Original Study

The impact of anaemia, leukocytosis and thrombocytosis on survival in patients with lung cancer resection

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SUMMARY.

INTRODUCTION: Previous studies have reported that preoperative leukocytosis, anaemia and thrombocytosis are related to the prognosis of non-small cell lung cancer (NSCLC). The aim of this study was to determine impact of these haematological parameters in patients of different ages with NSCLC. **MATERIAL AND METHODS:** Among 2,050 patients who underwent lung resection for NSCLC in the 5-year period 2002-2007, 200 were reviewed, of whom 93 were aged above 70 years. **RESULTS:** The frequency of preoperative leukocytosis, anaemia and thrombocytosis was 21% (42/200), 32.5% (65/200), 16.5% (33/200), respectively. The 5-year survival of the patients with and without leukocytosis, anaemia and thrombocytosis was 26.5% vs 27.4%, 28.9% vs 27.2% and 31.7% vs 26.6%, respectively. No significant difference was observed in the 5-year survival according to either the presence or absence of preoperative leukocytosis, anaemia and thrombocytosis, or the age group, <70 years and ≥70 years. Significant difference was found in the haemoglobin (Hb) level between the different age groups, 3 ($p=0.0025$), 6 ($p<0.001$) and 12 ($p=0.033$) months postoperatively. Leukocytosis, anaemia and thrombocytosis were frequently found in earlier stages of NSCLC and in connection with extended types of surgical resection. **CONCLUSIONS:** Preoperative anaemia, leukocytosis and thrombocytosis are not related with patient survival after lung resection for NSCLC, although the measurement is inexpensive and routinely used. An abnormal blood cell count in patients with cancer is not always a tumour-related phenomenon. ***Pneumon 2011, 24(1):35-39.***

INTRODUCTION

Lung cancer results in over one million cancer-related deaths each year worldwide[1]. Approximately 85% of the patients have non-small-cell lung

cancer (NSCLC), and at the time of diagnosis the majority of patients have locally advanced or metastatic disease. Only 35% patients with the diagnosis of NSCLC present with early-stage disease, defined as stage I and II disease, and a select group of patients with stage IIIA have surgically resectable disease[2]. Although multiple prognostic factors have been reported for patients with NSCLC, the majority of these factors are relevant to advanced or metastatic disease[3]. Previous studies have demonstrated that preoperative leukocytosis, anaemia and thrombocytosis are related to the prognosis of patients who have undergone lung resection for NSCLC[4]. The estimation of the preoperative blood cell count is easy, readily available and economical, and is used routinely. The aim of this study was to analyze the impact of preoperative leukocytosis, anaemia and thrombocytosis on survival in patients in two age groups, <70 years and ≥70 years, undergoing lung resection for NSCLC.

PATIENTS AND METHODS

The records were reviewed of 200 consecutive patients with NSCLC who underwent surgical lung resection between 2002 and 2007. Patients were classified into two age groups, those older and those younger than 70 years. Of the 200 patients, 107 were aged <70 years (range 42-69 years), and 93 were aged ≥70 years (range 70-78 years), and 161 (80.5%) were males and 39 (19.5%) females. The patients were followed up for a period of 1-84 months, with a median of 25 months. The baseline characteristics of the study patients are summarized in Table 1. Almost all the patients (95%) were in the Eastern Cooperative Oncology Group status 0 or 1. The preoperative assessment included the medical history, clinical and pathological staging and routine blood tests. Clinical staging was based on bronchoscopy, computed tomography (CT) of the chest, abdomen and brain, and bone scintigraphy. Histological typing was made according to WHO criteria, and the clinical and histological stages were determined according to the International TNM classification for lung cancer[5,6]. The standard follow-up protocol included blood and laboratory tests 3, 6 and 12 months postoperatively, and then every 6 months for the first 2 years, and every 12 months until the 5th year. The preoperative white blood cell count (WBC), haemoglobin level (Hb) and platelet count were obtained before the surgical procedure. Leukocytosis as defined as WBC >10x10^9/L, anaemia was defined as Hb <130 g/L in men and <120 g/L in women, and thrombocytosis as a platelet count >420x10^9/L[7].

