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Increased Platelet Counts after Transthoracic En Bloc Resection for Esophageal Cancer is Associated with Significantly Improved Survival

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Abstract

Background We analyzed perioperative platelet counts as a potential clinical marker for survival after transthoracic en bloc resection for esophageal cancer. Recent data described preoperative thrombocytosis in malignancies to be associated with poor prognosis.

Methods A retrospective analysis from a prospective database (1997–2006) was performed for 291 consecutive patients with esophageal cancer who underwent transthoracic en bloc esophagectomy and extended lymphadenectomy. Squamous cell cancer was found in 47.0% and adenocarcinoma in 50.9% (2.1% had rare histologies). Neoadjuvant chemoradiation was performed in 152 (52%) patients. Platelet counts before surgery and on postoperative days (PODs) 1, 10, and 30 were evaluated. We used the published cutoff value of 293×10^9/l (mean of 80 healthy controls ± standard deviation) for platelet counts.

Results High platelet counts before surgery missed significance for poorer survival ($p = 0.054$). Following a perioperative fall in thrombocytes, a significant rise at POD 10 after surgery was evident. Platelet counts of more than 293×10^9/l at this time correlated with a significantly improved survival rate ($p = 0.027$). Patients with no increase in thrombocytes until POD 10 had significantly poorer survival ($p = 0.012$). Multivariate analysis confirmed that a thrombocyte increase between the preoperative count and that on POD 10 is an independent prognostic indicator ($p = 0.035$) for patients with completely (R0) resected tumors.

Conclusions An increase in platelet counts measured on POD 10 following transthoracic en bloc esophagectomy and extended lymphadenectomy is an independent prognostic indicator for improved survival in patients with esophageal cancer.

Introduction

Platelets contribute to cancer metastasis through promotion of tumor cell proliferation; they enhance tumor cell extravasation by potentiating tumor cell-induced endothelial cell retraction and enhance tumor cell adhesion and spreading on extracellular matrix [1].

Thrombocytes also play an important role in surgical wound healing. Futami et al. found platelets to be a potential source of increased serum vascular endothelial growth factor (VEGF) levels after major surgical injury [2]. They also produce another potent angiogenetic factor, thymidine phosphorylase (dThdPase), previously known as platelet-derived endothelial cell growth factor. It stimulates endothelial cell growth and chemotaxis in vitro and angiogenesis in vivo [3]. Interestingly, dThdPase expression is evident in multiple cancer cells, such as esophageal squamous cell carcinoma, with correlation to tumor size, depth of invasion, lymph node status, and tumor stage [4]. In linear regression analyses, dThdPase expression in esophageal carcinoma correlates with microvessel density, indicating its importance for neoangiogenesis.

Thrombocytosis has been found in several malignancies, including 21% of patients with esophageal squamous cell

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carcinoma [5]. Several studies described thrombocytosis to be associated with poor prognosis [5–8].

Our study focused on platelet counts before surgery and at days 1, 10, and 30 after operation for being a potential clinical marker for survival after transthoracic en bloc resection and extended lymphadenectomy for esophageal cancer.

Materials and methods

Patients

A retrospective study from a prospective database was performed in 305 patients who underwent transthoracic en bloc esophagectomy between January 1997 and October 2006 in the Department of General, Visceral and Cancer Surgery, University of Cologne, Germany. To exclude the effects of surgery-related postoperative complications, 14 patients (4.8%) dying within 90 days after the operation were excluded. Among the remaining 291 study patients, there were 234 men (80.4%) and 57 women (19.6%) with a median age of 62 years (range 18.9–83.2 years).

Histopathologic examination of the resected specimens revealed squamous cell cancer in 137 patients (47%), adenocarcinoma in 148 cases (50.9%), and other, rare entities in 6 patients (2.1%). Staging was performed according to the 6th edition of the UICC/AJCC TNM classification system.

