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Thrombocytosis portends adverse prognostic significance in patients with stage II colorectal carcinoma

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(Article begins on next page)



OBSERVATION ARTICLE

REVISED

Thrombocytosis portends adverse prognostic significance in patients with stage II colorectal carcinoma [v2; ref status: indexed, <http://f1000r.es/4k6>]

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Abstract

Thrombocytosis portends adverse prognostic significance in many types of cancers including ovarian and lung carcinoma. In this study, we determined the prevalence and prognostic significance of thrombocytosis (defined as platelet count in excess of $400 \times 10^3/\mu\text{l}$) in patients with colorectal cancer. We performed a retrospective analysis of 310 consecutive patients diagnosed at our Institution between 2004 and 2013. The patients (48.7% male and 51.3% female) had a mean age of 69.9 years (+/- 12.7 years) at diagnosis. Thrombocytosis was found in a total of 25 patients, with a higher incidence in those with stage III and IV disease (14.4% of patients). Although the mean platelet count increased with the depth of tumor invasion (pT), its values remained within normal limits in the whole patient cohort. No patient with stage I cancer (n=57) had elevated platelet count at diagnosis. By contrast, five of the 78 patients (6.4%) with stage II cancer showed thrombocytosis, and four of these patients showed early recurrence and/or metastatic disease, resulting in shortened survival (they died within one year after surgery). The incidence of thrombocytosis increased to 12.2% and 20.6%, respectively, in patients with stage III and IV disease. The overall survival rate of patients with thrombocytosis was lower than those without thrombocytosis in the stage II and III disease groups, but this difference disappeared in patients with stage IV cancer who did poorly regardless of their platelet count. We concluded that thrombocytosis at diagnosis indicates adverse clinical outcome in colorectal cancer patients with stage II or III disease. This observation is especially intriguing in stage II patients because the clinical management of these patients is controversial. If our data are confirmed in larger studies, stage II colon cancer patients with thrombocytosis may be considered for adjuvant chemotherapy.

Open Peer Review

Referee Status:

	Invited Referees	
	1	2
REVISED		
version 2	report	report
published 20 Oct 2014	↑	↑
version 1		
published 31 Jul 2014	report	report

- Ioannis A. Voutsadakis**, Sault Area Hospital Canada
- Judit Moldvay**, Semmelweis University Hungary

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REVISED Amendments from Version 1

We are grateful to the referees for their time and efforts in improving our manuscript. Whereas we share some of the reservations of the referees, we would like to point out that this is an Observational Study and not a full report. We agree that our observations need to be confirmed in a much larger cohort of patients (indeed, we emphasize this upfront in the Abstract). That said, we believe that despite the study limitations our conclusions are sound enough for publication as a preliminary report.

In the revised version, major changes include:

- 1) The major limitations of this study (small number of patients in the stage II group; no information on ethnicity, smoking history, medications and/or comorbidities) are now clearly stated in Patients and Methods.
- 2) The discrepancy in patient numbers between text/Tables and Figure 2 is now explained: our database contained 310 patients, however, our Cancer Registry contained survival data only on 253 of these patients (the remaining 57 patients most likely decided to seek treatment at another medical facility and were, thus, lost to our follow-up).
- 3) Multivariate analysis was done (see Results). With regard to tumor location (right-sided versus left-sided cancer), the results are now detailed in the text.
- 4) Reactive thrombocytosis is now defined and its most common causes are listed in Introduction.
- 5) Reference range as well as mean platelet count (\pm SD) are now given for the two patient groups (with and without thrombocytosis).
- 6) As suggested, both Abstract and Discussion have been modified by changing "treated as stage III" to "may be considered for adjuvant chemotherapy".

See referee reports

Introduction

Platelets play important roles in hemostasis, immunity and inflammation¹. Reactive thrombocytosis is an elevated platelet count ($> 400 \times 10^3/\mu\text{l}$) that develops secondary to another disorder. Some causes of reactive thrombocytosis include iron deficiency, acute infection, and chronic inflammatory disorders (<http://www.patient.co.uk/doctor/thrombocytosis>). Cancer is often associated with paraneoplastic thrombocytosis². Thrombocytosis was reported as a poor prognostic indicator in many types of cancers including lung cancer³, renal cell carcinoma⁴ and gynecological cancers⁵. A positive correlation between the depth of tumor invasion and platelet counts was demonstrated in a gastric cancer study, and thrombocytosis served as an adverse prognostic factor in clinical outcome in gastric cancer patients⁶. Recent studies have shown that thrombocytosis in cancer may be correlated with serum cytokine levels that stimulate thrombopoiesis. For example, elevated plasma levels of IL-6 and thrombopoietin were reported in ovarian cancer patients⁵.

