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RESEARCH

Thrombocytosis of Liver Metastasis from Colorectal Cancer as Predictive Factor

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Abstract There is increasing evidence that thrombocytosis is associated with tumor invasion and metastasis formation. It was shown in several solid tumor types that thrombocytosis prognosticates cancer progression. The aim of this study was to evaluate preoperative thrombocytosis as a potential prognostic biomarker in isolated metastases, in patients with liver metastasis of colorectal cancer (mCRC). Clinicopathological data of 166 patients with mCRC who had surgical resection between 2001 and 2011 were collected retrospectively. All primary tumors have been already resected. The platelet count was evaluated based on the standard preoperative blood profile. The patients were followed-up on average for 28 months. Overall survival (OS) of patients with thrombocytosis was significantly worse both in univariate (HR=3.00, p=0.03) and in multivariate analysis (HR=4.68, p=0.056) when adjusted for gender, age, tumor size and surgical margin. Thrombocytosis was also a good prognosticator of disease-free survival (DFS) with HR=2.7, p=0.018 and nearly significant in multivariate setting (HR=2.26, p=0.073). The platelet count is a valuable prognostic marker for the survival in patients with mCRC.

Keywords Thrombocytosis · Liver metastasis of colorectal cancer · Prognostic factor · Survival

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Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide. In Europe the incidence of the disease corrected according to the population's age distribution is 12.3 % in men and 13.1 % in women [1]. The cornerstone of the therapy is surgical resection, however, one third of patients following curative resection die up to 5 years after the diagnosis [2]. Mainly metastases are responsible for this high mortality rate, primarily located in the liver. In approximately one fourth of patients hepatic metastases are found already at the time of diagnosis of colon cancer. Approximately the same percentage of patients develop metastases later, even years after the resection of the primary tumor [2]. Taken

together liver metastasis occurs in nearly every second patient with CRC. Therefore, it is important to find reliable prognostic markers that can predict the survival of patients with liver metastasis of CRC.

The correlation between thrombocytosis and tumor was first described by Leopold Riess in 1872 who found considerably elevated platelet count in patients with malignant disease [3]. Several hypotheses have been presented about the possible mechanisms by which thrombocytosis promotes the invasion of the tumor and the metastatization [4–10]. Several details were elucidated regarding the pathomechanism of this process, but the exact causative relationship between thrombocytosis and the tumor needs further clarification. Recently, it was shown in several tumor types mainly in gynecological [4, 11–17], pulmonary [5, 18], breast [6], kidney [7], esophageal [8], gastric [9] and pancreatic [10] cancer that concomitant thrombocytosis is associated with poorer survival. Similarly, preoperative thrombocytosis was reported to be associated with worse prognosis in colorectal cancer [19–23]. Despite the growing number of reports about the role of elevated platelet count in more and more types of solid tumors there are only little studies available about metastases. The aim of our study was to determine the prognostic role of thrombocytosis in mCRC.

Materials and Methods

Each patient signed an informed consent form approved by the Committee of Scientific Research Ethics of the Medical Research Council and the Institutional Research Ethics Committee. No animals were used for this study.

One hundred ninety seven patients with mCRC who had surgical resection between 2001 and 2011 were evaluated retrospectively. One of the inclusion criteria was curative (R0) resection. The number and size of metastases was not a limiting aspect during patients' enrollment.

Exclusion criteria were the followings: other synchronous tumor in addition to the hepatic metastases, inflammatory disorders (pneumonia, wound infection, abscess, cholecystitis, Crohn's disease, ulcerative colitis), non-curative resection and steroid therapy. A total of 31 patients were excluded and the clinical data of 166 patients were evaluated. The demographical and clinical distribution of our patients is shown in Table 1 (Table 1).

The liver metastases were removed on average 22 months after the resection of the primary tumor. At the time of the liver operation none of the patients had confirmed recurrence of the colorectal cancer or distant metastasis in another organ.

Demographical, surgical, histopathological and laboratory data were collected. Preoperative blood samples drawn within 2 weeks prior the date of the operation were assessed.

