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# The impact of thrombocytosis on clinicopathological prognostic factors and survival in patients with vulvar cancer

## Wpływ trombocytozy na prognostyczne czynniki kliniczno-patologiczne i przeżycie pacjentek z rakiem sromu

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### Abstract

***Purpose:*** *Reactive thrombocytosis in many solid tumors has widely been studied. In the present study we aimed to investigate whether thrombocytosis is a common and prognostic factor in women with vulvar cancer.*

***Material & Methods:*** *The preoperative platelet counts of 41 women, treated for vulvar cancer in our onco-gynecology center between March 1994 and January 2007, were retrospectively reviewed and correlated to clinical and pathological prognostic factors and 5-year survival. The chi-square or Fisher exact tests were used to compare categorical variables. P value <0.05 was accepted for statistical significance.*

***Results:*** *The mean age was 65.4±11.3 years (range 39-83y). All patients had squamous histology. The mean platelet count was 335.42x109/L ± 82.03 (range 142–1155x109/L). Thrombocytosis was detected in 8 (19.5%) patients. No correlation was found between thrombocytosis and grade (p=0.65), LVSI (p=0.82), tumor size (p=0.73), depth of invasion (p=0.18), lymph node metastasis (0.93), and FIGO stage (p=0.78). The mean follow up time was 118.0±43.1 months (range 60-213 months). At the end of the study period 14 patients (34.2%) had died, 8 (19.5%) had recurrence, 19 (46.3%) were disease-free. General 5-year survival was 68.3% (28/41). The 5-year survival rate for patients with thrombocytosis was 75.0% (6/8), which was not significantly different from the 5-year survival of patients with normal platelet counts (22/33; 66.7%) (p=0.75).*

***Conclusion:*** *Our study showed that, overall, thrombocytosis was found in about 20% of patients with vulvar cancer and proved to be not linked to the best known prognostic factors and survival. Thus, disease stage and inguinofemoral lymph node status continue to be the best prognostic factors for this disease.*

Key words: **thrombocytosis** / **vulvar cancer** / **prognostic factors** / **survival** /

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## Streszczenie

***Cel pracy:*** *Reaktywna trombocytoza w licznych guzach litych była już przedmiotem wielu badań. W naszej analizie badaliśmy czy trombocytoza jest częstym i prognostycznym czynnikiem u kobiet z rakiem sromu.*

***Materiał i metoda:*** *Retrospektywnie przeanalizowano i skorelowano z prognostycznymi czynnikami kliniczno-patologicznymi i 5-letnim przeżyciem, liczbę płytek krwi od 41 pacjentek, przed operacją z powodu raka sromu w naszym centrum onkologiczno-ginekologicznym w latach od marca 1994 do stycznia 2007. Zmienne kategoryczne porównano przy pomocy testów chi2 i Fishera.*

***Wyniki:*** *średnia wieku wynosiła 65.4±11.3 lat (zakres 39-83). Wszystkie pacjentki miały rozpoznanie raka płaskonabłonkowego. Średnia ilość płytek krwi wynosiła 335.42x109/L ±82.03 (zakres 142-1155x109/L). Trombocytoza została wykryta u 8 (19.5%) pacjentek. Nie znaleziono korelacji pomiędzy trombocytozą a stopniem zróżnicowania (p=0.65), LVSI (p=0.82), wielkością guza (p=0.73), głębokością naciekania (p=0.18), przerzutami do węzłów chłonnych (p=0.93) i stopniem FIGO (p=0.78). Średni czas obserwacji wynosił 118.0±43.1 miesięcy (zakres 60-213 miesięcy). Pod koniec okresu badania 14 (34,2%) pacjentek zmarło, 8(19.5%) miało wznowę, 19 (46.3%) nie miało oznak choroby. Ogólny 5-letni czas przeżycia wynosił 68.3% (28/41). 5-letnia przeżywalność dla pacjentek z trombocytozą wyniosła 75.0% (6/8), co nie różniło się istotnie od 5-letniej przeżywalności pacjentek w prawidłową liczba płytek (22/33; 66.7%) (p=0.75).*