Due to locally advanced diseases (cT3/4), 152 patients (52.2%) underwent standardized neoadjuvant chemoradiation as described in detail elsewhere [9] and 139 (47.8%) did not. At 4–5 weeks after completion of chemoradiation, transthoracic en bloc esophagectomy with two-field lymphadenectomy was performed. Histomorphologic regression was categorized based on the percentage of vital residual tumor cells [9]. The relevant clinical and histopathologic data are summarized in Table 1.

A time period of 30 days after operation was chosen for the analysis of platelet counts. An automated complete blood count was routinely obtained before surgery (preoperative) and at postoperative day 1 (POD1), POD10, and POD 30. Within this time period, 287 patients (98.6%) got no platelet transfusion, three patients received one unit, and one patient two units of thrombocytes. Fresh frozen plasma was administered to 86 patients (29.6%). Blood transfusions were given to 185 patients (63.6%), and 106 patients (36.4%) received no transfusion. The decision for transfusion was made by the attending physician—surgeon, anesthesiologist, intensive care unit (ICU) staff—for various reasons. Most blood products were given during and within the first 2 days after the operation to improve the cardiovascular situation and to minimize the use of catecholamines to protect the anastomosis. Unfortunately, during the 1990s and early 2000s, blood products were given liberally without defined criteria (e.g., hematocrit <25%). With increasing knowledge about the risks of immunomodulation, transfusion criteria were defined. Indeed, over the described time period (1997–2006), a tendency for restrained use of blood products was clearly seen [10].

Table 1 Patient characteristics ($n = 291$)

Parameter	No. of patients (%)
Age (years), median and range 62 (18.9–83.2)	
Sex	
Male	234 (80.4%)
Female	57 (19.6%)
Histology	
SCC	137 (47%)
AC	148 (50.9%)
Other	6 (2.1%)
Neoadjuvant treatment	
No	139 (47.8%)
Yes	152 (52.2%)
T category	
pT0/ypT0	27 (9.3%)
pT1/ypT1	68 (23.4%)
pT2/ypT2	58 (19.9%)
pT3/ypT3	136 (46.7%)
pT4/ypT4	2 (0.7%)
N category	
pN0/ypN0	149 (51.2%)
pN1/ypN1	142 (48.8%)
M category	
cpM0/ycpM0	249 (85.6%)
cpM1aycpM1a	42 (14.4%)
Grade	
G1	5 (1.7%)
G2	145 (49.8%)
G3	138 (47.4%)
G4	3 (1%)

SCC squamous cell carcinoma, *AC* adenocarcinoma, *pT* local invasiveness, *pN* lymph node metastases, *c/pM* distant metastases, *y* neoadjuvant therapy (all according to the UICC TNM classification, 6th edition)

Statistical analysis

Platelet counts followed Gaussian normal distribution. Therefore, a paired-samples *t*-test was chosen for analyzing values preoperatively and at POD1, POD10, and POD30 as well as differences between preoperative values and POD1 (ΔPOD1), preoperatively and POD10 (ΔPOD10), or

preoperatively and POD30 (ΔPOD30). Platelet counts of patients with or without neoadjuvant treatment and with or without blood transfusion were compared by independent-samples *t*-test. To evaluate associations of platelet values with histopathologic parameters or transfusions, Mann–Whitney testing was performed.

The median follow-up of the patients was 4.9 years (range 1.1–11.0 years). All living patients had a follow-up of more than 12 months. Currently, 133 patients are alive, and 158 died of cancer-related causes.

Based on Shimada et al., we used the cutoff value of 293 × 10^9/l (mean of 80 healthy controls ± SD) for thrombocytes [5]. Differences between platelet counts before surgery and at 1, 10, and 30 days after operation (ΔPOD1, ΔPOD10, ΔPOD30) were calculated and dichotomized for positive or negative changes.

Kaplan–Meier plots were used to describe survival distribution [11]. The log-rank test was applied to evaluate for survival differences [12]. In addition, 95% confidence intervals (95% CI) for the various survival curves were calculated. The multivariate analysis of survival rates used Cox regression analysis to identify independent prognostic variables.

