ORIGINAL RESEARCH

The Correlation Between Platelet Count and Survival in Prostate Cancer

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Purpose: A number of studies have confirmed that elevated platelet count accompanying various solid tumours is associated with worse survival. However, only meagre data are available on the relationship between thrombocytosis and survival in prostate cancer.
Methods: We conducted a retrospective analysis on clinical-pathological data accumulated from 316 patients during on average 51 months of follow-up after laparoscopic prostatectomy performed for prostate cancer. We analyzed the relationship between platelet count, risk factors, prostate-specific antigen (PSA) and cancer stage with use the Tumor, Node, Metastase system (TNM), as well as surgical margin, and prognosis.
Results: Thrombocytosis occurred in only one out of the 316 patients. The multivariate Cox proportional hazard model showed that preoperative PSA, risk group, preoperative haemoglobin level, and surgical margin status were significant, independent predictors of biochemical progression-free survival. By contrast, age at diagnosis and thrombocytosis had no such predictive value.
Conclusion: We could not demonstrate an association between elevated platelet count and worse survival in our study population of patients with prostate cancer.
Keywords: prostate cancer, thrombocytosis, prognosis, pathomechanism, solid tumor

Introduction

Cancer of the prostate is the second most common malignancy in males. In 2017, nearly 1.3 million cases were diagnosed and 416,000 related deaths were recorded. During the past decade, the incidence of the disease increased by 42%. Twenty-one per cent of this increment is due to changes in the age distribution and 13% is related to the growth of the population, as well as 8% is the result of changes in age-specific rates.[1]

While standard assessment tools for risk stratification are informative, prostate cancers may behave uncharacteristically with natural history or relapse patterns that are sometimes unpredictable Similar clinical and histologic patterns at diagnosis may lead to variable clinical outcomes across patients. Consequently, biomarkers that are capable of significantly improving risk stratification, distinguishing indolent versus aggressive prostate cancer, remain an unmet need.[2] The measurement of prostate-specific antigen (PSA) level is suitable for establishing the diagnosis and to follow-up the effectiveness of the management of prostate cancer; however, it is inadequate by itself for estimating prognosis. Prostate-specific antigen velocity (PSAV) and PSA doubling time (PSA-DT) may have a prognostic role in treating prostate cancer (PCa) but have limited diagnostic use because of background noise (total prostate volume, and benign prostatic hyperplasia), different intervals between PSA determinations, and acceleration/deceleration of PSAV and PSA-DT over time. Free/total PSA is of no clinical use if the total serum PSA is >10 ng/mL or during follow-up of known PCa. The

clinical value of f/t PSA is limited in light of the new diagnostic pathways incorporating Magnetic Resonance Imaging (MRI).[3]

Increasing evidence suggests that inflammation plays an essential role in cancer development and progression. Several studies demonstrated that inflammation marker neutrophil–lymphocyte ratio (NLR) had prognostic value in localized and advanced PCa; on the contrary, other studies reported that high serum NLR had no prognostic value in patients with PCa.[4]

Other study shows that systemic immune-inflammation index (SII), which is calculated as SII = platelet × NLR, appear to be a significant diagnostic marker in patients with high-grade PCa.[5]

Thrombocytosis observed in oncology patients has been reported to entail a worse prognosis in a variety of solid tumours: colorectal,[6,7] breast,[8] lung,[6,9] renal,[6,10] cervical,[11] ovarian[12] and brain tumours.[13] Only meagre data are available in the literature on the relationship between thrombocytosis and prostate cancer. MOUNCE et al suggests little or no true association between high platelet counts (or thrombocytosis) and prostate cancer.[14] By contrast, WATTS et al found that a higher platelet count was associated with an increased risk of prostate cancer diagnosis, but platelet indices were not associated with prostate cancer mortality.[15]

Our objective was to ascertain whether prostate cancer is similarly associated with elevated platelet count in our study population, as well as whether any relationship exists between thrombocytosis and progression-free survival or overall survival.[5] Due to the meagre results available, we try to place our results in the international literature.