***Wnioski:*** *Nasze badanie wykazało, że trombocytoza wystąpiła u około 20% pacjentek z rakiem sromu i nie jest związana ze znanymi czynnikami prognostycznymi i przeżyciem w tym nowotworze. W związku z tym stopień zaawansowania choroby i obecność przerzutów w węzłach chłonnych pachwinowo-udowych nadal pozostają najlepszymi czynnikami prognostycznymi w tej chorobie.*

Słowa kluczowe: **trombocytoza** / **rak sromu** / **czynniki prognostyczne** / **przeżywalność** /

## Introduction

Vulvar cancer accounts for 0.3% of human malignancies and 3-5% of female genital tract cancers. It is usually observed in older women and diagnosed at advanced stages, with squamous cell carcinoma as the predominant (90%) histologic type [1, 2]. The most important factors related to disease outcome are FIGO (International Federation of Gynecology and Obstetrics) stage, tumor size, depth of invasion, groin lymph node status, presence or absence of lymphovascular space invasion (LVSI), histologic grade, and patient age at the time of diagnosis [3, 4].

Although the threshold for clinically significant thrombocytosis depends on underlying clinical situation and etiology, and the exact definition of thrombocytosis also varies in the literature, a platelet count of >450X10$^9$/L is a generally accepted cut-off. Either primary (essential thrombocytosis) or secondary (reactive) causes can present and the differential diagnosis for thrombocytosis is extremely broad and sometimes a dilemma [5]. Prognosis of thrombocytosis generally depends on the underlying pathology. On the other hand, clinical outcome of the primary disease can be modified by a concurrent (secondary) thrombocytosis, resulting in microvascular and macrovascular thrombotic morbidities. Thrombocytosis can also affect disease outcome through non-thrombotic processes in some clinical situations, especially cancer [6-10]. Many studies postulate the existence of a relationship between thrombocytosis and negative prognostic factors and shortening of the overall survival in several malignant diseases such as breast cancer, gastrointestinal cancers, gynecologic cancers, lung cancer, pancreatic cancer, and Hodgkin disease [11-28]. Although the pathogenesis of this action is not completely clear, some reasonable explanations have been presented, suggesting a role of several humoral factors, including growth factors, cytokines, and cellular enzymes. For instance, a great amount of thymidine phosphorylase (TP), a thrombocyte-derived endothelial growth factor, has been detected in solid tumors compared to normal tissues [6]. High tissue level of TP has been associated with angiogenesis, biologically aggressive tumors, higher metastasis potential, and poor prognosis [7, 8, 9].

In the literature, there are some reports on the relationship between thrombocytosis and characteristics and prognosis of the underlying disease. The general conclusion was that secondary thrombocytosis in ovarian, [16] endometrial, [17] and cervical cancer [18] patients is related to poor prognosis and decreased survival. However, to the best of our knowledge, only two studies about such an effect of thrombocytosis in vulvar cancer have been carried out until today, and both failed to demonstrate the expected correlation [19, 22]. In the present study, once again, we aimed to investigate the frequency of thrombocytosis in vulvar cancer and to test whether thrombocytosis is associated with clinicopathological prognostic factors and survival in patients with vulvar cancer.

## Methods

The pretreatment platelet counts of 41 women, treated between March 1994 and January 2007 at the onco-gynecologic surgery clinic for vulvar cancer, were reviewed and correlated to clinical and pathological prognostic factors and 5-year survival. The clinical and pathological records of the entire study population were screened retrospectively. Follow up data were obtained from patient files with the permission of the head of the department. The approval of the Institutional review board of the hospital was also obtained.

