

# Hematological Toxicity in Carcinoma Cervix Patients Undergoing Concurrent Chemo Radiation Therapy or Radiation Therapy alone in a Tertiary Hospital of North East India: A Prospective Study

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**Introduction:** The current standard of treatment for locally advanced cancer of cervix is cisplatin based concurrent chemo radiation therapy followed by brachytherapy. Concurrent chemo radiotherapy causes acute hematological toxicities, which in turn leads to prolongation of therapy.

**Objective:** The main purpose of our study, was to analyze the acute hematological toxicity in cervical cancer patients undergoing radiation or chemo radiation therapy.

**Materials and Methods:** This is a hospital based observational study done at department of Radiation Oncology, Assam medical college and hospital. All the biopsy proven cervical cancer patients attending the department, within the study period from September 2020 to May 2021 are included in the study.

**Results:** Out of 26 patients in the study sample, grade 1 hematological toxicity is seen in 2 patients (7.5%), grade 2 hematological toxicity seen in 20 patients (77%), grade 3 hematological toxicities in 4 patients (15.5%) and none of the patients developed grade 4 nor grade 5 hematological toxicity or any other life threatening complications.

**Conclusion:** Hematological toxicity is more common with conventional external beam therapy in locally advanced carcinoma cervix patients. Compared to conventional external beam radiotherapy and 3DCRT, patients undergoing treatment with IMRT experiences significantly less acute grade  $\geq 2$  hematological toxicities.

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## Introduction

Carcinoma of cervix is a major health problem in developing countries like India with almost half a million women diagnosed with cancer of cervix each year and in developing countries, it is the leading cause of cancer death in women [1]. In india cervical cancer is the second most common cancer, with an estimated 132,314 new cases and 73,337 deaths in the year 2015 [2]. Carcinoma of cervix is one of the three most common cancer types in India, and is more prevalent and lethal in north east India compared with the rest of India. It is primarily due lack of knowledge about the risk factors among women, delay in diagnosis, late presentation and subsequent treatment, which is often inadequate [3].

In the management of cervical cancer, radiation therapy plays an Important role. The current standard of treatment for locally advanced cancer of cervix is cisplatin based concurrent chemoradiation therapy followed by brachytherapy. Concurrent chemoradiotherapy although it is superior than radiotherapy alone, it causes some toxicities especially acute hematological toxicities, which in turn leads to prolongation of therapy. In women undergoing pelvic radiation therapy for

cervical cancer, hematological toxicity has been particularly noted, due to the increased radiosensitivity of pelvic bone marrow. 40% of red marrow is found in pelvic bone and 11% is found in the lumbar spine. Conventional two-dimensional field radiation therapy in cervical cancer patients irradiate large volume of bone marrow, on the other hand concurrent chemotherapy agents also have some myelotoxic effect on the patient, so more severe acute hematological toxicities is noted in the patient during the treatment [4].

## **Aim**

Assessment of acute hematological toxicity in cervical cancer patients undergoing radiation or chemoradiation therapy.

## **Objectives**

1. To assess the prevalence of hematological toxicities in patients with cervical cancer.
2. To study the socio-demographic status of the study population.

## **Materials and Methods**

This is a hospital based observational study done at department of radiation oncology, Assam medical college and hospital. All the biopsy proven cervical cancer patients attending the radiation oncology department, fulfilling all the inclusion and exclusion criteria and giving an informed written consent within the study period from September 2020 to May 2021. Such 26 cases could be studied.

### **Inclusion criteria**

All the biopsy proven case of cervical cancer. All of them giving informed written consent for the study. Patients undergoing concurrent chemoradiation therapy with weekly cisplatin 40 mg/m<sup>2</sup> or radiation therapy alone. Patients with karnofsky performance score more than 70 or above.

### **Exclusion criteria**

Patients not willing to give consent. Patients with karnofsky performance score less than 70.

