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ORIGINAL ARTICLE

Postoperative failure of platelet recovery is an independent risk factor for poor survival in patients with oral and oropharyngeal cancer

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Abstract
Objective The aim of this study was to evaluate the postoperative platelet count changes in patients with oral and oropharyngeal squamous cell carcinoma undergoing preoperative chemoradiotherapy in order to test the hypothesis that the failure of platelets to recover to normal range within 7 days after surgery represents a significant risk factor for poor survival.

Materials and methods A cohort of 102 patients with primary locally advanced oral and oropharyngeal squamous cell carcinoma undergoing neoadjuvant chemoradiotherapy and surgery was retrospectively analyzed. For each patient, platelet counts were evaluated prior to neoadjuvant treatment, prior to surgery and throughout postoperative days 1 to 7. The Kaplan–Meier method and Cox regression models were used to assess the impact of platelet count changes on survival.
Results Overall survival rate at 5 years was 28 % for patients whose platelets did not recover by day 7, with 52 % for patients whose platelets remained within a normal level or recovered to this by day 7 ($p=0.005$). In multivariate analysis, failure of platelet recovery by day 7 was independently associated with shorter overall survival ($p=0.03$).
Conclusions We demonstrated that the failure of platelets to recover to normal range by the seventh postoperative day is an independent adverse prognostic factor in patients with oral and oropharyngeal cancer undergoing neoadjuvant treatment and surgery.
Clinical relevance Our results indicate that physicians should pay closer attention to monitoring the postoperative platelet count course, as it may predict the clinical outcome of patients with oral and oropharyngeal cancer.

Keywords Platelet count · Oral and oropharyngeal cancer · Risk factor · Prognosis

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Introduction

Thrombocytopenia is a common complication in patients undergoing major surgery [1, 2]. The main causes of postoperative thrombocytopenia are hemodilution and increased

platelet consumption due to bleeding or surgical trauma, followed by other less common causes, such as sepsis, disseminated intravascular coagulation, increased immunological platelet destruction (i.e., immune-mediated heparin-induced thrombocytopenia), and increased platelet sequestration [3–6].

Commonly observed postoperative platelet count kinetics shows a marked fall immediately after surgery, usually reaching a nadir 1 to 4 days later with a platelet recovery to the baseline level typically occurring on postoperative days 5 to 7 [3, 7, 8]. The specific dynamics of the postoperative platelet count course and their impact on clinical outcome have, however, not yet been systematically explored in patients with oral and oropharyngeal squamous cell carcinoma (OOSCC) undergoing neoadjuvant chemoradiotherapy and major surgery. The objective of this study was to analyze the early postoperative platelet count kinetics in patients with OOSCC undergoing neoadjuvant treatment in order to test the hypothesis that the failure of platelet recovery to normal range within 7 days after surgery represents an independent risk factor for poor survival.

Patients and methods

Study population and treatment

A total of 102 patients, diagnosed with primary locally advanced oral and oropharyngeal cancer between 2000 and 2009, were retrospectively included in this study. Each patient had to meet the following inclusion criteria: (1) biopsy-proven, previously untreated primary oral or oropharyngeal squamous cell carcinoma; (2) no history of another cancer in the head and neck region; (3) clinical tumor–lymph nodes–metastasis (TNM) stage III or IV without evidence of distant metastatic disease (M0) [9]; (4) multi-modality treatment with curative intent; (5) WHO performance status of ≤2 with adequate laboratory values compatible with chemotherapy and surgery; (6) clear resection margins (R0); (7) available complete blood counts obtained: (a) immediately before chemoradiotherapy, (b) immediately before surgery, and (c) throughout postoperative days 1 to 7; and (8) baseline platelet count prior to chemoradiotherapy $\geq 150 \times 10^9$/L. The Institutional Ethics Committee approved this study.

