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Original Research Article

## Is thrombocytosis a valid indicator of advanced stage and high mortality of gynecological cancer?

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### ABSTRACT

**Background:** Cytokines that stimulate thrombopoiesis are often elevated in cancer, and as a result, various cancers have been associated with thrombocytosis. In addition thrombocytosis has been found to be an adverse prognostic factor in many types of common cancers.

**Methods:** A cross sectional study was designed to evaluate the factors associated with prognosis of the cases of carcinoma cervix in the Department of Gyne-Oncology, GMCH, Aurangabad from August 2016 to August 2017. Variables analysed were the sociodemographic details, literacy level, symptoms, duration, stage of the disease at diagnosis, pretreatment platelet counts were noted.

**Results:** 85% patients were having squamous cell carcinoma, 6% patients were having adenocarcinoma and 9% patients had adenosuamous carcinoma. 29% patients have platelet count less than 3 lakhs and 18 patients has tumour less than 4 cm. 71% patients have platelet count more than 3 lakhs, only 6% patients belonged to early stage and 65% belonged to late stage of cancer cervix.

**Conclusions:** Seventy one percent of the cases had platelet count >3 lakh, of which only 6% were in early stage of disease, whereas 65% belonged to late stage of the disease. All the patients with tumour size of >4 cm had platelet count more than 3 lakh, this shows strong association of platelet count with tumour size >4 cm and advanced stage of the disease. This can be used as independent prognostic factor for prognosis of cancer cervix.

**Keywords:** Cancer cervix, Thrombocytosis

### INTRODUCTION

Cancer cervix is the most common gynecological malignancy in the developing countries and is the leading cause of mortality in women in the third world. According to the recent figures the global annual incidence of cervical cancer is around 529,800 new cases, with 275,100 deaths.<sup>1</sup> In India cervical cancer is one of leading causes of cancer mortality among women 30 to 69 years of age, accounting for 17% of all cancer deaths. Current estimates reveal 132,000 new diagnosed cases and 74,000 deaths annually in India, accounting for nearly 1/3<sup>rd</sup> of global cervical cancer deaths. High mortality rates are largely the result of

70% of cervical cancer cases in India being diagnosed at an advanced stage (stage III or IV).<sup>2</sup>

The huge case load of cancer cervix poses a big question mark about the disease progression and the outcome in this cases. The prognosis of the disease determines the morale of the patients and relatives to continue the treatment. Research confirms that a simple laboratory investigation can be used as a prognostic marker in cases of cancer cervix, e.g. platelet count. The current study was undertaken to find out the role of thrombocytosis in the prognosis of the cancer patient in terms of stage of the disease and histopathological grading of the cancer cervix.

Platelets are important cellular particles for hemostasis and vascular integrity. They are produced from bone marrow precursor cells, megakaryocytes. Abnormalities in their normal circulating number either in the form of thrombocytosis or thrombocytopenia are associated with many pathologic conditions.<sup>1</sup> Cytokines that stimulate thrombopoiesis are often elevated in cancer, and as a result, various cancers have been associated with thrombocytosis. In addition thrombocytosis has been found to be an adverse prognostic factor in many types of common cancers

Squamous cell carcinoma (SCC) is the predominant histological type accounts for three-fourths of all cervical cancers. Adenocarcinoma and adenosquamous cell carcinoma represent 10-15%, and other or unspecified histology represent the remaining 10-15%.<sup>3,4</sup> Since histopathology is a cornerstone in the detection and the diagnosis of cervical cancer, we believe that clarifying the prognostic value of pathological type is an important issue that might influence the management, treatment and surveillance planning of newly diagnosed cervical cancer.

## METHODS

### Study type

A cross sectional study was designed to evaluate the factors associated with prognosis of the cases of carcinoma cervix.

### Study place

This study was conducted at Department of Gynaecology, GMCH, Aurangabad.

### Study period

The study took place for a period of 1 year August 2016 to August 2017.

### Inclusion criteria

All women diagnosed with carcinoma cervix by histopathology report and consenting to be a part of the study were included. The study subjects were 100 that were included in the study.

### Exclusion criteria

Recurrence cases and metastasis due to any other malignancy in the body were excluded.

### Procedure

With the ethical approval this study was conducted. Statistically analysis was done. Variables analysed were the sociodemographic details, literacy level, symptoms, duration, stage of the disease at diagnosis, pretreatment platelet counts were noted, and were co-related with the

stage of the disease and the histopathological type and grading of the disease. The slides were opined by a senior professor of pathology. Results were expressed as means and percentages, and statistical significance was calculated using software Epiinfo.