### **Treatment plan**

Patients have undergone external beam teletherapy (EBRT) with BHABHATRON-2 teletherapy unit using Cobalt-60 isotope, total dose of 50 Gray to be given in daily fraction of 2 Gy over a period of 5 week at 5 day per week. Some patients also received concurrent chemotherapy with Cisplatin at the dose of 40 mg/m<sup>2</sup> weekly during radiation therapy.

### **Patient evaluation**

History taking of all the patients is done in detail. All of them are clinically examined and

investigated. Routine blood and biochemistry investigations were done. CT Scan, USG abdomen, ECG, chest x-ray also done. After the start of the treatment routine blood investigations are done on weekly basis till completion of the treatment and any toxicity in the respective blood reports are noted and further evaluated according to the NCI CTCAE grading of hematological toxicity.

## Results

Out of 26 patients included in the study all of them completed their respective scheduled radiation therapy and the patients attended for follow up 6 week after the completion of therapy. All the patients in our study group were married and all of them had the past history of chewing tobacco with betel nut and smoking tobacco. No one out of the 26 patients have family history of cancer and any other hematological disorders. The socio-economic status of the study population is demonstrated in the Table 1.

Sociodemographic factors	Frequency	Hematological toxicity (%)	
		Grade <2	Grade 2 or more
Age			
Less than 30	0	0	0
30-50	11	2 (19)	9 (81)
50-70	14	0	14 (100)
More than 70	1	0	1 (100)
Religion			
Hindu	22	2 (9)	20 (91)
Muslim	4	0	4 (100)
Education			
Illiterate	4	0	4 (100)
Primary education	7	0	7 (100)
Secondary education	12	1 (8)	11 (92)
Above	3	1 (33)	2 (67)
Parity			
0	0	0	0
1-3	21	2 (9)	19 (91)
4-6	4	0	4 (100)
More than 6	1	0	1 (100)
Modified kuppuswamy Socio-economic scale			
I (upper)	0	0	0
II (upper middle)	0	0	0
III (lower middle)	13	2 (15)	11 (85)
IV (upper lower)	8	0	8 (100)
V (lower)	5	0	5 (100)

**Table 1. Socio-demographic Profile of Patients.**

In our study sample 53.8% patients belonged to age group 50-70 year and 84.6% patients belonged to Hindu by religion and rest belonged to Muslim community. Our study showed that 57.69% patients have done secondary education and above while 15.38% were illiterate. Among the 26 patients, 80.76% have parity of 1-3, 15.38% have parity of 4-6 and 3.84% patients have parity of more than 6. According to Modified Kuppuswamy socioeconomic scale 13 (50%) patients in our study belonged to lower middle, 8 (30.76%) patients belonged to upper lower and 5 (19.24%) patients belonged to lower socioeconomic class.

The commonest histopathology observed was squamous cell carcinoma 25 (96%) and rest 1 (4%)

adenocarcinoma (Table 2).

Hematological toxicity	Histopathology		Staging			
	SCC	Adenocarcinoma	IIIA	IIIB	IVA	IVB
Grade <2	2 (8%)	0	1	1	0	0
Grade 2 or more	23 (92%)	1 (100%)	1	4	17	2
Total	25	1	2	5	17	2

**Table 2. Histopathology and Staging of Study Population.**

The patients are staged according to the clinical staging i.e International Federation of Gynecology and Obstetrics (FIGO) for the cervical cancer. 7 out of total patients are presented in stage III (26.92%) and 19 (73.08%) in stage IV (Table 3).

Blood elements	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophil	18	4	0	0	0
Platelets	11	0	0	0	0
Hemoglobin	2	20	4	0	0
Lymphocytes (total)	16	0	0	0	0
CD4	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0

**Table 3. Hematological Toxicity with Respect to Blood Elements.**

Out of the 26 patients 7 (26.92%) received only radiation therapy while 19 (73.08%) patients received concurrent chemo radiation therapy with cisplatin (Table 4).