Table 1 Clinicopathological data

Patients' characteristics	
Case number (n)	166
Gender (male/female)	108/58
Mean age (years)	62
Mean overall survival (OS) (months)	28
Mean disease-free survival (DFS) (months)	22
Recurring metastasis later (n)	58
Died (n)	37

Reviewing the literature we found that several authors used different cut-off regarding thrombocytosis and tumor prognosis [6, 23, 24]. We defined thrombocytosis as number of platelets in blood exceeding $380 \times 10^3/\mu L$. Patients were divided in two groups: with and without thrombocytosis.

The size of metastases was evaluated based on the pathological finding. None of the patients had a CT volumetry measurement. In addition to the type of surgery the presence of positive surgical margin and the need for blood transfusion in the perioperative period were also recorded. In addition to the histopathological subtype data on CK7, CK20, EGFR, Ki67 and K-Ras were collected, however, during the studied period these data were available only in a few patients.

The follow-up lasted until the end of the study. The required data were collected from oncological and surgical follow-up examinations. Local recurrence of the primary tumor and recurrent metastases occurring at later time were also recorded. Overall survival was defined as the time from the operation until death caused by the liver tumor, thus it is cancer-specific. Disease-free survival was counted from the date of the hepatic surgery until the date of recurrence in the liver.

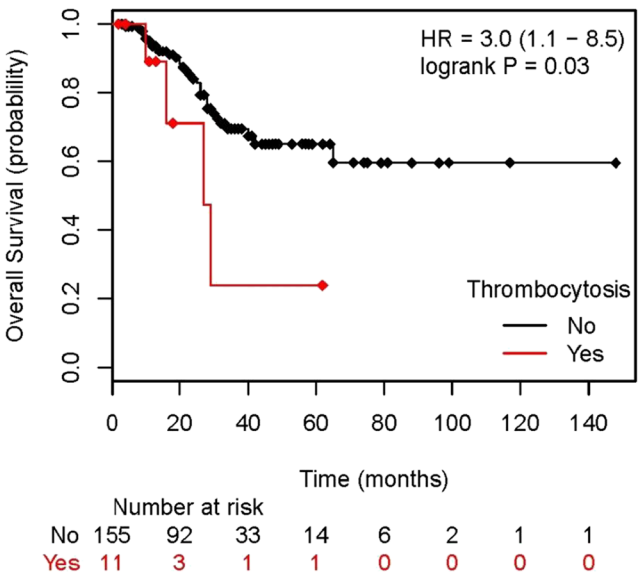

Fig. 1 Kaplan-Meier plot showing the overall survival of patients with and without thrombocytosis

Table 2 Multivariate analysis of patients' data

Variable	No (%)	Univariate			Platelet count (median)	Multivariate		
		HR	95 % CI	Pr(>|z|)		HR	95 % CI	Pr(>|z|)
Platelets [1/mm3]								
>380×10^3	11 (6.6)	3.0	1.06–8.53	0.03	416000	2.84	0.97–8.33	0.056
≤380×10^3	155 (93.4)				219000			
Sex								
Male	58 (34.9)	0.78	0.38–1.61	0.50	211500	0.82	0.39–1.72	0.60
Female	108 (65.1)				259500			
Age (years)								
>65	109 (65,7)	0.71	0.35–1.45	0.35	205000	0.75	0.36–1.53	0.42
≤65	57 (34.3)				234000			
Tumor volume [cm^3]								
>28 (median)	83 (50)	0.71	0.37–1.36	0.30	231000	0.70	0.36–1.35	0.28
≤28 (median)	83 (50)				226000			
Surgical margin								
Free	159 (95.8)	1.51	0.36–6.33	0.57	250000	1.16	0.26–5.12	0.84
Not free	7 (4.2)				226000			

Statistical Analysis

All calculations were made using R version 2.15.0 and packages 'beeswarm', 'survplot', 'survival' and 'stats'. Survival curves were generated using the Kaplan-Meier method. Hazard ratios with 95 % confidence intervals were obtained using Cox proportional hazards regression. P values were calculated using the log-rank test. The relationships between the platelet count and the different clinical parameters were investigated using uni- and multivariate Cox regression adjusted for gender, age, tumor volume and surgical margin.

