

Thrombocytosis Has a Negative Prognostic Value in Lung Cancer

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Abstract. *Background: Solid tumours have worse prognosis when associated with thrombocytosis. Our study assessed the prognostic value of thrombocytosis, and its relation with smoking habits in lung cancer. Patients and Methods: A total of 398 patients were operated on then divided into two groups, those with normal platelet counts (n=312), and those with thrombocytosis (n=86); 348 out of 398 patients had data for smoking habits (99 non-smokers, 249 smokers). Results: The frequency of thrombocytosis was 18.6%, 19.3%, 27.5 and 28.6% in patients with tumor stages I to IV, respectively. Thrombocytosis appeared most frequently in patients with squamous cell lung cancer, and among smokers. The overall 5-year survival was worse in patients with thrombocytosis (p<0.001). By uni- and multivariate analyses, platelet count, and T and N status were found to be independent prognostic factors. Conclusion: Our study indicates that the presence of perioperative thrombocytosis in patients undergoing surgery should be considered as an independent prognostic factor of poor survival, and should be taken into account in regard to therapy.*

Survival after lung cancer resection is mainly dependent on tumor stage (1), but other factors are also known to influence it. In resected stage I lung cancer cases, the tumor size, smoking index, and number of dissected mediastinal lymph nodes are all prognostic factors for overall and disease-free survival (2). Poor tumor differentiation is a risk factor for recurrence and carries an unfavorable prognosis (3). The impact of smoking on survival is widely discussed. Smoking was significantly predictive of a poor prognosis after resection of different stages of lung cancer (4) and in stage I adenocarcinomas (5), but there was no difference in terms of survival between smokers and non-smokers with advanced

non-small cell lung cancers (6). Thrombocytosis has been proven to have a fundamental impact on survival in advanced cervical (7) and renal cell cancer (8). Unfavorable outcome in association with thrombocytosis has been described in patients with esophageal (9), gastric (10) and soft tissue cancer (11). Currently only a few articles exist, discussing the impact of thrombocytosis on lung cancer survival, or in resected cases. Previous studies have reported mainly unfavorable (12, 14, 16-18) or no impact (19) on survival of a high thrombocyte count among patients with non-small cell lung cancer. In several studies, thrombocytosis was detected as an independent prognostic factor (14, 16, 18). In this retrospective study, we evaluated the incidence and potential impact of thrombocytosis on outcome, also analyzing the smoking habits of patients who underwent lung cancer resection.

Patients and Methods

The study was conducted in full accordance with the institutional regulations and all the patients gave their written informed consent prior to participation in the surgery.

Study population. Patients operated on for lung cancer at the Department of Surgery in a 5-year period between January 2003 and December 2007 were eligible for analysis in this study. For each patient, the treatment plan was designed by a multidisciplinary onco-team.

Surgical, histological and staging procedures. Resections performed for the 398 lung cancer cases were as follows: 124 pneumonectomies, 214 lobectomies, 6 bi-lobectomies, 27 atypical resections and 27 explorations. In all cases systematic mediastinal lymphadenectomy was performed. Preoperative staging examinations routinely included a chest X-ray, chest CT, bone scintigraphy, brain CT, abdominal ultrasound, bronchoscopy and spirometry based on the conventional protocol. The primary tumor and the mediastinal lymph nodes were histologically analyzed by the use of a standard pathological local protocol and AJCC TNM classification, sixth edition (1). Patient files were reviewed, and relevant data were collected.

Definition of thrombocytosis and smoking habits. The platelet counts were assessed three times during the perioperative period: just before surgery, and on the first and seventh postoperative days. If

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Key Words: Lung cancer, prognosis, thrombocytosis, smoking.

Table I. Distribution of thrombocytosis and smoking habits according to the pathological stage in the entire population.

| Stage | All patients n=398 | All patients, N=398 | | Patients with known smoking history, N=348 | |
|-------|-----------------------|---------------------------------------|--------------------------------------|---|------------------|
| | | PLT <400×10 ³ /μl n=312 | PLT >400×10 ³ /μl n=86 | Non-smokers n=99 | Smokers n=249 |
| IA | 18.6% | 20% | 14% | 21% | 16% |
| IB | 28.6% | 29.2% | 26.7% | 31% | 28.9% |
| IIA | 1.8% | 1.9% | 1.2% | 1% | 2% |
| IIB | 20.4% | 20.8% | 18.6% | 18% | 19.7% |
| IIIA | 19.8% | 17.9% | 26.7% | 15% | 22.1% |
| IIIB | 7.3% | 7.1% | 8.1% | 7% | 8.4% |
| IV | 3.5% | 3.2% | 4.7% | 6% | 2.8% |