Hematological toxicity	Total case (n=26)	RT alone (n=7)	CCRT (n=19)
Grade 1	2 (7.69%)	2 (28.57%)	0
Grade 2	20 (76.90%)	4 (57.14%)	16 (84.21%)
Grade 3	4 (15.38%)	1 (14.29%)	3 (15.79%)
Grade 4	0	0	0
Grade 5	0	0	0

**Table 4. Hematological Toxicity in Radiation Therapy Alone and in Concurrent Chemoradiation Therapy.**

Our study have reported that grade 1 hematological toxicity is seen in 2 (7.5%) patients, grade 2 hematological toxicities in 20 (77%) patients, grade 3 hematological toxicities in 4 (15%) patients and none of the patients developed grade 4 nor grade 5 hematological toxicity or any other life threatening complications (Table 4).

Out of 7 patients receiving only radiation therapy 2 patients developed grade 1, 4 patients developed grade 2, and 1 patients developed grade 3 hematological toxicity. On the other hand patients receiving concurrent chemo radiation therapy 16 patients developed grade 2, and 3 patients developed grade 3 hematological toxicity (Table 4).

Out of the 11 patients with below 50 years 9 (81%) patients developed grade 2 or higher hematological toxicity and 2 patient (19%) developed less than grade 1 toxicity, while all the 15 (100%) patients above 50 years developed grade 2 or more hematological toxicity (Table 1). The 25 patients who reported to be squamous cell carcinoma 23 (92%) developed grade 2 or more hematological toxicity and 2 (8%) patient developed grade 1 hematological toxicity. All the patients with adenocarcinoma 1 (100%) developed grade 2 or more toxicity. All the patients of stage IV

(100%) and 5 (71%) patients of stage III developed grade 2 or more hematological toxicity. In the study population grade 2 or more hematological toxicity is more prevalent in muslim population (100%), illiterate people (100%), patients with parity more than 3 (100%) and people with kuppuswamy class IV (100%) and V (100%) (Table 1).

## Discussion

Cervical cancer is one of the leading cause of cancer death among women in developing countries. Globally it is estimated that of 500,000 women develop cervical cancer and almost 274,000 of them die from the disease per year. Cancer cervix is most common in women in underdeveloped and developing nation which bear more than 80% of the global burden of the disease. This reveals the lack of effective control measures in these countries [5]. There were limited health campaigns about the importance of screening for cervical cancer, eligible age groups for screening, access to screening centers, and the government screening program. There is also a significant correlation between education status, and income level and the knowledge and attitude toward cervical cancer. The health-seeking behavior of the community and understanding of the need to undertake cancer screening among the patients and the normal population is low which in turn patients get diagnosed more in late stage of cervical cancer [3].

Out of the 26 patients in our study, the incidence of cervical cancer was found to be the most in the range of 50- 69 years of age, which constituted 14 patients, i.e., 53.84% of the study patients. The next highest incidence was reported in the age group of 30-49 years of age, which constituted 11 patients, i.e., 42.30% of the study patients and only 1 patient in the age group of >70 years. In contrast to our study majority of patients (50-60%) were in the age group of 40-59 years in some previous studies in other high-incidence regions in India [6-8].

In the study population 22 (84.61%) belongs to Hindu religion while 4 (13.39%) belong to Muslim religion similar to previous study [9,10]. On the basis of modified kuppuswamy socioeconomic scale 13 female belongs to grade III (upper middle), 8 female belongs to grade IV (upper lower) and 5 female belongs to grade V(lower) socioeconomic class in aggrement to previous study [9]. In the study population, 4 female are illiterate while rest 22 female are literate. Out of the 22 female 7 had completed primary education, 12 had completed secondary education while 3 had done more than secondary education.

In our study, out of the 26 patients, the histopathological type of the tumors showed a dominance of squamous cell carcinoma (96.15%) followed by adenocarcinoma (3.85%) similar to some studies [6,8].

