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Is there a role for pre-operative thrombocytosis in the management of colorectal cancer?☆

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Background: High circulating platelet counts have been associated with poor prognosis in a variety of solid tumours such as breast, renal and lung cancer. We investigated the significance of a high pre-operative platelet count on overall survival in patients with stages I–IV colorectal cancer.
Patients and methods: 630 Consecutive patients who colorectal cancer resection between 2004 and 2007 with a full blood count taken 14 days prior to the surgery were assessed. Male:female 7:5, median (range) age 73 (40–99 years). Thrombocytosis was defined as platelet count of $\geq 450 \times 10^9$/L. The relationship between platelet count, pathological features and overall survival was assessed.
Results: : Mantel–Cox regression showed that platelet count does not predict survival on multivariate analysis ($p = 0.067$). Thrombocytosis was present in 51/627 (8.1%) of cases. There was no statistically significant difference in mean survival ($p = 0.067$) observed in patients with platelet count $<450 \times 10^9$/L ($n = 576$; 95%CI: 1550.5–1405.4 SE 37.0) versus $\geq 450 \times 10^9$/L ($n = 51$, CI: 1261.6–955.0, SE 78.2). There was also no correlation between Dukes stage and thrombocytosis.
Conclusion(s): In our study, pre-operative thrombocytosis is not a prognostic indicator of survival in colorectal cancer patients regardless of pathological stage.

1. Introduction

Colorectal adenocarcinoma is a very common tumour and a leading cause of cancer death in the UK.[1,2] Surgical resection remains the only option for long-term survival. Multiple factors significantly affect survival in resected patients, including lymph node status, resection margins, tumour differentiation, and adjuvant treatment.

Various studies have associated thrombocytosis with poor survival in breast,[3] gastric, oesophageal,[4] colorectal,[5] pancreatic, renal,[6–8] gynaecologic,[9] and lung malignancies.[10] Thrombocytosis may be excited by proteolysis of the basement membrane and neo-angiogenesis, processes common in colorectal cancer.[11–13] Thrombocytosis has been evaluated in colorectal cancer, but the results have been often conflicting and have included limited patient numbers. The aim of the present study was to evaluate the prognostic relevance of pre-operative platelet count in a large cohort of patients with resected colorectal cancer.

2. Methods

We performed a retrospective review of 629 consecutive patients presenting with pathologically proven colorectal cancer between Jan 2004 and Dec 2007. Demographic, surgical, pathologic, and laboratory variables were collected. Patients who were diagnosed with colorectal cancer during the study period were identified from a database of colorectal cancer patients. All patients, including those who did not undergo any surgical procedure were included. The database is prospectively maintained and all patients are followed-up regularly by a team of colorectal nurse specialists. Age, sex, mode of presentation (emergency or elective), Dukes stage, TNM Classification and neo-adjuvant therapy were recorded for all patients.

Thrombocytosis was defined as platelet count of $\geq 450 \times 10^9$/L. All the patients were followed-up for at least 18 months post-operatively by the time of data collection. Overall survival and cancer-specific survival were recorded.

2.1. Statistical analysis

Results are presented as either median (with range) or mean (with standard deviation) for non-parametric and parametric data respectively. Chi-square was used for categorical variables and

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Table 1
Summary of patient demographics.

Parameter		Number of patients (%)
Age		73 (40–99) years (Median (range))
Site of tumour		
Colon	288	(46%)
Rectum	341	(54%)
Dukes' stage		
A	72	(11.4%)
B	294	(46.7%)
C	212	(33.8%)
D	15	(2.4%)
In-situ	36	(5.7%)

Student's *t*-test or the Mann–Whitney *U*-test were used for continuous variables with parametric or non-parametric distributions, respectively, after exploration analysis of normality. Potential prognostic factors were entered into univariate Kaplan–Meier models of intercurrent death and cancer-specific death and compared by the log-rank test in order to identify potential prognostic factors. Significant prognostic factors identified from the univariate analysis were entered into a multivariate Mantel–Cox regression model of survival to test for independence. The 5% level was considered significant.

3. Results

3.1. Patients

A total of 629 patients met the inclusion criteria (2 patient data unavailable), male:female 7:5; patient demographics are shown in Table 1. Thrombocytosis was defined as platelet count of $\geq 450 \times 10^9$/L. Overall median (range) age was 73 (40–99 years). Median age of patients with platelets $<450 \times 10^9$/L − 71.94 years and those with platelets $>450 \times 10^9$/L was 72.4 years. The relationship between platelet count, pathological features and overall survival was assessed in a multivariate model. At the last follow-up (31 July 2009) median time period of follow-up was 22 months (range 9–60), 474/627 patients (75.6%) were alive; and 153/627 (24.4%) had died.

3.2. Survival

Overall survival stratified by Dukes stage is shown in Table 2. Mantel–Cox regression showed that platelet count is not an independent marker of survival on multivariate analysis ($p = 0.067$). Thrombocytosis was observed in 51/627 (8.1%) of cases and its presence was not associated with extramural vascular invasion ($p = 0.058$, Fisher's Exact Test).