All patients had been staged surgically in accordance with the 1995 FIGO criteria. The recorded FIGO stages of the disease in all patients were adapted and restaged according to the revised

**Table I.** Demographic and disease-related characteristics.

| | | N or Mean±SD | % or Range |
|---|---|---|---|
| **Age at disease presentation (years)** | | **65.4±11.3 y** | **39-83 y** |
| **Marital status** | Married | 37 | 90.2% |
| | Non-married | 4 | 9.8% |
| **Smoking** | No | 33 | 80.5% |
| | Yes | 8 | 19.5% |
| **Parity** | None | 3 | 7.3% |
| | 1 | 10 | 24.4% |
| | 2 | 22 | 53.7% |
| | ≥3 | 6 | 14.6% |
| **Menopausal status** | Pre-menopausal | 7 | 17.1% |
| | Post-menopausal | 34 | 82.9% |
| **Co-morbidities** | Hypertension | 13 | 31.7% |
| | Diabetes | 11 | 26.8% |
| | Obesity | 15 | 36.6% |
| | Cardiac disease | 5 | 12.2% |
| | Second primary (breast) cancer | 2 | 4.9% |
| **Presenting symptoms** | Chronic irritation or vulvar dystrophy | 22 | 53.7% |
| | Vulvar lump or mass | 25 | 60.9% |
| | Vulvar bleeding | 5 | 12.2% |
| | Discharge | 3 | 7.3% |
| | Dysuria | 2 | 4.9% |
| | Groin mass | 2 | 4.9% |
| **Histologic type** | Squamous cell cancer | 41 | 100% |
| | Adenocarcinoma | none | 0% |
| **Location of primary lesion** | Labia majora | 21 | 51.2% |
| | Labia minora | 13 | 31.7% |
| | Posterior fourcette or perinea | 4 | 9.8% |
| | Clitoris or urethra | 3 | 7.3% |
| **Nodal status** | Negative | 29 | 70.8% |
| | Positive inguinofemoral node/nodes | 11 | 26.8% |
| | Positive pelvic node/nodes | 1 | 2.4% |
| **FIGO stage of disease*** | IA (microinvasive**) | 5 | 12.2% |
| | IB | 13 | 31.7% |
| | II | 9 | 21.9% |
| | III (including stage III A, B or C) | 8 | 19.5% |
| | IVA | 3 | 7.3% |
| | IVB | 3 | 7.3% |
| **Type of treatment** | Surgery alone | 24 | 58.5% |
| | Surgery plus RT with/without CT | 12 | 29.3% |
| | Surgery*** plus CT | 3 | 7.3% |
| | Neoadjuvant CTRT followed by surgery | 2 | 4.9% |
| **Type of the vulvar phase of surgical procedure** | Radical local excision (modified radical vulvectomy) | 11 | 26.8% |
| | Radical vulvectomy | 25 | 60.9% |
| | Extended vulvectomy with excision of distal perineal structures (distal uretra, vagina or anus) | 4 | 9.8% |
| | Resection of tumor bed (after neoadjuvant CTRT) | 1 | 2.4% |
| **Type of the groin phase of surgery****** | Unilateral complete inguinofemoral LND | 10 | 24.4% |
| | Bilateral complete inguinofemoral LND | 29 | 70.7% |
| | Excision of grossly enlarged inguino-femoral and pelvic lymph nodes alone | 2 | 4.9% |

* According to the 2009 FIGO; ** T≤ 2 cm and stromal invasion≤1 mm), *** for palliation, **** Groin surgery was performed by separate incisions in all cases and there were no sentinel lymph node biopsies because this technique was introduced at our clinical practice in 2008, CT: chemotherapy, RT: radiation therapy, CTRT: chemo-radiation therapy

**Table II.** Relationships between thrombocytosis and prognostic factors.

| | | Non-Thrombocytosis group (n=33) | Thrombocytosis group (n=8) | *P* |
|---|---|---|---|---|
| **Grade** | Grade I | 13 | 3 | 0.65 |
| | Grade II | 11 | 3 | |
| | Grade III | 9 | 2 | |
| **LVSI** | absent | 23 | 5 | 0.82 |
| | present | 10 | 3 | |
| **Tumor size** | ≤2cm | 12 | 2 | 0.73 |
| | >2cm | 21 | 6 | |
| **Depth of invasion** | ≤1mm | 9 | 3 | 0.18 |
| | >1mm | 24 | 5 | |
| **Lymph node status** | negative | 23 | 6 | 0.93 |
| | positive | 10 | 2 | |
| **Margin status after surgical resection** | Clear margins | 29 | 7 | 0.31 |
| | Positive or near margins | 4 | 1 | |
| **FIGO stage** | I | 15 | 3 | 0.78 |
| | II | 7 | 2 | |
| | III | 6 | 2 | |
| | IV | 5 | 1 | |

2009 FIGO staging system [29]. Vulvar melanomas and patients without surgical staging were excluded. Figure 1 shows the study flow-charts.