All patients were treated at the Departments of Radiotherapy and Cranio-Maxillofacial and Oral Surgery, at the Medical University of Vienna, and received neoadjuvant chemoradiotherapy followed by surgery. A multidisciplinary board determined the multimodal treatment according to institutional protocol as described previously [10, 11]. Chemotherapy consisted of mitomycin C (15 mg/m^2, an i.v. bolus injection on day 1) and 5-fluorouracil (750 mg/m^2/day, continuous infusions on days 1–5). Radiotherapy was delivered over 5 weeks with the cumulative dose of 50 Gy (25 fractions of 2 Gy/day). Surgery was performed 4–8 weeks after the finalization of radiotherapy. After the operation, all patients were transferred to the ICU, and controlled mechanical ventilation was then applied for at least 6 h. Low molecular weight heparins at prophylactic dose and antibiotics were given to all patients. The patients were followed up every 3 months for the first 2 years after surgery and bi-annually for a further 3 years.

We generated a patient database after reviewing patient medical records including clinical, surgical, laboratory, and outcomes data. Pre-existing comorbidities were assessed using the validated Charlson index, which scores comorbidities according to a weighted index of 19 medical conditions [12, 13]. The Charlson comorbidity index was dichotomized for further analysis as absence of comorbidity (score=0) or presence of comorbidity (score≥1). The surgical specimens were histopathologically evaluated by means of a standard protocol providing information on histological tumor type, resection margins, differentiation grade, perineural invasion, and pathological tumor response. In order to assign a pathological tumor regression grade, the vitality of tumor cells in surgical specimens was evaluated as follows [14]: no vital tumor cells, <5 % of vital tumor cells, 5–50 % of vital tumor cells, and more than 50 % of vital tumor cells [regression grades (RG) 1, 2, 3, and 4, respectively]. Tumor regression grades were bundled in responder (RG1/RG2) and non-responder (RG3/RG4) groups.

Definitions and study groups

The normal platelet count was defined as ranging between 150 and 450×10^9/L [15, 16]. Thrombocytopenia was defined as a platelet level of $<150 \times 10^9$/L [15]. Platelet recovery was defined as recovery of the platelet count to a level of $\geq 150 \times 10^9$/L within the first seven postoperative days. The patients in our study cohort were divided into two groups according to their platelet count kinetics achieved by day 7: (1) The first group comprised patients whose platelet count did not recover to $\geq 150 \times 10^9$/L, (2) the second group comprised patients whose platelet count recovered to $\geq 150 \times 10^9$/L, as well as patients who maintained a platelet count $\geq 150 \times 10^9$/L throughout the postoperative days 1 to 7.

Statistical analysis

Continuous data were expressed as mean±standard deviation in case of normal distribution and group differences are tested by unpaired *t* test. Skew data were described with median and interquartile range and tested between groups by Mann–Whitney *U* test. Categorical data are described with absolute and relative frequencies, and group comparisons were made by chi-square test or by Fisher's exact test in case of sparse data. The primary

endpoint of this study was overall survival (OS) defined as the time from surgery to death from any cause. The Kaplan–Meier method was used to estimate survival curves and the log-rank test to assess survival differences between groups. Hazard ratios (HR) and 95 % confidence intervals (CI) were calculated using univariate and multivariate (enter method) Cox proportional hazards regression models to assess the effect of clinicopathological factors and platelet counts on survival. A two-sided p value$\leq$0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®, version 19.0, SPSS Inc., Chicago, IL, USA).

Results

Study population

Patient characteristics are summarized in Table 1. The population studied had a mean age of 57±9 years, 75 % were male, 85 % had a primary tumor located in the oral cavity, and 96 % (n=98) had a clinical TNM stage IV disease. The majority of patients (n=56, 55 %) had a Charlson comorbidity score of 0. A Charlson's score 1 was recorded in 26 patients (25 %), score 2 in 8 (8 %), score 3 in 6 (6 %), score 4 in 4 (4 %), and score 5 in 2 (2 %).

Platelet count kinetics

Prior to the neoadjuvant chemoradiotherapy, all 102 patients studied showed a platelet count of $\geq 150\times10^9$/L, while later, prior to surgery, a preoperative platelet count of $\geq 150\times10^9$/L was observed in 94 patients. The remaining eight patients had developed a mild thrombocytopenia (platelet counts 100–149×10^9/L). In the course of the first seven postoperative days, platelet counts remained within a normal range in 17 of 102 patients (17 %), while in the remaining 85 patients (83 %), thrombocytopenia was recorded, with five patients (5 %) suffering from severe thrombocytopenia with platelet counts $<50\times10^9$/L. Of a total of 85 thrombocytopenic patients, 55 achieved platelet recovery by day 7 while the remaining 30 patients did not.

