

## Paraneoplastic thrombocytosis is associated with increased mortality and increased rate of lymph node metastasis in oesophageal adenocarcinoma



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### Summary

Paraneoplastic thrombocytosis has been associated with adverse outcomes in several cancers, but has not been described in oesophageal adenocarcinoma. The aim of our study was to examine the prognostic value of platelet counts in patients with oesophageal adenocarcinoma.

A cohort of 584 patients who underwent oesophagectomy for oesophageal adenocarcinoma was identified. Platelet counts, history of neoadjuvant chemoradiation, and clinicopathological factors such as T and N stage, and overall survival were recorded.

Patients with elevated platelet count (>450,000/ $\mu$ L) had a higher mortality rate than patients with normal platelet count (150,000–450,000/ $\mu$ L) (hazard ratio = 2.60,  $p$  = 0.0013). This effect was seen in patients with and without neoadjuvant chemoradiation therapy. Paraneoplastic thrombocytosis was also associated with increased likelihood of lymph node metastasis compared to normal platelet count (69% versus 31%,  $p$  < 0.01).

Paraneoplastic thrombocytosis is associated with increased rate of lymph node metastasis and mortality in oesophageal adenocarcinoma. Further studies are needed to examine the mechanisms behind this phenomenon.

**Key words:** Paraneoplastic thrombocytosis; platelet count; mortality; lymph node metastasis; oesophageal adenocarcinoma.

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### INTRODUCTION

Routine clinical laboratory studies often serve as prognostic or predictive markers in various types of cancer. Paraneoplastic thrombocytosis has been reported to be an independent prognostic factor for clinical outcome in a variety of human tumours such as lung cancer,<sup>1</sup> colon cancer,<sup>2</sup> ovarian cancer,<sup>3</sup> renal carcinoma,<sup>4</sup> and oesophageal squamous cell carcinoma.<sup>5,6</sup> While the underlying mechanism that explains the association between thrombocytosis and unfavourable outcome is unclear, recent studies suggest that platelets may guide the formation of early metastatic niches, which facilitates metastasis, which leads to faster disease progression.<sup>7</sup>

Even in the absence of a clear aetiology, the fact that thrombocytosis is an independent prognostic factor in early

stage disease raises the possibility that this simple laboratory test may help stratify patients who might benefit from aggressive treatment. Therefore, it is clinically relevant to identify all types of cancer in which thrombocytosis is an independent prognostic factor. Although the significance of paraneoplastic thrombocytosis has been investigated in oesophageal squamous cell carcinoma,<sup>5,6</sup> early and quite limited studies in oesophageal adenocarcinoma have not found a significant association with outcome. In our current study, we investigated the potential prognostic value of increased platelet counts in a large cohort of patients with oesophageal adenocarcinoma.

### MATERIALS AND METHODS

The study group consisted of 584 patients, derived from a series of 862 consecutive patients with oesophageal adenocarcinoma who underwent oesophagogastrectomy at Brigham and Women's Hospital between 1988 and 2009, either with or without pre-operative neoadjuvant chemoradiation therapy. Patients were included in the study group only if they had a pre-resection complete blood count with platelet count ( $n$  = 608), and were excluded if they received post-operative adjuvant chemotherapy ( $n$  = 24). Platelet counts were obtained a median of 5 days prior to surgical resection (range 1 hour – 47 days). A normal platelet count was defined as 150,000–450,000/ $\mu$ L, and thrombocytosis was defined as >450,000/ $\mu$ L.

For all patients, the clinical records and pathology reports were reviewed for determination of clinical and pathological characteristics, such as patient age and gender, history of pre-operative chemoradiation, tumour T stage, and N stage. Overall survival data were obtained by searching the Social Security Death Index database (average follow up time 54.6 months, range 2–290 months). Categorical variables were compared by Fisher exact test, and overall survival data were analysed by a Cox proportional hazards model. The statistical analysis was performed using R software for statistical computing v3.0.2 (<http://www.r-project.org/>). This study was approved by the Brigham and Women's Hospital Institutional Review Board.