The level of significance was set at $p < 0.05$. All statistical tests were calculated using the Software Package SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA).

Results

Platelet counts

The platelet counts distribution before surgery and at PODs 1, 10, and 30 is shown in Fig. 1. The paired-samples *t*-test showed a significant rise in the platelet counts up to 30 days after resection ($p < 0.001$). It further revealed a significant fall between the preoperative and POD1 counts ($p < 0.001$), but also a strong reactive rise between POD1 and POD10 ($p < 0.001$) with a slight but not significant fall ($p = 0.786$) up to day 30. There was no association between platelet counts before operation and the (y)pT-, (y)pN-, and (y)c/pM categories or neoadjuvant treatment; but there was a significant association with histology ($p = 0.001$). Differences in thrombocyte values and correlation with clinicopathologic parameters are listed in Table 2.

Influence of neoadjuvant therapy on perioperative platelet counts

Thrombocyte values of patients with or without neoadjuvant therapy are summarized in Table 3. The independent-samples *t*-test revealed no significant differences.

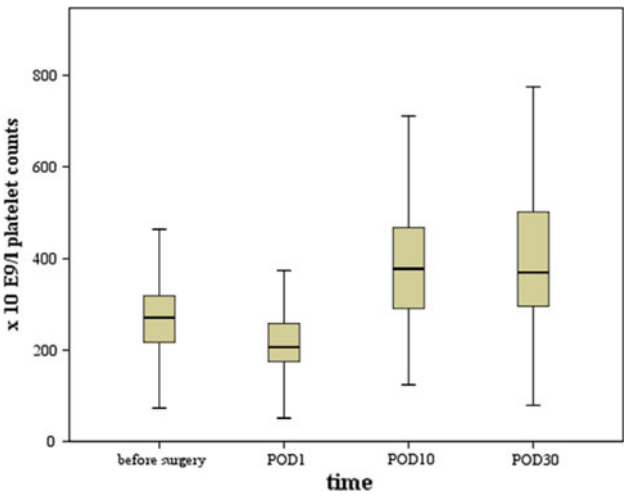

Fig. 1 Box plots showing platelet counts (all counts are × 10^9 per liter) of 291 patients with transthoracic en bloc resection for esophageal cancer before operation (267 ± 86) and on postoperative day 1 (*POD1*) (216 ± 85), *POD10* (421 ± 149), and *POD30* (393 ± 164)

Influence of platelet counts, fresh frozen plasma, or blood transfusions on platelet counts

Transfusion of platelet counts had no statistically significant influence on thrombocyte values; however, only 1.3% of the patients received platelet transfusions. Administration of fresh frozen plasma also had no statistical influence on platelet counts before operation or on POD1, POD10, and POD30. This is in contrast to blood transfusion with a significant difference between the preoperative ($p = 0.016$) and POD10 counts ($p = 0.030$), as shown in detail in Table 4.

A significant difference between the preoperative value and that on POD1 (ΔPOD1) between patients receiving blood or not (with blood transfusion −65 ± 101 vs. −26 ± 65 without transfusion, $p < 0.001$) was observed. The ΔPOD10 platelet counts were 135 ± 160 for transfused patients and 193 ± 119 for nontransfused patients ($p = 0.001$); the ΔPOD30 values were 117 ± 143 for the transfused ones and 178 ± 203 for nontransfused patients ($p = 0.353$).

Correlation between perioperative platelet counts and survival rates

Based on data by Shimada et al., platelet counts were dichotomized by use of a cutoff level of 293 × 10^9/l [5]. There was a strong tendency but no significant difference in survival when analyzing platelet counts from all patients before operation (log rank, $p = 0.054$). The median survival rate was 3.2 ± 0.5 years for patients with lowered