PLT, Platelet count.

all three samples were evaluated to be higher than 400×10³/μl, in agreement with other studies (7, 10, 12, 14, 15), thrombocytosis was diagnosed. Based on this data, the 398 patients were divided into two groups as to whether they had normal platelet counts or thrombocytosis in the perioperative period. Among all patients, two subgroups were formed regarding their smoking habits. A total of 348 out of the 398 patients had smoking habit data. Non-smokers either never smoked or smoked little in the past, but stopped 10 years or more prior to lung surgery, and smokers smoked at the time of surgery or had smoked in the past 10 years.

Statistical analysis. All analyses were carried out using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The associations between thrombocytosis and clinical factors (stage, histology, gender) were evaluated with the chi-square test, and the correlation between thrombocytosis and age were tested with independent samples *t*-test. Overall survival was analyzed by Kaplan-Meier analysis. The univariate- and multivariate analysis of the platelet count, T status, N status, stage and their impact on survival were evaluated with Cox regression test.

Results

Patients' characteristics. Three-hundred and ninety eight consecutive patients with primary lung cancer were included in the study. There were 293 (73.6%) males and 105 (26.4%) females, with a mean age (±SD) of 58.3 (±8.99) (range 36-79) years. Most of the patients had stage I cancer (47.2%). The performance status of the patients was good (ECOG 0 and 1, 44% and 56%, respectively). The histological type was squamous cell carcinoma in 175 (44%), adenocarcinoma in 163 (41%) and large cell, small cell lung cancer and carcinoid in 33 (8.3%), 13 (3.3%) and 14 (3.5%) cases, respectively.

Association of thrombocytosis and smoking habits with clinicopathological characteristics. Out of the 398 patients operated on for lung cancer, 86 (21.6%) were determined to have thrombocytosis. The incidence of thrombocytosis gradually elevated according to increasing cancer stage. In stage I, 18.6%

Table II. The association between thrombocytosis and smoking habit (*p*=0.001).

| | Non-smokers n=99 | Smokers n=249 |
|--|---------------------|------------------|
| Normal platelet count (<400×10 ³ /μl) | 89 (89.9%) | 184 (73.9%) |
| Thrombocytosis (>400×10 ³ /μl) | 10 (10.1%) | 65 (26.1%) |

of cases had thrombocytosis, in stage II, III and IV 19.3%, 27.8% and 28.6%, had thrombocytosis respectively. There were no significant associations between stage (*p*=0.074), histology (*p*=0.078), age (*p*=0.089), gender (*p*=0.516) and platelet count values. Only 348 out of the 398 patients had data concerning their smoking habits: 260 of these patients (75%) were male and 88 patients (25%) were female. A total of 249 (71.6%) out of the 348 patients were smokers and 99 (28.4%) were non-smokers. The distribution of thrombocytosis and smoking habit according to the pathological stage of all resected lung carcinomas is described in Table I; no significant differences were found. Thrombocytosis was significantly more frequent in smokers (26.1%) than in non-smokers (10.1%) (*p*=0.001) (Table II). This correlation was detected in the squamous cell subgroup (*p*=0.004), in contrast with patients with non-squamous cell histologies (*p*=0.082). The frequency of smokers was also higher in patients who suffered from squamous cell cancer than those with other histology. The incidence of thrombocytosis was also higher in the squamous cell subgroup, in which 94.9% of patients with thrombocytosis were smokers. The data for smoking habits and thrombocytosis in the squamous cell and other histological subtypes are detailed in Table III.

Association of thrombocytosis and smoking habit with outcome of patients. The median follow-up time of the entire population was 62.0 (range=1-103) months. The overall

Table III. The distribution of thrombocytosis and smoking habit according to squamous cell and other histological subtypes.