## RESULTS

Mean age of the patients was 57.35 years (30-82 years) 81% patients were illiterate and majority were from rural area.

**Table 1: Socio demographic characteristics of the study subjects.**

Variables	Percentage	Number
Age	30-39	9
	40-49	26
	50-59	21
	60-69	32
	70-79	11
	>79	1
	Total	100
Social status	BPL	71
	Non-BPL (APL)	29
Education	Illiterate	81
	Primary	15
	Secondary	4
Residential	Urban	22
	Rural	78
Religion	Hindu	70
	Muslim	8
	Christianity	0
	Buddhism	20
	Jainism	2
	Total	100

**Table 2: Distribution of the patients of cancer cervix according to staging.**

Stage of ca cervix	Total patients
I A	3
I B	7
II A	6
II B	18
III A	10
III B	40
IV A	8
IVB	8
<b>Total</b>	<b>100%</b>

Majority of the patients were of 3B staging (40%) followed by 2B (18%).

85% patients were having squamous cell carcinoma, 6% patients were having adenocarcinoma and 9% patients had adenosquamous carcinoma (Table 3).

**Table 3: Histopathological variant of study subjects.**

Stage of cancer cervix	LCK squamous	LCNK squamous	Adenocarcinoma	Adenosquamous
<b>IA</b>	-	2	-	4
<b>IB</b>	2	4	2	1
<b>IIA</b>	-	-	-	-
<b>IIB</b>	2	10	-	-
<b>IIIA</b>	-	2	-	2
<b>IIIB</b>	22	39	4	2
<b>IVA</b>				
<b>IVB</b>	2	-	-	
	28 (28%)	57 (57%)	6 (6%)	9 (9%)

**Table 4 showing correlation of platelet count with stage of cancer cervix and its size.**

Stage of ca cervix	<3 lakh	>3 lakh	Total	Tumour size <4 cm	Tumour size >4 cm
<b>I A</b>	1	2	3	3	-
<b>I B</b>	6	1	7	7	-
<b>II A</b>	3	3	6	6	-
<b>II B</b>	5	13	18	-	18
<b>III A</b>	4	6	10	-	10
<b>III B</b>	9	31	40	-	40
<b>IV A</b>	-	8	8	-	8
<b>IV B</b>	1	7	8	-	8
<b>Total</b>	29 (29%)	71 (71 %)	100%	18 (18%)	72 (72%)

29% patients had platelet count less than 3 lakhs and 18 patients had tumour less than 4 cm.

71% patients have platelet count more than 3 lakhs, only 6% patients belonged to early stage and 65% belonged to late stage of cancer cervix.

## DISCUSSION

In our study, early stage ca cervix IA, IB, II A were only 16%, whereas late stage IIB to IVB were 84% (Table 2).

This is important because the survival rate in early stage ca cervix are very good and surgical treatment is more accurate. It gives the advantage of removing primary disease, allowing accurate staging and allowing adjuvant therapy to be more accurately targeted. This gives excellent results with 5 year survival rate.

Majority of patients in our study (84%) reported late in stage. Late stage disease has lower 5 year survival rate and in addition it exposes the patient to chronic radiation damage to bladder, bowel and vagina (which is difficult to manage). Secondly, the late stage malignancy was associated with higher age group as elderly age group experiences more morbidity than younger patients.

In our study, we tried to correlate the platelet count along with stage of the disease (early versus late stage) and size of the lesion. Case records from our hospital information showed that among 100 patients of cancer cervix, 29% had

platelet count of less than 3 lakh/mm<sup>3</sup>. In this group 10 patients belong to early stage of cancer and 18 patients had tumour size less than 4 cm. This association was statistically significant for patient of early stage ca cervix and lesion less than 4 cm (Table 3).

The retrospective analysis shows that platelet count at the time of diagnosis can predict the tumour size. This can be explained on the basis that cytokines that stimulates thrombopoiesis often elevated in cancer cervix. Secondly the cancer cells use platelets as shield to protect themselves from the attack of immune system. Platelets also have new role in promotion of vascular integrity in cancer. They also serve as carrier of bio-active molecules and growth factor VEGF, EGF, PDGF, IGF. These substances contribute actively to the growth of the tumour and in the process of embolization in microcirculation. Thus platelet count reflects the VEGF concern in tumour and favourable environment needed to activate and to contribute to tumour angiogenesis which all together promote the growth of the tumour.<sup>5</sup>

Seventy one percent of the cases had platelet count >3 lakh, of which only 6% were in early stage of disease, whereas 65% belonged to late stage of the disease. All the patients with tumour size of >4 cm had platelet count more than 3 lakh, this shows strong association of platelet count with tumour size >4 cm and advanced stage of the disease. This can be used as independent prognostic factor for prognosis of cancer cervix.

