Preoperative thrombocytosis predicts poor survival in patients with glioblastoma

Marc A. Brockmann, Alf Giese, Kathrin Mueller, Finjap Janvier Kaba, Frank Lohr, Christel Weiss, Stefan Gottschalk, Ingo Nolte, Jan Leppert, Jochen Tuettenberg, and Christoph Groden

University Hospital Mannheim, Departments of Neuroradiology (M.A.B., K.M., I.N., C.G.), Radiation Therapy (F.J.K., F.L.), Neurosurgery (J.T.), and Statistics in Medicine (C.W.), Department of Neurosurgery, Georg-August-University of Göttingen, 37075 Göttingen (A.G.); Mannheim; 68167 University Hospital Schleswig-Holstein, Campus Luebeck, Departments of Neurosurgery (J.L.) and Neuroradiology (S.G.), 23538 Luebeck; Germany

Thrombocytosis, which is defined as a platelet count greater than 400 platelets/nl, has been found to be an independent predictor of shorter survival in various tumors. Release of growth factors from tumors has been proposed to increase platelet counts. Preoperative platelet counts and other clinical and hematological parameters were reviewed from the records of 153 patients diagnosed between 1999 and 2004 with histologically confirmed glioblastoma in order to evaluate the prognostic significance of preoperative thrombocytosis in these patients. The relationship between thrombocytosis and survival was initially analyzed in all patients regardless of further therapy. Univariate log-rank tests showed that the median survival time of 29 patients with preoperative thrombocytosis (19%) was significantly shorter (4 months; 95% confidence interval [95% CI], 3–6 months) compared to 124 patients with normal platelet counts (11 months; 95% CI, 8–13 months; $p = 0.0006$). Multivariate analysis (Cox proportional hazards model) confirmed preoperative platelet count, age, prothrombin time, and activated partial thromboplastin time to be prognostic factors of survival (all $p < 0.05$). In a subset of patients (only operated patients with radiation therapy with or without additional chemotherapy), survival was likewise significantly shorter when preoperative thrombocytosis was diagnosed (6 months; 95% CI, 4–12 months) compared to patients with normal platelet count (13 months; 95% CI, 11–15 months; $p = 0.0359$). In multivariate analysis, age, platelet count, preoperative prothrombin time, and degree of tumor resection retained significance as prognostic factors of survival (all $p < 0.05$). The results of our study demonstrate preoperative thrombocytosis to be a prognostic factor associated with shorter survival time in patients with glioblastoma. *Neuro-Oncology 9, 335–342, 2007 (Posted to Neuro-Oncology [serial online], Doc. D06-00054, May 15, 2007. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2007-013)*

Keywords: angiogenesis, malignant glioma, platelets, prognostic parameter

Thrombocytosis, which is defined as a platelet count greater than 400 platelets/nl, has been found to be associated with significantly shorter survival times in malignant mesothelioma[1]; in lung,[2–5] renal,[6,7] colorectal,[4,8] and esophageal cancer[9]; and in different gynecological malignancies and breast cancer.[10–16] It has been suggested that growing tumors induce thrombocytosis by secretion of different cytokines and growth factors.[17–20] But platelets might also influence tumor growth. Increased activation, adhesion, and aggregation of circulating platelets within pathologically altered and prothrombotic tumor vessels, with subsequent secretion of different growth factors from activated platelets, have been suggested to result in increased angiogenesis and tumor growth rates.[21,22] It remains questionable whether thrombocytosis is simply an end result of growth factors

Received April 5, 2006; accepted September 5, 2006.

Address correspondence to Marc A. Brockmann, University Hospital Mannheim, Department of Neuroradiology, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany (brockmann@gmx.de).

secreted by tumor cells or whether thrombocytosis is an event that directly increases the risk of disease spread and worsened prognosis.

For glioblastoma, the impact of various histopathological,[23–25] genetic,[26,27] and clinical[28–30] prognostic factors has been documented in several studies. To our knowledge, there are no studies investigating the prognostic significance of thrombocytosis as a survival factor in patients with glioblastoma. This retrospective study is the first to assess the influence of pretreatment thrombocytosis on survival in these patients.

