with improve local control rate. As per our knowledge this is the only study where 7Gy per fractions on twice weekly basis with acceptable complications.

However some drawback was also present in this study.

1. It was not randomized.
2. Number of patient in less.
3. Study period in short.
4. Follow up is poor.
5. Cause of death of patient is not known.

This study indicates that for better tumour control OTT should be less than 50 days, to decrease OTT, brachytherapy given on twice weekly basis, twice weekly brachytherapy seems to be safer and better therapeutic outcome with improve local control rate.courses of paclitaxel can be given as CCRT with manageable adverse effect in the management of locally advanced cervical carcinoma.

However a large randomized study is needed to pin point if any. CT and RT controlled only tumor and tumor related death. It cannot improve the expected age; hence cause of death in every treated cancer patients should be evaluated.

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Table 1 : Patient's Characteristics

Total No. of Patient	100	
Follow up (Median, Range)	26 Months (21to 46)	
Stage IIB	24	
Stage IIIB	62	
Stage IVA	14	
Age (Median, Range)	47.8 Years (28 to 65)	
Resident	Rural	70
	Urban	30
Degree of differentiations (SCC)	Moderately	48
	Well	28
	Poorly	24

SCC squmous cell carcinoma

Table 2 : Over all response after completion of treatment

Response	IIB	IIIB	IVA	Total
CR	21	51	11	83
PR	2	9	3	14
SD	1	2	0	3
Total	24	62	14	100

CR- complete response, PR- partial response, SD- stable disease

Table 3 : Acute Reactions

Acute Reactions	Grade-0	I	II	III	IV
Neutropaenia	84	13	3	0	0
Thrombocytopenia	88	8	4	0	0
Hypersensivity reaction	92	6	2	0	0
Nausea	20	38	52	10	0
Vomiting	26	52	22	0	0
Diarrohea	13	61	20	6	0
Urinary symptoms	40	54	6	0	0
Rectal symptoms	46	38	14	2	0

Table 4 : Late Reactions

Late Reactions	No. of cases
Vaginal fibrosis	24
Rectovaginal fistula	1
Bleeding per rectal	8
Hematurea	2

Table 5 : Comparison of Response between OTT ≤50 days vs. >50 days

Completed treatment ≤50 days				Completed treatment >50 days		
Stage	CR	Total no. of patients	%	CR	Total no. of patients	%
IIB	17	17	100	10	12	83.3
IIIB	19	23	82.6	30	34	88.2
IVA	8	11	72.7	0	3	0

CR- complete response, OTT- overall treatment time

Table 6 : Follow-up after 2 years

Response	Percentage
Follow-up	73
DFS	58

DFS- disease free survival