

## “The effect of treatment prolongation in treatment of cervical cancer patient” –treated patients at rural center in India”

Sanjay Singh Chandel<sup>1</sup>, K K singh<sup>2</sup>, A K Nigam<sup>3</sup>, Rajesh Singh Baghel<sup>4</sup>

<sup>1</sup>Department of Radiotherapy & oncology G R Medical College, Gwalior, Madhya Pradesh 474009, India

<sup>2</sup>Department of Radiotherapy & oncology, RMC, PMT, PIMS, Loni Bk, distric Ahmednagar, M S, India

<sup>3</sup>Department of Radiotherapy & oncology G R Medical College, Gwalior, Madhya Pradesh 474009, India

<sup>4</sup>Department of Radiology G R Medical College, Gwalior, Madhya Pradesh 474009, India

---

### **Abstract:**

#### **Introduction:**

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 adverse effect of treatment prolongation for cervical cancer treated with HDRICBT.

#### **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/m<sup>2</sup> 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 83%, partial response (PR) 14% and progressive disease 3%. At 26 months of median follow up 73 patients alive out of 58 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.

**Key words:** Treatment prolongation, paclitaxel, cervical carcinoma, HDR brachytherapy.

---

### **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] Carcinoma cervix is one of the most common cancers among rural Indian women[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 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 [4], [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[6]. Metanalysis[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/m<sup>2</sup> weekly as a chemotherapy agent to be used along with radiation.

Many drugs like Cisplatin, 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]

Traditional prognostic 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]

## **II. 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 2010 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.
- Histological/cytological diagnosis of cervical cancer.
- Age between 28-65years.
- HB >10gm.
- 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 creatinine, 1.5mg%.
- SGOT or SGPT <2 upper normal, creatinine clearance 50ml/min.
- No clinically significant medical problem like heart disease.
- No prior radiation therapy to pelvis.

Patients characteristic are shows in [Table no. 1]

### **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.

### **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/m<sup>2</sup> was diluted in 100 ml of normal saline and administered by 30 minute infusion. Dexona 8 mg, Ranitidine 50 mg and Ondansetron 8 mg IV bolus, given 30 min 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. During CT all patient were admitted in ward. 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 serum examination and 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.

### **III. 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, Loco regional relapse free survival and disease free survival mention in [Table no.6], eight patients have locoregional 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. Heamaturia 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.

### **IV. 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 [21]. [22] [23]). Paclitxel was also used along with RT either alone or in combination with cisplatin or carboplatin by many workers, [24] 2005, [25], [26]. Shows that paclitaxel either alone or in combination with other agents act as radiosensitizer with good pelvic control. In our study shows that concurrent administration of paclitaxel at the weekly dose of 40 mg/m<sup>2</sup> 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, [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. [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.

[27] and [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.

Mandal Abhijit 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 multiorgans failure.

ABS recommendations for HDRICBT [30]: 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, to keep 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.

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 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.

Table No. 1 Patient’s characteristics

Total No. of Patient	100	
Follow up (Median, Range)	37 Months (33to 57)	
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	Moderately	48

(Squamous Cell Carcinoma)	Well	28
	Poorly	24

**Table no.2 overall 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

Y CR complete response, ψ PR partial response, ũ NR no response

**Table no.3 acute reactions**

Acute reaction	Grade 0	I	II	III	IV
Neutropaenia	84	13	3	0	0
Thrombocytopaenia	88	8	4	0	0
Hypersensitivity reaction	92	6	2	0	0
Nausea	20	38	52	0	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
Hematuria	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	percentage	CR	Total no. of patients	Percentage
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