Thrombocytosis was defined as the platelet count above 450.000/μL (>450X10$^9$/L). All patients with thrombocytosis were also screened for an incidental myelo/lympho-proliferative disorders, especially polycythemia vera, according to the American Society of Hematology (ASH) guidelines [30].

The data was computerized and statistical analysis was performed using SPSS software (Windows version 10.0, SPSS, Chicago, IL). The chi-square or Fisher exact tests (2x2 table) were used to compare categorical variables. Significance level was established at $P < 0.05$ in 2-sided tests.

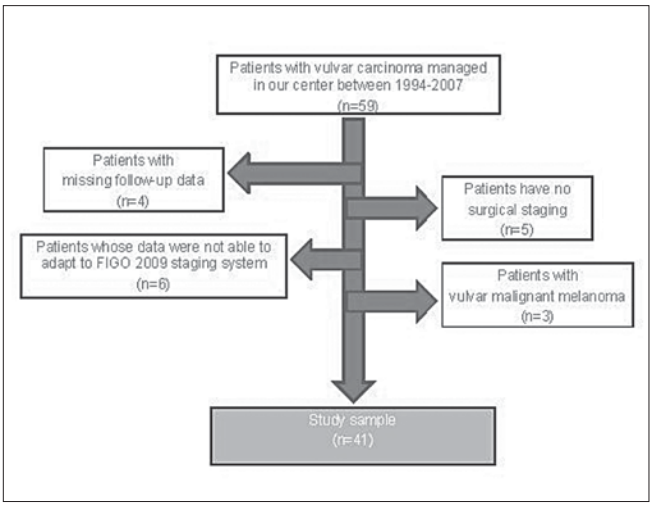


**Figure 1.** Study population and flow-chart.

## Results

Mean patient age at presentation was 65.4±11.3 years (range 39-83). All patients had squamous histology, there was no adenocarcinoma. While 24 (58.5%) patients underwent surgery alone, the remaining 17 (41.5%) received one or more additional multimodal therapies. Table I shows demographic, disease, and treatment related characteristics of the patients.

Mean pretreatment platelet count was 335.42x10$^9$/L ± 82.03 (range 142–1155x10$^9$/L). Thrombocytosis was detected in 8 (19.5%) patients. No correlation was found between thrombocytosis and grade (p=0.65), LVSI (p=0.82), primary tumor size (p=0.73), depth of invasion (p=0.18), incidence of lymph node metastases (0.93), margin status (p=0.31), and stage of the disease (p=0.78). Relationships between thrombocytosis and prognostic factors were presented in Table II.

Mean follow up time was 118.0±43.1 months, ranging from 60 to 213 months. At the end of study period 14 patients (34.2%) had died, 8 (19.5%) had recurrence (local, regional or distant), 19 (46.3%) were disease-free. General 5-year survival was 68.3% (28/41). The 5-year survival rate for patients with thrombocytosis was 75.0% (6/8), which was not significantly different from the 5-year survival of patients with normal platelet counts (22/33; 66.7%) (p=0.75). Survival Curves according to FIGO, nodal status, and thrombocytosis status are shown in Figure 2 (A, B, C).

## Discussion

Thrombocytosis has been linked to many solid tumors, especially non-small cell lung cancer (NSCLC). The incidence of thrombocytosis has been reported to be as high as 60% in patients