Materials and Methods

We performed a retrospective analysis of the clinical-pathology data of the patients treated with laparoscopic prostatectomy at the "Jahn Ferenc" South-Pest Hospital (Budapest, Hungary) between 2011 and 2014. During this period, all surgical operations were performed at our institute by laparoscopy. The criterion for inclusion was the presence of a histologically confirmed prostate tumour (with the exception of clinical T4, N2, and M+ cases); data from 321 patients in total were analyzed. The presence of a synchronous tumour (other than the prostate cancer), any inflammatory disease (such as pneumonia, abscess, cholecystitis, endocarditis, urinary tract infection, Crohn's disease, ulcerative colitis), thromboembolic events (deep-vein thrombosis, pulmonary embolism, myocardial infarction), corticosteroid therapy or other diseases that may affect the platelet count (myelodysplastic disease, etc.) were criteria for exclusion, which eliminated five patients altogether from the study. The data gathered during follow-up were analyzed along with the abnormalities detected by physical examination, as well as with the changes in PSA levels. PSA level was measured one month after surgery – then, at 3-month intervals in the first, and at 6-month intervals during the second to fifth postoperative year, and at yearly intervals thereafter.

Platelet count was determined preoperatively within 14 days prior to surgery or before the start of neoadjuvant therapy and assessed in the same laboratory.

Thrombocytosis was defined as a platelet count exceeding the upper limit of the normal range (>400 G/L), but we also performed analysis between elevated platelet count and survival at other cut-off values (for example, mean platelet value). Anaemia was diagnosed when the haemoglobin level was lower than 130 g/L. The patients were categorized into low-, intermediate-, and high-risk groups according to the classification by D'Amico.[16] Within the framework of multimodal management, a proportion of the high-risk patients received neoadjuvant therapy in the form of androgen deprivation (ADT). During surgery, lymph node dissection was performed as recommended by the guideline.[3,17] In particular, lymph node dissection was not performed in low-risk cases but was always carried out in high-risk patients. In intermediate-risk patients, the decision to perform lymphadenectomy was based on the Briganti nomogram.[18] Patients exhibiting disease progression received ADT, irradiation, or the combination of these modalities. In conformity with the European consensus, progression-free survival (PFS) was defined as survival until biochemical relapse (>0.2 ng/mL increase of PSA level between two subsequent measurements after radical prostatectomy),[19] which was the primary endpoint of our study. Overall survival (OS) was calculated from the time of surgery to the tumour-related death of the patient, or to the end of follow-up.

Statistical Methodology

Statistical analyses for categorical variables were performed by the χ2 or the Fisher's exact tests and for continuous variables by the Mann–Whitney test. PFS and OS data were analyzed by the Log rank test and Kaplan–Meier estimates were computed. In multivariate survival analyses, Cox proportional hazard models were adjusted for age, PSA levels, Gleason score, risk scores, and wound edge positivity. The analyses were performed with the SPSS Statistics Software, version 22. Result is significant if the p-value is less than 0.05.

Results

Clinical pathology data from 316 patients with prostate cancer were analyzed. Patients with T4 stage disease were not operated upon based on the inclusion criteria, as well as those with T1 stage prostate cancer were missing from the study population. The majority of patients belonged to the intermediate-risk group (Table 1).

The mean duration of follow-up was 51 (5 to 80) months during which disease progression occurred in 25.9% of the patients. Importantly, mean survival was not significantly different between the patient subsets with or without disease progression (48 versus 52 months). Eighty-two per cent of patients with biochemical relapse underwent adjuvant therapy by pelvic irradiation (n = 21), hormone therapy (n = 16), or the combination of these two modalities (n = 30). Six patients (1.89%) died of tumour progression during follow-up. Before surgery, 87 patients (27.5%) were treated with platelet aggregation inhibitors: 68 received acetylsalicylic acid and 19 clopidogrel. The administration of these agents was discontinued before the operation and hence, their effects did not interfere with preoperative laboratory testing. In addition to platelet count, we studied the impact of other factors known to influence survival by performing the Kaplan–Meier univariate analysis (Table 2).

Higher haemoglobin levels were associated with significantly longer survival. This correlation was significant (p < 0.0005) even if the median haemoglobin concentration (Hgb <147 g/L) was defined as the cut-off level. Mean platelet count was 214 (114–569) G/L. Thrombocytosis occurred in just one patient and this made further statistical analysis inappropriate. We could not demonstrate a statistically significant correlation between elevated platelet count and survival at other cut-off values either (mean PLT: 214 G/L, p = 0.333, or PLT: 300 G/L, p = 0.149). We also examined whether a lower platelet count is associated with worse survival. Mean platelet count did not increase with the progression of the tumour stage, although there were only six patients with T2b stage disease in the study population (Table 3).

