Volume : 4 | Issue : 6 | June 2015 • ISSN No 2277 - 8179

Research Paper

Clinical Significance of Overall Treatment Time and Concurrent Chemo Radiation in the Treatment of Cervical Cancer Patients – 5 Years Follow-Up

Medical Science

KEYWORDS : overall treatment time, paclitaxel, cervical carcinoma, HDR brachytherapy.

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ABSTRACT

Background and rationale: The potential risk of prolongation of treatment time in cervical cancer has been reported for many low-dose rate (LDR) studies, with an estimated loss of local control ranging from 0.3 to 1.6% per day of treatment prolongation. Since the treatment schedule for fractionated high-dose rate intracavitary brachytherapy (HDRICBT) is not directly comparable with that for LDR studies. Many studies are also present with different results. Aims: To evaluate the clinical significance of overall treatment time with clinical response and overall survival cervical cancer treated with concurrent chemoradiation. Methods and Materials: Hundred patients with biopsy proven squamous cell carcinoma of the cervix with stage IIB to IVA (according to FIGO classification) were entered into protocol using concurrent paclitaxel and radiation. 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⁄m2 during entire course of external beam radiotherapy. Results: Treatment response was evaluated three months after the end of radiotherapy by means of clinical examination and ultrasonography. Complete Regression (CR) in 78%, partial response (PR) 16% and progressive disease 6%. At 52 months of median follow up 56 patients alive out of 42 patients are diseases free. Conclusion: The results of this study suggest that to achieve better treatment outcome, avoid treatment prolongation and overall treatment time should be less than 50 days.

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 (National Institute of Health consensus Development Conference Statement on cervical Cancer, 1997).[1] Of these, 80% occur in developing countries and 20% in developed countries (Parkins et al, 1999).[2]Carcinoma cervix is one of the most common cancers among rural Indian women (Stewart and Kleihues, 2003) [3]. Usually cervical carcinoma presents as a locally advanced disease with parametrial infiltration. Treatment of locally advanced carcinoma of cervix had undergone paradigm shift over the last decade. Results of five randomized trials (Keys et al, 1999; Morris et al, 1999; Rose et al, 1999;Whitney et al, 1999; Peters et al, 2000) coerced National Cancer Institute (NCI) to flash an alert regarding the use of concurrent chemoradiotherapy using cisplatin. There were many issues like lacunae in the design of many of these trials, inadequate eligibility criteria, use of improper control arm, toxicity etc (Saibishkumar et al,2005[4]; Datta and Agrawal, 2006) [5]. In spite of these issues it is used as a routine clinical practice in majority of oncology centres in our country. Results of the trial by NCI of Canada clinical trial group did not reveal any benefit with concurrent chemoradiotherapy (Pearcey et al, 2002) [6]. Metanalysis by Green et al [7] revealed significantly better survival using concurrent chemoradiotherapy as compared to radiotherapy alone (Green et al, 2006). In their subgroup analysis survival advantage was more pronounced among early stage disease. Although there was the heterogeneity among the trials included in the metanalysis, author recommended Cisplatin 40 mg/m2 weekly as a chemotherapy agent to be used along with radiation.

Many drugs like Cisplstin, 5-Fluorouracil and more recently Paclitaxel are used as radiosensitizer. In addition to direct cytotoxic effect show the theoretical advantage to sensitize malignant tissue to the effect of radiation. Chemotherapy in fact may act synergistically with radiotherapy inhibiting the repair of sub lethal damage, promoting the synchronization of cell into a radiation sensitive phase of the cycle, and reducing the fraction of hypoxic cells resistant to radiation. Furthermore chemotherapy may independently increase the rate of death of tumour cells. 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. [8], [9]

Traditionalprognostic factors in cervical cancer have been studied. Patients related prognostic factors include age, anaemia and smoking [10], [11], [12], [13]. Tumour related factors include stage, tumour size, nodal involvement, and hypoxia [14]. 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. [15], [16], [17], [18].

MATERIALS AND METHODS:

Hundred patients with biopsy proven squamous cell carcinoma of the cervix with stage IIB, III and IVA were entered into the protocol using Concurrent paclitaxel and radiation from July 2007 to June 2009 respectively. Before enrolment of patients, our institutional review board and clinical research committee approved the trial.

ELIGIBILITY CRITERIA WERE:

- No previous oncology treatment except biopsy.
- Age less than 65years.
- HB >l0gm.
- Complete haemogram, Renal function test &Liver function test within normal limit.
- Informed consent oral and written from patients.
- No clinically significant medical problem like heart disease.

Patients characteristic are shows in [Table no. 1]

PRETREATMENT EVALUATION:

- Detailed history and complete physical examination including bimanual pelvic examinations.
- Radiographic studies like X-rays chest, USG abdomen and pelvis, if possible CT scan and MRI of pelvis also done.
- Laboratory studies including complete haemogram, biochemistry and Liver function test.
- Clinical staging based on FIGO staging.

