



Prognostic Significance of Thrombocytosis in Locally Advanced Carcinoma Cervix Patients Treated with Chemoradiotherapy

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Abstract

Background: The outcome of locally advanced carcinoma cervix patients treated with chemoradiotherapy is highly variable and depends on various prognostic factors.

Objectives: The aim of this study is to evaluate the prevalence and prognostic significance of thrombocytosis in this group of patients of our institution.

Methods: Between January 2008 and December 2012, 195 patients with locally advanced carcinoma cervix [International Federation of Gynecology and Obstetrics (FIGO) stage IIB-IIIIB], were treated with external beam radiotherapy (EBRT) to a dose of 45 Gy in 25 fractions along with concurrent chemotherapy (cisplatin 40 mg/m²), followed by HDR brachytherapy EQD2 of 30 Gy. The platelet counts were recorded pre treatment and during treatment in all the patients.

Results: Among the 195 patients, 101 (51.5%) belonged to stage IIB and 94 (48.5%) to stage IIIIB. Thrombocytosis (platelet count > 400 × 10⁹/L) was seen in 31 (15.8%) patients. The overall survival in thrombocytosis group is 41% which is significantly less than the OS of the non-thrombocytosis group which is 62%.

Conclusions: Thrombocytosis is not a frequent finding in patients with locally advanced carcinoma cervix in our population, but when present it is associated with poor outcome in terms of survival.

Keywords: Thrombocytosis, Carcinoma Cervix, Platelet Count and Outcome

1. Background

The association between thrombocytosis and malignancies has been known for over a century (1). Numerous studies have been carried out to evaluate thrombocytosis as a prognostic marker (2-8). Thrombocytosis is associated with various gynecological and non-gynecological cancers, especially in thoracic and gastrointestinal malignancies (2, 3, 6). Malignancy related to thrombocytosis is seen in about 4% to 55% of the patients, more so in the advanced stage (9).

Most studies that have investigated the prognostic implications of thrombocytosis in cancer cervix patients have yielded inconsistent results, few have shown positive correlation while others found no such correlation (4, 5, 10-16). India has the largest burden of cervical cancer, but there is a lack of studies regarding the incidence of thrombocytosis and its correlation with response and survival.

2. Objectives

We have undertaken the present study to investigate the incidence and prognostic significance of thrombocytosis in patients with cervical cancer, treated with definitive chemoradiotherapy.

3. Methods

Between January 2008 and December 2012, 195 patients with locally advanced cervical cancer (International Federation of Gynaecology and Obstetrics [FIGO] stage IIB-IIIIB) were treated with external beam radiotherapy (EBRT) with a dose of 45 Gy in 25 fractions, on Cobalt 60, along with weekly concurrent cisplatin. High dose rate (HDR) brachytherapy, to a dose of 7 Gy in 3 fractions, was delivered either by intracavitary or interstitial brachytherapy. All patients included in the study had completed the planned radiation.

The response to the treatment was assessed 3 months post-treatment according to response evaluation criteria in solid tumors (RECIST). Patients underwent periodic detailed clinical evaluation and imaging (computerized tomography scan) during the follow-up period.

Thrombocytosis was defined as a platelet count greater than $400 \times 10^9/L$ on at least 2 separate occasions. Blood tests of all the patients were carried out, including complete blood count at the time of diagnosis and before the start of chemoradiation. Patients who had a previous history of cancer or predisposing conditions to thrombocytosis, such as a history of splenectomy, rheumatoid disease, myeloproliferative disorders, acute inflammatory disease, and history of malignancy were excluded from the study.

3.1. Statistical Analysis

This is a retrospective analytical study. The Kaplan-Meier method was used for determining the overall survival (OS) and disease-free survival (DFS). Statistical significance was defined to be a probability value of ≤ 0.05 . The significance of potential prognostic factors was assessed by the Cox proportional hazards model. The SPSS software version 15 was used for statistical analysis.

4. Results

The 195 patients evaluated were divided in two groups based on their platelet count. The patients having a platelet count greater than $400 \times 10^9/L$ were placed in the thrombocytosis group at presentation (31 patients, 15.8%) and those with platelet counts less than $400 \times 10^9/L$ were placed in the non-thrombocytosis group (164 patients, 84.2%). The patient characteristics in both the groups are compared in Table 1.

The mean age of the entire cohort was 45 years. The total number of patients with stage II and stage III disease was 101 and 94, respectively, and were comparable in both the groups. The hemoglobin level at presentation was more than 10 mg/dL in 167 patients as compared to 28 patients who had levels less than 10 mg/dL. Concurrent chemotherapy with weekly cisplatin to a cumulative dose of 250 mg or more was received by 113 patients in the non-thrombocytosis and 21 patients in thrombocytosis group. The response to treatment was evaluated clinically and by imaging.