Colon cancer is a leading cause of cancer-related death in developed countries (<http://seer.cancer.gov/statfacts/html/colorect.html>). A significant portion of patients receiving potentially curative resection dies within five years of diagnosis⁷. Since both chemo- and radiation therapies cause very significant side-effects, it is critical to define reliable prognostic factors to identify patients who might benefit from more aggressive adjuvant treatment options. The prognostic role of thrombocytosis in colorectal cancer patients has not

been fully investigated, although there are some reports supporting the negative impact of thrombocytosis on the survival of patients with colorectal cancer^{8,9}.

In this study, the aim was to analyze the association between platelet count at diagnosis or pre-surgery and cancer stage, and to determine the prognostic significance of thrombocytosis in patients with colorectal cancer.

Patients and methods

After approval by the Monmouth Medical Center Institutional Research Review Board (IRB Study # 213-041), the medical records of 310 consecutive colorectal cancer patients who underwent biopsy (47 patients), surgical resection and/or neoadjuvant treatment (263 patients) at our Institution between 2004 and 2013 were retrospectively reviewed. The patient cohort included 62 patients with *in-situ* or stage I disease, 78 patients at stage II, 98 patients at stage III, 34 patients at stage IV, and 38 patients with biopsy diagnosis only (stage could not be determined). The mean age of the patients was 69.9 ± 12.7 years (range = 32 to 98 years). The data gathered included platelet counts, tumor location, histological type and differentiation, lymph node metastasis, depth of tumor invasion (T), and presence or absence of distant metastasis. The database did not include ethnicity, smoking habits, and comorbidities.

Pre-operative platelet counts were collected from our Laboratory Information System (LIS), and thrombocytosis was defined as platelet count $\geq 400 \times 10^3/\mu\text{l}$ (normal range = 150 to $400 \times 10^3/\mu\text{l}$). After resection of the tumor, all specimens were histologically examined by a pathologist and the pathological TNM stage was determined according to the American Joint Committee on Cancer, 7th edition. Stage I and II cancers are lymph node negative (N0) whereas stage III is defined by the presence of lymph node metastasis. Patients with distant metastatic disease are classified as stage IV.

Survival data for 253 patients were provided by the Cancer Registry at the Leon Hess Cancer Center, Monmouth Medical Center (57 patients were lost to follow-up). 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. Long-rank test was used for the analysis of significance.

Results

The characteristics (including age, gender, pT stage, tumor differentiation and platelet count) of the patients in our study cohort are shown in Table 1. Of the 310 patients with colorectal cancer, 25 (8.1%) had thrombocytosis at diagnosis or pre-surgery with the highest incidence detected in stage IV patients (20.6%) [Table 2]. Importantly, none of the 57 patients with stage I carcinoma had elevated platelet count. The mean platelet counts ($\times 10^3/\mu\text{L}$) in patients with or without thrombocytosis were 494.7 ± 83.0 and 246.2 ± 72.3 , respectively.

Although the mean platelet count increased with the depth of invasion (pT), it remained within the normal limits in all patients groups (pT1 to pT4) [Figure 1]. Mean platelet counts ($\times 10^3/\mu\text{L}$) were

Table 1. Patient characteristics.

	Number (%)
Total	310
Gender	
Male	151 (48.7%)
Female	159 (51.3%)
Age	69.9 ± 12.7 years ^a
Pathologic category of primary tumor (pT) ^b	
pTis	5 (1.6%)
pT1	17 (5.5%)
pT2	60 (19.4%)
pT3	137 (44.2%)
pT4	44 (14.2%)
pTx (unclassified)	47 (15.2%)
Grade ^c	
well differentiated	42 (13.5%)
moderately differentiated	149 (48.1%)
poorly differentiated	67 (21.6%)
unclassified	52 (16.8%)
Platelet count (× 10 ³ /μL)	
≥ 400	25 (8.1%)
< 400	285 (91.9%)

a: Data presented as mean ± SD; b: staging according to AJCC Cancer Staging Manual 7th Edition); c: Grading according to WHO grading system

216 ± 71 (pT1), 252 ± 83 (pT2), 274 ± 109 (pT3), and 291 ± 104 (pT4); this increase was significant at P = 0.001. By contrast, in multivariate analysis, there were no significant differences in thrombocytosis with regard to gender, age, location, or tumor differentiation (data not shown). For example, our database included 193 patients with right-sided (from cecum to splenic flexure) and 102 patients with left-sided (from splenic flexure to rectosigmoid colon) cancer. Furthermore, we had one patient with rectal adenocarcinoma and 14 patients with metastatic (stage IV) colorectal carcinoma of unknown (at least to us) primary location. Fourteen of the 193 patients with right-sided (~7%) and 8 of the 102 patients with left-sided (~7%) carcinoma showed thrombocytosis at diagnosis, indicating that thrombocytosis is not predictive of the location of the tumor (right- versus left-sided).