Figure 1 illustrates the mean platelet counts over time. The pretreatment and preoperative mean platelet counts were 282×10^9/L±86 and 247×10^9/L±85, respectively. On day 1, the mean platelet count fell by 47 % from the preoperative level to 132×10^9/L±49. The mean platelet count nadir was reached on day 2 (125×10^9/L±40) and maintained on day 3 (125×10^9/L±43). A platelet count recovery began on day 4 (137×10^9/L±48) and increased further on days 5 (149×10^9/L±55), 6 (174×10^9/L±66), and 7 (200×10^9/L±80).

Correlations between clinicopathological variables and platelet recovery

Platelet recovery status by day 7 was significantly associated with smoking (p=0.04), pathological response (p=0.046), and baseline leucocytes (p=0.028). No statistically significant association between platelet recovery status and clinicopathological variables, such as age, sex, Charlson index, tumor localization, grade, perineural invasion, and baseline hemoglobin was observed (Table 1).

Survival analyses

At a median follow-up of 4.1 years, 52 patients were still alive (50 without and two with tumor recurrence) and 50 patients had died (22 without and 28 with tumor recurrence). Kaplan–Meier survival curves according to platelet count kinetics by the seventh postoperative day are shown in Fig. 2. Overall survival rate at 5 years was 28 % for patients whose platelet counts did not recover by day 7 (n=30), with 52 % for patients whose platelet counts remained within a normal level or recovered to this by day 7 (n=72; log-rank test: p=0.005).

Survival analyses using Cox proportional hazards regression models are shown in Table 2. In univariate analyses, failure of platelet recovery by day 7 (HR 2.23, 95 % CI 1.26–3.96, p=0.006), age (HR 1.04, 95 % CI 1.00–1.07, p=0.02), perineural invasion (HR 2.77, 95 % CI 1.22–6.29, p=0.02), and pathological non-response (HR 2.35, 95 % CI 1.33–4.16, p=0.003) were all found to be statistically significant risk factors for poor OS. A multivariate regression model, adjusted for age, sex, smoking, Charlson index, tumor localization, tumor grade, perineural invasion, pathological response, baseline leucocytes, and baseline hemoglobin, confirmed that failure of platelet recovery by day 7 was independently associated with shorter overall survival (HR 2.19, 95 % CI 1.06–4.54, p=0.03).

Discussion

The main finding of this study is that the failure of platelet recovery by the seventh postoperative day represents an independent risk factor for poor survival in patients with oral and oropharyngeal cancer undergoing neoadjuvant chemoradiotherapy. On the first postoperative day, we observed in our cohort a sharp decrease of approximately 50 % in the platelet counts when compared to preoperative levels. This was probably due to hemodilution and increased platelet consumption due to bleeding or surgical trauma [3]. A nadir in the mean platelet count was reached and maintained on days 2 and 3 after surgery and was followed by a reactive platelet recovery starting on day 4 and continuing throughout days 5 to 7. It is likely that the initial acute platelet

Table 1 Correlations between clinicopathological variables and platelet count kinetics in 102 patients with OOSCC