Table 2 Platelet counts in correlation to clinicopathologic parameters

Parameter	Preoperative (Ø ± SD)	Count *p*	ΔPOD10 (Ø ± SD)	*p*
Histology		0.001*		0.025*
SCC	283 ± 89		142 ± 156	
AC	252 ± 82		175 ± 141	
T category		0.294		0.377
(y)pT0	272 ± 91		129 ± 144	
(y)pT1	267 ± 77		174 ± 146	
(y)pT2	252 ± 87		144 ± 129	
(y)pT3	271 ± 89		159 ± 158	
(y)pT4	463		4	
N category		0.231		0.013*
(y)pN0	259 ± 82		175 ± 135	
(y)pN1	275 ± 90		136 ± 160	
M category		0.825		0.057
(y)c/pM0	268 ± 89		163 ± 151	
(y)c/pM1	263 ± 70		118 ± 128	
Neoadjuvant treatment		0.489		0.667
No	263 ± 78		151 ± 143	
Yes	269 ± 91		166 ± 149	

All platelet counts are the number of platelets $\times 10^9$ per liter

Ø, average value; ΔPOD10, difference on postoperative day 10

Table 3 Perioperative platelet counts with and without neoadjuvant chemoradiation

Platelet count ($\times$ 10^9/l)				
Parameter	Preoperative	POD1	POD10	POD30
Without neoadjuvant treatment				
No. of patients	136	136	138	45
Ø ± SD	263 ± 78	218 ± 59	413 ± 138	393 ± 165
SCC	280 ± 85	217 ± 59	416 ± 152	428 ± 171
AC	247 ± 68	216 ± 56	416 ± 130	363 ± 161
With neoadjuvant treatment				
No. of patients	145	147	148	53
Ø ± SD	271 ± 94	214 ± 104	429 ± 159	393 ± 165
SCC	284 ± 92	209 ± 72	423 ± 163	388 ± 126
AC	257 ± 95	223 ± 132	439 ± 156	411 ± 219
p	0.534	0.666	0.414	0.628

Table 4 Perioperative platelet counts with and without blood transfusion

Platelet count ($\times 10^9$/l)				
Parameter	Preoperative	POD1	POD10	POD30
Without blood transfusion				
No. of patients	102	105	106	14
Ø ± SD	251 ± 75	226 ± 72	445 ± 136	430 ± 229
With blood transfusion				
No. of patients	179	178	180	84
Ø ± SD	276 ± 91	210 ± 92	407 ± 156	386 ± 151
p	0.016*	0.117	0.030*	0.508

* significance is achieved

platelet counts versus 2.0 ± 0.7 years for the group with increased counts.

The day after operation, no significant difference in survival was obvious ($p = 0.890$). Interestingly, however, patients with lower platelet counts had a comparatively shorter median survival (2.4 ± 0.3 vs. 3.2 ± 0.9 years).

A significant survival benefit, however, was achieved on POD10 for patients with increased thrombocytes ($p = 0.027$) (Fig. 2). The median survival was 1.8 ± 0.3 years for patients with lowered platelet counts and 3.0 ± 0.4 years for the elevated group. At POD 30, again there was no difference in survival ($p = 0.546$), and the median survival was 2.4 ± 0.5 vs. 3.2 ± 0.5 years.

Perioperative increase of thrombocytes and survival

To determine whether there was a high number of platelets themselves or a postoperative reactive increase differences in platelet counts between the preoperative and POD1 (ΔPOD1), POD10 (ΔPOD10), and POD30 (ΔPOD30) were calculated. For detailed data see Table 5.

Platelet differences were dichotomized for cases >0 and ≤0. ΔPOD1 revealed a nearly significant survival benefit for patients with platelet increase (median survival