Results

In the perioperative period none of the patients received blood transfusion. At the time of blood test none of the patients had anemia (red blood cell count $<3.9\times10^6/\mu L$, Hematocrit: 0.36 %), elevated C-reactive protein level (CRP) (>10 mg/L) or leukocytosis (white blood cell count $>10.8\times10^3/\mu L$). During our follow-up none of the patients developed recurrence of the primary tumor, while 58 patients developed repeatedly liver metastasis that were independent from surgical margin, total volume of the liver metastasis or localization. Oncologic therapies before and after the hepatic surgery were so heterogeneous that they could not be used for statistical analysis.

The overall survival of patients with liver metastasis from colorectal cancer was evaluated with respect to thrombocytosis using Kaplan-Meier analysis. We found that risk of death of patients with elevated platelet count was significantly higher (HR=3.00, p=0.03) than the rest of the cohort (Fig. 1). Median OS in the group with thrombocytosis was 27 months while median OS for the rest of the cohort could not be established because the surviving fraction of patients in this group never dropped below 50 %. The follow-up time in both groups was 18 and 28 months, respectively.

In a multivariate setting we adjusted for gender, age, tumor volume and surgical margin the analysis showed that elevated platelet count is an independent prognosticator of patient survival in colorectal cancer (Table 2) with hazard ratio of 4.68, and nearly significant p-value of 0.056. The log-rank p-value

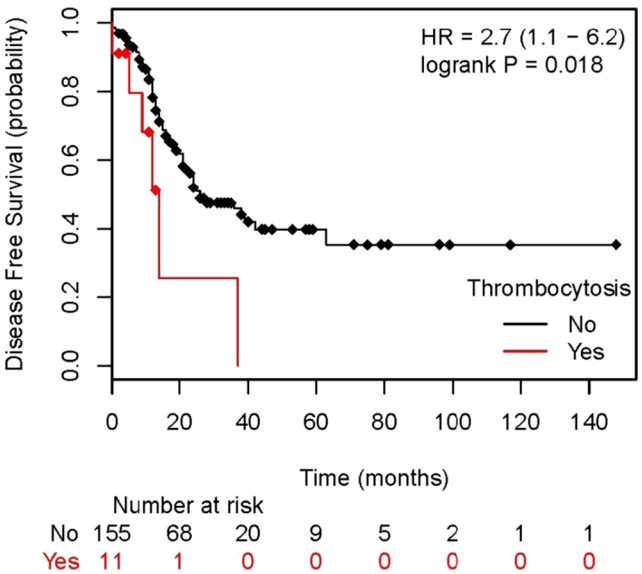

Fig. 2 Kaplan-Meier plot showing the disease-free survival of patients with and without thrombocytosis

Table 3 Differences of the evaluated data according to the histopathological subtypes

Histological subtypes	No.	Percentage	Average platelet count	Mean OS	Mean DFS
Adenocarcinoma	151	90,97	244	26	20
Mucinous adenocarcinoma	15	9,03	308	21	16

was slightly above the 0.05 due to small number of available data points.

The analysis also showed that DFS was significantly shorter in patients with thrombocytosis (HR=2.70, p=0.018) (Fig. 2). Multivariate analysis showed the same trend, however, this could not be reliably confirmed in the multivariate analysis (Table 2) probably due to insufficient number of data points.

Regarding the histological classification of colorectal cancer we found cases of mucinous adenocarcinoma in addition to adenocarcinoma. The mean platelet count of the mucinous subgroup was higher than that of the adenocarcinoma subgroup (Table 3 and Fig. 3). Consistently with our findings above we noticed lower mean overall survival (OS) in the mucinous subgroup with higher mean platelet count, however, the number of those cases was too low in the cohort to show a significant difference (Fig. 4).