In the non-thrombocytosis group, 131 patients showed complete or partial response and 33 had stable or progressive disease. In the thrombocytosis group, 15 patients showed complete or partial response and 16 patients had

stable or progressive disease. This study shows a significant association between platelet levels at diagnosis and the response to treatment (P value < 0.001). The 5-year OS for the non-thrombocytosis group was higher (62%) compared to the thrombocytosis group (41%); similarly, the 5-year DFS was 61% and 39%, respectively. The OS and DFS had statistical significance in both the arms (P value < 0.001) across platelet counts at diagnosis (Figures 1 and 2). In multivariate analysis, platelet counts greater than $400 \times 10^9/L$ and age less than 45 years had poor survival, and no other factor had any significance (Table 2).

5. Discussion

Few studies on cervical cancer have assessed thrombocytosis as a prognostic indicator in patients receiving

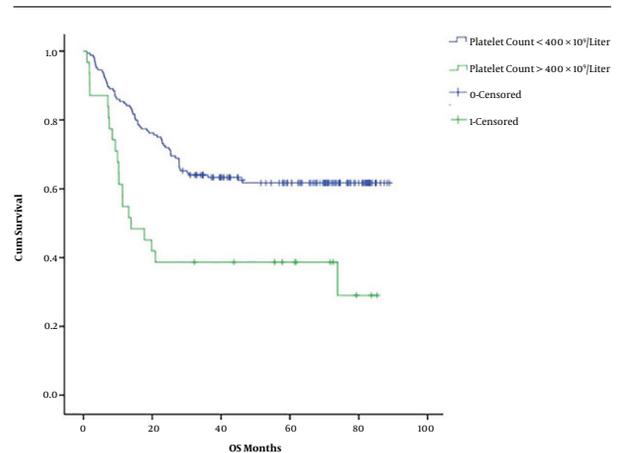


Figure 1. Overall survival of thrombocytosis and non thrombocytosis group

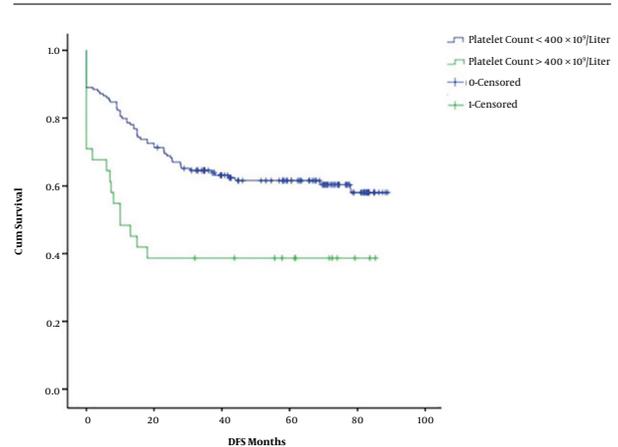


Figure 2. Disease free survival of thrombocytosis and non thrombocytosis group

Table 1. Patient Characteristics Stratified According to Platelet Level

Characteristics	All Patients (195)	Patients Without Thrombocytosis (164)	Patients with Thrombocytosis (31)	P Value
Age, y				0.721
Mean	45	45	44	
< 45	113	93	20	
> 45	82	71	11	
Stage				1.009
II	101	85	16	
III	94	79	15	
Hemoglobin, mg/dL				0.401
< 10	28	20	8	
> 10	167	144	23	
Cumulative cisplatin dose, mg				0.441
≤ 250	134	113	21	
> 250	61	51	10	
Treatment response				0.001
Partial or complete response	146	131	15	
Stable or progressive disease	49	33	16	

Table 2. Multivariate Cox Proportional Hazards Analysis of Variables That Could Impact Survival

	P Value	95.0% Confidence Interval	
		Lower	Upper
Age group			
< 45 years vs. > 45 years	0.006	2.503	233.106
Cumulative chemotherapy received			
> 250 mg vs. < 250 mg	0.506	0.742	1.832
Staging			
II vs. III	0.439	0.766	1.847
Hemoglobin level			
< 10 mg% vs. > 10 mg%	0.553	0.426	1.580
Platelets level			
< $400 \times 10^9 /L$ vs. $> 400 \times 10^9 /L$	0.004	1.290	3.784

chemoradiation (5,10-16). Two of them were review articles by Sharma and Singh, and Cheng et al., published in 2017, positively correlating the association between thrombocytosis and poor outcome (14, 15). We defined platelet count greater than $400 \times 10^9 /L$ as thrombocytosis in our study as most of the above papers have considered the same cut-off (Table 3). Our intention was to assess thrombocytosis as a prognosticator in the Indian scenario.

We observed thrombocytosis in 15.8% patients during diagnosis, which was similar to most of the published studies (4, 10-12), except for one by Hernandez et al. (10) where

it was 30%.