ϐ OTT- overall treatment time, ± CR complete response

**Table no.6 Follow-up after 2 years**

Response	Percentage
OS	73
DFS	58

¿ OS- overall survival, \*DFS

### References

- [1]. National Institute of Health consensus Development Conference Statement on cervical Cancer, 1997.
- [2]. Parkin DM, Bray F, Ferlay J.: Global cancer statistics, 1999. CA Cancer J Clin 55:74-108, 2000.
- [3]. Stewart BW, Kleihues P, eds. (2003) World cancer report. Lyon, IARC Press, 215-224.
- [4]. Saibishkumar EP, Patel FD, Sharma SC (2005) Results of a phase II trial of concurrent chemoradiation in the treatment of locally advanced carcinoma of uterine cervix: an experience from India. Bull Cancer 92, 7-12.
- [5]. Datta NR, Agrawal S (2006) does the evidence supports the use of concurrent chemoradiotherapy as a standard in the management of locally advanced cancer of the cervix, especially in developing countries? Clin Oncol (R Coll Radiol) 18, 306-12.
- [6]. Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, et.al (2002) Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 20, 966-72.
- [7]. Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, et.al (2006) Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. The Cochrane Database of Systematic Reviews.
- [8]. Chen M.D et al Phase I trial of Taxol as a radiation sensitizer in advanced cervical cancer. Gynecol Oncol1997, 67,131.
- [9]. Pignata S, Frezza P, Tramontana S, Perrone F, Tambaro R, Casella G, et al. Phase I study with weekly cisplatin–paclitaxel and concurrent radiotherapy in patients with carcinoma of the cervix uteri. Ann Oncol 2000:455–9.
- [10]. Monk BJ, Tewari KS: Invasive cervical cancer, in DiS aia PJ, Creasman WT (eds): Clinical Gynecologic Oncology (ed 7). Philadelphia, PA, Mosby Publishers, 2007
- [11]. Huang H-J, Chang T\_C, HongJ-H,Tseng C-J, Chou H-H, Huang K-G, et al. Prognostic value of age and histologic type in neoadjuvant chemotherapy plus radical surgery for bulky (>=4 cm) stage IB and IIA cervical carcinoma.Int J Gynecol Cancer.2003; 13:204-11.

- [12]. Los Santos JF, Thomas GM. Anemia correction in malignancy management: threat or opportunity *Gynecol Oncol* 2007; 105:517-29.
- [13]. Waggoner SE, Darcy KM et al. Association between cigarette smoking and prognosis in locally advanced cervical carcinoma treated with chemoradiation: A Gynecology oncology Group study. *Gynecol Oncol*.2006; 103:853-8.
- [14]. Nordmark M, Lancaster J, Aquino-Parsons C, Chou SC. The prognostic value of pimonidazole and tumor p02 in human cervix carcinomas after radiation therapy: A prospective international multicenter study. *Radiother Oncol*.2006; 80; 123-31.
- [15]. Lanciano RM, Won M, Coia LR.: Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys* 20:667-676, 1991.
- [16]. Fyles AW, Pintilie M. Prognostic factors in patients treated cervix cancer treated by radiation therapy: results of multiple regression analysis. *Radiotherapy Oncol*.1995; 35:107-17.
- [17]. Peterit DG, Sarkaria JN, Chappell R, Fowler JF, Hartmann TJ. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Onco Biol Phys* 1995; 32:1301-7.
- [18]. Eifel PJ, Thoms WW Jr, Smith TL, Morris M. The relationship between brachytherapy dose and outcome in patient with bulky endocervical tumor treated with radiation alone. *Int J Radiat Onco Biol Phys*. 1994; 28:113-8.
- [19]. Perez C. A. "Radiation therapy alone in treatment of carcinoma of the uterine cervix". I. Analysis of tumor recurrence *Cancer*, 1983, 51, 1393
- [20]. Jacobs A. J. "Short term persistence of carcinoma of uterine cervix after radiation" An indicator of long term prognosis. *Cancer*. 1986, 57, 944.
- [21]. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999; 340:1137–43.
- [22]. Rose PG, Bundy BN, and Watkins EB.: Concurrent cisplatin-based chemoradiation improves progression free and overall survival in advanced cervical cancer: Results of a randomized Gynecologic Oncology Group study. *N Engl J Med* 340:1144-1153, 1999
- [23]. Whiteny. "Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative Para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Group study". *J. Clin. Oncol.*, 1999,17,1339.
- [24]. Cerrotta A, Garden G, Cavina R, Raspagliesi F, Stefanon B, Garassinol, et al. Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A study with intensification of dose. *Eur J Gynaecol Oncol* 2002; 23:115–9
- [25]. Kim K. Efficacy of paclitaxel and carboplatin as a regimen for post operative concurrent chemotherapy of high risk uterine cervix cancer. *Gynecol Oncol*. 2006 Jun; 101(3):398-402 Epub 2006 sep22.
- [26]. Rao G.G. et al. Phase I clinical trial of weekly paclitaxel and concurrent radiotherapy for primary cervical cancer. *Gynecol. Oncol*. 2005 Jan, 96(1):168-72.
- [27]. Delaloye JF, Coucke PA, Pampallona S, Peltecu G, De Grandi P. Radiation therapy duration influences overall survival in patients with cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1991;20:667-676.
- [28]. Abhijit Mandal, Anupam Kumar Ashtana, Lalit Mohan Aggarwal., Clinical Significance of cumulative biological effective dose and overall treatment time in the treatment of carcinoma cervix. *Journal of Medical Physics*, Vol. 32 No.2, 2007
- [29]. Y Hama. "Carcinoma of uterine cervix: Twice-verses Once weekly High-Dose-Rate Brachytherapy" *Radiology*. 2001; 219; 207-212.
- [30]. Nag S, Erickson B, Thomadsen B.: The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 48:201-211, 2000.