Materials and Methods

Patients and Parameters

For this retrospective study, we tried to identify as many patients as possible diagnosed with glioblastoma multiforme (GBM) between October 1999 and July 2004 by searching medical records in the archives of the Mannheim University Hospital and the Schleswig-Holstein University Hospital (Campus Luebeck). A total of 187 patients treated for GBM could be identified. Of these 187 patients, 26 could not be included in the study because they were lost to follow-up and/or no definite information regarding survival time could be obtained. In three cases, relevant preoperative laboratory investigations were missing, and in five cases, the patient chart was missing in the archive. Finally, the medical records of the remaining 153 patients with histologically confirmed GBM (WHO glioma grade IV), who underwent treatment at either participating center, were included for retrospective analysis.

The data assessed from the patient charts included gender, patient age, preoperative platelet count (platelets/nl), fibrinogen (g/l), prothrombin time (%), activated partial thromboplastin time (aPTT; seconds), KPS, tumor volume (ml), and other details of the patient history such as smoking habits, treatment modalities (complete/incomplete tumor resection based on the surgeon's report, biopsy only, postoperative radiation therapy [RT] with or without additional chemotherapy [CT]), and postoperative survival time (in months, with 95% confidence interval [95% CI]). If patients did not undergo complete or incomplete tumor resection but only biopsy, the survival time after histopathological diagnosis of GBM was used for statistical analyses.

All preoperative hematological analyses were taken within 14 days prior to tumor resection or biopsy. Thrombocytosis was considered as a platelet count greater than 400/nl, in accord with the literature.[4,6,31] Patients with a history of myeloproliferative disorders, acute inflammatory disease, or splenectomy were not included in this study.

Analysis of Preoperative Tumor Volume

If available at the time of data analysis, digitally stored preoperative computed tomography or MR images were used for volumetric analyses of tumors using Argus software (Argus VA 60C; Siemens, Erlangen, Germany) as supplied with one of the hospital's MRI scanners. Only preoperative images acquired and digitally stored in one of the study centers were considered for volumetric analyses. Preoperative images acquired off-site were not available for analysis.

Statistical Analysis

Gross total resection has been found to be associated with significantly improved survival compared with biopsy only.[32–34] In addition to the group containing all patients, we decided to analyze a subpopulation of patients with complete or incomplete tumor resection and RT with or without additional CT ($n = 98$) in order to evaluate the specific characteristics of this group.

Differences in clinical factors and hematological parameters between patients with and without thrombocytosis were examined with the chi-square, Mann-Whitney, Fisher's exact, and two-sample *t*-test according to the type of underlying parameter. The survival time was estimated by the Kaplan-Meier method, in which the response variable (survival time) was related to one explanatory variable (e.g., platelet count). Kaplan-Meier curves were compared with the log-rank test. The Cox proportional hazards model was used to assess the significance of potential prognostic factors as predictive parameters for patient survival. After univariate and multivariate analysis of all potential confounding factors, we tried to identify the best prognostic model with a relatively small number of variables. This procedure was chosen to make sure that none of the important factors was omitted. Effects with a p value equal to or less than 0.05 were considered to be statistically significant.

Results

All Patients

The records of 153 patients (63 female, 90 male) with histopathologically confirmed glioblastoma were analyzed. Of these 153 patients, 89 were treated at the Mannheim University Hospital and 64 at the Schleswig-Holstein University Hospital (Campus Luebeck). Clinical parameters and associations between presence and absence of thrombocytosis of all patients are presented in Table 1.

Macroscopically complete resection (based on the surgeons report) was achieved in 80 patients (52.3%), while a partial resection was performed in 33 patients (21.6%). Forty patients (26.1%) were considered inoperable due to tumor location in inaccessible areas or because of the patient's poor condition.