In our study, early stage of cancer cervix (I to IIA) comprise of 16 cases. The distribution was two cases of LCK. Six cases of LCNK and 2 cases of squamous cell carcinoma. This early stages have low risk of lymph node metastasis and recurrences. They can also be cured by cone biopsy with clean surgical margin and extrafascial hysterectomy and radical trachelotomy. The incidence of lymphovascular invasion is very less and find positive correlation between depth of invasion and presence of lymphovascular invasion (Table 4).

Eighty four percentage of our cases belong to advanced stage i.e. from IIB to IVB. The causes of majority of the cases reporting late were many like financial reason, family problem, ashamed of, nobody paid attention, taken mistaken as AUB, not diagnosed at periphery early. This patients were also found to widow, left by husband without any active support from family. Late advanced stage cases of cancer cervix unique problem of limited survival and morbidity in the favour of vesicovaginal and rectovaginal fistula. They are associated with other co-morbidity like distant metastasis, anaemia, malnutrition and chronic pelvic pain.

An elevated platelet count may have various causes and is either primary due to essential thrombocytosis or other myeloproliferative disorders or secondary to infection, trauma or surgery, iron deficiency, or malignancy. Thrombocytosis appears to be a universal marker of adverse outcomes in cancer. Its association with worse oncologic outcomes has been also reported in oesophageal squamous cell carcinoma, gastric adenocarcinoma, renal cell carcinoma, ovarian carcinoma.<sup>6</sup>

Initially, Hernandez et al reported that thrombocytosis was an independent indicator of poor prognosis in 113 stage I-IV cervical cancer patients treated with radiotherapy.<sup>7</sup> Surgical pathologic variables were not available in this study. Rodriguez et al found that an elevated platelet count ( $>300,000/\text{L}$ ) was an independent prognostic factor for poor survival of 219 surgically treated patients with stage IB cervical carcinoma. The authors noted a significant association between elevated platelet count and large lesion size (greater than 4 cm) and low preoperative hematocrit levels, whereas age, race, pelvic node metastases, histology and tumor grade showed no statistical correlation with thrombocytosis.<sup>8</sup>

The squamous cell carcinoma, which includes LCK and LCNK constitute the major bulk of our patients (85%). This may be because of the more prevalence of HPV 16 subtype which is said to be causative agent in squamous cell carcinoma. HPV 18 subtype is associated with endocervical (adeno and adenosquamous) carcinoma which is less prevalent than 16 type.

In our study, 19% were LCK, 44% were LCNK and squamous cell carcinoma were 12%, remaining were adeno and adenosquamous carcinoma i.e. 15%. Adenocarcinoma are associated with less five year

survival rate and greater degree of lymph node metastasis. Adenosquamous carcinoma have still poorer outcome with respective stage, size of lesion, nodal status and the age.

We would like to emphasize that the squamous cell carcinoma, which includes LCK and LCNK constitute the major bulk of our patients (85%). This may be because of the more prevalence of HPV 16 subtype which is said to be causative agent in squamous cell carcinoma. HPV 18 subtype is associated with endocervical (adeno and adenosquamous) carcinoma which is less prevalent than 16 type.

This agrees with Jain et al where squamous cell carcinoma accounted for 75-80%, adeno carcinoma 15-25% and adenosquamous 3-5% of cervical cancer. Saini et al showed adenocarcinoma 5%.<sup>9,10</sup>

Limitations of the study are the patient survival should have been followed up for at least 2 years but it has not been followed in this study due to time constraint and other external factors.

## CONCLUSION

In our study, early stage ca cervix IA, IB, IIA were only 16%, whereas late stage IIB to IVB were 84%.

Seventy one percent of the cases had platelet count  $>3$  lakh, of which only 6% were in early stage of disease, whereas 65% belonged to late stage of the disease. All the patients with tumour size of  $>4$  cm had platelet count more than 3 lakh, this shows strong association of platelet count with tumour size  $>4$  cm and advanced stage of the disease. This can be used as independent prognostic factor for prognosis of cancer cervix.

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