TABLE 1. The baseline characteristics of the patients with non-small cell lung cancer (NSCLC) treated by surgical resection (n=200).

	No of patients (%)
Age	
<70 years	107 (53.5%)
≥70 years	93 (46.5%)
Gender	
Male	161 (80.5%)
Female	39 (19.5%)
Histological stage	
I	30 (15%)
II	99 (49.5%)
III	67 (33.5%)
IV	4 (2%)
Histology	
Squamous cell carcinoma	140 (70%)
Adenocarcinoma	55 (27.5%)
Large cell carcinoma	5 (2.5%)
Type of resection	
Pneumonectomy	54 (27%)
Extended pneumonectomy	31 (15%)
Lobectomy	93 (46.5%)
Extended lobectomy	14 (7%)
Bilobectomy	5 (2.5%)
Wedge resection	3 (1.5%)

The protocol was approved by the Ethics Committee of the institution.

Statistical analysis

Data are reported as mean ± standard deviation (SD). The survival rate was estimated by the Kaplan-Meier method, and the log-rank test was used to compare survival rates between the two age groups. Other comparisons were made using the Mann-Whitney test, Pearson Hi^2 test, Fisher exact test, and Wilcoxon signed rank test. Significance was accepted as a p value of <0.05.

The statistical package used was R (version 2.8.0 (2008-10-20); Copyright (C) 2008 the R Foundation for Statistical Computing; ISBN 3-900051-07-0.

RESULTS

The frequencies of preoperative leukocytosis, anaemia and thrombocytosis were 21% (42/200), 32.5% (65/200), 16.5% (33/200), respectively. Leukocytosis was found in 15 patients ≥70 years and in 27 patients <70 years. Ac-

cording to TNM staging, in the patients with leukocytosis aged ≥70 years, 5 were in stage I, 7 in stage II and 3 in III, while in the group aged <70 years, 2 were in stage I, 17 in stage II and 8 in stage III of the disease. As shown in Figure 1, the 5-year survival of the patients with and without leukocytosis was 26.5% and 27.4% respectively (p=0.357). In patients aged <70 years, the 5-year survival with and without leukocytosis was 27.2% and 26.1% respectively (p=0.393), and in patients aged ≥ 70 years it was 21.4% and 29.9% respectively (p=0.757).

Preoperative anaemia was found in 29 patients aged ≥ 70 years and in 36 patients aged <70 years. Of the patients with anaemia aged ≥70 years, 5 were in stage I, 12 in stage II, 9 in stage III and 3 in stage IV, while in the group aged < 70 years, 1 was in stage I, 25 were in stage II and 10 in stage III. In the whole cohort, the 5-year survival of patients with anaemia was 28.9% and of those without anaemia 27.2% (p=0.631). In the group aged <70 years the corresponding 5-year survival rates were 30.7 vs 25.8% (p=0.821) (Figure 2). Poorer results were noted in the group aged ≥70 years, 24.4% vs 30% (p=0.345), but not to a statistically significant degree.

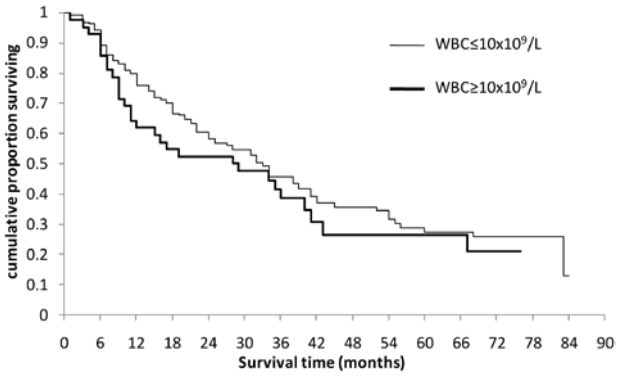
Thrombocytosis was found in 9 (27.27%) patients aged ≥70 years, and in 24 (72.72%) of those aged <70 years. Of the patients with thrombocytosis aged ≥70 years, 3 were in stage I, 3 in stage II, and 2 in stage III and 1 was in stage IV, while of those aged <70 years, 1 was in stage I, and 16 were in stage II and 7 in stage III of the disease. Similar 5-year survival was observed in the patients with and without thrombocytosis, 31.7% and 26.6% respectively (p=0.504). In the patients aged <70 years, the corresponding 5-year survival rates were 32.5% vs 25.1% (p=0.997), while in those aged ≥70 years the rates were 24.3% vs 29.2% (p=0.177) (Figure 3).