In our study, all of the 26 patients belong to Stage III and Stage IV as per the FIGO staging. Out of the 26 enlisted patients, 19 of the patients in our study were in AJCC Stage IV disease (73.07%), whereas only 7 (26.93%) of the patients belonged to the stage III disease at presentation. This is similar to the finding of a south Indian study [9] and a study from Manipur [11]. This findings reflect lack of awareness about the disease in the general population of this region.

In this study, all patients (100%) were married; 17 of them i.e. 65.0% married before the age of 20yrs this findings were in accordance with the observations of a study done in manipur [11]. Among the patients, 8 (30.76%) had history of abortion, 21 patients (80.76%) had parity of 1-3 and 16 patients (61.53%) had history of child birth at home by local dais. 2 patients (7.69%) had co-morbidity; both having Hypertension and Diabetes [10]. In all patients presentation were within 3 months from the onset of symptoms. Many patients (80%) had more than one symptom at the time of presentation. The commonest presenting symptoms were abnormal vaginal bleeding followed by white discharge per vagina and irregular menstruation similar to a study done in western india [10].

In our study, grade 2 or more hematological toxicity is seen in 24 (92.30%) patients while 2 (7.70%) patients developed grade 1 hematological toxicity. With respect to the blood elements, in neutrophil 18 (69.23%) patients develop grade 1 while 4 (15.38%) patients developed

grade 2, while 4 (15.38) patients donot develop any hematological toxicity. In platelet and lymphocyte 11 (42.30%) and 16 (61.53%) patients developed grade 1 hematological toxicity respectively and others did not developed any toxicity. With respect to hemoglobin all the 26 (100%) patients developed hematological toxicity. Grade 1, grade 2, grade 3 hematological toxicity is developed by 2 (7.69%) patients, 20 (76.92%) patients and 4 (15.38%) patients respectively. No patients develop any grade of hematological toxicity with respect to CD4 count or febrile neutropenia.

In our study group 7 patients were given radiotherapy alone while 19 patients were given concurrent chemoradiation therapy with weekly cisplatin. All the patients in both group develop hematological toxicity but in our study it is seen that patients taking concurrent chemoradiation therapy develop more higher grade of hematological toxicity. Out of the 7 patients taking radiation alone 5 (71.42%) patients developed grade 2 or more hematological toxicity, while patients taking concurrent chemoradiation therapy, all the 19 (100%) patients developed grade 2 or more hematological toxicity.

In our study out of the 19 patients of stage IV cervical cancer all of them (100%) develops grade 2 or more hematological toxicity, while out of the 7 patients of stage III, 5 (71.42%) patients developed grade 2 or more hematological toxicity.

In our study grade 2 or more hematological toxicity is found more in patients with age 50 years or more i.e. 100% compared to age below 50 years i.e. 81%. In the study group grade 2 or more hematological toxicity is found mainly with respect to socioeconomic class in upper lower and lower socioeconomic class i.e. 100%, with respect to education more common in patients with primary education and illiterate. Again in our study all the patients with parity more than 3 developed grade 2 or more hematological toxicity.

#### *Limitations of the study*

1. The statistical estimation of the sample size of the study could not be done properly as it was a hospital-based observational study with a limited number of cases and hence a small sample size.
2. The short duration of follow up of the patients.

In conclusions, incidence of hematological toxicity in cervix cancer patients undergoing radiation therapy or chemoradiation therapy is usually very common. Patients having concurrent chemoradiation therapy usually develop higher grade of hematological toxicity compared to patients having only radiation therapy. Moreover compared to conventional external beam radiotherapy and 3DCRT, patients undergoing treatment with IMRT experiences significantly less acute grade  $\geq 2$  hematological toxicities which again improves the treatment compliance by avoiding unnecessary treatment breaks owing to toxicities.

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