The multivariate Cox proportional hazard model showed that preoperative PSA, preoperative haemoglobin, risk group, and surgical margin status were significant, independent predictors of biochemical PFS. By contrast, age at diagnosis and thrombocytosis had no such predictive value (Table 4).

Discussion

The pathomechanism of the relationship between solid tumour-associated thrombocytosis and survival is not known. Several hypotheses have been proposed. Platelets may be activated by tumour cells in a process known as the tumour cell-induced platelet aggregation. Platelet activation may occur either by direct interaction with tumour cells,[20] or indirectly, through the mediation of adenosine diphosphate (ADP), thromboxane A2, or metalloproteinases.[21] Additionally, tumour cells may secrete thrombin, or may stimulate pro-thrombotic activity in other tissues, and can thereby contribute to enhanced platelet activation.[22] Activated platelets facilitate the growth of tumour cells by releasing a number of angiogenic and tumour growth factors. These include thrombospondin, platelet factor 4, transforming growth factor-beta, vascular endothelial growth factor (VEGF), and platelet-derived growth factor.[23–27] These processes induce angiogenesis, which also leads to the acceleration of tumour growth.[28–33] Additionally, tumour cells secrete VEGF which activates the coagulation cascade – this has an activating effect also on platelets and enhances the adhesion of the latter to the endothelial surface of blood vessels in the tumour.[31] Accordingly, the tumour cells and the platelets are involved in a mutually potentiating interaction. Activated platelets release micro-vesicles which increase the invasive potential of the tumour cells.[34] These observations led to the conclusion that the emboli containing platelets and tumour cells contribute to the formation of tumour metastases. Moreover, the platelets form a cloak around tumour cells and thereby prevent their recognition by the natural killer cells.[35] Platelets can also interfere with dendritic cells, neutrophils, macrophages and lymphocytes and modulate their immunological function.[36] In their studies conducted on patients

Table 1 The Clinical Pathology Data of the Subjects

Characteristics	Number of Patient (%) n=316
Mean age (years), [range]	66 [48–80]
Mean BMI (kg/m^2), [range]	27.9 [19.8–39.8]
Mean Haemoglobin (g/l), [range]	147 [112–177]
Baseline PSA (ng/mL)	
Median [range]	9 [2.5–83]
<10	173 (54.7)
10–20	110 (34.8)
>20	33 (10.5)
Risk group	
Low	48 (15.2)
Intermediate	142 (44.9)
High	126 (39.9)
Lymph node dissection	
Positive	32 (16.1)
Negative	152 (42.1)
Not performed	132 (41.8)
Neoadjuvant androgen deprivation	
Yes	53 (16.8)
No	263 (83.2)
Postoperative Gleason score	
<7	51 (16.1)
7A (3+4)	107 (33.9)
7B (4+3)	75 (23.7)
>7	83 (26.3)
Tumour stage	
pT2a	32 (10.1)
pT2b	6 (1.9)
pT2c	152 (48.2)
pT3a	76 (24)
pT3b	50 (15.8)
Surgical margin	
Positive	88 (27.8)
Negative	228 (72.2)

Abbreviations: BMI, body mass index; PSA, prostate specific antigen.

Table 2 The Impact of Platelet Count and of the Known Factors Influencing Survival on PFS (Kaplan–Meier Univariate Analysis)

Factors	Subgroups	n	Mean Survival (Month)	PFS at 60m	95% CI	p-value
Age (years)	<66	149	68.5	83%	64.4–72.4	0.002
	>66	167	58.5	64%	53.8–63.2	
PSA (µg/L)	<9	149	73.1	88%	70.0–76.2	<0.0005
	>9	167	54.5	58%	60.1–66.4	
Surgical margin	negative	228	70.9	83%	67.9–73.8	<0.0005
	positive	88	41.5	52%	35.0–48.0	
Gleason score	<8	256	66.1	78%	62.8–69.4	<0.0005
	>8	60	51.1	52%	42.5–59.7	
Risk	low	48	75.7	93%	71.1–80.4	<0.0005
	intermediate	142	65.7	77%	61.4–70.1	
	high	126	55.6	60%	48.9–61.4	
Hgb, mean (g/L)	<147	161	56.9	82%	52.0–61.7	<0.0005
	≥147	155	68.1	61%	64.4–71.8	
PLT, mean (G/L)	<214	159	64.5	72%	60.0–68.9	0.333
	≥214	157	60.6	68%	59.3–65.0	
PLT, dichotomous (G/L)	<300	294	62.6	72%	59.2–65.9	0.149
	>300	22	70.4	85%	62.3–78.5	

Abbreviations: PSF, progression free survival; PSA, prostate specific antigen; Hgb, haemoglobin level; m, months; PLT, platelet count.