The combined incidence of thrombocytosis in stage III and IV disease was 14.4%. Stage II disease had the lowest incidence (6.4%) and stage IV cancer showed the highest incidence of elevated platelet count (20.6%) [Table 2]. The overall survival of patients with stage I to stage III colorectal cancer with thrombocytosis was significantly lower than those without thrombocytosis [Figure 2]. Although patients with Stage IV carcinoma had the highest prevalence of thrombocytosis, these patients did uniformly poorly and the difference in survival was no longer observed in patients with or without elevated platelet count (not shown). Patients with thrombocytosis (PLT ≥ 400 × 10³/μL) at stage I to stage III had a hazard ratio of 2.2 compared to the patients without thrombocytosis (PLT < 400 × 10³/μL) as shown in Figure 2.

Dataset 1. Data of thrombocytosis in colon cancer patients

<http://dx.doi.org/10.5256/f1000research.4856.d33371>

This data set contains the medical records of patients diagnosed with colon cancer at the Monmouth Medical Center between 2004 and 2013.

Table 2. Incidence of thrombocytosis in each stage of colorectal cancer.

	Number of cases with thrombocytosis	Number of cases without thrombocytosis	Total number of cases	% of thrombocytosis
Stage 0	0	5	5	0.0
Stage I	0	57	57	0.0
Stage II	5	73	78	6.4
Stage III	12	86	98	12.2
Stage IV	7	27	34	20.6
Stage X (unclassified)	1	37	38	2.6
Overall	25	285	310	8.1
*Stage IV and III combined	19	113	132	14.4

Note: There are 403 cases in our data pool. 310 cases were diagnosed as colon cancer among the 321 cases with available platelet counts (82 cases without platelet counts). 11 non-colorectal cancer cases including 5 cases labeled as "appendix" and 6 cases labeled as "not colon cancer" were taken out of the pool.

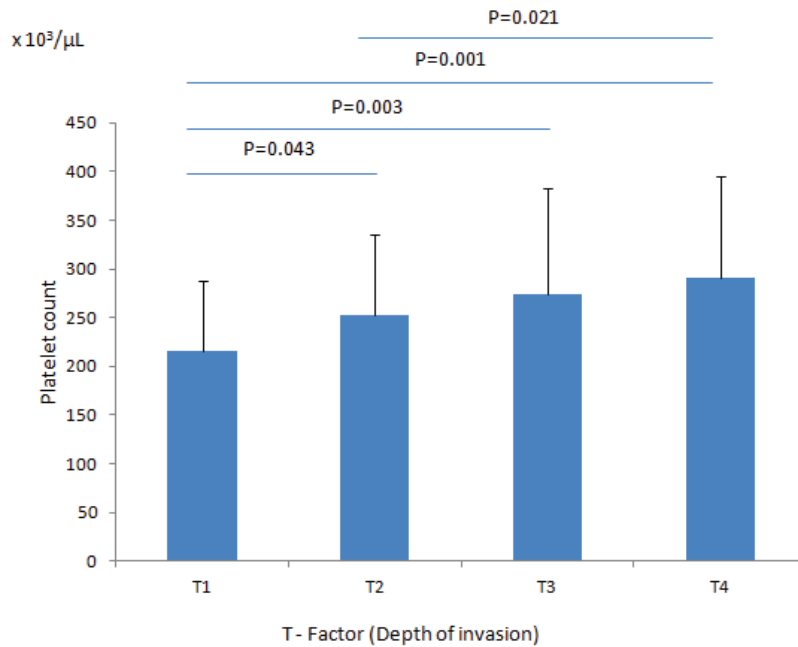


Figure 1. Mean platelet count according to the depth of tumor invasion. The mean platelet count of patients with pT1, $(216 \pm 71) \times 10^3/\mu\text{L}$ is significantly lower than patients with pT4 $(291 \pm 104) \times 10^3/\mu\text{L}$, $P = 0.001$.