Of all 153 patients, 127 patients (83.0%) were treated by postoperative RT, performed as three-dimensional irradiation with a median dose of 60 Gy (mean ± 1 SD, 56.0 ± 6.4 Gy). Of these 127 patients, 61 received additional CT (temozolomide = 28, temozolomide + rofecoxib = 12; imatinib = 11; nimustine hydrochloride = 7; other chemotherapies = 3). No patient was treated by

Table 1. Clinical parameters and associations between presence and absence of thrombocytosis in all patients with glioblastoma ($n = 153$)

Parameter	< 400 Platelets/nl ($n = 124$)	> 400 Platelets/nl ($n = 29$)	Test	*P* Value
Age (years)	64.9 ± 11.1 ($n = 124$)	64.8 ± 10.4 ($n = 29$)	*t*-test	0.9498
KPS	80 (40–100; $n = 124$)	80 (20–90; $n = 26$)	Mann-Whitney test	0.7636
Tumor volume (ml)	24.8 ± 21.8 ($n = 55$)	38.9 ± 22.5 ($n = 12$)	*t*-test	0.0481
Platelet count (per nl)	276 ± 62 ($n = 124$)	451 ± 54 ($n = 29$)	*t*-test	< 0.0001
Hemoglobin (g/100 ml)	14.5 ± 1.4 ($n = 124$)	14.3 ± 1.6 ($n = 29$)	*t*-test	0.3978
aPTT (s)	23.6 ± 3.2 ($n = 117$)	24.4 ± 3.4 ($n = 28$)	*t*-test	0.2471
Prothrombin time (%)	98.8 ± 13.8 ($n = 122$)	99.0 ± 10.3 ($n = 29$)	*t*-test	0.9377
Fibrinogen (g/l)	2.9 ± 1.0 ($n = 79$)	3.7 ± 1.7 ($n = 23$)	*t*-test	0.0323
Smokers	16 (14.3%)	5 (18.5%)	Fisher's exact test	0.5588
Nonsmokers	96 (85.7%)	22 (81.5%)		
Female	49 (39.5%)	14 (48.3%)	Chi-square test	0.3882
Male	75 (60.5%)	15 (51.7%)		
Biopsy only	29 (23.4%)	11 (38.0%)	Chi-square test	0.0392
Incomplete resection	24 (19.4%)	9 (31.0%)		
Complete resection	71 (57.3%)	9 (31.0%)		
No RT or CT	17 (13.7%)	9 (31.0%)	Chi-square test	0.079
RT only	55 (44.4%)	11 (38.0%)		
RT and CT	52 (41.9%)	9 (31.0%)		

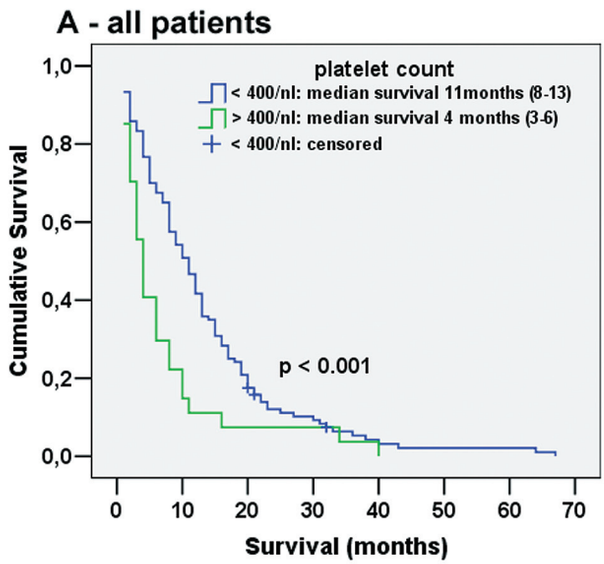
Abbreviations: aPTT, activated partial thromboplastin time; RT, radiation therapy, CT, chemotherapy. Note that for these analyses, all patients with glioblastoma, regardless of their further therapy or other parameters, were included. All quantitative parameters are given as mean ± 1 SD; KPS is given as median and range; the qualitative parameters are expressed in frequencies or number of patients (%). The degree of tumor resection was based on the surgeon's report.