All the survival data collected as part of our study passed normality tests. A detailed analysis of platelet count stratified by Dukes stage is shown in Table 3. Patients with thrombocytosis did not have any significant difference in overall mean survival, (CI: 1384.74, 1067.25 SE 80.99, $p = 0.067$, Mantel–Cox). There is no statistically significant difference in mean survival ($p = 0.067$) (Fig. 1) observed in patients with platelet count $<450 \times 10^9$/L ($n = 576$ of 627; 95%CI: 1550.5–1405.4 SE 37.0) versus $\geq 450 \times 10^9$/L ($n = 51$ of 627, CI: 1261.61–955.05, SE 78.2, Mantel–Cox) (Fig. 2). By univariate analysis, Dukes staging, T staging, metastatic lymph nodes, and vascular invasion were associated with poor survival (Table 4).

Table 2
Overall survival of patients with resected colorectal adenocarcinoma (measured to 31 July 2009).

Dukes stage	Mean survival in months	Std. Error	95% Confidence interval	
			Lower bound	Upper bound
A	55.277	2.299	50.771	59.783
B	53.238	1.445	50.405	56.070
C	46.662	1.637	43.454	49.871
Overall	51.961	1.055	49.893	54.028

Table 3
Platelet count of patients stratified according to Dukes staging.

Dukes stage	Mean survival in weeks	N	Std. Deviation
A	240.06	71	73.207
B	307.30	294	115.991
C	292.26	175	113.423
D	320.87	15	65.124
Total (overall)	295.36	592	110.930

4. Discussion

The presence of thrombocytosis in some solid tumours has been associated with poor prognosis. The state of cancer is strongly associated with hypercoagulability, which is due to direct influence of the cancer cells themselves and various indirect mechanisms not fully explained by releasing endothelial and tumour cell-based proteolytic enzymes, thrombocytosis contributes to the process of proteolysis of basement membrane.[12,14] Due to unknown mechanisms, several studies noted an increased platelet count in the presence of malignancy, often thought of as a paraneoplastic syndrome. This study shows no relationship between pre-operative platelet count and survival.

Previous smaller studies reported association between platelet count and survival. Monreal et al. (1998)[5] found that in their cohort of 180 consecutive patients, a high pre-operative platelet level (RR: 2.467; 95%C.I.: 1.117–5.452) independently predicted poor prognosis. In another study, Tweedle et al.[15] (398 patients) found that thrombocytosis was observed in 39/398 (9.8%) of cases and its presence was associated with extramural vascular invasion, depth of tumour invasion and lymph node involvement. They also reported a significant reduction in survival of patients with thrombocytosis from 41 months to 15 months in those without

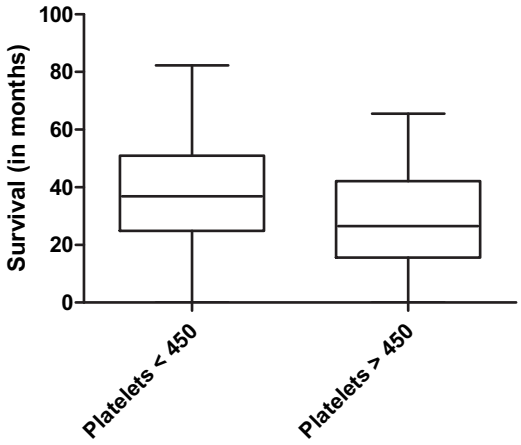

Fig. 1. Box-whisker plot showing survival in patients with higher and lower pre-operative platelet count.

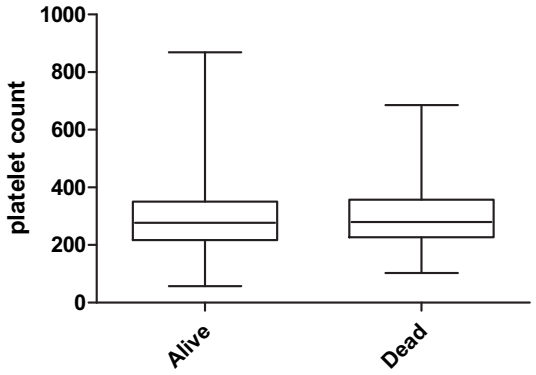

Fig. 2. Platelet count stratified by the event of death.

Table 4
Clinicopathological characteristics and survival.

Factor	Chi-Square	df	Sig.
T Category	14.423	1	.0001
N Category	8.880	1	.003
Dukes stage	8.377	1	.004
Vascular invasion	2.891	1	0.046
Thrombocytosis	9.261	1	0.067

($p < 0.0001$, Mantel–Cox). These findings were not supported in our larger series of patients.

In summary, this large cohort of patients with adenocarcinoma of the colon and rectum, with complete follow-up shows no statistical evidence to support that pre-operative platelet count is an adverse prognostic factor. The follow-up period for patients with colorectal cancer in our study is limited. Although a longer follow-up (>5years) or higher platelet cut-offs could potentially show a difference in survival, the number of patients needed to demonstrate this would be very large. In our series of over 600 patients, we have demonstrated a lack of association between thrombocytosis and survival from colorectal cancer.

Conflict of interest

None to declare.

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Ethical approval

None declared.

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