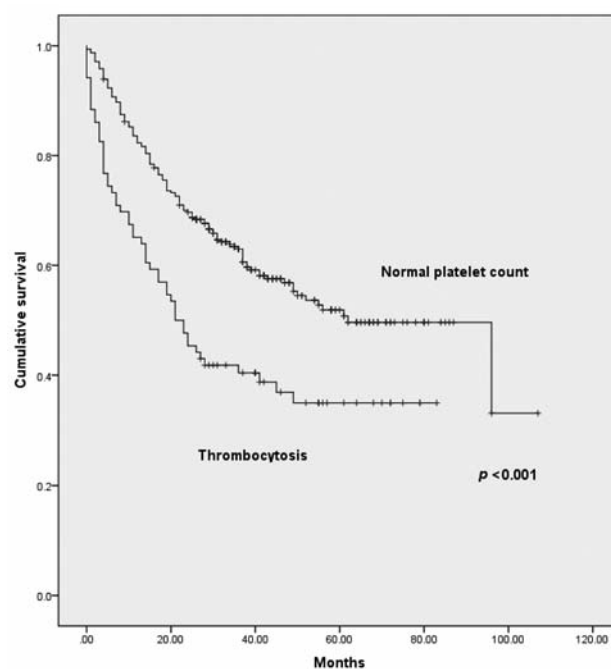
| | All patients, N=398 | | Patients with known smoking history, N=348 | |
|-----------------------------------|---------------------------------------|--------------------------------------|---|------------------|
| | PLT <400×10 ³ /μl n=312 | PLT >400×10 ³ /μl n=86 | Non-smokers n=99 | Smokers n=249 |
| Squamous cell lung cancer | 130 (74.3%) | 45 (25.7%) | 35 (21.5%) | 128 (78.5%) |
| Other histology | 182 (81.6%) | 41 (18.4%) | 64 (34.6%) | 121 (65.4%) |
| <i>p</i> -Value (Chi-square test) | 0.001 | | 0.007 | |

PLT, Platelet count.

survival of the entire population was 31.0 months, and 14.8% of the patients were still alive after five years of follow-up. The overall 5-year survival was 35% among patients with thrombocytosis, and 50.8% among patients with a normal thrombocyte count ($p < 0.001$). The overall survival time was 63.1 months in the group without and 38 months in the group with thrombocytosis ($p < 0.001$) (Figure 1). There were no significant associations between the overall survival and gender ($p = 0.392$), smoking habit ($p = 0.724$) or histology ($p = 0.148$). A significant association was detected in the case of overall survival in the squamous histological subgroup according to the patient's platelet count (thrombocytosis *vs.* normal) ($p < 0.001$), but such an association was not found in the other histological subgroups ($p = 0.916$). The survival of the patients significantly correlated with tumor stage for the whole study group ($p < 0.001$) and also in the subgroup of patients with normal platelet counts ($p < 0.001$), but there was no difference among the patients with thrombocytosis ($p = 0.13$), presumably because of the relatively small number of cases (Table IV). By univariate analysis, except histology ($p = 0.148$), advanced stage of lung cancer ($p < 0.001$), greater tumor size ($p < 0.001$), lymph node involvement ($p < 0.001$) and the presence of thrombocytosis ($p < 0.001$) were significantly associated with a decreased survival. By multivariate analysis, the presence of thrombocytosis, greater tumor size and lymph node involvement were all independent factors related to poorer survival (Table V).

Discussion

The present study demonstrated that an increased platelet count can help to predict unfavorable outcome in lung cancer. We observed a strong association not only between the T and N status and stages, but also between the presence of thrombocytosis and the 5-year survival of the patients after surgery. Thrombocytosis was significantly more frequent among smokers than non-smokers. The novelty of our study lies in the analysis of a high platelet count as a potential prognostic marker in relation to the outcome of lung cancer and on which few data have been published.



Patients at risk.

| | 0 year | 1 year | 2 years | 3 years | 4 years | 5 years |
|------|--------|--------|---------|---------|---------|---------|
| G I | 312 | 258 | 214 | 139 | 75 | 47 |
| G II | 86 | 56 | 40 | 29 | 19 | 12 |

Group I: Patients with normal platelet count, Group II: patients with thrombocytosis.

Figure 1. Kaplan-Meier survival curves for patients with lung cancer patients according to platelet count.