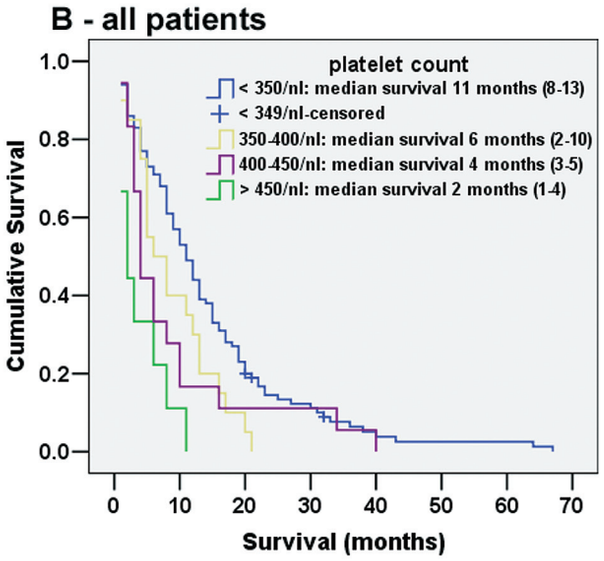
CT alone. In 26 of all 153 patients (17.0%), no radiation or CT was performed. Of these 26 patients, 11 underwent biopsy only, 10 underwent incomplete tumor resection, and only 5 underwent macroscopically complete tumor resection. Reasons to refrain from RT and/or CT were refusal of patients to undergo RT and/or CT, a poor postoperative performance status, or the fact that patients were considered primarily inoperable and presented with rapidly deteriorating performance. Analysis of the medical records revealed 21 of the patients to be chronic smokers (15.1%), while 118 patients (84.9%) identified themselves as nonsmokers. For the remaining 14 patients, no information on smoking behavior was available. Twenty-nine patients (19.0%) presented with preoperative thrombocytosis. The mean (± 1 SD) preoperative tumor volume was acquired in 67 patients (27.3 ± 22.4 ml). Platelet counts were higher in female ($n = 63$) than in male ($n = 90$) patients (326 ± 97 vs. 297 ± 86; $p = 0.0555$, *t*-test). Nevertheless, platelet count retained significance in multivariate analysis as a factor influencing survival, whereas gender did not affect survival time in univariate or multivariate analyses ($p = 0.7081$, log-rank test).

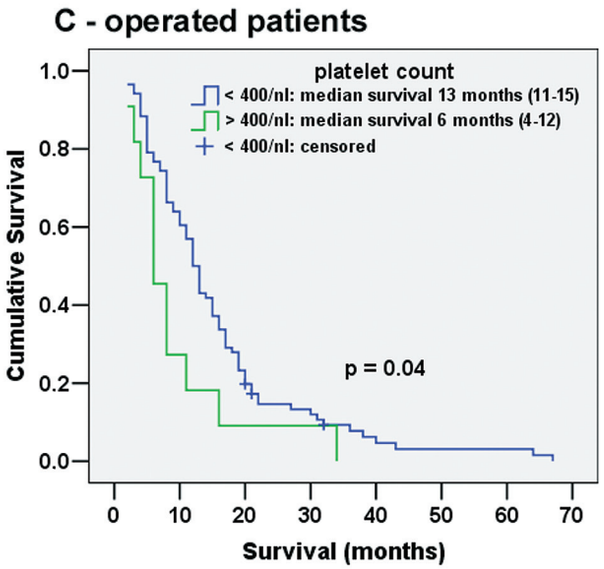
The median survival time for all 153 patients was nine months (95% CI, 7–11). Univariate analysis (log-rank test) revealed preoperative thrombocytosis to be significantly associated with reduced survival times (4 months; 95% CI, 3–6 months) compared to patients with normal platelet counts (11 months; 95% CI, 8–13 months; $p = 0.0006$; Fig. 1A). Fig. 1B indicates how platelet levels affect survival time and shows that even elevated platelet levels still within the normal range (350–400 platelets/nl) are associated with shorter survival. Continuous variables significantly associated with shorter survival time were elevated preoperative platelet count ($p = 0.0002$), elevated fibrinogen levels ($p = 0.0178$), higher age ($p = 0.0001$), decreased prothrombin time ($p = 0.0535$), and prolonged aPTT ($p = 0.0340$). There was a trend that larger preoperative tumor volume likewise was associated with shorter survival ($p = 0.0545$). In our population, the KPS showed no significant association with survival time ($p = 0.1356$) when applied as a quantitative variable. A highly significant difference in median survival time was detected when comparing a group of patients with a KPS of 60 or less (5.5 months; 95% CI, 5–9 months) with patients with a KPS of 70 or higher (11 months; 95% CI, 8–13 months; $p = 0.0047$).