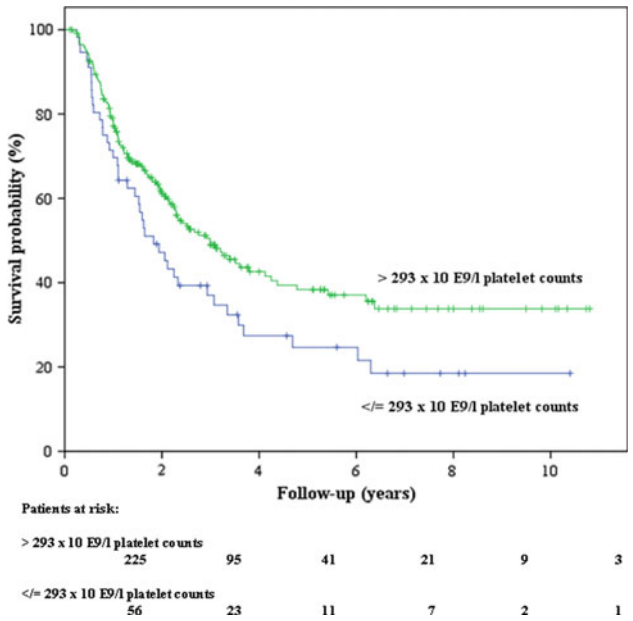

Fig. 2 Kaplan-Meier survival curves for patients undergoing transthoracic en bloc resection for esophageal cancer classified by platelet counts of $>293 \times 10^9$/l and $\leq 293 \times 10^9$/l on POD10 ($p = 0.027$)

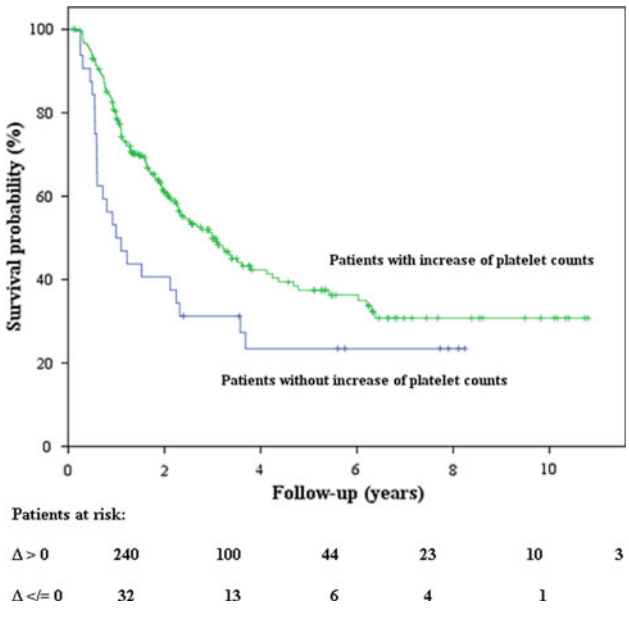

Fig. 3 Kaplan-Meier survival curves of patients undergoing transthoracic en bloc resection for esophageal cancer classified by the existence of a thrombocyte increase between preoperative values and POD10 ($p = 0.012$)

2.33 ± 0.35 vs. 4.69 ± 1.53, $p = 0.051$). Analysis of ΔPOD10 however, showed a clearly significant result ($p = 0.012$). The median survival was 1.0 ± 0.3 years (without increase) vs. 3.0 ± 0.4 years for patients with a positive difference in platelet counts (Fig. 3). This is in contrast to ΔPOD30 (1.11 ± 0.86 vs. 3.24 ± 0.33, $p = 0.392$).

Subgroup univariate analysis of patients with neoadjuvant treatment (Table 6) and without neoadjuvant treatment (Table 7) showed no significant survival advantage in the neoadjuvant chemoradiation group for increased or decreased platelet counts. On the other hand, in the group of the nonneoadjuvant-treated patients, ΔPOD1 and ΔPOD10 >0 were associated with significantly better survival ($p = 0.015$ and $p = 0.02$, respectively).