In this case series we significant differences were not observed in the 5-year survival of patients with and without leukocytosis, anaemia and thrombocytosis, nor between the two age groups, < and ≥ 70 years.

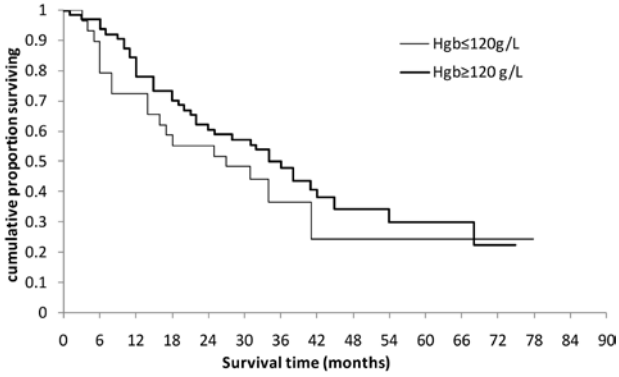
The distribution of preoperative leukocytosis, anaemia and thrombocytosis according to the type of surgical resection is shown in Table 2.

No significant difference was found among preoperative Hb levels (mean±SD) according to the type of surgical resection (Table 3).

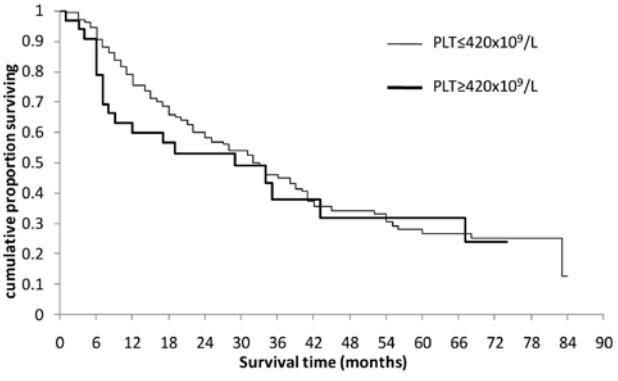
Significant differences were found in the Hb levels between the two age groups, < and ≥70 years, 3 (p=0.00248), 6 (p< 0.001) and 12 (p=0.03263) months postoperatively, with higher Hb levels in the younger patients at all follow-up periods, as shown in Table 4.



ΕΙΚΟΝΑ 1. Η αθροιστική ποσοστιαία επιβίωση ανάλογα με την προεγχειρητική παρουσία ή όχι λευκοκυττάρωσης δεν είχε στατιστικά σημαντική διαφορά (log-rank test, X-2=0,85, P = 0,357).



ΕΙΚΟΝΑ 2. Η αθροιστική ποσοστιαία επιβίωση ανάλογα με την προεγχειρητική παρουσία ή όχι αναιμίας δεν είχε στατιστικά σημαντική διαφορά (log-rank test, X-2=0,891, P = 0,345).



ΕΙΚΟΝΑ 3. Η αθροιστική ποσοστιαία επιβίωση ανάλογα με την προεγχειρητική παρουσία ή όχι θρομβοκυττάρωσης δεν είχε στατιστικά σημαντική διαφορά (log-rank test, X-2=0,448, P = 0,504).

TABLE 2. Distribution of preoperative leukocytosis, anaemia and thrombocytosis according to type of surgical resection in patients with non-small cell lung cancer (NSCLC) (n=200).

	No of patients (%)		
Type of resection	**Leukocytosis**	**Anaemia**	**Thrombocytosis**
Pneumonectomy	14 (33.33%)	21 (32.31%)	10 (30.30%)
Extended pneumonectomy	7 (16.67%)	7 (10.77%)	9 (27.27%)
Lobectomy	18 (42.86%)	28 (43.07%)	11 (33.33%)
Extended lobectomy	1 (2.38%)	7 (10.77%)	3 (9.09%)
Bilobectomy	2 (4.76%)	1 (1.54%)	0
Wedge resection	0	1 (1.54%)	0
Total	42	65	33

TABLE 3. Preoperative haemoglobin level (Hb) according to type of resection in patients with non-small cell lung cancer (NSCLC) (n=200).