After univariate and multivariate analyses of all potential confounding factors, we identified the best prognostic model with a relatively small number of variables, to make sure that none of the important factors was omitted in the model. After multivariate analysis, the following variables retained significance as prognostic factors (Table 2): preoperative platelet count ($p < 0.0001$), age ($p = 0.0002$), preoperative prothrombin time ($p = 0.0163$), and aPTT ($p = 0.0263$).

We additionally analyzed the correlation of preoperative platelet count and other preoperative clinical parameters using Spearman's rho (correlation coefficient, *p* value). Preoperative platelet count correlated positively with tumor volume ($r_s = 0.305$, $p = 0.0122$, $n = 67$) and negatively with degree of tumor resection ($r_s = -0.233$,







$p = 0.0037$, $n = 153$). Other significant correlations found were tumor volume (ml) and survival ($r_s = -0.271$, $p = 0.028$, $n = 66$), degree of tumor resection and preoperative fibrinogen levels ($r_s = -0.342$, $p = 0.0004$, $n = 102$), age and degree of tumor resection ($r_s = -0.219$, $p = 0.0067$, $n = 153$), and age and KPS ($r_s = -0.179$, $p = 0.0304$, $n = 146$).

Definite information on cause of death (COD) was available in eight patients: venous thrombosis ($n = 1$), pneumonia and sepsis ($n = 3$), intracerebral hemorrhage ($n = 2$), and basilar and median cerebral artery thrombosis (each $n = 1$). Both patients with intracerebral artery thrombosis belonged to the group of patients with preoperative thrombosis and died within the first month after the operation. The patient with venous thrombosis died five months after diagnosis of GBM and initially presented with a platelet count of 388/nl.

Factors Influencing Survival in Operated Patients with Subsequent RT with or without CT

This subpopulation consisted of 98 patients who underwent complete or incomplete tumor resection with subsequent RT with or without additional CT. Nonoperated patients and patients with complete or incomplete tumor resection but without subsequent RT were excluded from this subanalysis to better control the factor of postoperative RT. Table 3 shows the associations between the presence or absence of thrombocytosis and clinical parameters in these patients and demonstrates that both groups are approximately balanced for all factors, including degree of tumor resection. Platelet count and tumor volume were the only unbalanced factors and again correlated positively with each other ($r_s = 0.370$, $p = 0.0173$, $n = 41$). Median survival time in this group was 12 months (95% CI, 10–14 months).

Univariate analysis (log-rank test) revealed the following factors to be significantly associated with survival time: incomplete tumor resection (8 months; 95% CI, 6–10 months) versus complete tumor resection (13

Fig 1. Effect of elevated platelet counts on survival duration in patients with glioblastoma: survival in months (95% confidence interval [95% CI]). (A) Patients with glioblastoma with preoperative thrombocytosis had a statistically significantly shorter overall survival (log-rank test). The composition of the patient groups is described in Table 1. (B) Overall survival of all patients with glioblastoma after creating four strata of platelet counts. Note that patients with platelet counts elevated within the normal range (350–400 platelets/nl) had a significantly reduced survival time compared to patients with a platelet count below 350/nl ($p = 0.022$). Patients with thrombocytosis below 450 platelets/nl can be expected to have a median survival time of four months (95% CI, 3–5 months) compared to two months (95% CI, 1–4 months) in patients with thrombocytosis greater than 450 platelets/nl ($p = 0.057$). (C) Overall survival of only patients with complete or incomplete tumor resection and subsequent radiation therapy, with or without additional chemotherapy. The composition of this patient group is described in Table 3.