Table 3 Survival Data by Disease Stage and Platelet Count

Stage	n	PFS (Month)	Deaths	Mean/Median Platelet Count (G/L)
T2a	32	51.2	1	206/203
T2b	6	74.5	0	175/185
T2c	152	47.9	2	222/209
T3a	76	40	0	220/214
T3b	50	29.1	3	220/220

Abbreviation: PFS, progression free survival.

with ovarian cancer, STONE et al found a significant correlation between elevated platelet count, as well as thrombopoietin (TPO) and serum interleukin 6 (IL-6) levels.[37] Based on their findings, the authors suggested the possible existence of a paracrine-mediated, paraneoplastic pathway, where IL-6 expressed and secreted by the ovarian tumour enhances the synthesis of TPO by the liver. The latter increases – through its stimulatory effect on bone marrow – the number of platelets. This process results in tumour-induced thrombocytosis.

IL-6 is a multifunctional pro-inflammatory cytokine which is expressed in clinical specimens obtained from patients with prostate cancer and in multiple cell lines.[38] The review by NGUYEN et al suggests that IL-6 is a key mediator in several steps of prostate cancer pathogenesis, including the initiation of prostate tumorigenesis, stimulation of tumour growth, induction of aggressive prostate cancer phenotype and promotion tumour metastasis. IL-6 can regulate the expression of androgen-responsive genes in low-androgen conditions and thereby contribute to the emergence of castration-resistant prostate cancer.[39] First ADLER et al and WISE et al observed in clinical studies that patients with metastatic or castration-resistant prostate cancer have elevated serum IL-6 levels when compared to that of healthy patients or patients with localized prostate cancer.[40,41] CHUNG et al found that only hormone-refractory cell lines express IL-6.[42]

Table 4 Multivariate Cox Proportional Hazards Model for the Variables Used to Predict the Risk of Disease Progression

Variable	HR	CI	p
Age at surgery (y)			
≤66	1		
>66	1.51	0.7–3.27	0.29
Surgical margins			
negative	1		
positive	5.58	3.39–9.2	<0.0005
PSA (ng/mL)			
≤9	1		
>9	3.04	1.7–5.4	<0.0005
Platelet count (G/L)			
≤400	1		
>400	0.99	0.98–1.01	0.871
≤300	1		
>300	0.523	0,12–2,26	0.386
≤214	1		
>214	1.33	0.64–2.76	0.44
Risk group			
low	1		
intermediate, high	2.15	1.19–3.88	0.01
Haemoglobin (g/L)			
≤130	1		
>130	0.47	0.23–0.99	0.047

Abbreviations: PSA, prostate specific antigen; HR, hazard ratio; CI, confidence interval.

Biochemical progression-free survival varies between 38% and 51% at 10 years if patients are treated with radical prostatectomy as monotherapy.[3] In our study population, biochemical progression-free survival is 74.1% at the mean follow-up of 51 months.

So far, all instances of solid tumour-related thrombocytosis were associated with worse survival. However, the definition of thrombocytosis is dependent on the selected cut-off value, and this often makes the comparison of the published data difficult. For example, SHIMODAIRA et al used 300 G/L as cut-off value,[43] whereas GUTIONTOV et al used 187 G/L.[44] According to the literature, the prevalence of thrombocytosis ranges between 8% and 49% in colorectal cancer, 2.7% and 8.2% in hepatic tumours, and 16% and 27% in pancreatic tumours.[7] In contrast with the findings from studies conducted in other malignancies, we could not demonstrate a statistical relationship between elevated platelet count and poor survival in patients with prostate cancer. We measured a platelet count corresponding to the upper limit of the normal range (400 G/L) in just one patient (0.3%) – this proportion is lower than that characteristic of the general population without malignancy (1.5 to 2.2%).[45]