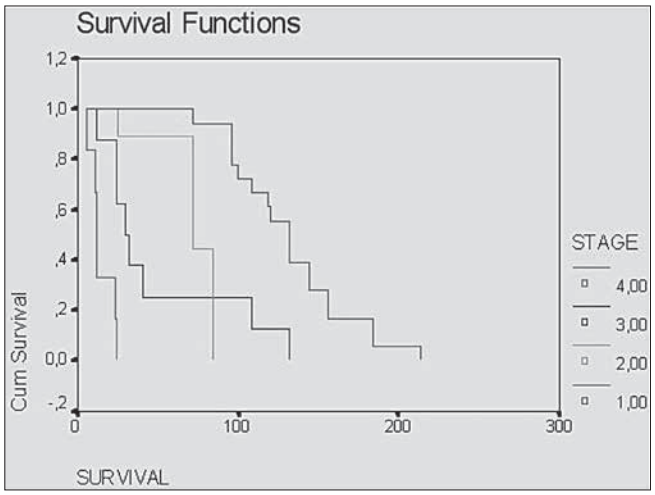


**Figure 2 a.** Kaplan Meier Survival Curves: Survival According to the FIGO stage of disease.

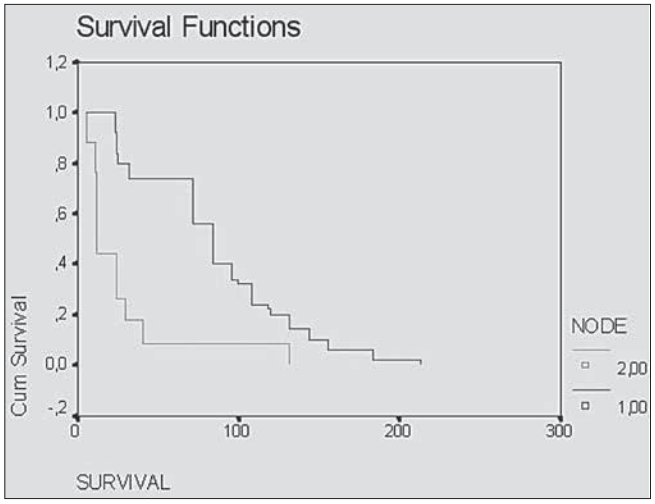


**Figure 2 b.** Kaplan Meier Survival Curves: Survival according to regional lymph node status.

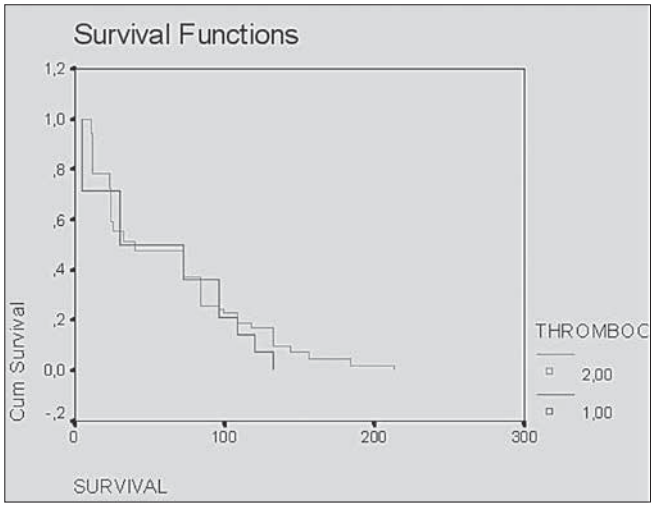


**Figure 2 c.** Kaplan Meier Survival Curves: Survival according to thrombocytosis status.

with NSCLC [20]. In a comparative study, thrombocytosis was found in 42.5% and 13% of patients with malignant and benign pelvic masses, respectively [21]. However, in accordance with our study (19.5% of thrombocytosis rate), the two previous studies were not able to detect an increased incidence of thrombocytosis in vulvar cancer. We suggest that when thrombocytosis is detected in patients with no solid tumors, they should be comprehensively evaluated for all primary (clonal or essential) and secondary (reactive) causes of this hematological finding. Essential thrombocytosis is a clonal disorder of myelocyt progenitor cells in bone marrow, which results in abnormal platelet production. Platelets are one of well-known acute phase reactants; therefore their number increases in response to several endogenous stimulants, including trauma and major surgery, inflammatory diseases, bacterial or viral infections, iron deficiency anemia, bleeding disorders, drugs, and malignancy. This type of abnormal platelet count usually involves benign (generally transient) forms of thrombocytosis [31, 32]. In our study, to make differential diagnosis, all patients were referred to hematology clinic for diagnostic evaluation and bone marrow biopsy. The latter proved to be unaffected and no etiology for thrombocytosis was detected.