Table 2. Multivariate Cox proportional hazards analysis of potential prognostic factors on overall survival in patients with glioblastoma

Variable	Unit	Hazard Ratio	95% Confidence Interval	*P* Value
Preoperative platelet count	100 counts	1.597	1.427–1.747	<0.0001
Age	10 years	1.406	1.283–1.541	0.0002
Preoperative prothrombin time	10%	0.868	0.818–0.921	0.0163
aPTT	1 s	1.069	1.037–1.102	0.0263

Abbreviation: aPTT, activated partial thromboplastin time. For this analysis, all patients with glioblastoma, regardless of their further therapy or other parameters, were included. Age, preoperative platelet count, and preoperative prothrombin time were analyzed as continuous variables.

Table 3. Clinical parameters and associations between presence and absence of thrombocytosis in all operated patients with subsequent radiation therapy with or without additional chemotherapy

Parameter	< 400 Platelets/nl ($n = 87$)	> 400 Platelets/nl ($n = 11$)	Test	*P* Value
Age (years)	63.3 ± 11.1 ($n = 87$)	65.8 ± 6.4 ($n = 11$)	*t*-test	0.4620
KPS[a]	80 (50–100; $n = 86$)	80 (50–90; $n = 11$)	Mann-Whitney test	0.6618
Tumor volume (ml)	23.5 ± 20.3 ($n = 37$)	48.7 ± 23.1 ($n = 4$)	*t*-test	0.0248
Platelet count (per nl)	275 ± 65 ($n = 87$)	440 ± 42 ($n = 11$)	*t*-test	<0.0001
Hemoglobin (g/100 ml)	14.5 ± 1.4 ($n = 87$)	14.2 ± 1.7 ($n = 11$)	*t*-test	0.6376
aPTT (s)	23.2 ± 2.9 ($n = 81$)	24.4 ± 2.7 ($n = 10$)	*t*-test	0.2069
Prothrombin time (%)	99.8 ± 11.0 ($n = 86$)	97.5 ± 13.4 ($n = 11$)	*t*-test	0.5382
Fibrinogen (g/l)	2.7 ± 1.0 ($n = 51$)	3.2 ± 1.5 ($n = 7$)	*t*-test	0.4248
Smokers	12 (15%)	3 (30%)	Fisher's exact test	0.3610
Nonsmokers	68 (85%)	7 (70%)		
Female	36 (41.4%)	5 (45.5%)	Fisher's exact test	1.0000
Male	51 (58.6%)	6 (54.5%)		
Incomplete resection	20 (23.0%)	3 (27.3%)	Fisher's exact test	0.7164
Complete resection	67 (77.0%)	8 (72.7%)		
RT only	43 (49.4%)	4 (36.4%)	Chi-square test	0.4139
RT and CT	44 (50.6%)	7 (63.6%)		

Abbreviations: aPTT, activated partial thromboplastin time; RT, radiation therapy, CT, chemotherapy. Nonoperated patients or operated patients without subsequent RT were excluded from this analysis. All quantitative parameters are given as mean ± 1 SD or number of patients (%); KPS is given as median and range; the qualitative parameters are expressed in frequencies.

months; 95% CI, 12–16 months; $p = 0.0077$), and preoperative thrombocytosis (6 months; 95% CI, 4–12 months) versus normal platelet count (13 months; 95% CI, 11–15 months; $p = 0.0359$; Fig. 1C). A KPS of 60 or less was clearly, although not significantly, associated with shorter survival (9 months; 95% CI, 5–14 months) compared to a score of 70 or higher (13 months; 95% CI, 11–16 months; $p = 0.0871$). There was a tendency for RT with additional CT to prolong survival times (14 months; 95% CI, 12–17 months) compared to RT alone (8.5 months; 95% CI, 6–12 months), and for survival time to be prolonged in patients presenting with a preoperative tumor volume of less than 20 ml (14 months; 95% CI, 11–17 months) compared to patients with tumor volumes exceeding 20 ml (7 months; 95% CI, 4–10 months). These differences, however, were not statistically significant ($p = 0.1173$ and p = 0.16, respectively).