Type of resection	**Preoperative Hb ± SD**	***p***
Pneumonectomy	123.5±13.36	0.08
Extended pneumonectomy	127.5±13.7	0.25937
Lobectomy	127±15.01	0.33496
Extended lobectomy	124.6±18.13	0.77565
Bilobectomy	119.8±21.03	0.35168
Wedge resection	133±16.76	0.31987

TABLE 4. Postoperative follow-up haemoglobin levels (Hb) in the two age groups (< and ≥70 years).

	Mean Hb ± SD		
Age groups	**3 months**	**6 months**	**12 months**
<70 years	131.4 ± 15,55	127.9 ± 13.81	129.8 ± 15.54
≥70 years	121.8 ± 12.55	123,3 ± 11,94	127.3 ± 11.25
p value	0.00248	<0.001	0.03263

DISCUSSION

In the present study, the frequencies of preoperative leukocytosis, anaemia and thrombocytosis were 21%, 32.5% and 16.5%, respectively. In previously published studies based on advanced stage NSCLC or small cell carcinoma (SCLC), higher frequencies of leukocytosis (28-60%), anaemia (48-80%) and thrombocytosis (16-48%) were reported[3,8-10]. Only a few published papers are focused on resectable NSCLC[4]. A possible explanation for differences in the frequencies might be due to differences in distribution of clinical and histological staging. In the present case series, leukocytosis, anaemia and thrombocytosis were found frequently (p=0.03) in patients aged younger than 70 years. Leukocytosis in patients with malignancy is usually caused by infection, bone marrow metastasis or the use of corticosteroids. In patients with NSCLC, leukocytosis may present without previous underlying conditions[3,9,11], or it may be caused by unregulated production of haematopoietic cytokines, such as granulocyte-colony-stimulating factor[12]. Similarly to tumour related leukocytosis, anaemia and thrombocytosis might be regarded as a paraneoplastic phenomenon[13]. Anaemia is commonly observed in patients with lung cancer, and according to some reports it estimated to occur in up to 50% of preoperative patients[14]. Lower baseline Hb levels have been associated with decreased survival[15]. Anaemia also has been considered to be a sign of a more aggressive tumour, which can influence the treatment modality, being associated with worsening of tumour hypoxia within solid tumours and an increase in radio-resistance[16]. Regarding the platelets, tumour associated elevation of bone marrow-stimulating cytokines such as interleukin (IL)-6, IL-1 beta and macrophage colony-stimulating factor (M-CSF) might be one of possible mechanisms for development of thrombocytosis in patients with lung cancer[17]. Thrombocytosis might affect survival by facilitating cell invasion and metastasis[18]. It is well known that platelets have been reported to play an important role in the process of tumour angiogenesis[19].

In this case series leukocytosis was found in 15.5% (31/200) of patients who were in stage I/II, and in 5.5% (11/200) of patients in stage III/IV. Anaemia was noted in 21.5% (43/200) of patients in stage I/II, and in 11% (22/200) of patients in stage III/IV. Thrombocytosis was found in 11.5% (23/200) of patients in stage I/II, and in 5% (10/200) of patients in stage III/IV. Patients in stage IV have been

operated on because of a single brain or adrenal gland metastasis in the presence of T1/T2 tumour. In this case series leukocytosis, anaemia and thrombocytosis were more frequently found in earlier stage of diseases, which had not been found in previously published studies[7,12,20]. The present study was based on patients with resectable NSCLC, whereas previous studies included patients at more advanced stages of NSCLC or SCLC. Regarding the type of resection, preoperative leukocytosis, anaemia and thrombocytosis were more frequently found in patients requiring extended resection than in those undergoing limited resection (p=0.03), as shown on Table 3.

In conclusion, while the preoperative measurement of the blood cell count is a routinely used examination that is easy, readily available and economical, abnormal blood cell counts are not useful for estimation of survival in either older or younger patients operated on for lung cancer. The histological staging and the grade of aggressiveness of the tumour behaviour are the only predictors of long-term survival.

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