Secondary, or reactive thrombocytosis is observed in a variety of underlying conditions, which may cause either an acute and transient elevation of platelet count (trauma, major surgery, acute bleeding) or more sustained thrombocytosis (infection or neoplasia) in patients. Thrombocytosis has a prevalence as high as 30% in patients with lung cancer, and has been associated with extensive and/or metastatic disease and a worse prognosis. The percentage of patients with elevated platelet counts was 21.6% among all our resected

Table IV. The association between 5-year survival, platelet count and stage.

| Stage | PLT <400×10 ³ /μl n=312 | PLT >400×10 ³ /μl n=86 | All |
|------------|---------------------------------------|--------------------------------------|--------|
| IA, n=78 | 81% | 44% | 75% |
| IB, n=110 | 62% | 48% | 59% |
| IIA, n=7 | 50% | 0% | 43% |
| IIB, n=81 | 46% | 31% | 43% |
| IIIA, n=80 | 25% | 26% | 25% |
| IIIB, n=28 | 15% | 28% | 20% |
| IV, n=14 | 44% | 25% | 34% |
| p-Value | <0.001 | 0.130 | <0.001 |

PLT, Platelet count.

lung cancer cases, the frequency of the incidence was higher in more advanced stages (18.6% in stage I and 27.5% in stage III), which is similar to the proportion of thrombocytosis in the study of Pedersen and Milman (20% in stage I and 30% in stage IIIA) (12). The study by Hamilton *et al.* presented comparable data, as thrombocytosis occurred in 26% of lung cancer cases (13). In our study, thrombocytosis appeared most frequently in squamous cell lung cancer (52%) than in other histological subtypes. Similar data were presented in the study by Pedersen and Milman (12). Smoking habit can have an impact on the type of lung cancer. Nakamura *et al.* reported squamous cell cancer as being most frequent among smokers (4). Among the smokers participating in our study, the incidence of squamous cell lung cancer was also the most frequent, in addition, we discovered that thrombocytosis was significantly more frequent in smokers than in non-smokers. There was no difference in 5-year survival between smokers and non-smokers in patients with normal platelet counts or thrombocytosis. There was no significant difference in survival between smokers and non-smokers in advanced lung cancer cases presented by Toh *et al.* (6), but Nakamura *et al.* presented smoking as being significantly predictive of a poor prognosis after resection of different stages of lung cancer (4). The impact of thrombocytosis on the survival was analyzed from different aspects. Using the current TNM lung cancer classification (1), there was a significant difference in the survival based on the stages, using an overall comparison. In our study, analyzing all patient data or only data for patients with normal platelet counts, we found the same significant correlation in survival rates in the different stages. When we analyzed the survival among patients with thrombocytosis during the perioperative period, there was no significant difference in survival among the stages, presumably, because thrombocytosis resulted in the unfavorable outcome of the whole group, or because of the relatively small

Table V. Multivariate analysis of survival.

| | p-Value | HR | 95% CI | |
|----------------|---------|-------|--------|-------|
| | | | Lower | Upper |
| Thrombocytosis | 0.006 | 1.576 | 1.141 | 2.176 |
| T status | 0.001 | 1.341 | 1.129 | 1.594 |
| N status | <0.001 | 1.726 | 1.474 | 2.020 |

CI: Confidence interval; HR: hazard ratio.

number of cases. Thus the survival rates among the different stages in patients with thrombocytosis did not show a wide range. According to Mountain (1), the five-year survival in pathological stage IA and IB cases was 67% and 57%, close to the five-year survival for our patients overall (75 and 59%, respectively). The survival rate was significantly reduced in patients with preoperative thrombocytosis according to Pedersen and Hamilton (12), and in the evaluated patients in the trial of Aoe *et al.* (14), while in our study there was also a significant difference in the overall survival between the high and normal platelet level groups. Using univariate analysis of the gender, smoking habit, histology, T status, N status, stage and platelet count, only the latter four had a significant impact on survival. Multivariate analysis of the T status, N status and platelet count showed that all were independent factors for survival. This finding is in accordance with the results of Pedersen and Milman (12), and also of Aoe *et al.* (14) among patients treated with resection or conservative treatments for lung cancer. To sum up, thrombocytosis had a significant negative impact on survival by both uni- and multivariate analyses, and in the separately evaluated squamous histological subgroup. Survival after lung resection was remarkably lower in patients with thrombocytosis during the perioperative period compared to patients with normal platelet counts. Thrombocytosis was evidently more frequent in smokers. In conclusion, the present study has revealed that thrombocytosis during the perioperative period in patients undergoing lung cancer resection can be considered as a potential negative independent factor for survival, and should be taken into account in the decision regarding indication for adjuvant therapy.

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