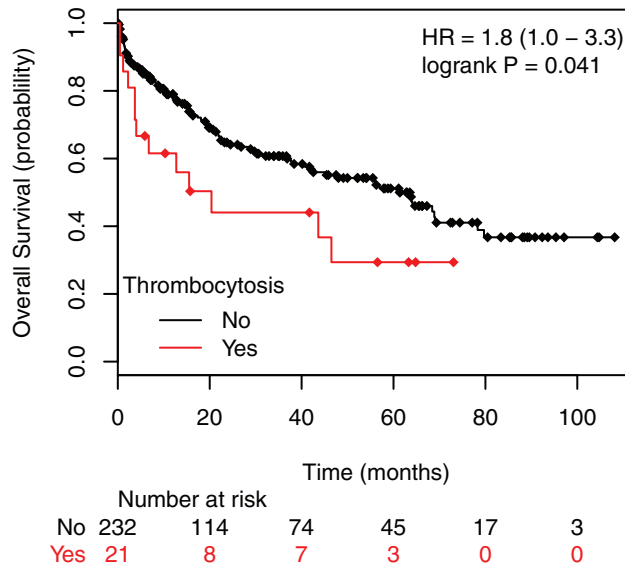


Figure 2. Overall survival plots of patients with stage I to stage III colorectal cancer according to the preoperative platelet counts. Patients were allocated into two groups: with thrombocytosis, $\text{PLT} \geq 400 \times 10^3/\mu\text{L}$ (labeled as Exceeds) and without thrombocytosis) $\text{PLT} < 400 \times 10^3/\mu\text{L}$ (labeled as Normal). The patients with thrombocytosis have a hazard ratio of 1.8 compare to the patients without thrombocytosis ($P < 0.041$).

Discussion

It was noted more than 100 years ago that thrombocytosis is often seen in patients with malignant diseases. Indeed, thrombocytosis correlates with both worse disease free survival and shortened overall survival in patients with ovarian cancer⁵, and worsens overall survival in patients with gastric cancer (reviewed in 10). The prognostic significance of thrombocytosis in colorectal cancer, however,

remains controversial¹¹, although the majority of literature suggests a negative impact of thrombocytosis on the survival of patients with colorectal cancer^{8,9}.

In the present study, we identified a mild, T stage-dependant increase in mean platelet counts in patients with colorectal carcinoma that reached statistical significance when comparing T1 to T4;

however, the mean platelet count remained within the normal limits in the whole patient cohort. Importantly, thrombocytosis was more common among patients with advanced disease: its prevalence increased from 6.4% in stage II to 20.6% in stage IV cancer patients. Our data are comparable to those reported in the literature (12.1–13.9%;^{7,8}).

In our study, thrombocytosis showed adverse prognostic significance in patients with stage I to stage III colorectal carcinoma; this was no longer apparent in patients with stage IV disease, presumably because these patients did poorly regardless of the platelet count.

Probably the most intriguing observation of our study is the fairly uniformly dismal clinical outcome of stage II patients with thrombocytosis (five out of 78 patients): four of these five patients did very poorly (they died within a year) and the fifth was lost to follow-up. At present, the National Comprehensive Cancer Network guidelines do not recommend routine administration of adjuvant chemotherapy to stage II colorectal cancer patients whose cancer was completely resected¹². Clearly, the small number of patients in this group precludes a definitive conclusion. However, if confirmed in future larger studies, our data indicate that stage II colorectal cancer patients with thrombocytosis may benefit from adjuvant chemotherapy.

The molecular mechanisms underlying thrombocytosis in cancer patients are incompletely understood. Recently, plasma levels of IL-6 and thrombopoietin were found to significantly correlate with platelet counts in ovarian cancer patients⁵. Indeed, silencing of the IL-6 and thrombopoietin genes markedly abrogated thrombocytosis (and halted tumor progression) in a mouse model of epithelial ovarian cancer⁵. These findings are promising because an anti-IL-6 agent (siltuximab) has already been approved by the United States Food and Drug Administration (FDA) to treat patients with Castleman's

disease (<http://www.cancer.org/cancer/new/fda-approves-sylvant-siltuximab-for-castleman-disease>). Another series of study showed that immobilized platelets support human colon carcinoma cell tethering, rolling, and firm adhesion under dynamic flow conditions in colon cancer cell lines, suggesting a role of platelets in hematogenous dissemination of tumor cells in colorectal cancer¹³. Taken together, these studies imply that inhibition of thrombocytosis may represent a potential novel target in cancer therapy.