TREATMENT DESIGNED

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

CHEMOTHERAPY

Paclitaxel a dose of 40mg/m2 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, given30 min

Volume : 4 | Issue : 6 | June 2015 • ISSN No 2277 - 8179

before paclitaxel.

RADIOTHERAPY

External beam radiotherapy (EBRT),50.4Gy / 28 fractions, was delivered using Cobalt-60 unit with 80 cm SSD one fraction per day, five days in a 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 HDR-Intracavitary brachytherapy (ICBT) 4 fractions of 7 Gy each (total 28 Gy) 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).

EVALUATION OF FOLLOW-UP: Before each course of CT patients were evaluated and during RT they were seen at least once a week 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. Patients were examined after completion of RT, than after 6 weeks followed by 3 monthly intervals for two year than six monthly bases. Blood count, x-ray chest, USG abdomen. Patients belong to rural area were also motivated to come for regular follow up.

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 blood cell counts. Patient symptoms like diarrhoea, vomiting, dysuria were reported. Toxicity was scored according to WHO criteria.

STATISTICAL METHODS:

Patient characteristics, safety profile of the concurrent modality treatment administration, and response rates were characterized by descriptive methods. Locoregional relapse free survival (LRFS), Disease free survival (DFS) and overall survival (OS) curves were calculated according to the Kaplan- Meier method. For LRFS all local and /or regional recurrences and deaths due to disease were taken as events, for DFS all the deaths because of disease were taken as events, while for overall survival (OS) all deaths regardless of any cause were taken as events.

RESULTS:

All patients completed planned course of RT. Complete Regression in 78 patients (78%), partial response in 16 patients (16%), while six patients had progressive disease (6%) 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 5 years from last patents treated analysis done, only 56 patients on regular follow up, overall survival, Loco regional relapse free 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). No cases of cardiac toxicity and alopecia were recorded.

DISCUSSION:

Definitive RT represents the standard treatment for locally advanced (FIGO stage IIB-IVA) squamous cell carcinoma of uterine cervix. 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 [19] 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, verses 41% when CR is not achieved[20]. 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.

In locally advanced cervical carcinoma CCRT with cisplatin or cisplatin in combination with fluorouracil to external and ICBT improved the survival rate (Morris et al. [21] Rose et al. [22] Whitney et al. 1999[23]). Paclitxel was also used along with RT either alone or in combination with cisplatin or carboplatin by many workers (A. Cerrotta et al. 2002, [24] Kim K et al 2005, [25] Rao GG et al. 2005, [26]. 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/m2 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. In conclusion to completed treatment less than 50 days, twice weekly HDRICBT to be done, which are safer regimen and lesser complication rates? A complete response of 83% considered as satisfactory results.

Overall treatment time (OTT) is one of most important prognostic factor, Fyles et al [16]. 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[13], 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.

Delaloye et al. [27] and Lanciano et al. [15]: 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):[28] 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. (1991) [29] 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.

Subir Nag, M.D (2000) [30] ABS recommendations for HDRICBT: 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 keep the total treatment duration less than 8 weeks.

OTT would be unduly prolonged if the HDR was started after completion of EBRT as a weekly session. If disease is advanced due to large tumour volume, brachytherapy implant was not possible during EBRT. So it is advisable to perform two implants per week after the EBRT has been completed, tokeep the total treatment duration to less than 50days.The difference in outcome could be attributable to the change in the dose per fraction, not necessarily the twice-weekly aspect of schedule. HDRICBT should always fractionated, and prolongation of OTT should be avoided because of risk of tumour repopulation.Different fractionations schedule are available for HDR with good results. 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 to decreases OTT, brachytherapy started after completion of EBRT and two implants per week were done. Result shows that patents completed treatment less than 50 days has better tumor control as compare to more than 50 days.

However some drawback was also present in this study like -it was not randomized, number of patient is less, Follow-up is poor and Cause of death of patient is not known.

This study indicates that for better tumor control treatment should completed within 50 days, 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.

TABLES

Table No. 1 Patient's characteristics

Total No. of Patient	100	
Follow up (Median, Range)	52 Months (38 to 82)	
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
Ω		

Table no.2 overall response after completion of treatment

Response	IIB	IIIB	IVA	Total
CR	21	49	8	78
PR	2	11	3	16
SD	1	2	3	6
Total	24	62	14	100

΄Y CR complete response, ψ PR partial response, ύ NR no response

Table no.3acutereactions

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 no.4 late reactions

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

Table No. 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

ɐ OTT- overall treatment time, ± CR complete response

Volume : 4 | Issue : 6 | June 2015 • ISSN No 2277 - 8179

Table no.6 Follow-up after 52 months

Response	Percentage
OS	56
DFS	42
LRFS	59

? OS- overall survival, *DFS, ¥ LRFS- loco regional relapse free survival

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