Table 5 Perioperative differences in absolute platelet counts

Parameter	ΔPOD1	ΔPOD10	ΔPOD30
No. of patients	274	277	91
Ø ± SD	−50 ± 91	156 ± 149	124 ± 152
Dichotomized data (≤0 vs. >0)			
Number			
≤0	217 (79.2%)	32 (11.6%)	19 (20.9%)
>0	57 (20.8%)	245 (88.4%)	72 (79.1%)
Median survival			
≤0	2.33 ± 0.35	1.00 ± 0.30	1.11 ± 0.86
>0	4.69 ± 1.53	3.00 ± 0.38	3.24 ± 0.33
p	0.051	0.012*	0.392

* significance is achieved

Multivariate survival analysis

Multivariate analysis for all R0-resected patients was performed including the following parameters: (y)pT, (y)pN, and (y)c/pM categories, histopathologic response to neoadjuvant therapy, blood transfusion, fresh frozen plasma (FFP) transfusion, platelet transfusion, and platelet counts preoperatively and at POD10 as well as ΔPOD10. Significance was obtained for: (y)pT [$p < 0.001$ for stage T1 vs. T2, the hazard ratio (HR) and 95% CI (in parentheses) were 1.99 (0.81–4.91) and for T1 vs. T3 they were 3.89 (2.01–7.50)]; (y)pN [$p < 0.001$, HR 2.27 (1.57–3.29)]; (y)c/pM [$p = 0.040$, HR 1.56 (1.02–2.39)]; and ΔPOD10 [$p = 0.035$, HR 0.60 (0.37–0.97)].

Table 6 Perioperative differences in absolute platelet counts for patients with neoadjuvant treatment

Parameter	ΔPOD1	ΔPOD10	ΔPOD30
No. of patients	139	140	46
Ø ± SD	−54 ± 106	166 ± 149	135 ± 148
Dichotomized data (≤0 vs. >0)			
Number			
≤0	110 (79.1%)	13 (9.3%)	9 (19.6%)
>0	29 (20.9%)	127 (90.7%)	37 (80.4%)
Median survival			
≤0	1.96 ± 0.23	1.52 ± 0.61	1.11 ± 0.46
>0	2.30 ± 0.17	2.25 ± 0.22	2.34 ± 0.24
p	0.904	0.195	0.289

Table 7 Perioperative differences in absolute platelet counts for patients without neoadjuvant treatment

Parameter	ΔPOD1	ΔPOD10	ΔPOD30
No. of patients	133	135	44
Ø ± SD	−45 ± 70	150 ± 142	115 ± 157
Dichotomized data (≤0 versus >0):			
Number			
≤0	105 (78.9%)	18 (13.3%)	10 (22.7%)
>0	28 (21.1%)	117 (86.7%)	34 (77.3%)
Median survival			
≤0	3.07 ± 0.46	0.60 ± 0.34	0.67
>0		6.2 ± 1.38	6.3
p	0.015*	0.02 *	0.46

Subgroup analysis in patients without neoadjuvant therapy showed significance for pT ($p = 0.008$), pT1 vs. pT2 [HR 1.63 (0.63–4.20)], and pT1 vs. pT3 [HR 3.1 (1.42–6.80]; for pN [$p = 0.011$, HR 2.40 (1.22-4.81)]; and blood transfusion (no or yes) [$p = 0.059$, HR 1.81 (0.98–3.35)].

In cases with neoadjuvant chemoradiation, significance could be shown for pN0 vs. pN1 [$p < 0.001$, HR 2.42 (1.49–3.93)] and POD10 [$p = 0.009$, HR 0.52 (0.32–0.85)]. For a minor versus major response, there was a strong tendency that just missed significance [$p = 0.056$, HR 0.61 (0.37–1.01)].

Discussion

In patients with esophageal cancers who underwent transthoracic en bloc esophagectomy with extended abdominal and mediastinal (two-field) lymphadenectomy, platelet counts showed, following an initial fall, a significant rise at POD 10 and partial normalization at POD30. This observation is in line with data from Spence et al., who demonstrated elevated amounts of platelet counts on POD 10 with return to preoperative levels by 6 weeks [13].

In a previous report, Shimada and coworkers reported a preoperative platelet count of more than 293×10^9/l to be associated with tumor progression and poor survival in patients with squamous cell carcinoma of the esophagus [5]. In our population, this result could be confirmed as a tendency but just missed significance ($p = 0.054$). This might have been influenced by our mixed population, with 47% squamous cell carcinomas and 51% adenocarcinoma of the esophagus. Subgroup analysis showed higher platelet counts preoperatively in patients with squamous cell cancer than in those with adenocarcinoma, with switched postoperative (data not shown). Based on the presented data, both values could be seen as a predictor for a poorer prognostic outcome in patients with SCC [5].