Thrombocytosis was shown to be associated with advanced stage, bulky disease, and pelvic node positivity (10-12). Only Lopes et al. did not show any association of thrombocytosis with nodal positivity, mainly because most of the patients had early-stage disease, where the incidence of nodal metastasis was low (11, 12). As all our patients had locally advanced disease, we found no correlation of thrombocytosis with age, stage, and pre-treatment hemoglobin levels. We did not look for correlation with the nodal status. A study by Kawano et al. (12) and Kozasa et al. (16)

Table 3. Studies on Prognostic Significance of Thrombocytosis in Patients of Carcinoma Cervix Treated with Chemoradiotherapy

Study	No of Patients	Treatment	Platelet Level Cut Off	Incidence of Thrombocytosis, %	Results	Significance	P Value
Hernandez et al. (4)	113	Radiotherapy alone	$> 400 \times 10^9/L$	18	The 5-year survival for patients with normal platelet counts was 65%, whereas it was 25% for patients with thrombocytosis.		< 0.0001
Hernandez et al. (10)	294	Radiotherapy and concurrent hydroxyurea or misonidazole	$> 400 \times 10^9/L$	30	Thrombocytosis had a 55% greater chance of dying than those who had a normal platelet count.	Risk ratio: 1.55 95% confidence interval: 1.08 - 2.21	0.02
Kawano et al. (12)	286	Radiotherapy with or without platinum-based concurrent chemotherapy	$> 350 \times 10^9/L$	14	Thrombocytosis is an independent predictor of compromised survival.	Hazard ratio of 1.65 for death 95% confidence interval: 1.03 - 2.56	0.0395
Lopes et al. (11)	643	Surgery or radiotherapy with or without chemotherapy	$> 400 \times 10^9/L$	17	The 5-year survival rate for patients with thrombocytosis was 57.1%, which was significantly worse than the 76.5% for those with normal platelet counts.	No significance on multivariate analysis	< 0.01
Kozasa et al. (16)	684	Surgery or radiotherapy with or without chemotherapy	$> 400 \times 10^9/L$	12.7	Pretreatment thrombocytosis and elevated PLR were identified as independent predictors in cervical cancer patients.	Elevated platelet count is significant predictor of outcome on multivariate analysis	

showed an association of thrombocytosis with young age (< 50 years) and low hemoglobin (< 11 mg%), and only young age (< 50 years), respectively; however, no such correlation was seen in any of the other studies, including our study. The only factor where we found significance was better response to treatment in patients without thrombocytosis (P value ≤ 0.001).

The patients with thrombocytosis had significantly poor OS and DFS of 41% and 39%, respectively, at 5 years in our study. A similar trend was seen in all the studies with chemoradiation (Table 3) (4, 10-12, 16). The first study by Hernandez et al. published in 1992, showed a 5-year survival advantage of 65% in non-thrombocytosis versus 25% in patients with thrombocytosis. Again in the year 2000, the same authors showed that patients with thrombocytosis had a 55% greater chance of dying than those who had a normal platelet count (4, 10). Kawano et al. also showed that patients with thrombocytosis had poor outcomes in terms of survival, with a hazard ratio of 1.65 for death (12). The recent study by Kozasa et al. showed elevated platelet

count and was associated with poor OS and DFS. In addition, the authors showed elevated platelet lymphocyte ratio, also associated with poor survival outcomes (16).

In our study, multivariate analysis showed that thrombocytosis as an independent prognostic factor (Table 3). Only Lopes et al. found no significant difference in survival when the patients were analysed by the stage of the disease (11).

Irrespective of the platelet count at diagnosis, survival in young patients (< 45 years) is associated with poor outcome on multivariate analysis (Table 2), which is similar to the studies by Hernandez et al. and Kawano et al. where age less than 50 years was associated with poor outcome (10, 12).

Most of the studies have shown that patients with thrombocytosis fail locally as compared to systemically (12). The increased risk of local recurrence is probably due to poor response of the tumor to chemoradiation as seen in our study; also increased platelet counts have a role in stimulating tumor growth. However, platelet count may

not influence the process of metastasis (17, 18).

The drawback of our study is that it is a retrospective study and the results need to be verified in a prospective trial. The cut off value for thrombocytosis is variable ranging from $350 \times 10^9/L$ in Japanese studies to $> 400 \times 10^9/L$ in European studies. We considered a platelet count $> 400 \times 10^9/L$ as cut off for our study as this is the value taken in most of the studies, but there is no data available regarding the same for Indian patients. However, to establish an optimal cut off value for the platelets, there needs to be a large, multicentric study, including patients from various ethnicities.

The data from our study and previous studies suggested that thrombocytosis could be a potential marker of prognosis especially in patients with locally advanced and bulky disease.

5.1. Conclusions

In conclusion, our study found thrombocytosis could be a potential prognostic marker in locally advanced cervical cancer treated with concurrent chemoradiation. We need further larger prospective studies to categorize thrombocytosis as a prognostic factor for poor response.

Footnotes

Authors' Contribution: Nanda Ramanand: developing the idea for the study, manuscript preparation. Shamsundar Sunkappa Dayashankara: manuscript preparation, editing, and data collection. Aradhana Katke: editing manuscript, data collection, Thejaswini Boraiah: help in developing idea for study and editing.

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