In summary, thrombocytosis appears to herald adverse clinical outcome in patients with stage II and III colorectal carcinoma. We suggest that elevated platelet count may identify a subset of patients with stage II colon cancer who could benefit from close follow-up and adjuvant chemotherapy.

Data availability

F1000Research: Dataset 1. Data of thrombocytosis in colon cancer patients, [10.5256/f1000research.4856.d33371](https://doi.org/10.5256/f1000research.4856.d33371)¹⁴

Author contributions

Tianhua Guo: collected data.

Marcin Krzystanek: analysed data.

Zoltan Szallasi: initiated project, supervised data analysis.

Arpad Szallasi: supervised project, prepared MS.

All authors revised the manuscript and agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this study.

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Open Peer Review

Current Referee Status:



Version 2

Referee Report 10 November 2014

doi:[10.5256/f1000research.5910.r6678](https://doi.org/10.5256/f1000research.5910.r6678)



Ioannis A. Voutsadakis

Medical Oncology, Sault Area Hospital, Ontario, Canada

The report is now acceptable for indexing.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 27 October 2014

doi:[10.5256/f1000research.5910.r6456](https://doi.org/10.5256/f1000research.5910.r6456)



Judit Moldvay

Department of Pulmonology, Semmelweis University, Budapest, Hungary

The Authors have corrected the manuscript according to the referees' comments and completions, therefore, this revised manuscript is acceptable for indexation.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Version 1

Referee Report 06 October 2014

doi:[10.5256/f1000research.5184.r6229](https://doi.org/10.5256/f1000research.5184.r6229)



Judit Moldvay

Department of Pulmonology, Semmelweis University, Budapest, Hungary

It is an interesting work providing new information on the issue of thrombocytosis in colon cancer patients. It contains relevant clinicopathologic parameters, however, there is no data on ethnicity, smoking habits, inflammatory processes, comorbidities, or medications of the studied patients, all which might have impact on platelet count (Msaouel *et al.*, 2014).

The main factors that can influence the platelet count should at least be discussed.

In Figure 1. the Authors discussed the mean platelet count according to the depth of tumor invasion. Although it might change statistically significantly, the mean platelet count remains much within the normal range, therefore, the conclusion that "... we identified a mild, T stage-dependant increase in mean platelet count ..." is not well-founded.

One of the most critical aspects of the investigation is the number of patients, especially in stage II, as disproportionately firm conclusions have been drawn regarding correlation between overall survival and thrombocytosis on the basis of only four patients with thrombocytosis in stage II.

Another weakness of the study is the lack of information on the precise localizations of the primary tumors, as this in itself may be of prognostic value, e.g. Majek *et al.* (2012) .

Although neoadjuvant treatment has been mentioned, it was not discussed in details, similarly, adjuvant treatments in advanced cases were not detailed either. These issues should be discussed in the "Discussion".

In Figure 2. the value of HR is not in accordance with the HR in the legend.

In the 4th line of the Discussion there is a mistake with the Ref. 3., this – most probably – is the Ref. 5.

Similarly, in the 18th line of the Discussion the Ref. 6. – most probably – is the Ref. 8.

In conclusion, this study yielded clinically very interesting results that might have therapeutic consequence, however, these results need to be confirmed in a much larger cohort of colorectal patients.

All in all, in my opinion this manuscript is acceptable for indexation, but only after corrections and completions based on the above mentioned comments.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response (Member of the F1000 Faculty) 13 Oct 2014

Arpad Szallasi, Department of Pathology, Monmouth Medical Center, USA

Whereas we share some of the reservations of the referee, we would like to point out that this is an Observational Study and not a full report. We believe that despite the limitations of this study, this is an interesting observation with potential implications for patient management. That said, we wholeheartedly agree with the referee that "these results need to be confirmed in a much larger

cohort of colorectal patients."

Changes done in response to points raised by the referee in the revised MS include:

1. Our study has a number of limitations such the lack of data on ethnicity, smoking habits, comorbidities, or medications: this is now clearly stated in Patients and Methods. We believe that such a detailed, multifactorial analysis would surpass the confines of a preliminary Observational Report. Of note, the patient database is available for review for the interested reader (please follow link under Reference 14 to "data source").
2. The most common causes of reactive thrombocytosis are now briefly listed in the Introduction.
3. The statement between platelet count and depth of invasion has been toned down - the reference to significance has been eliminated.
4. As emphasized in the MS, our conclusions are preliminary and are based on a limited number of patients. It is our hope that our findings will be confirmed (or refuted) based on a much larger patient cohort.
5. The localization of the primary tumor (right-sided versus left-sided) seems to have no impact on the presence or absence of thrombocytosis: both groups had an incidence of ~7%. This is now clearly stated in Results.
6. References have been corrected.