### RESULTS

The mean age of the study group was 63.3 years and 87% were male. Of the 584 patients included in this study, 531 (91%) had a normal platelet count (150,000–450,000/ $\mu$ L), whereas 14 (2.4%) had thrombocytosis and 39 (6.8%) had thrombocytopenia. Among the 14 patients with thrombocytosis, the mean platelet count was 506,000/ $\mu$ L (range 457,000–635,000/ $\mu$ L). Of these 14 patients, there were 12 deaths (86%) upon follow-up with a median survival time of 23.2 months (Table 1). This was in contrast to patients with a normal platelet count in which only 266/531 (50%) patients

**Table 1** All patients (*n* = 584)

CRT: ALL	High PLT ( <i>n</i> = 14)	Normal PLT ( <i>n</i> = 531)	Low PLT ( <i>n</i> = 39)	Total ( <i>n</i> = 584)
Age (>65 years)	6 (43%)	236 (44%)	19 (49%)	261 (45%)
Gender (male)	13 (93%)	460 (87%)	35 (90%)	508 (87%)
T stage				
T0	0 (0%)	88 (17%)	8 (21%)	96 (16%)
Tis	0 (0%)	16 (3%)	0 (0%)	16 (3%)
T1a	1 (7%)	75 (14%)	7 (18%)	83 (14%)
T1b	4 (29%)	110 (21%)	5 (13%)	119 (20%)
T2	3 (21%)	97 (18%)	5 (13%)	105 (18%)
T3	6 (43%)	136 (26%)	14 (36%)	156 (27%)
T4	0 (0%)	6 (1%)	0 (0%)	6 (1%)
N stage				
N0	4 (31%) <sup>a</sup>	367 (69%)	25 (64%)	396 (68%)
N1	7 (54%) <sup>a</sup>	96 (18%)	10 (26%)	113 (19%)
N2	1 (8%)	46 (9%)	2 (5%)	49 (8%)
N3	1 (8%)	16 (3%)	2 (5%)	19 (3%)
Deaths, <i>n</i>	12 (86%)	266 (50%)	25 (64%)	303 (52%)
Median survival, months	23.2	76.9	33.9	
Hazard ratio	2.60 <sup>a</sup>	1.00	1.50	

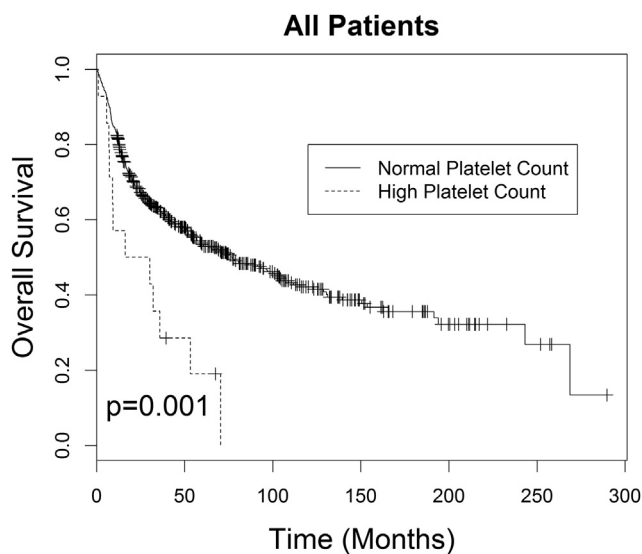
PLT, platelet count.

<sup>a</sup> *p* < 0.01 compared to normal platelet count.

died, with a median survival time of 76.9 months, yielding a significantly elevated hazard ratio (HR) of 2.60 (*p* = 0.0013). A Kaplan–Meier curve illustrates these differences in Fig. 1.

Patients with thrombocytosis also had a higher rate of lymph node metastases; 9/14 (69%) patients had nodal disease (at least N1) compared to 158/531 (31%) in patients with a normal platelet count (*p* = 0.015). Among other clinical/pathological variables, such as age, gender, and tumour T stage, there were no statistically significant differences.