Discussion

It is not completely understood how platelets affect the development of the tumor. According to the most widely accepted hypothesis they take part in the metastasis formation by covering and protecting the tumor cells from mechanic damage [25, 26] and the body's immune response [27, 28]. Tumor cells circulating in the vascular system have to face the body's immune response, specifically the NK-cells. Activated platelets adhere to the circulating tumor cells [29] and release PDGF and TGF-β that decrease the activation of the NK-cells [30, 31]. MHC-I molecules expressed on the surface of the platelets impair the recognition of the tumor cells by the immune system [30]. Furthermore, platelets covering the tumor cells promote their adhesion to the endothelial cells. Additionally, embolization of the small vessels with tumor-platelet aggregates makes extravasation faster [25].

Furthermore, elevated platelet count was suggested to stimulate tumor growth and angiogenesis by secreting proangiogenic cytokines [32, 33]. Under normal conditions inactive platelets circulate in laminar blood flow in the vascular system and the endothelial cells hinder the platelets to adhere to the vessel wall. Proangiogenic cytokines released from the tumor cells make the vascular system of the tumor permeable where the physiologic blood flow becomes turbulent. In addition to other factors platelets are activated by their contact to subendothelial structures and the turbulent blood flow. Cytokines released from the activated platelets stimulate the proliferation and migration of tumor cells and promote angiogenesis [25]. The hypothesis that platelet-induced angiogenesis is partially mediated by glycoproteins is supported by the finding of Trikha et al.: they found that the inhibition of

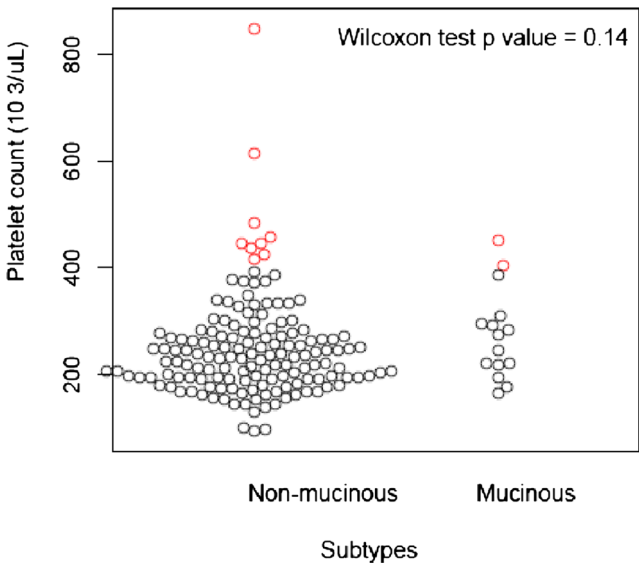

Fig. 3 Comparison of the cases with and without thrombocytosis in non-mucinous and mucinous adenocarcinoma

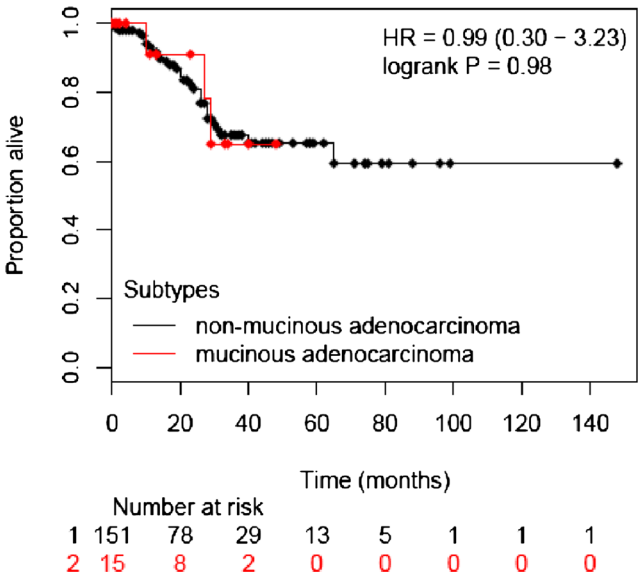

Fig. 4 Comparison of overall survival in the different histopathological subtypes

GPIIb/IIIa on platelets negatively influences endothelial cell proliferation stimulated by platelets. Furthermore, the concomitant inhibition of integrin αβγ3 on endothelial (and tumor) cells and the GPIIb/IIIa on platelets significantly reduced the angiogenesis and melanoma growth in mice [34].