SYLMAN et al found that the use of historical platelet counts greatly improved prediction efforts in prostate cancer (early- and late-stage patient survival both increased by approx. 30%) and temporal evaluation of platelet counts preceding a cancer diagnosis was superior to a single time-point evaluation.[46] VIDAL et al demonstrate that in men undergoing RP, there were no significant associations between platelet counts and biochemical recurrence in either white or black men.[47] In a retrospective analysis of 364 prostatectomy patients, WONG et al found that only a specific subpopulation of total platelets are an independent predictor of early biochemical recurrence, and they revealed that there was no significant difference between the total platelet counts of tumour-free patients and patients with recurrence.[48] GUTIONTOV et al demonstrate that a lower platelet count is associated with an increased biochemical recurrence and a twofold increased rate of distant metastases after prostate radiation therapy.[44]

NIEDER et al, by contrast, reported worse outcomes in patients with metastatic prostate cancer and thrombocytopenia.[49]

Between 2011 and 2014 there were 55 patients in our institute who were diagnosed with prostate cancer with bone metastasis (Tany, Nany, M1). 87% of the patients had multiple and 13% had oligo metastasis. Mean PLT count was 237 G/L (114–355). Two patients had thrombocytopenia (3,6%) and none of them had thrombocytosis. Neither thrombocytopenia (p = 0.248) nor thrombocytosis was related to overall survival based on Kaplan–Meier analysis.

By contrast, SHIMODAIRA et al found that platelet counts were independent prognostic factors in patients with metastatic prostate cancer.[43] LEBLANC et al revealed that patients with bone metastases, which are the most frequent metastases in prostate cancer, have higher platelet counts and bad prognoses.[50]

Our objective was to ascertain whether any relationship exists between thrombocytosis and worse survival in prostate cancer. Prostate cancer has a good prognosis, as the five-year survival rate is 97.8%.[51] In our study population, the survival rate is 98.1% after 51 months. We could not demonstrate a statistical relationship between elevated platelet count and poor survival in patients with prostate cancer, because they have a good survival compared with other solid tumors. The 5 year survival rate is 20.5% in lung cancer and 64.6% in colon cancer.[51] In both lung and colon cancer, a relationship has been observed between thrombocytosis and worse prognosis.[6,7,9] BAILEY et al found the same trend after they investigated 40,000 patients with thrombocytosis in their study, that is, lung and colorectal cancer were much more commonly diagnosed in patients with thrombocytosis than in the general population, whereas breast and prostate cancer were much less commonly diagnosed.[45] In a case where a patient's prognosis is already good, there might be less inclination to use platelet counts as a measure of prognosis.

In contrast with other solid tumours, the absence of thrombocytosis in prostate cancer appears intriguing. The prostate is enveloped by a dual-layer capsule: the inner capsule is a thin, fibrous shell – the visceral layer of the pelvic fascia, actually. The venous plexus of the prostate gland is located between the two layers of the capsule. The inner capsule might have a protective function and if this is the case, the tumour is not exposed to the factors that possibly induce thrombocytosis. However, this is contradicted by the fact that we could not detect thrombocytosis even in Stage T3 disease where the tumour extends beyond the capsule. Another possible explanation is the existence of a possible prostate-blood barrier,[52] which has been suggested during the management of chronic prostatitis. The active component of the blood-prostate barrier is still unknown; some researchers consider that vascular endothelial cells and the basement membrane constitute this barrier, whereas epithelial cells are deemed essential by others.[53] However, even if this prostate-blood barrier existed and functioned similarly to the blood-brain barrier, this hypothesis is contradicted by the fact that thrombocytosis has been detected in patients with brain tumours.[13] Furthermore, it should also be noted that prostate cancer most often metastasizes to the bone marrow, that is, to a location where platelets are generated.

If we accept that thrombocytosis is caused by the IL-6 produced by prostate cancer cells, while IL-6 is only produced by the hormone-refractory cells, it can explain why none of our patients had thrombocytosis. However, it does not account for the discrepancies found in the literature.

The findings of this study have to be seen in light of some limitations. First, this is a single-center, retrospective study. In particular, we studied patients treated by surgery, therefore our study population was not representative of cases with early-stage or advanced metastatic disease.

Conclusion

One can only wonder why we found lower platelet counts in prostate cancer than those published for other solid tumours. Elucidating the underlying cause of this difference might contribute to a better understanding of the relationship between thrombocytosis and solid tumours. It appears worthwhile to repeat our study in a larger patient population with a wider range of tumour stages.

Data Sharing Statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

Ethical approval for this study was obtained from The Hungarian Scientific and Research Ethics Committee of Medical Research Council, approval number: 8951-0/2015/EKU (0444/15).

Informed consent was obtained from the subjects in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrolment in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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