Competing Interests: None

Referee Report 14 August 2014

doi:[10.5256/f1000research.5184.r5655](https://doi.org/10.5256/f1000research.5184.r5655)



Ioannis A. Voutsadakis

Medical Oncology, Sault Area Hospital, Ontario, Canada

This is an interesting retrospective study of an extensive series of colorectal cancer patients and authors are to be congratulated on undertaking this academic endeavour. Nevertheless there are several points that need to be addressed. A major concern is that all stages of the disease have been included. In general a comparison between stage I and IV, for example, has no meaning clinically and the only statement that one can make is that thrombocytosis is more common. Another major concern is that no multivariate analysis is done or presented.

Some other specific points:

- The title mentions specifically stage II disease (as the authors probably recognize the importance of prognostic factors in this sub-group for therapeutic decisions) but no statistical comparison is offered anywhere in the article. In any case the number of patients with thrombocytosis in this group (5) is prohibitive for definite conclusions.

- In the last line of the Abstract and in the Discussion it should be: “*treated as stage III*” or even better “*considered for adjuvant chemotherapy*” (stage IV patients are treated with palliative intent).
- Data on tumor grade and location have been collected (dataset) but not summarized or presented in the article. It would be of particular interest to present and include in an eventual multivariate analysis tumor location (right versus left from the splenic flexure versus rectal).
- In Patients and methods the normal range of platelets in authors’ institution should be mentioned.
- In the Results it would be interesting to provide the mean and SD of the platelet number in the 2 groups (normal and thrombocytosis).
- In fig. 2 there is a discrepancy between HR and p values in the body and the legend. In addition the numbers at risk do not match. Is that a mistake in calculations or data missing? Authors should address this.
- In the 4th line of the 1st paragraph of the Discussion” the reference does not seem to be correct. Same with reference 6 in the 2nd paragraph.
- In the discussion on metastatic patients - this is an over-simplification. If any useful comparison is to be made, other data have to be entered in the equation such as oligometastatic versus polymetastatic disease and treatments.
- Treatments should be mentioned. For example have all stage III patients received adjuvant chemotherapy? And have any of the stage II patients received any such treatment?
- In the 4th paragraph of the Discussion the explanation of “*false negative node examination*” is improbable as there is no reason to suspect that such false negative occurs more commonly in patients with thrombocytosis. Instead a difference in biology as briefly discussed in the next paragraph is more probable.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response (Member of the F1000 Faculty) 13 Oct 2014

Arpad Szallasi, Department of Pathology, Monmouth Medical Center, USA

We are grateful for the referee for his thoughts in making this a better MS. Whereas we agree with most of the reservations of the referee, we would like to point out that this is an Observation Study, and not a full report. We believe that despite the limitations of our study, our conclusions are sound and (if confirmed) may have important implications for patient management.

Major changes done in response to points raised by the referee include:

1. We agree with the referee that the small number of patients (5) in the stage II group precludes a definitive conclusion; this is now clearly stated in the MS. Again, this is an

Observational Study within the confines of our hospital database on colorectal carcinoma patients.

2. Both the Abstract and the Discussion have been modified as suggested by the referee ("treated as stage III" has been changed to "may be considered for adjuvant chemotherapy").
3. The multivariate analysis with special regard to the location of the tumor (right-sided versus left-sided) is now detailed in the Results.
4. The normal range of platelets at our Institution (150 to 400 K/ul) is now provided in the MS.
5. The mean +/-SD of the platelet counts in the two patient groups (with and without thrombocytosis) is now provided in Results.
6. Indeed, there is a discrepancy between the body of the text and Figure 2 with regard to the patient numbers; this should have been addressed before to avoid any confusion. As clearly stated now in Patients and Methods, our database included 310 patients. Of these patients, our Cancer Registry had long-term survival data on 253 patients (hence the discrepancy): the remaining 57 patients most likely decided to seek treatment at a different facility.
7. References have been corrected.
8. Discussion on metastatic patients has been modified.
9. Unfortunately, our Cancer Registry has no full details on chemotherapy regimens (some of our patients receive chemotherapy in a private practice setting).
10. The reference to "false negative node examination" has been eliminated.

Competing Interests: None