Among the 39 patients with thrombocytopenia, the mean platelet count was 124,000/μL (range 41,000–149,000/μL). Of these 39 patients, there were 25 deaths (64%) upon follow up, with a median survival time of 33.9 months (Table 1).



**Fig. 1** Kaplan–Meier curve shows increased mortality associated with paraneoplastic thrombocytosis in patients with oesophageal adenocarcinoma. Patients with an elevated platelet count had a median survival time of 23.2 months, whereas patients with a normal platelet count had a median survival time of 76.9 months, yielding a significantly elevated hazard ratio (HR) of 2.60 (*p* = 0.0013).

This was in contrast to patients with a normal platelet count in which 266/531 (50%) patients died with a median survival time of 76.9 months, yielding an elevated HR of 1.43 that did not reach statistical significance (*p* = 0.053). In this comparison, there were no significant differences in age, gender, tumour T stage or N stage.

Of the 584 patients in this study, 358 (61%) underwent neoadjuvant chemoradiation therapy and 226 (39%) did not. In the non-neoadjuvant treated group, 5/226 (2.2%) had thrombocytosis, and 4 (80%) of these patients died on follow up with a median survival time of 35.8 months (Table 2). This was in contrast to the patients with normal platelet count in which only 97/215 (45%) died with a median survival of 112 months. This yielded a significantly elevated HR of 3.02 (*p* = 0.032), which is also illustrated by a Kaplan–Meier curve in Fig. 2. In this subgroup of patients, there were no statistically significant differences in age, gender, T stage or N stage.

Finally, in the neoadjuvant treated group, 9/358 (2.5%) had thrombocytosis, and 8 (89%) of these patients died on follow up with a median survival time of 16.2 months (Table 3). This was in contrast to the patients with normal platelet count in which only 169/316 (53%) died with a median survival of 52.1 months. This also yielded a significantly elevated HR of 2.31 (*p* = 0.021) as illustrated by a Kaplan–Meier curve in Fig. 3. In this subgroup, patients with thrombocytosis had a trend toward higher rate of lymph node metastasis with 6/9 (67%) patients with nodal disease compared to 105/316 (33%) in patients with normal platelet count (*p* = 0.067). Among the remaining clinical/pathological variables such as age, gender, and tumour T stage, there were no statistically significant differences.

## DISCUSSION

Our study is the first to show that patients with oesophageal adenocarcinoma and paraneoplastic thrombocytosis have a higher mortality rate than patients with normal platelet count, regardless of neoadjuvant chemotherapy status, and an

**Table 2** Patients without neoadjuvant treatment (*n* = 226)

CRT: N	High PLT ( <i>n</i> = 5)	Normal PLT ( <i>n</i> = 215)	Low PLT ( <i>n</i> = 6)	Total ( <i>n</i> = 226)
Age (>65 years)	1 (20%)	118 (55%)	3 (50%)	122 (54%)
Gender (male)	5 (100%)	181 (84%)	5 (83%)	191 (85%)
T stage				
T0	0 (0%)	3 (1%)	0 (0%)	3 (1%)
Tis	0 (0%)	12 (6%)	0 (0%)	12 (5%)
T1a	1 (20%)	60 (28%)	2 (33%)	63 (28%)
T1b	1 (20%)	63 (29%)	1 (17%)	65 (29%)
T2	1 (20%)	30 (14%)	0 (0%)	31 (14%)
T3	2 (40%)	44 (20%)	3 (50%)	49 (22%)
T4	0 (0%)	3 (1%)	0 (0%)	3 (1%)
N stage				
N0	2 (40%)	160 (74%)	4 (67%)	166 (73%)
N1	2 (40%)	29 (13%)	1 (17%)	32 (14%)
N2	1 (20%)	17 (8%)	0 (0%)	18 (8%)
N3	0 (0%)	7 (3%)	1 (17%)	8 (4%)
Deaths, <i>n</i>	4 (80%)	97 (45%)	6 (100%)	107 (47%)
Median survival, months	35.8	111.8	116.6	
Hazard ratio	3.02 <sup>a</sup>	1.00	1.55	

PLT, platelet count.

<sup>a</sup> *p* < 0.05 compared to normal platelet count.

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