Variable	Patients	Platelet count kinetics by the 7th postoperative day		p[a]
	n (%)	Platelets recovered to/ maintained ≥150×10^9/L, *n* (%)	Failure of platelet recovery, *n* (%)	
Total *n* of patients	102 (100)	72 (71)	30 (29)	
Age				0.15[b]
Mean±SD, years	57±9	56±9	59±8	
Sex				0.86
Male	77 (75)	54 (75)	23 (77)	
Female	25 (25)	18 (25)	7 (23)	
Smoking				0.04
Current	87 (85)	65 (90)	22 (73)	
Former or never	15 (15)	7 (10)	8 (27)	
Charlson index				0.051
Score 0	56 (55)	44 (61)	12 (40)	
Score ≥1	46 (45)	28 (39)	18 (60)	
Tumor localization				0.30
Oral cavity	87 (85)	60 (83)	27 (90)	
Oropharynx	15 (15)	12 (17)	3 (10)	
Tumor grade				0.06
G1	10 (10)	8 (11)	2 (7)	
G2	80 (78)	59 (82)	21 (70)	
G3	12 (12)	5 (7)	7 (23)	
Perineural invasion				0.39
No	92 (90)	64 (89)	28 (93)	
Yes	10 (10)	8 (11)	2 (7)	
Pathologic response				0.046
Response	69 (68)	53 (74)	16 (53)	
Non-response	33 (32)	19 (26)	14 (47)	
Baseline leucocytes				0.028[c]
Median—×10^9/L	8.1	8.4	6.9	
IQR	6.5–9.7	6.9–10	5.9–8.7	
Baseline hemoglobin				0.27[c]
Median—g/dL	13.7	13.7	13.7	
IQR	12.8–14.9	12.6–15.2	12.9–14.4	

SD standard deviation, *G1* well differentiated, *G2* moderately differentiated, *G3* poorly differentiated, *IQR* interquartile range

[a]Chi-square test (or Fisher's exact test) unless otherwise specified

[b]*t* test

[c]Mann–Whitney *U* test

reduction lead to an increase in circulating thrombopoietin and subsequent stimulation of megakaryocytes [17]. Accumulated evidence suggests that following thrombopoietin stimulation an increased production of new platelets by megakaryocytes requires a minimum time of 3 days, a fact that may explain why platelet recovery started on the fourth postoperative day in our cohort [3, 18]. The postoperative platelet count changes found in our study are similar to those reported in literature for patients after major cardiac, vascular, abdominal, or trauma surgery [7, 19–21]. Patients undergoing the above types of surgery show only slight differences in their postoperative platelet count profiles with regard to the initial platelet decrease, the time to the nadir, and platelet recovery. Warkentin et al. examined the platelet count changes in patients undergoing major orthopedic surgery and found that the vast majority of them had reached a platelet nadir by the third postoperative day [15]. In addition, Akca et al. observed in a large mixed population of both medical and surgical intensive care unit patients that their platelets reached a mean nadir on day 4, followed thereafter by a reactive increase above baseline levels [7].

In our study, we demonstrated that a failure of platelet recovery by the seventh postoperative day was significantly associated with worse survival in patients with OOSCC undergoing chemoradiotherapy and surgery. In particular, patients whose platelets did not recover by day 7 after surgery had a 5-year survival probability of 28 %, which was significantly worse (p=0.005), when compared with a 5-year survival