It is reported that thrombocytosis has an independent prognostic value in many solid tumors by increasing tumor growth, angiogenesis (by IL-6 and other cytokines derived from inflammatory tissue in rapidly growing tumors), and metastasis (by increasing interaction between vessel wall/endothelium and tumor cell and increasing interaction between tumor cell and extracellular matrix) [17, 23, 24, 35, 26, 27, 28, 33]. Tomita et al., noted that preoperative thrombocytosis had a prognostic effect on the 5-year survival in patients with resectable NSCLC [26]. In a 2009 study performed in ovarian cancer population, Gungor et al., reported that thrombocytosis was associated with advanced stage, high grade and biologically aggressive tumors and poor prognosis [16]. Gorelick et al., observed similar findings for advanced stage endometrial cancers [17]. Contrary to these reports, some studies noted no prognostic significance of thrombocytosis in malignancy. Nyasavajjala et al., evaluated a total of 630 patients with colorectal cancer and found that thrombocytosis was frequent but had no prognostic effect on the survival [34]. Taking into consideration vulvar cancer, both 1999 study by Lavie et al., (n=201) and 2000 study by Hefler et al., (n=62) did not reveal a significant relationship between pretreatment thrombocytosis and survival [19, 22]. Lavie et al., reported thrombocytosis rate of 14.92% for patients with vulvar malignancies and 15.46% for squamous cell carcinoma of the vulva. They found no correlation between thrombocytosis and tumor size, incidence of lymph node metastases or stage of the disease. The 5-year survival rate was not significantly different between the groups (89.29% for thrombocytosis group vs. 76.47% for non-thrombocytosis group). They reported that among several factors including thrombocytosis only stage of disease, number of tumors, and histological differentiation were associated with unfavorable prognosis [19]. Hefler et al., studied the prevalence and prognostic effect of tumor anemia and thrombocytosis in patients with vulvar cancer. Their cut-off value for thrombocytosis was 300.000 and the authors concluded that 27.4% of the subjects had thrombocytosis and tumor thrombocytosis was associated with a poor prognosis but was not an independent predictor of the outcome [22]. In the present

study, we analyzed a total of 41 vulvar cancer patients and found that the 5-year survival rates were 75.0% and 75.8% for patients with and without thrombocytosis, respectively. We also found that there were no correlations between thrombocytosis and several prognostic factors, including grade, LVSI, tumor size, depth of invasion, lymph node metastasis and disease stage.

As for the reported shorter survival in cancer patients with thrombocytosis, it may be a reasonable hypothesis that thrombocytosis can cause undiagnosed but fatal arterial or venous thrombotic events, which result in decreased cumulative survival in that group of patients. Disease and treatment-related arterial thrombosis or venous thromboembolism (VTE) are one of the most common reasons for morbidity and deaths not attributed to cancer in cancer patients [35]. However, in contrast to clonal ones, reactive thrombocytosis alone is not a risk factor for thromboembolic complications unless additional risk factors such as age≥60, leukocytosis, platelets ≥1500 x $10^9$/L, previous thrombosis, JAK2V617F mutation are present [10, 36]. Cancer, as a cause of reactive thrombocytosis, may also contribute to thrombotic processes in many different ways and VTE prophylaxis is an important issue in patients diagnosed with cancer. While some authors have recommended low molecular weight heparin (LMWH), others recommend low dose (100 mg/day) aspirin for cancer patients with additional risk factors [37]. In our clinical practice, we have routinely used low dose aspirin to prevent VTE events in patients with platelets >1000 x$10^9$/L if not contraindicated. In the present study we used this protocol in two patients and did not observe any thrombotic complications during their follow-up periods.

In conclusion, despite the fact that increased frequency and prognostic value of thrombocytosis had been previously shown for many solid tumors, this hypothesis does not seem to be valid for vulvar squamous cell carcinoma. Thus, the prognosis of women with vulvar cancer depends mostly on classical independent prognostic factors, especially FIGO stage of the disease and the status of regional lymph nodes.

**Conflict of Interest Statement**

The authors declare that there are no conflicts of interest.

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