Most recent reports propose thrombocytosis to be a paraneoplastic phenomenon as cytokines secreted by the tumor itself also induce thrombopoiesis [35]. The most promising pathway has been recently described in ovarian cancer [35]. According to the hypothesis ovarian cancer cells secrete IL-6 that stimulates thrombopoietin production in the liver. Thrombopoietin induces platelet production in the bone marrow that leads to thrombocytosis. In several tumor types such as gastrointestinal [36], renal cell [37], prostate [38], epithelial ovarian [39], lung cancer [40] and Kaposi sarcoma [41] elevated IL-6 levels were observed. Tumor cells can also directly secrete IL-6 [25]. Additionally, it was found in c-Mpl knocked-out mice that IL-3, IL-6, IL-11 and LIF restore normal platelet count only in the presence of thrombopoietin [42, 43]. Kaser et al. found in mice that the hepatic thrombopoietin mRNA expression is also increased concomitantly with the IL-6 induced thrombocytosis [44]. Other studies reported in different solid tumors that human recombinant IL-6 accelerates the restoration of platelet count after chemotherapy [45, 46].

If all three hypotheses are true a vicious circle will develop: the platelet count will be raised by the tumor that induces tumor growth, angiogenesis and metastasis formation, which, in turn, will further increase the platelet count [25].

Many authors believe that thrombocytosis in tumors is a reactive phenomenon. Grieshammer found that 643 out of 732 (88 %) surgical patients had reactive thrombocytosis ($\geq 500 \times 10^3/\mu L$). The most common underlying cause was operations with extensive necrosis, infection, tumor and chronic inflammation [47]. Another study reported that thrombocytosis ($\geq 1000 \times 10^3/\mu L$) was reactive in 82 % of patients (231/280), in 4 % (11/280) of uncertain origin and in only 14 % (38/280) myeloproliferative [48]. Reactive thrombocytosis was thought to be correlated with anemia and the consequent iron deficiency caused by the malignant disease. Iron deficiency is a well-known cause of reactive thrombocytosis [49–51]. In order to exclude the phenomenon of reactive thrombocytosis the patients' red blood cell count was also reviewed. None of the patients had anemia or received blood transfusion, therefore, elevated platelet count was not of reactive origin.

Although it is obvious that tumor development has genetic background, the body's inflammatory response plays an important role in carcinogenesis and in tumor progression [52, 53].The tumor can form an inflammatory microenvironment around itself [52, 54, 55] that has a very complex mechanism. One of the potential hypotheses is that hypoxia and tumor necrosis stimulate the inflammatory process [56, 57]. The increased inflammatory response is associated with worse survival in malignant diseases. Elevated C-reactive protein was found to have prognostic value in CRC [58], gastroesophageal [59], pancreatic [60], kidney [61], bladder [62] and non-small cell lung cancer [63]. The CRP was not elevated and no leukocytosis was found in patients included in the current study, therefore, the underlying cause of worse prognosis cannot be attributed to the patients' different immune response.

Carcinoembryonic antigen (CEA) is widely used to monitor tumor progression in CRC. It would be useful to compare the predictive value of this tumor marker with that of thrombocytosis. In our cohort CEA was documented only in a handful of patients, therefore, no such comparison could be made.

Based on our results it can be stated that similarly to other solid tumors thrombocytosis is correlated independently with significantly worse OS and DFS in patients with liver metastasis of colorectal cancer. Our findings lead to the conclusion that preoperative thrombocytosis is a useful factor that can be used to predict the postoperative prognosis of patients with mCRC. The examination is simple, cheap and readily accessible for everyone.

Conflict of Interest None of the authors has conflict of interest.

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