Continuous variables associated with shorter survival time were higher age ($p = 0.0083$), elevated preoperative platelet counts ($p = 0.018$), and elevated fibrinogen levels ($p = 0.087$). In this patient population, KPS and aPTT failed to retain significant influence on patient survival time.

Multivariate analysis (Cox proportional hazards model) rendered age ($p = 0.0115$), prothrombin time ($p = 0.0228$), degree of tumor resection ($p = 0.0349$), and elevated preoperative platelet counts ($p = 0.0384$) to be valuable predictors of survival time in this group of operated patients with subsequent RT with or without additional CT (Table 4). Because the degree of tumor resection is based on the surgeon's report, an inadequate estimation of the degree of tumor resection in this group cannot be completely ruled out. Furthermore, few studies have convincingly shown an advantage to gross total versus partial resection. Lacroix et al.[35] is a good example of the latter, but even its authors concede that some degree of selection bias is likely present. The results describing the effects of the degree of tumor resection thus require critical interpretation by the reader.

We additionally analyzed the influence of thrombocytosis on survival time in a subpopulation of all patients with complete tumor resection ($n = 75$). We found a

Table 4. Multivariate Cox proportional hazards analysis of potential prognostic factors on survival in operated patients (complete or incomplete tumor resection) with subsequent radiation therapy (with or without additional chemotherapy)

Variable	Unit	Hazard Ratio	95% Confidence Interval	*P* Value
Age	10 years	1.316	1.180–1.438	0.0115
Preoperative prothrombin time	10%	0.785	0.706–0.873	0.0228
Preoperative platelet count	100 platelets	1.327	1.157–1.521	0.0384
Degree of tumor resection	—	0.562	0.428–0.738	0.0349

Age and preoperative prothrombin time were analyzed as continuous variables; degree of tumor resection was analyzed as nominal variable. The degree of tumor resection was based on the surgeon's report and defined as complete or incomplete tumor resection.

striking disadvantage regarding median survival time in patients with preoperative thrombocytosis ($n = 8$) compared to patients without thrombocytosis ($n = 67$; 13 months vs. 18 months, respectively; log-rank test: $p = 0.235$). This finding, however, was not significant in this subpopulation, which is most likely due to the smaller number of patients.

Discussion

The relation of thrombocytosis with malignant disorders has been known for more than a century.[36] Higher platelet counts are known to be an independent poor prognostic marker associated with advanced tumor stage and decreased survival rates in solid tumors.[3,6,9,14,31,37] The frequency of thrombocytosis and thrombocyte counts vary in malignant diseases. The ranges of frequencies for thrombocytosis as previously reported are 9.5%–38% in gynecological cancer,[11,16,37] 13%–60% in bronchial cancer,[5,38,39] and 56.8% in renal cancer.[6] In our study, 19% of all patients with GBM presented with thrombocytosis. Likewise, our results demonstrate pretreatment thrombocytosis to be associated not only with reduced survival time but also with larger preoperative tumor volumes, which similarly has been reported for hepatocellular carcinoma.[40]

Thrombocytosis is most likely a result of tumor burden. Excessive amounts of cytokines were found to be associated with thrombocytosis in solid cancers. Interleukin-6 (IL-6), IL-1, vascular endothelial growth factor (VEGF), macrophage colony-stimulating factor, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor-α are some of the cytokines that have been studied in malignancy-associated thrombocytosis.[41–45] Furthermore, platelet counts have been found to correlate well with blood VEGF levels in cancer.[44] Some of the cytokines associated with increased platelet levels have also been found to be secreted by GBM or to be increased in the blood of patients with GBM. Choi et al.[46] and van Meir et al.[47] reported increased IL-6 levels in GBM, while Valter et al.[48] and Ross et al.[49] reported increased levels of IL-1 in gliomas. Another study found IL-1α and IL-1β to induce the production of GM-CSF and G-CSF in human astroglial cell lines.[50] These findings, and the fact that, compared to a normal population with a mean platelet count of 250/nl,[51,52] our patients present with an obviously increased mean platelet count of 309 platelets/nl, which positively correlates with tumor volume, suggest thrombocytosis results from tumor growth.