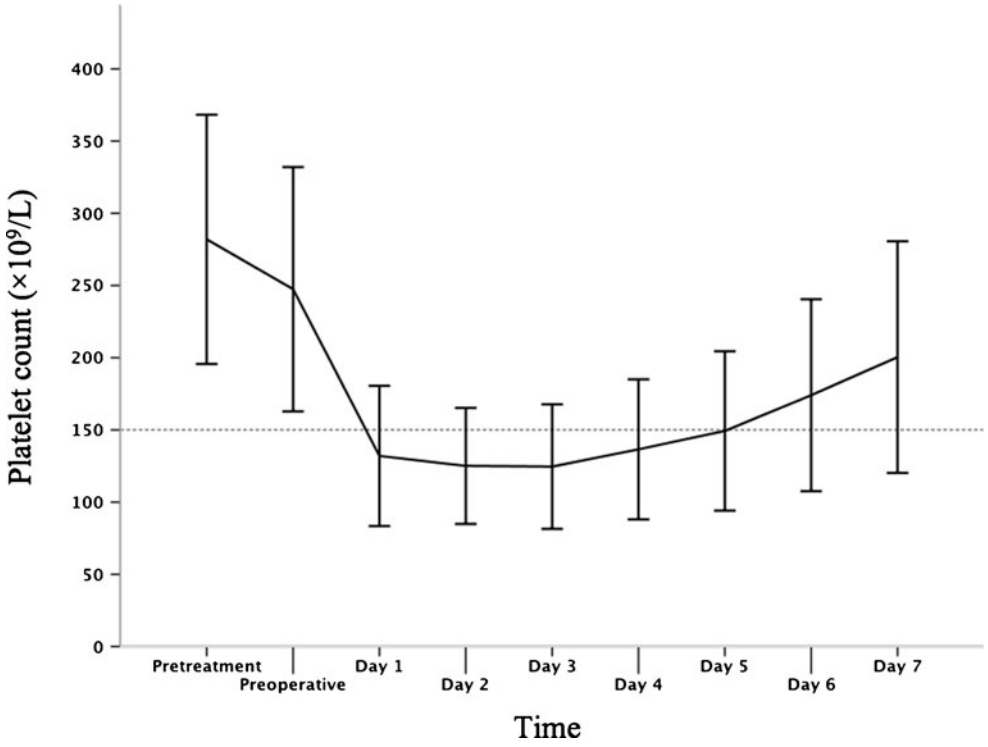

Fig. 1 Mean platelet counts± standard deviation during the observation period

probability of 52 % in patients whose platelets recovered to or maintained a normal level by the seventh postoperative day. A multivariate analysis further strengthened the hypothesis that postoperative failure of platelet recovery represents an independent adverse prognostic factor in patients with oral and oropharyngeal cancer. Our results are in accordance with Ling et al.

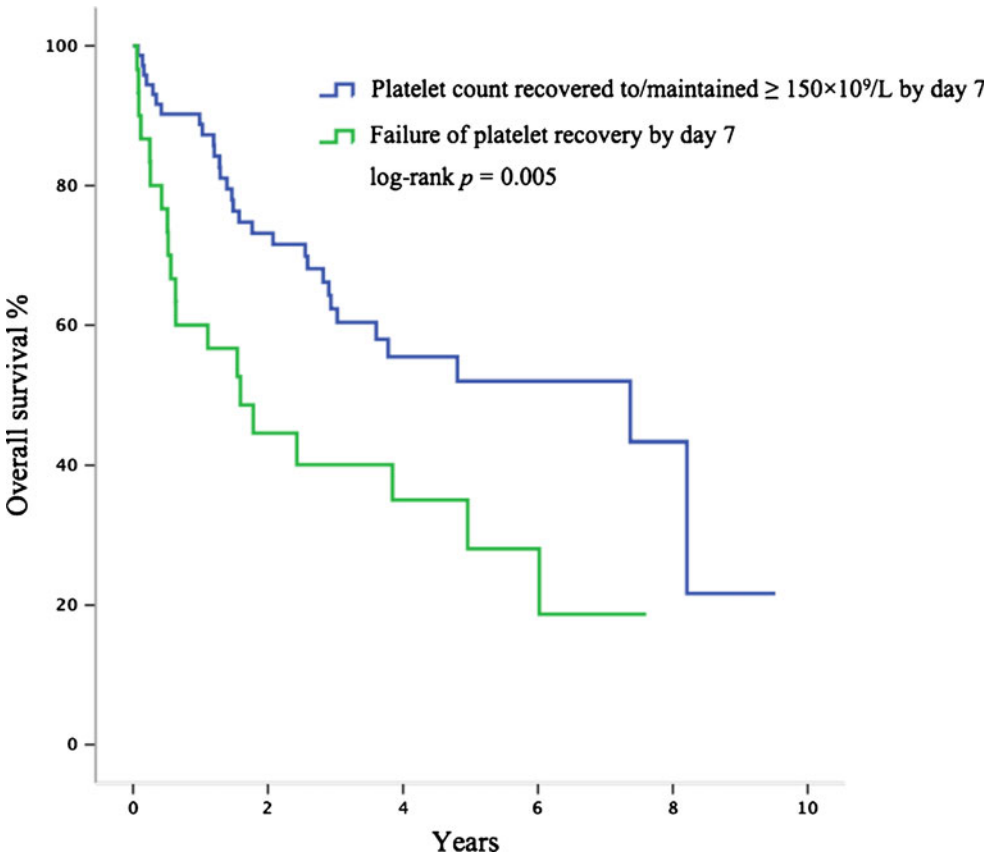

Fig. 2 Kaplan–Meier survival curves separated by platelet count kinetics by the seventh postoperative day