This tendency of a survival disadvantage with preoperatively elevated platelet counts, however, switched completely into a highly significant survival benefit 10 days after resection. Furthermore, the increase between the preoperative and POD10 counts (ΔPOD10) indicated a significant survival advantage. Multivariate analysis confirmed ΔPOD10 as an independent prognostic factor next to the (y)pT, (y)pN, and (y)c/pM categories. These results have not been published yet to the best of our knowledge.

We hypothesize that the bone marrow is stimulated due to surgical stress and produces and/or releases higher amounts of thrombocytes. In the literature, major surgery (esophagectomy) caused a twofold increase of VEGF compared to laparoscopic cholecystectomy (minor surgery). Maximum VEGF levels correlated with maximum platelet counts in the study by Futami et al. [2]. Although exact mechanisms of platelet production stimulation are largely unknown, interactions with cytokines in a systemic inflammatory reaction are discussed [14]. Interleukin-6 (IL-6) was shown to support megakaryocytic proliferation and differentiation in megakaryocytopoiesis [15]. Perioperative administration of steroids was reported to reduce postoperative serum IL-6 levels caused by surgical stress [16].

Furthermore, restriction through the malignant tumor or damage to the bone marrow through chemotherapeutic agents or irradiation appears possible. Especially, the S-phase-specific agent 5-fluorouracil is known to inhibit DNA synthesis in continuous intravenous infusion [17]; and myelosuppresion is sometimes observed [18]. Suwa et al. supposed that the normal bone marrow response of releasing band cells from the postmitotic marrow pool after surgery is disturbed by neoadjuvant therapy. Because of missing differences in white blood cell and neutrophil counts, this marrow response was not predictable until surgery was performed [19]. This is in line with our data showing no difference in platelet counts between patients undergoing chemoradiation and those who did not.

In contrast, univariate analysis of the differences between preoperative values and POD1, POD10, and POD30 (ΔPOD1, 10, or 30) showed a significant survival advantage for increasing values in the nonpretreated subgroup. No significant survival benefit could be detected in the neoadjuvant treated subgroup. In the multivariate subgroup analysis, the nonpretreated group showed pT, pN, and blood transfusion categories as significant factors, whereas in the neoadjuvant-treated subgroup ypN, histopathologic response category, and POD10 showed significance. These data are difficult to interpret and further studies are necessary to clarify this issue.

Interestingly, transfusion of FFP had no statistical influence on platelet counts or in the multivariate survival

analysis. The small number of patients receiving platelets (1.4%) allows no conclusions but clearly eliminates its influence on our data. This is in contrast to blood transfusions, where higher platelet counts before the resection and a lower value after surgery were detected. Even differences between preoperative and postoperative data were less in comparison to nontransfused patients. Based on the available data, including our recently published series [10], transfused patients are at higher risk for reduced survival. We cannot absolutely rule out a potential reciprocal dependence, however, by multivariate analysis as only differences in platelet counts (ΔPOD10) and not blood transfusion categories achieved significance. Therefore, perioperative platelet counts appear to be an interesting prognostic parameter that is easy to obtain.

Interestingly, absolute platelet counts seem to be independent of perioperative complications. Futami and coworkers found that postoperative inflammatory lung complications led to significantly increased serum VEGF levels but did not influence platelet counts. They suggested that inflammatory cells are an additional source of VEGF [2].

Conclusions

We demonstrate a significant perioperative fall of thrombocytes followed by a highly significant rise on POD10 after transthoracic en bloc esophagectomy and extended lymphadenectomy for esophageal cancer. An increase between preoperative platelet counts and values 10 days after resection is an independent good prognostic factor for patients with esophageal cancer. Further studies are necessary to elucidate whether differences in platelet counts are a surrogate marker or if they indeed have a pathogenetic impact.

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