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Original research

Relationship of postoperative thrombocytosis and survival of patients with colorectal cancer

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HIGHLIGHTS

- The predictive power of postoperative thrombocytosis was evaluated, and compared with preoperative thrombocytosis.
- After surgery platelet counts significantly decreased, suggesting a causative link between primary tumor and thrombocytosis.
- Not only preoperative but also postoperative thrombocytosis is predictive for survival, reinforcing the prognostic power of thrombocytosis.

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ABSTRACT

Introduction: Thrombocytosis accompanying solid tumors and predicting the prognosis of malignant tumors has been the subject of intensive research lately. Reports so far have evaluated the role of preoperative platelet count. In our present study we looked at the effect of tumor removal on platelet count and the predictive power of postoperative thrombocytosis on the survival of patients with colorectal cancer (CRC).

Methods: We retrospectively evaluated the clinical and histopathological data of 336 patients operated due to CRC between 2001 and 2011. Thrombocytosis was defined as a platelet count exceeding $400 \times 10^3/\mu L$. Preoperative platelet count was compared with the value measured 1 month postoperatively.

Results: The platelet count significantly decreased after the removal of the primary tumor (paired Wilcoxon test $p < 0.001$). In univariate analysis preoperative thrombocytosis was a significant marker of overall survival (OS) with HR 2.2, $p < 0.001$ while the postoperative thrombocytosis was nearly significant with HR = 1.59, $p = 0.087$. In multivariate setting, when corrected for location, stage, tumor size and controlling for gender and age (>65 years vs. ≤65 years), both pre- and postoperative thrombocytosis were significant independent prognostic markers with HR 1.80, $p = 0.20$ and HR = 1.98, $p = 0.018$, respectively.

Discussion and conclusion: Although the pathomechanism of thrombocytosis related to solid tumors is not known the decrease of platelet count after the removal of the primary tumor raises the possibility that the tumor may play an active role in the development of thrombocytosis. Furthermore, the observation of postoperative thrombocytosis with significant worse outcome underlines the predictive power of elevated platelet count.

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Units and abbreviations

CRC	colorectal cancer
CEA	carcinoembryonic antigen
IL-1	interleukin-1
IL-6	interleukin-6
LMWH	low molecular weight heparin
mRNA	messenger ribonucleoprotein
TPO	thrombopoietin
ULN	upper limit of normal
5-FU	5-fluorouracil
μL	microliter

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancy all over the world. In Europe the age-adjusted incidence in men and women is 12.3% and 13.1%, respectively [1].

During cancer research with novel molecular biology techniques there is emphasis on elucidating the molecular background of the disease and to develop methods for early diagnosis. There is an urge to find biomarkers that may be used to screen for malignant diseases. In oncological practice the ideal help would be if tumor markers identified cancer in its early stages and provided information on tumor growth, disease progression, metastasis formation and the effectiveness of treatment.

Carcinoembryonic antigen (CEA) is the most commonly used tumor marker in the follow-up of CRC. However, this examination has also its limitations partially due to the biological nature of the tumor cells, and partially due to the characteristics of the procedure. Apart from a few exceptions this technique is not suitable for screening or early diagnosis of the tumor, however, it is exceptionally useful and reliable for the follow-up of CRC.

The cornerstone of the therapy of CRC is still the resection of the tumor, however, one third of patients following curative surgery die within 5 years [2]. Therefore, it is essential to find reliable prognostic markers that can predict the outcome of CRC patients who underwent surgery.

Platelets play an important role in several physiological and pathophysiological processes, such as hemostasis, thrombosis, immunological defense mechanisms and the development of inflammation. A possible connection between platelets and cancer was suggested more than a century ago in 1872, when Leopold Riess noticed elevated platelet counts in patients with malignant disease [3]. Since then it has been shown repeatedly that thrombocytosis at the time of diagnosis is associated with tumor invasion, metastatic progression and less favorable survival in several solid tumors [4–8].

There are plentiful reports in the literature on the relationship of solid tumors and thrombocytosis, but they assessed only the preoperative platelet count. We intend to give the first report on the evaluation of the platelet count after the resection of the primary tumor.

2. Material and methods

2.1. Patient data

Clinical, demographic, surgical, histopathological and laboratory data of 357 patients with primary CRC who underwent surgery in Uzsoki Hospital, Hungary, between 2001 and 2011 were reviewed retrospectively (Table 1). The study has been approved by the Committee of Scientific Research Ethics of the Medical Research Council (ETT TUKEB), Hungary, with approval number: 4963-0/2010-1018EKU (328/PI/010). Written informed consent was given by participants for their clinical records to be used in this study. Patients were enrolled only if they underwent R0 resection of the primary (CRC) tumor. Exclusion criteria were as follows: synchronous tumor in addition to the colorectal tumor, steroid therapy and any disease or postoperative complication with inflammation (anastomosis insufficiency, pneumonia, wound infection, abscess formation, urinary tract infection, line infection, endocarditis, cholecystitis, ulcerative colitis, Crohn's disease). Thromboembolic complications were intended to be recorded (heart attack, deep vein thrombosis, embolism, stroke), however, none occurred. Altogether 21 patients were excluded for the reasons above.

Preoperative (within the shortest time, usually 1–2 weeks prior the surgery) and postoperative (1 month after surgery) platelet counts were assessed. In the institute conducting the study laboratory examination is performed routinely 1 month postoperatively (30 ± 4.7 days). It is both part of the surgical follow-up and the establishment of the patients' condition before the initiation of the adjuvant therapy. This laboratory examination was chosen from all other postoperative tests because it was assumed that enough time passed between the surgical intervention and the blood draw in order to exclude the inflammatory effects of the surgery and the interfering effect of the adjuvant therapy as it was not started in any patient.

Thrombocytosis was defined as a platelet count greater than the upper limit of normal (ULN), $400 \times 10^3/\mu L$. During the examined period the test were performed by the same laboratory and with the same technique. Patients' overall survival (OS) started at the date of surgery and ended at the time of death or when the patient was censored.

2.2. Statistical tests

All calculations were made using R version 2.15.0 and packages 'beeswarm', 'survplot', 'survival' and 'stats'. If not stated otherwise statistical tests between two groups were performed using the Wilcoxon rank sum test. To compare more than two groups the Kruskall–Wallis rank sum test was used. To compare pre- and postoperative platelet levels the Wilcoxon signed rank test was used.

2.3. Survival analysis

Survival curves were estimated using the Kaplan–Meier method. Hazard ratios with 95% confidence intervals were obtained using Cox proportional hazards regression. The relationships between the platelet count and the various clinical parameters were investigated using uni- and multivariate Cox regression adjusted for tumor stage, grade, location (given as: 'colon' and 'rectum') and anemia (red blood cell count $< 3.9 \times 10^6/\mu L$).

3. Results

The clinical cohort showed a balanced distribution (Table 1) in terms of stage, sex and age. The mean age was 66.9 years and it slightly varied across the stages (Table 1). The distribution of patients regarding stages was even, with a slight underrepresentation of stages I and IV.

Neoadjuvant chemoradiotherapy was administered only in patients with rectal cancer (57 out of 115) and 43 of them received 5-fluorouracil (5-FU). We found no correlation between the neoadjuvant 5-FU administration and the predictive role of thrombocytosis.