Table 2 Cox proportional hazards regression models

Variable	Univariate analysis			Multivariate analysis		
	HR for death	95 % CI	*p*	HR for death	95 % CI	*p*
Age	1.04	1.00–1.07	0.02	1.04	1.01–1.08	0.02
Sex	0.71	0.34–1.46	0.35	0.63	0.27–1.46	0.28
Smoking	1.30	0.63–2.68	0.48	1.01	0.43–2.35	0.98
Charlson index	1.05	0.60–1.84	0.85	0.81	0.42–1.57	0.53
Tumor localization	1.03	0.48–2.20	0.95	1.01	0.42–2.41	0.99
Tumor grade	0.99	0.53–1.85	0.98	0.74	0.36–1.50	0.40
Perineural invasion	2.77	1.22–6.29	0.02	2.95	0.98–8.90	0.054
Pathological tumor response	2.35	1.33–4.16	0.003	1.34	0.64–2.83	0.44
Baseline leucocytes	0.96	0.87–1.06	0.46	1.00	0.88–1.14	0.96
Baseline hemoglobin	0.93	0.78–1.10	0.39	0.94	0.78–1.14	0.54
No platelet recovery by day 7	2.23	1.26–3.96	0.006	2.19	1.06–4.54	0.03

Variables were coded as described in Table 1

HR hazard ratio, *95 % CI* 95 % confidence interval

who analyzed the prognostic importance of platelet count kinetics in patients who had undergone surgery for esophageal cancer [22]. They found a marked drop in platelet counts on the first postoperative day and a significantly poorer survival outcome for patients who failed to increase their platelets between surgery and the tenth postoperative day.

This retrospective study has several limitations. Firstly, we used stringent inclusion criteria, which may introduce a selection bias. Our analysis, however, was based on a relatively homogeneous cohort of uniformly treated OOSCC patients. Furthermore, to avoid a bias related to the potential prognostic effect of baseline thrombocytopenia, all patients studied had to have a pre-chemoradiotherapy platelet count $\geq 150 \times 10^9$/L. Moreover, we limited our analyses to the seventh postoperative day because several lines of evidence suggested that reactive platelet recovery should have been achieved by this time [3, 7, 8]. Secondly, several factors that might have an impact on the postoperative platelet count course were not considered in our analysis. For example, early sepsis, which is one of the most common causes of persistent severe thrombocytopenia, is characterized by a major postoperative platelet count fall of less than 50×10^9/L that remains beyond the fourth postoperative day [3]. Heparin-induced thrombocytopenia, which is often considered as a potential cause for postoperative thrombocytopenia, is rather uncommon with an incidence of approximately 0.5 %. The clinical diagnosis of heparin-induced thrombocytopenia requires a platelet count fall of more than 50 % from the postoperative peak platelet count, which is usually observed within 4 to 14 days of starting heparin treatment [19]. Other unmeasured, rare causes of postoperative thrombocytopenia include disseminated intravascular coagulation, transfusions of blood products, and increased platelet sequestration. Thirdly, although a significant association between postoperative failure of platelet recovery and poor survival was evident in univariate and multivariate analyses, causality cannot be established because confounding factors may not have been taken into account. Fourthly, in this study, we did not explore the pathophysiological mechanisms underlying the postoperative platelet count changes in patients treated for oral and oropharyngeal cancer. Thus, additional studies are required to determine whether there indeed is a link between defective compensatory mechanisms and poor survival in patients who failed to achieve postoperative platelet recovery. The above-mentioned limitations, together with the relatively small cohort size, suggest that our findings need to be validated in further studies.

To the best of our knowledge, this is the first study examining the clinical value of postoperative platelet count changes in OOSCC patients. We provide evidence that the failure of platelets to recover to normal range by the seventh postoperative day is a significant independent risk factor for poor survival in patients with oral and oropharyngeal cancer undergoing neoadjuvant chemoradiotherapy and surgery. Our findings suggest that physicians should pay closer attention to monitoring the postoperative platelet count course, as it may predict the clinical outcome of patients with oral and oropharyngeal cancer.

Conflict of interest The authors declare that they have no conflict of interest.

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