Although an influence of tumor growth on thrombocytosis is generally accepted, the reverse remains unclear: does thrombocytosis influence tumor growth and angiogenesis? It has been proposed that the release of growth factors from platelets activated within prothrombotic tumor microcirculation increases angiogenesis and tumor growth. If so, this could result in a vicious circle, whereby tumor growth induces thrombocytosis, and elevated platelet counts lead to increased tumor growth and angiogenesis. Our recent results have demonstrated that platelet-derived growth factors as well as VEGF, which is also stored in platelets, exert strong chemotactic effects on the migration of human cerebral microvascular endothelial cells, which is an essential step in angiogenesis.[53] Our ongoing unpublished investigations indicate a strong influence of platelets on glioma and endothelial cell growth and migration in vitro, but there also have been contradicting results from in vivo studies of intratumoral microthrombosis and platelet adhesion. Manegold et al.[54] assessed platelet adherence by intravital fluorescence video microscopy of Lewis lung carcinoma (LLC 1) and fibrosarcoma (BFS 1) using a dorsal skinfold chamber model and found only slightly increased rolling of fluorescence-labeled platelets and no obvious platelet adhesion. These results, however, might not represent the physiological situation, since they were observed in a highly artificial setting with fluorescence-labeled platelets and short observation periods.

If thrombocytosis is associated with platelet-promoted tumor growth, then selective and controlled reduction of platelet counts (e.g., using cytapheresis) to normal levels, without increasing the risk of intratumoral hemorrhage, might provide a treatment option in patients with significantly elevated platelet counts. Because of the increased risk for intratumoral hemorrhage, antiplatelet drugs may not be a good solution. Nevertheless, Arrieta et al.[55] treated C6 glioma-bearing rats with acetylsalicylic acid (ASA) and found a reduction in tumor size after administration of low-dose ASA, although higher doses seemed paradoxically to promote tumor growth. Other groups have also investigated the influence of inhibitors of the arachidonic acid metabolism on tumor cell growth and migration.[56,57] These studies demonstrated that inhibitors of cyclooxygenases and thromboxane synthase block the migration of endothelial cells[58] and malignant glioma cells, induce apoptosis, and sensitize migration-arrested cells to drug-induced apoptosis.[56,59,60]

The significant correlation between increased prothrombin time and shortened survival observed in this study cannot be easily explained, especially because mean prothrombin time in both patient groups (with and without thrombocytosis) was within the normal range and no significant differences could be observed. We also investigated the effect of smoking habits on survival in our patient population, because smoking has been controversially discussed to have prothrombotic and platelet-activating effects.[61–63] However, no significant correlations with platelet count or patient survival were found in our study.

Regarding COD, we have definite information only for eight of our patients. In the remaining patients, no autopsy was performed and no definite COD could be extracted from patients' charts. How many of our patients definitely died as a direct result of tumor growth is unknown. Because COD in patients with supratentorial glioblastoma has been found to be multifactorial,[64] the actual COD is often difficult to determine. In three of the patients with known COD, however, possible thrombosis-related mechanisms (median cerebral and basilar artery thrombosis and venous thrombosis) were identified as COD.

In conclusion, our retrospective study identified pretreatment thrombocytosis as an independent risk factor for survival time in patients with glioblastoma. Because patients with GBM present with increased platelet counts compared to a normal population, increased platelet levels are likely to be the result of tumor growth. Whether increased platelet counts increase tumor growth and angiogenesis remains open for discussion.

Acknowledgment

We thank Thomas Nebe, M.D. (Institute of Clinical Chemistry, Mannheim University Hospital), for his assistance in acquisition of patient data.

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